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Stereoselective Synthesis of 1,2-Aminoalcohols by [2,3]-Wittig Rearrangements

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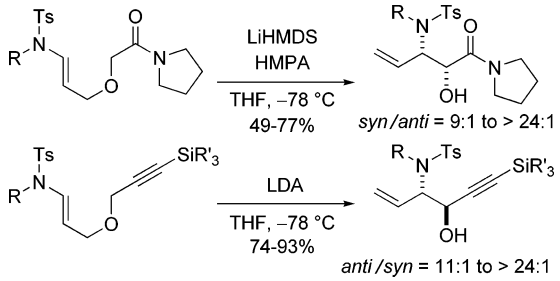
ABSTRACT



[2,3]-Wittig rearrangements of (*E*)-3-aza-allylic alcohol derivatives can provide access to functionalized 1,2-aminoalcohols with high *syn* or *anti* diastereoselectivity depending on the anionic stabilizing group (amide or alkyne).

1,2-Aminoalcohols are encountered in a large number of natural products and/or biologically active compounds.[1] Moreover, optically enriched 1,2-aminoalcohols are often used as building blocks for the preparation of chiral catalysts used in a variety of enantioselective processes.[2] Numerous strategies have been developed to synthesize 1,2-aminoalcohols. Among the different possible routes, those that involve formation of the σ bond between the two heterosubstituted carbons, with control of their configuration, essentially rely on the addition of α-amino or α-alkoxy carbon nucleophiles to carbonyl compounds or imines.[3,4] Alternatively, reductive coupling reactions between C═N and C═O bonds can also be carried out.[5] The preparation of α-alkoxy-β-aminoesters has also been described from α-alkoxy-γ,δ-unsaturated esters that can be obtained by a [3,3]-glycolate Claisen rearrangement. In this latter approach, oxidative cleavage of the double bond to the corresponding acid and subsequent Schmidt reaction were used to introduce the amino substituent.[6] However, to our knowledge, there are no examples of direct formation of the σ bond between the two heterosubstituted carbons in 1,2-aminoalcohols that relies on sigmatropic rearrangements. Herein, we report our results on the [2,3]-Wittig rearrangement of derivatives of

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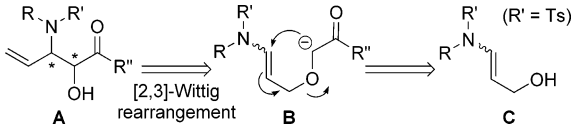
acyclic 3-aza-substituted allylic alcohols as a diastereoselective route to 1,2-aminoalcohols.

With the goal of synthesizing α-hydroxy-β-amino-γ,δ-unsaturated carbonyl derivatives of type **A**, in which the double bond and the carbonyl group could undergo several transformations and hence give access to a variety of functionalized 1,2-aminoalcohols, it was envisaged to carry out the [2,3]-Wittig rearrangement of enamine derivatives of type **B**.[7] The latter compounds would be synthesized from the 3-aza-allylic alcohols of type **C**. Although there has been one previous report dealing with [2,3]-Wittig rearrangements of substrates bearing an enol ether moiety,[8] related reactions have apparently not been studied with enamine derivatives. As compounds of type **B** contain an enamine moiety and a potential allylic alkoxy leaving group, the nitrogen atom was substituted by an electron-withdrawing tosyl substituent (R′ = Ts) to obtain stable enamide derivatives (Scheme 1).

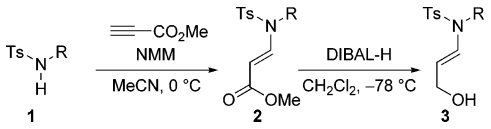
Scheme 1. Synthesis of α-Hydroxy-β-aminocarbonyl Compounds by [2,3]-Wittig Rearrangement



A straightforward route toward allylic alcohols of type **C** starts with the conjugate addition of sulfonamides **1a**−**f** to methyl propiolate in the presence of *N*-methylmorpholine (NMM) (MeCN, 0 °C).[9] The corresponding β-aminoacrylates were obtained as a mixture of geometric isomers with acceptable stereoselectivity in most cases [(*E*)/(*Z*) ≥ 80:20] except when R is a *p*-anisyl group [(*E*)/(*Z*) = 70:30]. After separation by flash chromatography, the major (*E*)-β-aminoacrylates **2a**−**f** were isolated in good yields (55−91%) and were reduced (DIBAL-H, CH_2Cl_2, −78 °C) to the corresponding (*E*)-allylic alcohols **3a**−**f** (84−99%) without alteration of the stereoisomeric purity (Table 1).

