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Asymmetric Addition of Alkoxy Ethynyl Anion to Chiral *N*-Sulfinyl Imines

Charlie Verrier, Sébastien Carret, and Jean-Francois Poisson*

Département de Chimie Moléculaire (SERCO), UMR-5250, ICMG FR-2607, CNRS, Université Joseph Fourier, BP 53, 38041 Grenoble Cedex 9, France

jean-francois.poisson@ujf-grenoble.fr

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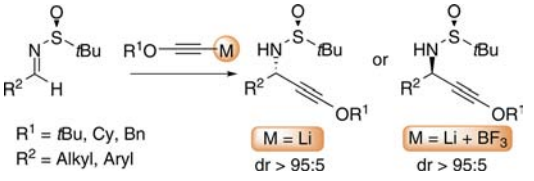
ABSTRACT



The addition of lithiated ynol ethers to chiral *N*-sulfinyl imines proceeds in high yield and diastereoselectivity. The selectivity is completely reversed by the addition of boron trifluoride. These alkoxypropargyl sulfinamides can be reduced to afford enol ethers, selectively oxidized to busyl derivatives, or the ynol ether can be hydrolyzed to afford *β*-amino esters.

Heterosubstituted alkynes such as ynamines, ynamides,[1] and ynol ethers have received considerable attention over the past decade due to their particular structure and synthetic potential as versatile key intermediates in organic chemistry. While the synthetic utility of ynamides has been particularly studied,[2] their oxygenated analogues, ynol ethers, are still underexploited. These oxygenated electron-rich alkynes have recently found applications in cycloadditions, gold catalysis, or carbocupration.[3] The ynol ether moiety is generally formed from a pre-existing function on the molecule, mainly by two methods: from an ester or a carbonyl derivative,[4] or by oxidation of a terminal alkyne.[5] In a complementary fashion, the ynol ether can be introduced by nucleophilic addition of an alkoxy ethynyl anion to a carbonyl derivative. This second strategy is very much underdeveloped, with only a few reports on the addition of lithiated alkoxy ethyne to ketone[6] and tosylimine.[7]

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Our research group has acquired expertise in ynol ether chemistry for the formation of chiral enol ethers.[8] The ynol ether is conveniently formed by treatment of a dichloroenol ether[9] with two equivalents of *n*-butyllithium: after a first deprotonation, the intermediate lithiated species **II** undergoes a β-elimination upon warming, leading to a chloroynol ether **III**; a subsequent chlorine lithium exchange with a second equivalent of *n*-butyllithium leads to the lithiated ethynyl ether which can be trapped by electrophiles (Figure 1).[9b] In the present study, we report the unprecedented selective addition of various ethynyl ether anions to *N*-sulfinyl imines,[10] offering a variety of useful substrates.

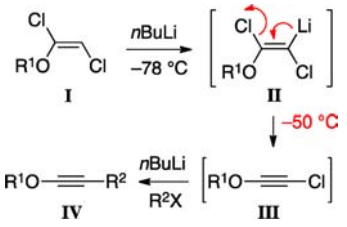

Figure 1. Ynol ethers formed from dichloroenol ethers.

We started our study with the synthesis of different ethynyl ethers. The dichloroenol ethers (**1a**–**c**), obtained by treatment of trichloethylene with the potassium alkoxides, were treated with *n*-butyllithium followed by hydrolysis. The obtained ethynyl ethers showed very different stabilities: the cyclohexyl ethyne ether **2a** could be purified by distillation and proved stable for weeks at −15 °C, in contrast to the benzyl derivative **2b** which proved unstable and the *tert*-butyl ether **2c** that could not be isolated in a pure form. With pure ynol ether **2a** in hand, we studied its addition to the sulfinyl imine **3a**. Using LiHMDS in hexane as the base, a solvent screening showed that THF was the most suitable: diethyl ether and pentane gave both lower yield and selectivity, whereas dichloromethane was inefficient (Figure 2). Using a THF solution of LiHMDS led to an increase in yield and selectivity in every solvent; the reaction in just THF afforded **4a** with the best diastereoselectivity (dr = 91:9) in 92% yield. Surprisingly, the Grignard derivative led to poorer results in terms of both efficiency and selectivity. Using *n*-butyllithium as the base was nearly as selective, a result that prompted us to investigate the direct conversion of dichloroenol ether **1a** to sulfinamide **4a**. Treatment of dichloroenol ether **1a** with *n*-butyllithium (2 equiv) followed by the addition of sulfinyl imine **3a** afforded the alkoxypropargylamine **4a** in similar yield and selectivity (dr = 89:11) compared to the two-step sequence. Overall, this one-pot procedure is much more attractive in terms of both efficiency and simplicity, allowing the formation of *tert*-butyl ynol ether derivatives.

