Stereocontrolled α-Alkylation of Oxime Ether Derived from Terpene: Efficient Synthesis of New Chiral γ- and δ-Amino Alcohols

Thomas Jennequin,[a] Stéphane Labat,[a] Loïc Toupet,[b] Jean-Claude Caille,*[c] Marc Mauduit*[a]

[a] 'Sciences Chimiques de Rennes', UMR 6226 CNRS – Equipe Chimie Organique et Supramoléculaire – Ecole Nationale Supérieure de Chimie de Rennes, Avenue du Général Leclerc, 35700 Rennes, France
E-mail: marc.mauduit@ensc-rennes.fr

[b] Groupe Matière Condensée et Matériaux, UMR CNRS 6626, Avenue du General Leclerc CS 74205, 35042 Rennes, France

[c] Zambon ZI la Croix-Cadeau, B.P. 10079, 49243 Avrillé, France
E-mail: jean-claude.caille@zambongroup.com

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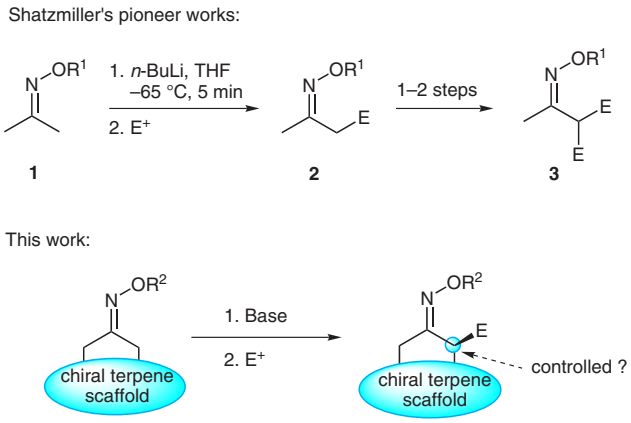
Abstract: The alkylation of (+)-nopinone oxime ether with various electrophiles afforded the corresponding adduct with a total stereoselectivity. Further reduction of the oxime ether afforded an easily access to new chiral γ-and δ-amino alcohols of high interest for catalysis and asymmetric synthesis.

Key words: oxime ether, (+)-nopinone, stereocontrolled alkylation, amino alcohols

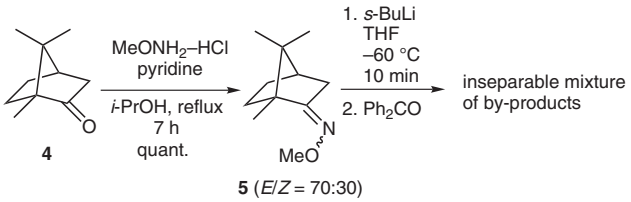
The oxime ether function represents a great interest in organic synthesis as it can easily be converted into ketone,[1] amine,[2] or nitrile[3] derivatives. Moreover, this function shows an interesting reactivity in radical reactions[4] and 'enol-like' reactions[5] or can be used as efficient substrates in 1,2-addition reactions of organometallics reagents.[6] Surprisingly, chiral organometallic additions and stereoselective radical cyclization have been fully studied, whereas no asymmetric 'enol-like' reaction has been described to date. Pioneers in the area of the 'enol-like' reaction of oxime ether derivatives, Shatzmiller and coworkers have fully studied the α-alkylation of linear oxime ether **1** toward several electrophiles using lithiated strong bases (such as *n*-BuLi or LDA).[5] Products **2**, resulting from lithiation of the α-carbon *syn* to the oxime ether, were obtained in excellent yields (Scheme 1). It is worth noting that the geometrically directed α-lithiation of the *O*-alkyl oxime led to a remarkable control of the regioselectivity during the alkylation, since only one adduct **3** was formed even if a double alkylation process was performed.

The aim of this work is to study an asymmetric version of the aforementioned oxime ether alkylation using a chiral scaffold derived from terpenes (Scheme 1). This method should promote a rapid and efficient access to new chiral γ- and δ-amino alcohols, which are components of many interesting biologically active molecules.

We started our study with the (+)-camphor (**4**), which is a cheap and readily available chiral terpene. Reaction of methoxylamine hydrochloride in the presence of pyridine



Scheme 1 α-Alkylation of oxime ether



Scheme 2 Attempt for alkylation of oxime methyl ether **5** derived from (+)-camphor

at 80 °C for seven hours in 2-propanol afforded the corresponding oxime methyl ether **5** in quantitative yield with an *E/Z* ratio of 70:30. Unfortunately, deprotonation of **5** using *s*-BuLi at –60 °C in THF followed by the addition of benzophenone afforded a mixture of inseparable byproducts (Scheme 2).