Though this access to 3-aza-allylic alcohols of type **C** was convenient, a stereoselective route to both geometric isomers of the latter compounds has also been secured. The copper-catalyzed coupling between sulfonamide **1a** and bromoalkyne **4** [$CuSO_4$·$5H_2O$, 1,10-phenanthroline, K_3PO_4, toluene, 60 °C] afforded the disubstituted ynamide **5** (99%).[10] The latter was reduced to the (*Z*)-allylic alcohol **7** by conversion to an (η^2-alkyne)Ti(II) complex followed by hydrolysis[11] and subsequent deprotection with TBAF (59%, two steps from **5**). On the other hand, deprotection of the hydroxyl group in

Table 1. Synthesis of 3-aza-Allylic Alcohols of Type **C**

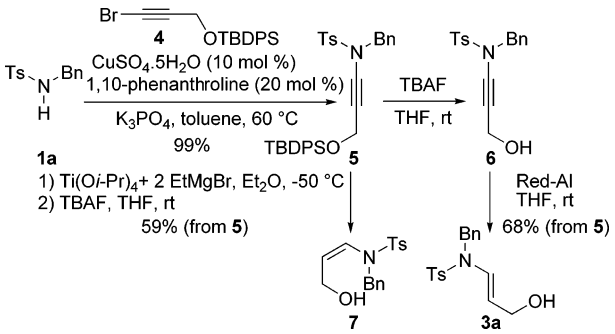


1	R	(*E*)/(*Z*)[a]	**2**	yield (%)[b]	**3**	yield (%)
1a	Bn	92:8	**2a**	91	**3a**	95
1b	$CH_2CH(OMe)_2$	87:13	**2b**	69	**3b**	99
1c	$(CH_2)_2CH{=}CH_2$	82:18	**2c**	82	**3c**	94
1d	$CH_2CH{=}CH_2$	88:12	**2d**	84	**3d**	99
1e	PMB	90:10	**2e**	90	**3e**	93
1f	PMP	70:30	**2f**	55	**3f**	84

[a] Determined by ^{1}H NMR and/or GC−MS. [b] Isolated yield of the (*E*) isomer.

ynamide **5** afforded the propargylic alcohol **6** which could be stereoselectively reduced (Red-Al, THF, rt) to the corresponding (*E*)-allylic alcohol **3a** (68%, two steps from **5**) (Scheme 2).

Scheme 2. Stereoselective Synthesis of 3-aza-Allylic Alcohols



The 3-aza-substituted allylic alcohols had to then be converted to allylic ethers of type **B**, required as substrates for the [2,3]-Wittig rearrangement, and derivatives bearing a carbonyl amide group were first considered.[12] Thus, alcohols **3a**−**f** were alkylated with *N*-(bromoacetyl)pyrrolidine **8** under phase-transfer catalysis (35% aq NaOH/toluene, cat. n-Bu_4NHSO_4) to provide amides **9a**−**f** in good yields (85−99%) (Table 2).

Metalation of amides **9a**−**f** was achieved by treatement with LiHMDS (1.5−2 equiv, THF, −40 °C to 0 °C; method A), and subsequent [2,3]-Wittig rearrangement took place to afford mixtures of the corresponding diastereomeric *syn*- and *anti*-α-hydroxy-β-amino amides **10a**−**f** and **11a**−**f**, respectively, with low to good diastereoselectivities (*syn*/*anti* = 2:1 to 10:1).[13] To improve these results, the effect of additives was investigated. Addition of the polar cosolvent

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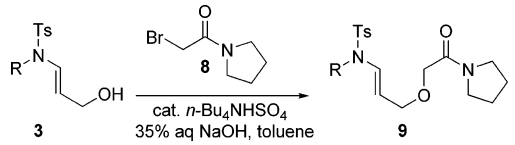
(11) (a) Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003**, *5*, 67−70. (b) (η^2-ynamide)Ti(II) complexes also react with aldehydes to afford 3-aza-allylic alcohols having a trisubstituted double bond: Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727−729.

(12) Mikami, K.; Takahashi, O.; Kasuga, T.; Nakai, T. *Chem. Lett.* **1985**, 1729−1732.