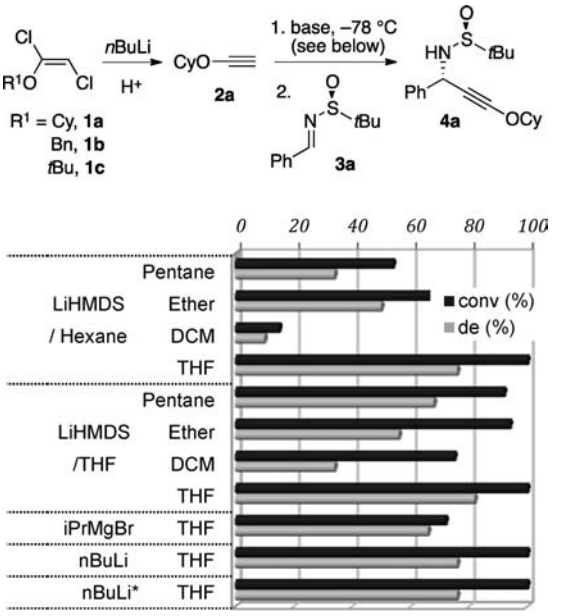

Figure 2. Optimization of the addition of the ynol ether anion to chiral *N*-sulfinyl imines. Ether: diethyl ether. DCM: dichloromethane. *Reaction sequence directly from **1a**.

The best reaction conditions were next applied to the addition of dichloroenol ether **1a,b** to a variety of sulfinyl imines (**3a**–**j**) (Scheme 1). The sequence is efficient starting with both the cyclohexyl (**1a**) and the *tert*-butyl (**1b**) dichloroenol ether, affording the sulfinamides in good yields and selectivities ranging from 92:8 with *p*-methoxybenzyl sulfinyl imine **3d** to a nearly 1:1 mixture with the *p*-nitrobenzyl imine **3e**. The interesting furan derivative **4d** was formed very efficiently with no influence of the heteroatom on the diastereoselectivity. There was no notable stability differences between the cyclohexyl or the *tert*-butyl ynol ethers **4a** and **4b**: both could be stored neat in a freezer (−18 °C) for weeks. In contrast, any reactions attempted with the benzyl derivative **1c** led to a crude addition product which could not be purified, as the substrate decomposed very quickly. Using primary, secondary, and tertiary alkyl sulfinyl imines afforded the addition product in slighlty lower selectivity.

The two diastereoisomers are, in all cases, easily separated by flash chromatography, and the S_S,*S* relative configuration of the crystalline major diastereoisomer **4a** could be assigned by X-ray analysis (Figure 3). The formation of this product can be explained by the attack of the sulfinyl imine by the ynol ether anion through a

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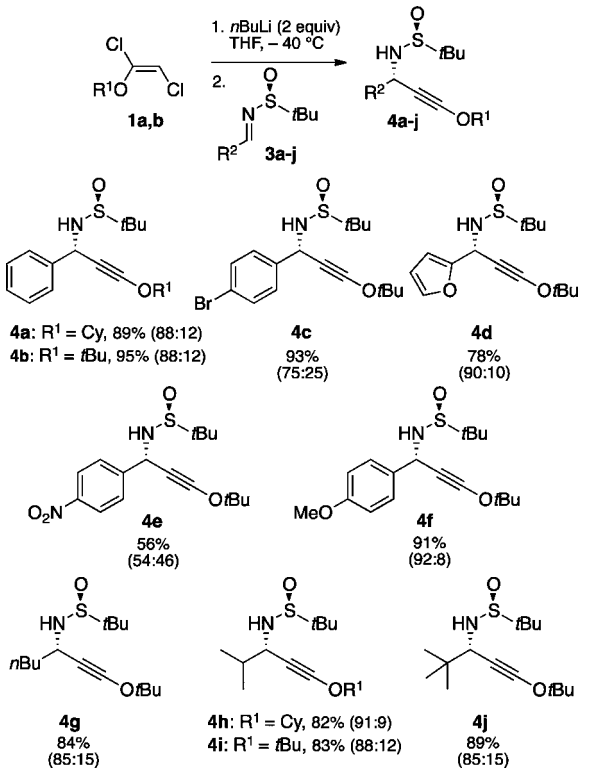
Scheme 1. Lithiated Ynol Ether Addition to *N*-Sulfinyl Imines[a]



