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Stereocontrolled Formation of Amino Acids and *N*-Heterocycles Bearing a Quaternary Chiral Carbon

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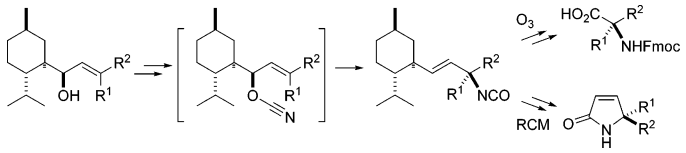
ABSTRACT



Stereocontrolled formation of tertiary or quaternary chiral carbons bearing nitrogen was achieved using the [3,3]-sigmatropic rearrangement of cyanate to isocyanate as a key element. A short and highly selective sequence of reactions, starting from *p*-menthane-3-carboxaldehyde, was developed leading to α,α-dialkylated α-amino acids or *N*-heterocycles, depending on the method of cleavage of the auxiliary.

Quaternary carbons bearing a nitrogen atom are fairly ubiquitous in nature, being found in many natural alkaloids such as daphniphylline and (−)-adaline (Figure 1).[1] In addition, α,α-dialkylated amino acids such as methylphenylalanine are useful molecular building blocks for the synthesis of peptides with specific properties.[2] Such peptides possessing constrained conformations due to the additional substituent may change their secondary or tertiary structure.[3] In addition, some α,α-dialkylated amino acids are powerful enzyme inhibitors.[4]

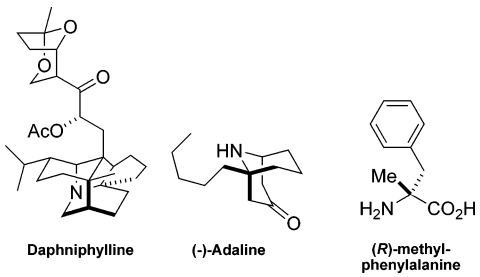


Figure 1. Natural products containing a quaternary chiral carbon bearing nitrogen.

The stereoselective preparation of quaternary carbons bearing nitrogen is a particularly difficult task.[5,6] We recently published[6] a stereodivergent approach to α,α-dialkylated amino acids that takes advantage of two stereospecific events, namely, the S_N2' displacement of allylic esters by cuprates and the Curtius rearrangement, using *p*-menthane-3-carboxaldehyde **1**[7] as a recyclable chiral auxiliary. The linear

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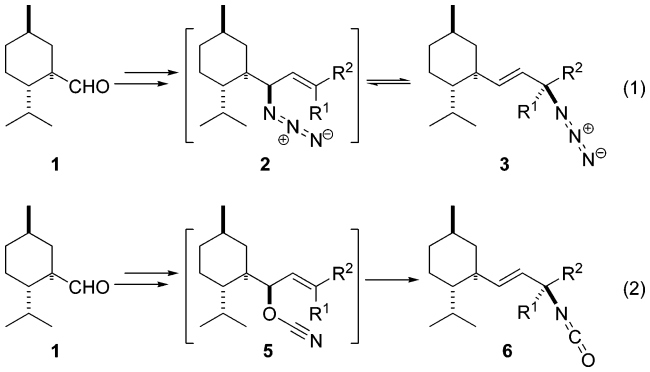
sequence included seven chemical steps, and we felt it could be improved. We now disclose a shorter sequence of reactions that starts with *p*-menthane-3-carboxaldehyde **1** and generates, in five steps, amino acids or *N*-heterocycles, depending on the method of cleavage, bearing a tertiary or quaternary chiral carbon.

The strategy is based on the stereospecific [3,3]-sigmatropic rearrangement of allylic cyanates **5** to allylic isocyanates **6** (Scheme 1, eq 2).[8,9] In an earlier communication,

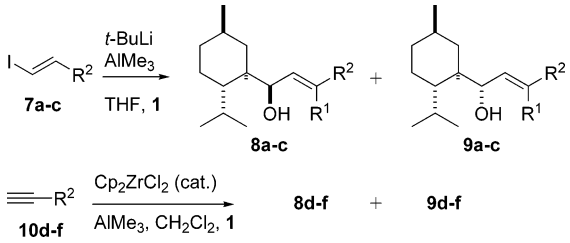
Scheme 1. Stereocontrolled Formation of the C−N Bond



we described the reversible [3,3]-sigmatropic rearrangement of allylic azides **2** to give principally compound **3** thanks to the steric bias provided by the menthyl fragment (Scheme 1, eq 1).[10] However, substituents capable of conjugation such as the phenyl group favored regioisomer **2**, and in addition, the method was not applicable to quaternary azides (**3**, R^1, $R^2 \neq H$). Contrary to azides, cyanates rearrange irreversibly to the corresponding isocyanates because of the strength of the carbonyl double bond. In addition, unlike the azide, making the cyanate does not require displacing the stereochemically pure alcohol (cf. alcohols **8**), thus eliminating a step that can potentially scramble stereochemistry.