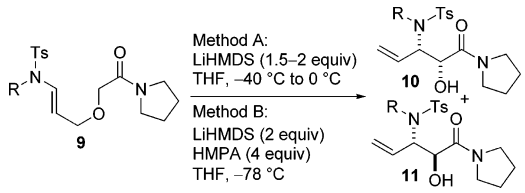
Table 2. Synthesis of Amides **9**



3	R	9	yield (%)
3a	Bn	**9a**	96
3b	$CH_2CH(OMe)_2$	**9b**	97
3c	$(CH_2)_2CH{=}CH_2$	**9c**	99
3d	$CH_2CH{=}CH_2$	**9d**	85
3e	PMB	**9e**	86
3f	PMP	**9f**	97

HMPA (4 equiv) enabled us to achieve the deprotonation of amides **9a**−**f** at a lower temperature (LiHMDS, THF, −78 °C; method B), and under these conditions, subsequent [2,3]-Wittig rearrangements occurred with a dramatic improvement of the diastereoselectivity (*syn/anti* = 9:1 to >24:1) (Table 3).

Table 3. [2,3]-Wittig Rearrangements of Amides **9**

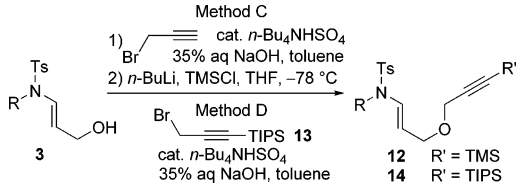


		method A		method B	
	R	*syn*/*anti* (**10**/**11**)	yield (%)	*syn*/*anti* (**10**/**11**)	yield (%)
9a	Bn	7:1	73	>24:1	77
9b	$CH_2CH(OMe)_2$	3:1	61	19:1	64
9c	$(CH_2)_2CH{=}CH_2$	6:1	60	>24:1	71
9d	$CH_2CH{=}CH_2$	10:1	58	>24:1	75
9e	PMB	6:1	66	>24:1	49
9f	PMP	2:1	55	9:1	52

Attempts to achieve the rearrangements of amides of type **B** synthesized from 3-aza-allylic alcohols of (*Z*) configuration, which may have potentially reverted the diastereoselectivity in favor of the *anti*-α-hydroxy-*β*-amino amides **11**, have not yet been successful.[14] Thus, with the aim of getting access to 1,2-*anti*-aminoalcohols by [2,3]-Wittig rearrangements of derivatives of (*E*)-3-aza-allylic alcohols, the remaining option was to replace the *π*-acceptor amide group by a stabilizing *π*-donor alkynyl substituent.

To prepare propargylic ethers from the alcohols **3a**−**e**, a two-step procedure involving alkylation with propargyl bromide under phase-transfer catalysis followed by silylation of the terminal alkyne moiety (*n*-BuLi, THF, −78 °C) was initially used (method C, Table 4). Under these conditions, alcohols **3a** and **3b** were efficiently converted to ethers **12a** (67%) and **12b** (91%), respectively, but **12c** was obtained in low yield (31%) from **3c**.[15] A one-step propargylation protocol of alcohols **3c**−**e** (method D, Table 4) was therefore developed under phase transfer conditions with the propargylic bromide **13**, bearing a TIPS group, and the propargylic ethers **14c**−**e** were thus obtained in high yields (86−91%) (Table 4).

Table 4. Synthesis of the Propargylic Ethers **12** and **14**



3	R	method	R′	12/14	yield (%)
3a	Bn	C	TMS	**12a**	67
3b	$CH_2CH(OMe)_2$	C	TMS	**12b**	84
3c	$(CH_2)_2CH{=}CH_2$	C	TMS	**12c**	31
		D	TIPS	**14c**	86
3d	$CH_2CH{=}CH_2$	D	TIPS	**14d**	89
3e	PMB	D	TIPS	**14e**	91

Despite the presence of other potential acidic hydrogens in substrates **12a**−**c** and **14c**−**e**, metalation at the propargylic position was successfully achieved by treatment with LDA (THF, −78 °C), and subsequent [2,3]-Wittig rearrangements proceeded cleanly to afford the corresponding 1,2-aminoalcohols **15a**−**c** and **16c**−**e** in good yields (74−93%) and with high 1,2-*anti* diastereoselectivity (*anti/syn* = 11:1 to >24:1). It is interesting that the propargylic ethers **14c**−**e** substituted by a TIPS group are not only easier to synthesize but also also underwent [2,3]-Wittig rearrangements with higher diastereoselectivities (dr > 24:1) (Table 5).[16]

Additionally, it is also noteworthy that the rearrangement of propargylic ethers derived from (*E*)-3-aza-allylic alcohols can also provide access to *anti*-α-hydroxy-*β*-amino methyl ketones of type **A** (R″ = Me). Indeed, the triple bond in compound **15a** can undergo hydration (cat. $HgSO_4$, cat. H_2SO_4, THF/H_2O, rt) to afford ketone **17** (86%) without epimerization (Scheme 3).