[a] All yields refer to the combined isolated yield of separated, pure, diastereoisomers; diastereoisomeric ratios were measured on the ^{1}H NMR spectra of the crude product.

six-membered cyclic transition state, where the lithium coordinated both the amine and the oxygen of the sulfoxide, as previously proposed for the addition of other lithiated species to chiral *N*-sulfinyl imines.[11]

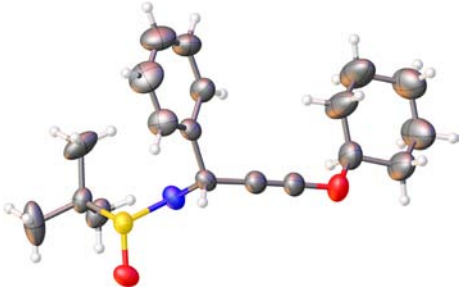


Figure 3. X-ray Ortep of the major diastereoisomer **4a**.

As it would be very interesting to synthesize both isomers from the same enantiomer of the sulfinamide, we looked for additives in order to reverse the diastereoselectivity (Figure 4).[10,12] The addition of DMPU led to a substantial decrease in selectivity, whereas the S_S,R isomer became the major product upon addition of HMPA. The organozincate, generated by addition of dimethylzinc to the lithioacetylenic ether, also led to an inversion of selectivity, but this was still unsatisfactory (dr = 22:78). Despite the high sensitivity of the acetylenic ether, we next tested the influence of Lewis acids. The sulfinyl imine was precomplexed with $AlMe_3$, but no reversal of the diastereoselectivity was observed. Switching to boron trifluoride diethyl etherate was much more rewarding, affording the S_S,R isomer with a complete inversion of selectivity in an excellent yield, showing an unexpected and productive compatibility of ynol ethers with strong Lewis acids.

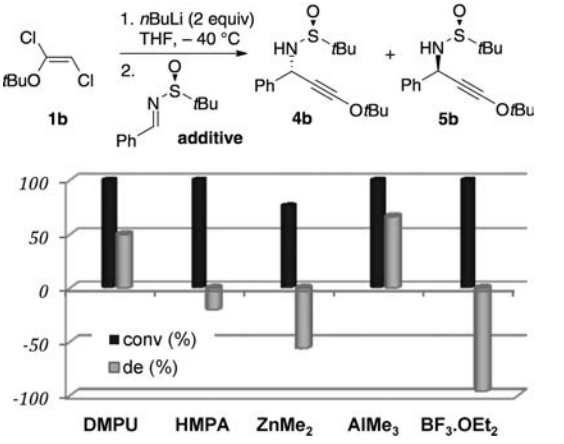


Figure 4. Influence of additives on diastereoselectivity.

The inversion of diastereoselectivity proved general for all the tested sulfinyl imines **3a**–**j**, either aromatic or aliphatic, affording the sulfinamides **5a**–**j** in excellent yield (Scheme 2). In addition, in all cases the selectivity is much higher compared to the reaction without Lewis acid. This reaction could be performed on gram-scale, with the formation of 600 mg of sulfinamide **5a** (83%) and 1.4 g of **5b** (84%), both still obtained as single diastereoisomers (dr > 2:98).

With these new substrates in hand, their potential transformations were next investigated. The hydrolysis of the ynol ethers **4b,j** and **5b,j** was selectively achieved using trifluoroacetic acid and methanol in dichoromethane, affording respectively the β-amino esters **6b,j** and **7b,j** in excellent yield as single diastereoisomers (Scheme 3). No sulfinamide cleavage was observed under these reaction conditions. The addition of ynol ethers to chiral *N*-sulfinyl imines thus affords a direct entry to β-amino acids.