Despite this result, we then decided to continue our effort with the (+)-nopinone (**6**) readily available from β-pinene terpene. The use of methoxylamine hydrochloride in ethanol with pyridine under reflux over one hour afforded the desired oxime methyl ether **7** in quantitative yield with an *E/Z* ratio of 90:10. Unfortunately, separation of isomers by silica gel chromatography was unsuccessful. And many attempts to improve the selectivity towards *E*-isomer using alkoxylamine bearing more bulky groups such as benzyl or *tert*-butyldimethylsilyl have failed leading to lower or similar selectivities. We then investigated the alkylation of the *E/Z* mixture of **7** using *tert*-butylbro-

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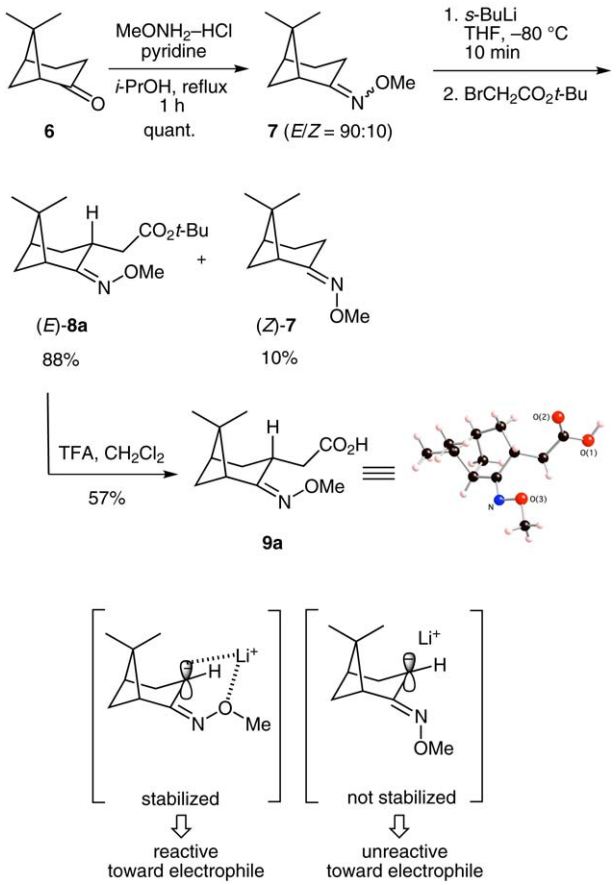
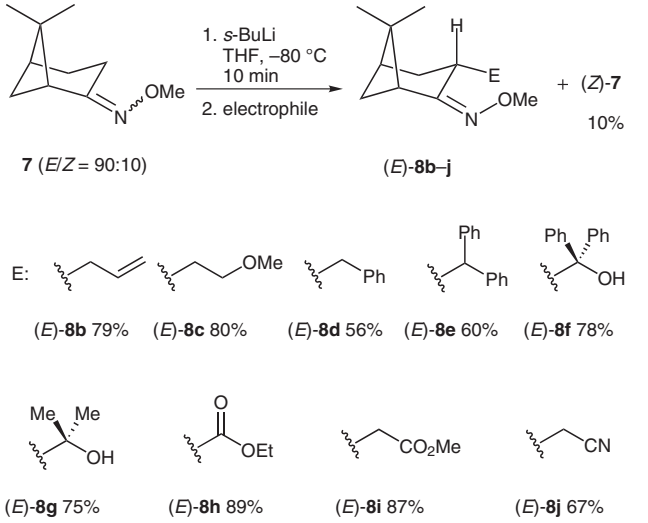