The stereochemical outcome observed in the [2,3]-rearrangement of the amides and the propargylic ethers derived from 3-aza-allylic alcohols is in perfect agreement with the

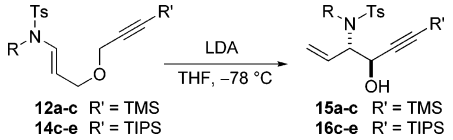
(13) The relative configurations of **10a**, **11a**, and **10f** were unambiguously ascertained by chemical correlations; see Supporting Information. The relative configuration of the other compounds **10b**−**e** was assigned by analogy.

(14) The [2,3]-Wittig rearrangement of the pyrrolidine amide derived from the (*Z*)-allylic alcohol **7** failed and resulted in extensive decomposition. Enolization of this substrate appears to be considerably more difficult to achieve, probably for steric reasons.

(15) For this substrate, metalation of the aromatic group also took place as a side reaction during the second stage of method C.

(16) The relative configuration of **15a** was unambiguously ascertained by a chemical correlation, and those of **15b**,**c** were assumed to be similar. Desilylation of **15c** and **16c** (TBAF, THF) led to the same 1,2-aminoalcohol indicating that the nature of the silicon substituent on the alkyne does not affect the stereochemical outcome; see Supporting Information.

Table 5. [2,3]-Wittig Rearrangements of Propargylic Ethers



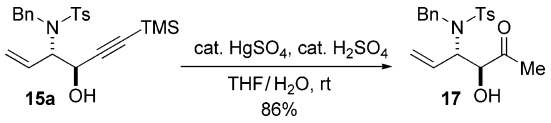
12a-c R' = TMS
14c-e R' = TIPS

15a-c R' = TMS
16c-e R' = TIPS

12/14	R	R′	**15/16**	*anti*/*syn*	yield (%)
12a	Bn	TMS	**15a**	13:1	89
12b	$CH_2CH(OMe)_2$	TMS	**15b**	23:1	81
12c	$(CH_2)_2CH{=}CH_2$	TMS	**15c**	11:1	74
14c	$(CH_2)_2CH{=}CH_2$	TIPS	**16c**	>24:1	76
14d	$CH_2CH{=}CH_2$	TIPS	**16d**	>24:1	79
14e	PMB	TIPS	**16e**	>24:1	93

transition state model used to rationalize the diastereoselectivities of the rearrangement of nonheterosubstituted alcohol derivatives. In this five-membered ring transition state model

Scheme 3. Hydration of Alkyne **15a**

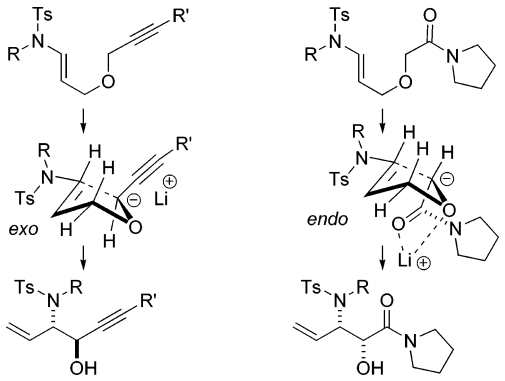


15a **17**

of envelope conformation, the π-donating stabilizing alkynyl group (of small steric demand) tends to occupy an *exo* orientation, whereas an *endo* orientation is favored for the π-acceptor amide moiety due to secondary orbital or electrostatic interactions with the negatively charged olefinic moiety (Scheme 4).[17]

(17) (a) Wu, Y.-D.; Houk, K. N.; Marshall, J. A. *J. Org. Chem.* **1990**, *55*, 1421−1423. (b) Mikami, K.; Uchida, T.; Hirano, T.; Wu, Y.-D.; Houk, K. N. *Tetrahedron* **1994**, *50*, 5917−5926.

Scheme 4. [2,3]-Wittig Rearrangements of the Derivatives of 3-aza-Allylic Alcohols of Type **C**



We have reported the first examples of [2,3]-Wittig rearrangements of acyclic 3-aza-substituted allylic alcohol derivatives that proceed with synthetically useful levels of 1,2-diastereoselectivity. Further work is currently underway to explore the scope of such [2,3]-Wittig rearrangements and in particular to control the absolute configuration of the newly formed heterosubstituted stereocenters by the use of a chirality transfer from secondary 3-aza-allylic alcohols.

Acknowledgment. Financial support from Glaxo-Smith-Kline and the CNRS (BDI grant to M.B.) is gratefully acknowledged.

Supporting Information Available: Experimental procedures, analytical data for all new compounds, evidence for stereochemical assignments, and copies of the ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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