We pursued investigations by a selective reduction of the triple bond by catalytic hydrogenation leading to the enol

(11) For the proposed transition states, see the Supporting Information. See also: (a) Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162–1186. (b) Chen, X.-Y.; Qiu, X.-L.; Qing, F.-L. *Tetrahedron* **2008**, *64*, 2301–2306.

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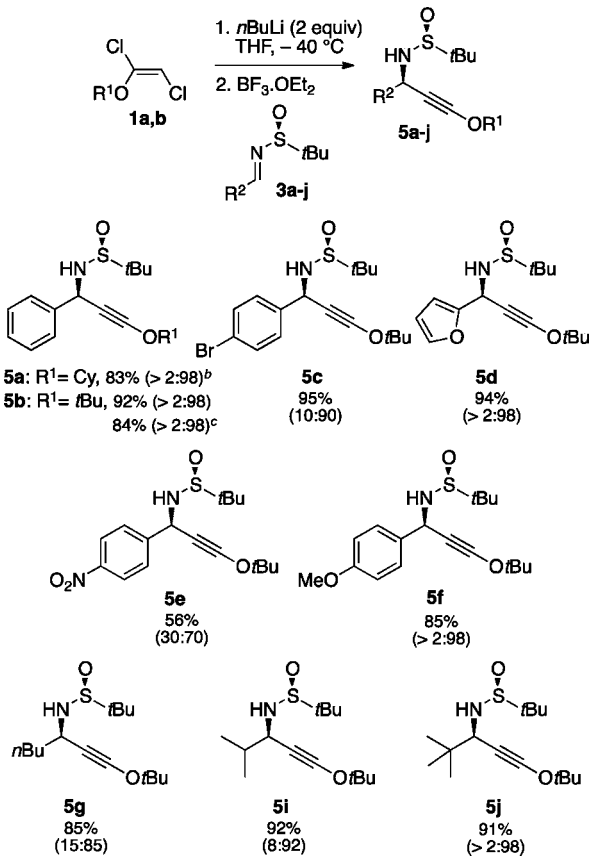
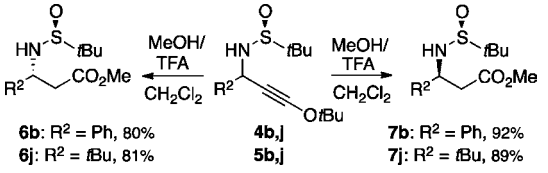
Scheme 2. Lithiated Ynol Ethers Addition to *N*-sulfinyl Imines **3a**–**j** Precomplexed with $BF_3 \cdot OEt_2$[a]



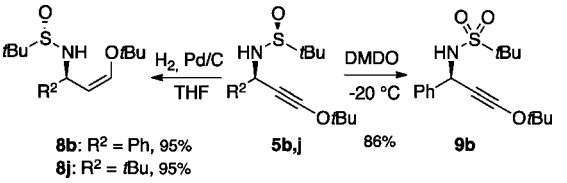
[a] All yields refer to combined isolated yield of separated pure diastereoisomers. [b] Performed on 600 mg scale. [c] Reaction on gram scale (synthesis of 1.4 g of **5b**).

Scheme 3. Synthesis of β-Amino Esters **6** and **7**



ether **8b,j** (95%, Scheme 4).[13] Finally, we have found that the selective oxidation of the sulfinamide to the sulfonamide, in the presence of the ynol ether, could be cleanly achieved using DMDO at −20 °C, affording the busyl protected amine **9b** (86%). This transformation offers an additional option for the derivatization of this class of compounds.

Scheme 4. Reduction and Oxidation of Alkoxypropargyl Sulfinamide **5**



In conclusion, we have reported the addition of lithiated ynol ethers to chiral *N*-sulfinyl imines producing functionalized alkoxypropargyl sulfinamide in good yield and selectivity; with or without boron trifluoride, a complete reversal of the diastereoselectivity is observed. These new densely functionalized substrates can be selectively reduced at the triple bond, oxidized at the sulfur, and upon hydrolysis afford β-amino esters in a very efficient manner. We are pursuing the study of the reactivity of these substrates, and the results will be reported in due course.

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Supporting Information Available. Detailed diastereoisomeric ratios for Figures 2 and 4, complete characterization data and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) Enol ether **8j** was obtained with 10% of over-reduction product.

The authors declare no competing financial interest.