Scheme 3 Stereoselective α-alkylation of (+)-nopinone oxime methyl ether **7**



Scheme 4 Scope of alkylation of oxime methyl ether **7**

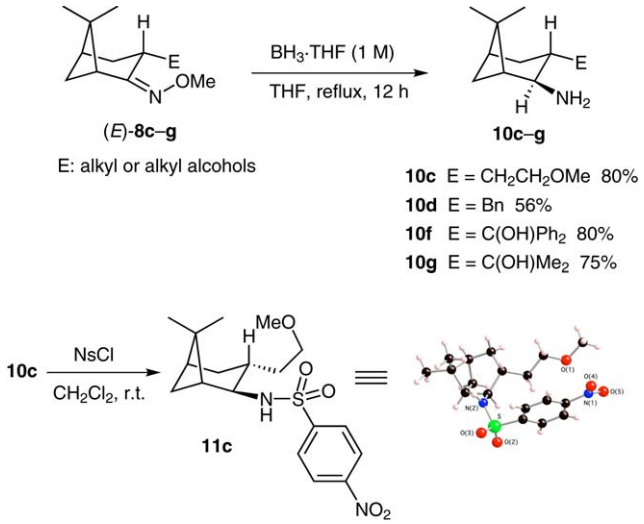
moacetate as electrophile. The deprotonation step using *s*-BuLi was performed at –80 °C in order to avoid the formation of byproducts. Remarkably, the reaction occurred on the *E*/*Z* mixture of isomers and only one adduct **8a** was observed by NMR in the presence of an unreactive oxime methyl ether (*Z*)-**7**. Taking into consideration, Shatzmiller results,[5a] we supposed that only the *E*-isomer of **7** is able to react through a *syn*-alkylation process. This reactivity can be explained by a possible stabilization of the carbanion intermediate with the oxygen lone pair of the oxime methyl ether function (Scheme 3). The initial 10% of (*Z*)-**7** can be separated after a silica gel chromatography and then adduct (*E*)-**8a** was isolated in 88% yield. The stereochemistry of the alkylated product was determined by usual NMR spectroscopical studies (COSY and NOESY) showing that the approach of the carbanion to the electrophile occurs from the opposite side of the *gem*-dimethyl bridge, as expected. The X-ray crystal structure analysis of acid **9a**,[7] resulting from the saponification of the *tert*-butylester **8a**, allowed us to confirm both the absolute configuration of the new chiral center and the *E*-configuration of the oxime ether functionality. Therefore, we clearly established the geometrically directed α-lithiation of oxime ether as previously proposed by Shatzmiller leading to the unique reactivity of the *E*-isomer towards the alkylation.

A wide range of electrophiles bearing different functions such as ketone, ester, nitrile, allyl, and ether were also used furnishing the corresponding single adducts **8b–j** in 56–89% of yields after purification by chromatography (Scheme 4).

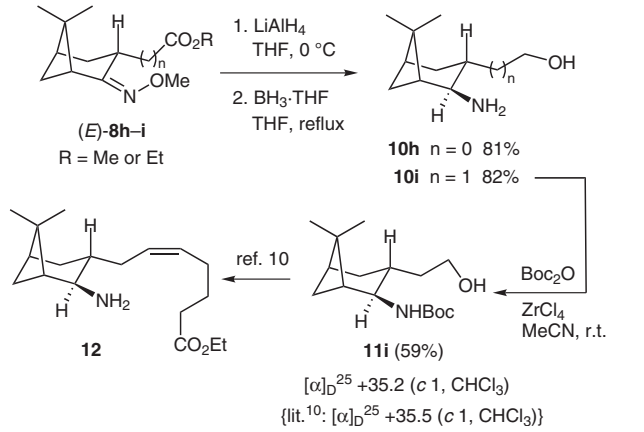
In order to prepare several functionalized chiral scaffolds of high interest in synthesis and catalysis, we then focused on the reduction of the oxime ether fragment. The usual procedure using lithium and aluminum hydrides only afforded byproducts resulting from the degradation of the nopinone scaffold. The hydrogenation was also investigated; however, no reaction occurred even under drastic conditions (PtO_2, H_2, 50 bar, 12 h). Finally, the use of BH_3·THF complex in THF at reflux condition appeared more suitable to reduce the oxime ether functionality (Scheme 5). Starting with **8c–g**, the corresponding amines **10c–d**, or γ-amino alcohols **10f–g** were isolated in moderate to good yields after chromatographic purification. Moreover, the X-ray analysis of the nosylamide **11**[7] derived from **10c** allowed us to determine the absolute configuration of the new stereogenic center bearing the amine function, which is in *anti* position with respect to the alkylated group (Scheme 5).

The alkylated oximes **8h** and **8j** required a prior reduction of the ester functionality by using lithium aluminum hydride at 0 °C (Scheme 6). The corresponding oxime alcohols were then reduced in the presence of BH_3·THF complex in THF at reflux condition yielding the desired γ-amino alcohols **10h** and δ-amino alcohol **10i** in good isolated yields. Moreover, the treatment of **10i** by Boc_2O in the presence of tetrachlorozirconium lead to the corresponding carbamate **11i** in 59% of yield, which is a key intermediate in the synthesis of a prostaglandin receptor antagonist **12**.[8,9]

As reported by Shatzmiller et al., aldehydes are excellent prochiral electrophiles for the alkylation of oxime alkyl ether promoting the formation of stereogenic alcohols.[5a] To complete our study, we were interested to evaluate the



