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Synthesis of α-Substituted Allylic Amines via a Modified Bruylants Reaction

Claude Agami, François Couty,* and Gwilherm Evano

Laboratoire de Synthèse Asymétrique associé au CNRS, Université Pierre et Marie Curie, 4 place Jussieu, 75005 Paris, France

couty@ccr.jussieu.fr

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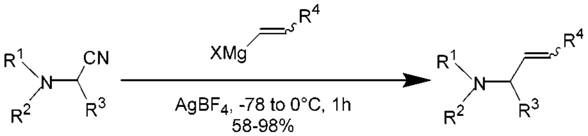
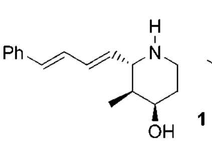
ABSTRACT



Silver tetrafluoroborate, used as an iminium ion promoter from α-amino nitriles, is an efficient additive in the Bruylants reaction involving vinylic Grignards. Improved yields of allylic amines were obtained when the starting α-amino nitrile was treated with this silver salt prior to its reaction with the vinylic Grignard. This improvement was not observed in the case of acetylenic Grignards. The reactivity of other vinyl organometallics (M = Zn, Li, Al, Cu, Si) was briefly examined.

The Bruylants reaction, namely, the reaction of an α-amino nitrile with a Grignard reagent in order to prepare α-substituted amines is an old, widely used procedure.[1] This reaction is most often described in relation to the preparation of aliphatic amines, starting with sp^3 Grignard reagents, and very few papers[2] report on the use of vinylic Grignards in this reaction, thus affording allylic amines. This is quite surprising since allylic amines, in addition to their synthetic utility[3] as aldehyde or ketone homoenolates precursors, are substructures found in a growing class of biologically active alkaloids, such as dienomicin C **1**,[4] pinidine **2**,[5] and clavepictine B **3**.[6] (Figure 1). Indeed, a Bruylants reaction would be an attractive strategy to introduce the unsaturated side chain of such targets.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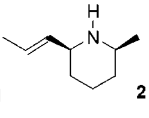
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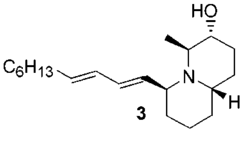
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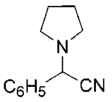
Figure 1. Naturally occurring alkaloids containing an allylic amine moiety.

For these reasons, we decided to delineate the scope of the Bruylants reaction for the synthesis of allylic (or propargylic) amines by varying the nature of the metal in the vinyl organometallic reagent (M = Mg, Li, Cu, Zn, Al, Si). Furthermore, since an iminium ion is actually the reactive intermediate in this reaction, we also examined the influence of silver tetrafluoroborate used as an additive to produce in situ the iminium ion from the starting α-amino nitrile, prior to its reaction with the organometallic reagent.

The four α-amino nitriles **4**−**7** selected for this study are shown in Figure 2, and some of the organometallics used are depicted in Figure 3. Our results are collected in Table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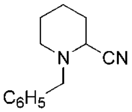
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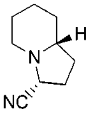
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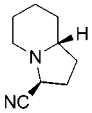
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Figure 2. Selected α-amino nitriles.

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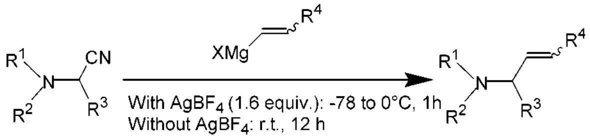
Table 1. Bruylants Reaction Performed on Amino Nitriles **4**−**7** with Vinylic Grignards



entry	substrate	Grignard reagent (equiv)	R^4	addition product	yield[a] (%) without $AgBF_4$	yield[a] (%) with $AgBF_4$
1	**4**	vinylMgBr (1.5)	H	**9**	27	91
2	**4**	vinylMgBr (4)	H	**9**	32	98
3	**4**	propenylMgBr[b](4)	Me	**10**	nd[c]	98 (*E*/*Z* 80/20)
4	**4**	**11**[d](3)	C_8H_{15}	**12**	nd[c]	60
5	**5**	vinylMgBr (1.5)	H	**13**	nd[c]	40
6	**5**	vinylMgBr (4)	H	**13**	30	91
7	**6** (de 84%)	vinylMgBr (4)	H	**14**	44 (de 50%)	60 (de 66%)
8	**7** (de 64%)	vinylMgBr (4)	H	**14**		58 (de 66%)
9	**7**	propenylMgBr[b](4)	Me	**15**[e]		70

[a] All yields refer to pure isolated products, except in the case of **14** and **15** which could not be obtained free of minor byproducts. In these cases, yields were estimated on the basis of GC and NMR analysis. [b] Obtained from insertion of Mg in a (*E*/*Z*) 60/40 mixture of 1-bromoprop-1-ene. [c] Only traces of addition product could be detected in the ^1H NMR spectra of the crude reaction mixture. [d] Obtained from Br/Li exchange (*t*-BuLi) from (*E*,*E*)-1-bromodeca-1,3-diene followed by transmetalation with $MgBr_2$. [e] Obtained as a mixture of four isomers.