The sequence starts with the stereoselective preparation of allylic alcohols **8** using either a trimethylaluminum-catalyzed[11] addition of vinyllithium (method A) or the direct addition of vinylalanes[12] (method B) to *p*-menthane-3-carboxaldehyde **4** (Table 1). Either of these methods proceeds

Table 1. Stereoselective Addition of Vinylmetals to **4**



entry	R_1	R_2	product	yield of **8** (%)[a]	ratio **8**:**9**[b]
1	H	*n*-Pr	**a**	72	99:1
2	H	*t*-Bu	**b**	66	200:1
3	H	TMS	**c**	69	6:1[c]
4	Me	*n*-Pr	**d**	87	30:1
5	Me	Ph	**e**	69	49:1
6	Me	Bn	**f**	81	24:1

[a] Isolated yield of pure **8**. [b] Measured by GC against authentic material. [c] Prepared without $AlMe_3$ as additive.

with high stereoselectivity, providing allylic alcohols **8a**−**f** in good yields and excellent diastereomeric ratios. The addition of vinyllithiums without $AlMe_3$ as additive usually proceeds with much lower selectivity (cf. entry 3). The formation of the major alcohol **8** can be rationalized using the Felkin−Anh model of addition to α-chiral carbonyls.[13] The diastereomeric alcohols were easily separated by flash chromatography in all cases to yield diastereomerically pure allylic alcohols **8a**−**f**.

Treatment of these allylic alcohols **8a**−**f** with trichloroacetyl isocyanate in dichloromethane at 0 °C followed by hydrolysis using potassium carbonate in an aqueous methanolic solution provided the corresponding carbamates **11a**−**f** in excellent yields (88% to >99%).[14] The carbamates **11a**−**f** were then treated with trifluoroacetic anhydride and triethylamine in dichloromethane at 0 °C to generate the isocyanates **6a**−**f** in only 10 min (Table 2), presumably via the intermediacy of the corresponding cyanates **5a**−**f** that rearranged in situ. The lower-energy transition state **5A** with

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(9) During the course of our work a conceptually similar approach was divulged; see: (a) Ichikawa, Y.; Yamauchi, E.; Isobe, M. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 939−943. (b) Ichikawa, Y.; Ito, T.; Isobe, M. *Chem. Eur. J.* **2005**, *11*, 1949−1957. (c) Matsukawa, Y.; Isobe, M.; Kotsuki, H; Ichikawa Y. *J. Org. Chem.* **2005**, *70*, 5339−5341. (d) Nishiyama, T.; Isobe, M.; Ichikawa, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4372−4375.

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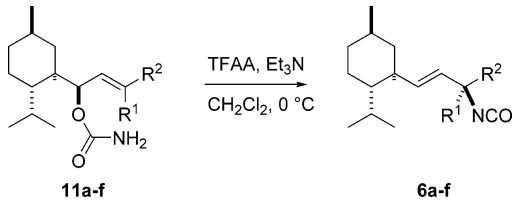
(14) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4, 1109−1111.

Table 2. [3,3]-Rearrangement of Allylic Cyanates from **11a−f**



entry	R_1	R_2	product	yield (%)[a]	dr **6**[b]
1	H	*n*-Pr	**a**	96	>99:1
2	H	*t*-Bu	**b**	93	>99:1
3	H	TMS	**c**	93	>98:2[c]
4	Me	*n*-Pr	**d**	99	>99:1
5	Me	Ph	**e**	80	97:3
6	Me	Bn	**f**	99	>99:1

[a] Isolated yield. [b] Measured by GC against authentic diastereomeric mixtures. [c] Measured by HPLC.

minimum $A^{1,3}$ strain leads to the major isocyanate with a *E*-double bond (Figure 2). The higher-energy transition state

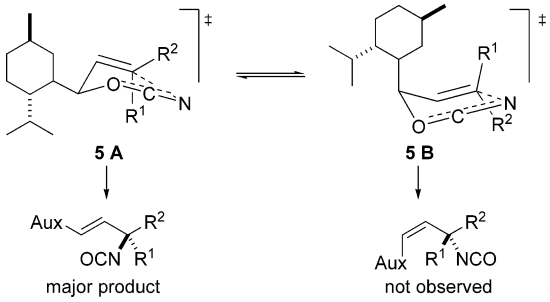


Figure 2. Possible transition states for the rearrangement.

5B with maximum $A^{1,3}$ strain would lead to an isocyanate having a *Z*-double bond, which was never observed. Isocyanates can be purified on silica gel and proved to be stable at room temperature for an extended period of time. Other conditions of dehydration were tried but invariably led to mixtures of products (see Supporting Information). Prominent in those mixtures were products resulting from elimination reactions. Importantly, carbamates **11d−f** possessing trisubstituted double bonds gave excellent yields and diastereomeric ratios of products having a chiral quaternary isocyanate.