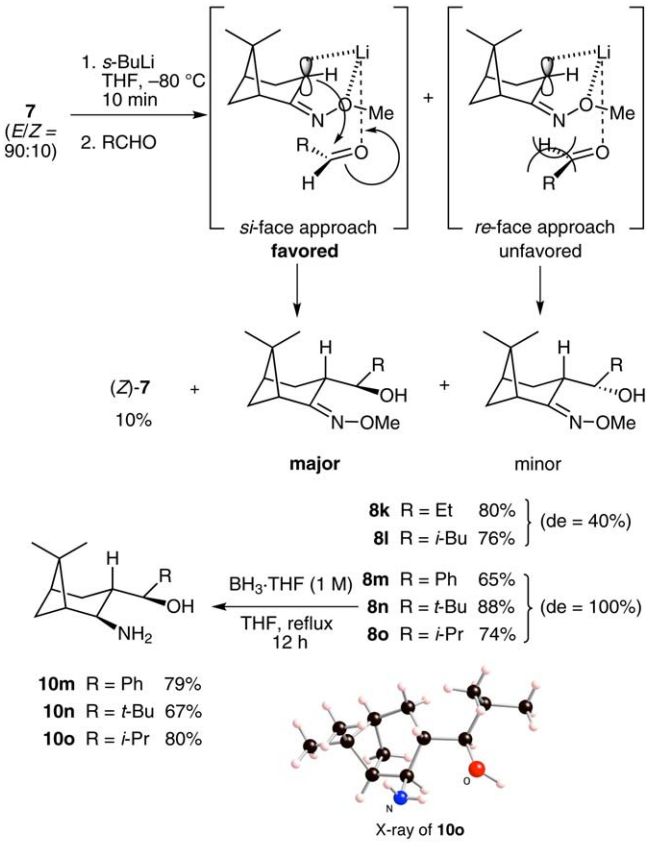
Scheme 5 Stereoselective reduction of the oxime methyl ether function



Scheme 6 Two-step reduction of the oxime methyl ether **8h** and **8i**; creation of a key intermediate of the prostaglandine receptor antagonist **12**

ability to control another asymmetric center. In this particular purpose, we performed the alkylation reaction using five different aldehydes (Scheme 7). Resulting alcohols **8k** to **8o** were obtained in 65–88% of isolated yields with a diastereoselectivity ranged between 40% de (**8k**,**l**) to 100% de (**8m**–**o**) depending on the steric hindrance of the aldehyde used. The further reduction of the oxime methyl ether function afforded the corresponding γ-amino alcohols **10m**–**o** in good yields after silica gel purification. The absolute configuration of these three new chiral centers formed were determined by the X-ray crystal structure analysis of **10o**[7] showing that the carbanion approach is preferentially occurred on the *Si* face of the aldehyde.

In summary, we have developed an efficient stereoselective α-alkylation of oxime ether derived from (+)-nopinone. This method led us to develop a convenient pathway in the asymmetric synthesis of a prostaglandin receptor antagonist. Additionally, a wide range of new chiral γ- and δ-amino alcohols have been synthesized, which could be useful in the design of new ligands for asymmetric



Scheme 7 Stereoselective alkylation of (+)-nopinone oxime methyl ether **7** with aldehydes; formation of chiral γ-amino alcohols

catalysis[10] and also as new chiral agents for kinetic resolution.[11]

Experimental Section

(+)-Nopinone Oxime Ether 7

To a solution of methoxylamine hydrochloride (1.1 mmol) in EtOH (30 mL) were added pyridine (1.1 mmol) and (+)-nopinone (**6**, 1.0 mmol). The mixture was heated to 80 °C for 1 h. Ethanol was then removed under vacuum. Aqueous HCl solution (1 N) was added to the residue and the oxime ether was extracted with Et_2O. The combined organic layers were washed with sat. aq $NaHCO_3$ solution and then with brine. The organic phase was dried on anhyd $MgSO_4$, and the solvent was carefully removed under vacuum to afford **3** in 90% yield with an *E*/*Z* ratio of 90:10. The *E*- and *Z*-isomers are only differentiated by the ^{1}H NMR chemical shift of the oxime methyl ether function.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.78 (s, 3 H, NOMe, *E*-isomer), 4.72 (s, 0.3 H, NOMe, *Z*-isomer), 2.68 (tt, 1 H, *J* = 5.5 Hz,), 2.53 (t, 1 H, *J* = 5.5 Hz), 2.33–2.46 (m, 2 H), 2.03 (m, 1 H), 1.83–1.90 (m, 2 H), 1.32 (d, 1 H, *J* = 10.2 Hz), 1.24 (s, 3 H), 0.78 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.89, 61.29, 61.15, 48.24, 41.47, 40.96, 30.06, 27.61, 25.43, 21.50.