1 (vinylic Grignards with or without $AgBF_4$), Table 2 (acetylenic Grignards with or without $AgBF_4$), and Table 3 (other vinylic metals with $AgBF_4$).

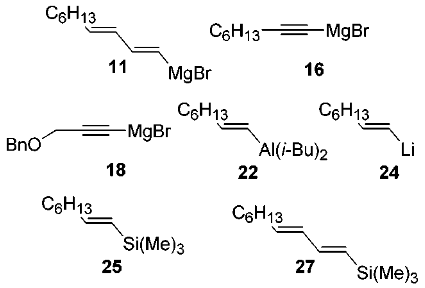
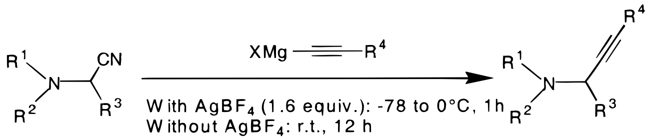


Figure 3. Some organometallics used in Tables 1−3.

The α-amino nitriles **4**−**7** selected for this study were synthesized as follows. Compound **4** resulted from a Strecker reaction.[2b] Piperidine **5** was prepared by Hg(II)-mediated oxidation of *N*-benzyl piperidine followed by treatment with HCN, using a procedure described for the preparation of similar compounds.[7] Cyano indolizidine **6** and **7** were prepared from available 2-piperidineethanol **8** following a three-step sequence involving (i) alkylation with bromoacetonitrile, (ii) treatment with thionyl chloride , and (iii) intramolecular alkylation of the amino nitrile anion generated by LiHMDS (Scheme 1). This reaction afforded **6** and **7** in a respective 60/40 ratio. Purification by chromatography on silica gel induced epimerization of this mixture to the more stable **7** (ratio **6**/**7**: 40/60).

The results collected in Tables 1−3 clearly demonstrate that the successful outcome of this reaction relies strongly not only on the conditions used but also on the nature of the starting α-amino nitrile. In regard to the organometallic, Grignard reagents gave the best results and the use of silver tetrafluoroborate as an additive invariably gave improved yields when vinylic Grignards were used (Table 1). Furthermore, in the presence of this additive, the reaction proceeded

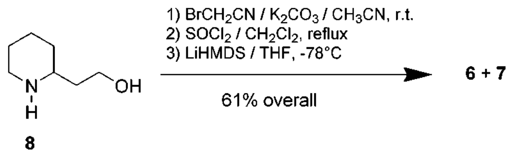
Table 2. Bruylants Reaction Performed on Amino Nitriles **4** and **5** with Acetylenic Grignards



entry	substrate	Grignard reagent (equiv)[a]	R^4	addition product	yield[b] (%) without $AgBF_4$	yield[b] (%) with $AgBF_4$
1	**4**	**16** (4)	C_6H_{13}	17	85	98
2	**4**	**18** (4)	CH_2OBn	19	87	40
3	**5**	**16** (4)	C_6H_{13}	20	98	45
4	**5**	**18** (4)	CH_2OBn	21	97	61

[a] Obtained by metalation (EtMgBr) of the corresponding alkyne. [b] All yields refer to pure isolated products.

Scheme 1. Synthesis of α-Amino Nitriles **6** and **7**



readily at ca. −40 °C, while Grignard reagent alone required protracted reaction time at rt to reach completion.

The beneficial outcome of the use of silver tetrafluoroborate was much less pronounced when acetylenic Grignards were used (Table 2). In these cases, similar or even better yields of addition product were obtained in the absence of additive.

The nature of the α-amino nitrile had also an influence on the success of these reactions: while very good yields were obtained under our standard conditions with substrates **4** and **5** (Table 1 entries 1−6), lower yields were observed with cyano indolizidines **6** and **7** (entries 7−9) though in these cases $AgBF_4$ still had a beneficial influence on both yield and diastereoselectivity. Using these substrates, byproducts were produced together with the vinylic indolizidines which could not be obtained in pure form.

The behavior of other vinylic reagents in the presence of $AgBF_4$ was next examined: vinylzinc[8] and vinyllithium reagents gave much lower yields compared to vinylic Grignards (Table 3, entries 1, 2, 5, and 6). Vinylic alane **22** and vinylic silanes[9] **25** and **27** (entries 4, 7, and 8) failed to give any addition product, and in the former case, a clean coupling of the vinylic alane was observed with the concomitant reduction of Ag^+.[10] Finally, an organocuprate gave unidentified products, but no addition was observed (entry 3).