With this method, compounds such as **6c** and **6e** possessing phenyl or silyl substituents, which were not previously accessible,[10] are now easily prepared in high stereoisomeric purity. However, in the case of **6e**, the diastereomeric excess of the isocyanate was slighly lower than for the other substrates. We believe that this could arise from a partial nonstereoselective collapse of the stabilized cationic intermediate **12** (Figure 3).[15] The isolation of a 3% yield of the regioisomer **13e** together with small amounts of elimination products is supportive of this hypothesis.

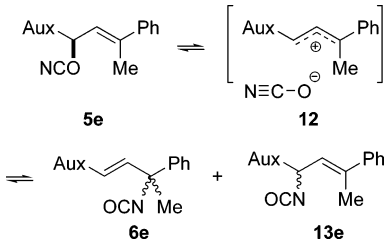
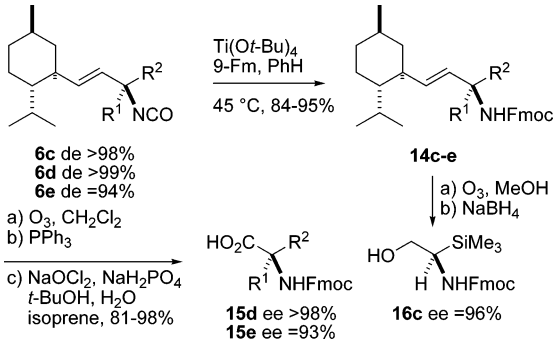


Figure 3. Possible cationic intermediates.

Isocyanates **6c−e** were further reacted with 9-fluorenemethanol in the presence of a catalytic amount of $Ti(O\textit{t}\text{-Bu})_4$ in benzene at 45 °C, providing Fmoc-protected allylic amines **14c−e** (Scheme 2). This catalyst is particularly

Scheme 2. Synthesis of α-Amino Acids **15**



useful when dealing with sterically crowded isocyanates.[16] Oxidative cleavage of the auxiliary afforded amino acids **15d** and **15e** in good to excellent yields and without loss of stereochemical purity. Ozonolysis of **14c** followed by a reductive workup provided Fmoc-protected 2-hydroxy-1-(trimethylsilyl)ethylamine **16c** in 60% yield. Compounds of this type could be useful as chiral oxazolidinones. Although **15c** could not be oxidized to the amino acid because of the labile trimethylsilyl group, amino-alcohols substituted with larger silyl groups can.[17]

Alternatively, isocyanate **6d** was treated with vinylmagnesium bromide in THF at 0 °C to afford acrylamide **17** (Scheme 3). Cleavage of the auxiliary[18] was then achieved using the second generation Grubbs[19] catalyst and afforded pyrrolone **18** in 60% yield. Compounds of type **18** are highly suited for the synthesis of more complex alkaloids possessing a quaternary carbon bearing nitrogen. The alkene **19** is highly

(15) Similar intermediates were previously suggested. See: Overman, L. E. *J. Am. Chem. Soc.* **1976**, 2901−2910.
(16) Spino, C.; Joly, M.-A.; Godbout, C.; Arbour, M. *J. Org. Chem.* **2005**, *70*, 6118−6121.
(17) Liu, G.; Sieburth, S. McN. *Org. Lett.* **2005**, *7*, 665−668.
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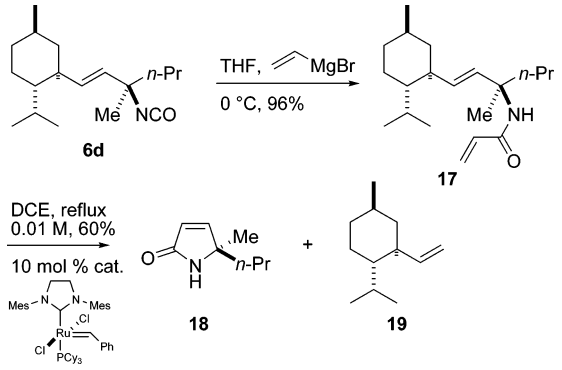
(19) (a) Scholl, M.; Ding, S.; Lee C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751−1753. Trnka, T. T.; Grubbs, R. B. *Acc. Chem. Res.* **2001**, *34*, 18−29.

Scheme 3. Synthesis of Pyrrolone **18**



volatile and can be easily removed from **18** under vacuum. Chiral auxiliary **1** can be recovered simply by ozonolysis of **9**.

In summary, we have achieved the stereocontrolled formation of chiral carbons bearing nitrogen. Our methodology gives rapid access to tertiary and quaternary centers in good to excellent yields and diastereomeric excesses. We have developed a short and highly selective synthesis of α,α-dialkylated amino acids and *N*-heterocycles possessing a chiral quaternary carbon atom, which are interresting building blocks for the synthesis of more complex peptides and alkaloids. This methodology is now being applied toward the synthesis of complex natural alkaloids.

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Supporting Information Available: Experimental procedures and ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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