$[\alpha]_D^{20}$ +11.9 (*c* 0.71, $CHCl_3$).

General Procedure for the Alkylation of (+)-Nopinone Oxime Ether

To a solution of **3** (1.0 mmol) in dry THF (10 mL) was added dropwise *s*-BuLi in a solution of hexane (1.1 mmol) at –80 °C. The mix-

ture was then stirred for 20 min at this temperature. Then the electrophile (1.0 mmol) was added slowly. The reaction mixture was stirred at –80 °C for 1–6 h. After the completion of the reaction, aq sat. $NaHCO_3$ solution was added at –80 °C to the mixture. The compound was extracted with Et_2O. The combined organic layer were washed with brine and then dried over anhyd $MgSO_4$. The solvent was removed under vacuum to afford the alkylated oxime ether in moderate to good yield.

tert-Butylacetate (+)-Nopinone Oxime Methyl Ether 8a

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75 (s, 3 H), 3.26 (tdd, 1 H, *J* = 11.9, 9.6, 2.6 Hz), 3.07 (dd, 1 H, *J* = 9.6, 6.3 Hz), 2.50 (t, 1 H, *J* = 5.5 Hz), 2.37 (ddt, 1 H, *J* = 8.5, 5.5, 2.8 Hz), 2.07–2.16 (m, 2 H), 1.98–2.02 (m, 1 H), 1.75–1.91 (m, 2 H), 1.40 (s, 9 H), 1.32 (d, 1 H, *J* = 5.1 Hz), 1.21 (s, 3 H), 0.71 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.78, 165.14, 80.65, 61.34, 48.31, 41.91, 41.22, 40.92, 30.11, 28.17 (3 C), 28.06, 25.91, 25.40, 21.58.

$[\alpha]_D^{20}$ +8.04 (*c* 0.26, $CHCl_3$).

2-Acetic Acid Nopinone Oxime Methyl Ether 9a

To **8a** (1.0 mmol) in dry CH_2Cl_2 (5 mL) was added TFA (5 mL) dropwise at r.t. The mixture was then stirred for 2 h at this temperature. The reaction mixture was quenched with aq sat. $NaHCO_3$ solution followed by the extraction of the acid with CH_2Cl_2. The combined organic layers were washed with brine and dried over anhyd $MgSO_4$. The solvent was then removed under vacuum to afford **9a** in 57% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.76 (s, 3 H), 3.38 (m, 1 H), 3.07 (dd, 1 H, *J* = 9.6, 6.7 Hz), 2.53 (t, 1 H, *J* = 5.5 Hz), 2.37–2.44 (m, 1 H), 2.16–2.31 (m, 2 H), 2.00–2.05 (m, 1 H), 1.51–1.57 (m, 2 H), 1.31 (d, 1 H, *J* = 5.3 Hz), 1.22 (s, 3 H), 0.72 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.92, 164.72, 61.39, 48.20, 41.24, 40.81, 30.35, 27.59, 25.95, 25.37, 21.63.

$[\alpha]_D^{20}$ +53 (*c* 0.05, $CHCl_3$).

General Procedure for the Reduction of the Oxime Ether Group

To the oxime ether (1.0 mmol) was added BH_3·THF solution (1 M) in THF (3.0 mmol). The mixture was stirred under reflux (80 °C) overnight. The mixture was quenched with aq NaOH solution (1 M) and the product was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhyd $MgSO_4$, and concentrated under vacuum to afford the corresponding compound in moderate to good yields.

(1*R*)-1-{(2*S*,3*S*)-2-amino-6,6-dimethylbicyclo[3.1.1]heptan-3-yl}-2-methylpropan-1-ol (10o)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.32 (m, 1 H), 3.04 (dd, 1 H, *J* = 7.5, 1.8 Hz), 2.23–2.27 (m, 1 H), 2.15 (m, 2 H), 1.85–1.95 (m, 2 H), 1.67–1.82 (m, 3 H), 1.17 (s, 3 H), 1.06 (s, 3 H), 0.96 (d, 3 H, *J* = 6.7 Hz), 0.79 (d, 3 H, *J* = 6.7 Hz), 0.64 (d, 1 H, *J* = 9.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 83.07, 59.15, 49.72, 40.31, 37.19, 31.98, 28.48, 28.15, 27.185, 21.54, 19.36, 12.96.

$[\alpha]_D^{20}$ +51.6 (*c* 0.62, $CHCl_3$).

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