A standard procedure using 1.6 equiv of silver tetrafluoroborate (rt, THF, 10 mn) with respect to the starting α-amino nitrile, followed by addition of 3−4 equiv of the vinylic Grignard at −78 °C, soon emerged as the best operative conditions.

The use of silver tetrafluoroborate to promote the formation of an iminium ion from an α-amino nitrile was first introduced by Husson et al.,[11] and the produced ions were reported to be conveniently reduced by zinc borohydride. However, to our knowledge, the addition of an aliphatic Grignard onto these iminium ions preformed by $AgBF_4$ was described only once[11] and occurred with a low yield, together with the formation of the corresponding enamine.

We verified that reaction of **4** or **5** with $AgBF_4$ in $CDCl_3$ followed by filtration of the precipitated AgCN produced almost quantitatively the corresponding iminiums (appearance of a signal in ^{1}H NMR at 8.98 and 8.73 ppm respectively for **4** and **5**). Furthermore, the fact that similar yields and selectivity were obtained in the case of substrates **6** and **7** (Table 1, entries 7−9) is also in agreement with the production of an intermediate iminium ion.

During the reaction of these iminiums with an organometallic reagent, an obvious side reaction is the deprotonation of the iminium ion. The produced enamine can then add to the starting iminium and oligomerization may follow. The occurrence of this competing deprotonation depends both on the basicity of the organometallic and on the structure of the iminium substrate: while this is not possible in the case of **4**, it appears to be particularly easy in the case of the strained indolizidinium ion derived from **6** or **7**. The deprotonation of these preformed iminiums is probably less effective when acetylenic Grignard reagents are used since they are less basic than vinylic Grignards. This might at least partially explain why the use of $AgBF_4$ is useless in these cases.

In regard to the nature of the reacting vinyl organometallic (Table 3), parameters governing this reaction remain unclear: though iminium ions are known to be soft electrophilic species,[12] the hard or soft character of the reacting vinyl organometallic does not explain the obtained results: vinyllithium (harder than vinylic Grignards) gave low yields, but dilithiumpropenylcuprate, considered as a softer nucleophile than vinylic Grignards, is ineffective. On the other hand, the presence of silver(I) salt in the reaction mixture can also induce undesired side reactions with the vinyl organometallic, as evidenced in the case of alane **22** (vide supra).

In conclusion, this work shows that silver tetrafluoroborate as an iminium promoter is a very efficient additive in the Bruylants reaction involving vinylic Grignards. Owing to the

Table 3. Bruylants Reaction Performed on Amino Nitriles **4** and **5** with Other Vinyl Metals in the Presence of $AgBF_4$ (1.6 equiv)

entry	substrate	organometallic	conditions	product	yield (%)
1	**4**	propenylLi[a] (1.5)	−78 to 0 °C, 1 h	**10** (R^4: Me)	32
2	**4**	propenylZnCl[b](1.5)	−78 to 0 °C, 1 h	**10** (R^4: Me)	13
3	**4**	dipropenylCuLi[c] (1.5)	−78 to 0 °C, 1 h	**10** (R^4: Me)	0
4	**4**	**22**[d] (2)	−78 to 0 °C, 1 h	**23** (R^4: C_6H_{13})	0
5	**4**	**24**[e] (3)	−78 to 0 °C, 1 h	**23** (R^4: C_6H_{13})	13
6	**5**	vinylZnCl[f] (1.5)	−78 to 0 °C, 1 h	**13** (R^4: H)	59
7	**5**	**25**	reflux 12 h	**26** (R^4: C_6H_{13})	0
8	**5**	**27**	reflux 12 h	**28** (R^4: C_8H_{15})	0

[a] Obtained from Br/Li exchange (*t*-BuLi) from a (*E*/*Z*) 60/40 mixture of 1-bromoprop-1-ene. [b] Obtained from Br/Li exchange (*t*-BuLi) from a (*E*/*Z*) 60/40 mixture of 1-bromoprop-1-ene followed by transmetalation with zinc chloride. [c] Obtained from Br/Li exchange (*t*-BuLi) from a (*E*/*Z*) 60/40 mixture of 1-bromoprop-1-ene followed by transmetalation with copper iodide (0.5 equiv). [d] Obtained by reaction of DIBALH with prop-1-yne. [e] Obtained from Br/Li exchange (*t*-BuLi) from (*E*)-1-bromooct-1-ene. [f] Obtained by transmetalation of vinylmagnesium bromide with $ZnCl_2$.

easy access to both α-amino nitrile moiety and vinylic Grignards, this reaction should find a new place in the synthesis of alkaloids.

Supporting Information Available: Standard experimental procedure for the modified Bruylants reaction and NMR spectra (^{1}H and ^{13}C) for unreported compounds **6**, **7**, **12**, **14**, **17**, **19−21**, and **23** and iminium ion derived from **4**. This material is available free of charges via the Internet at http://pubs.acs.org.

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