

Bifunctional Homoallylic Carbamates from Chiral Silane Additions to in Situ Generated *N*-Acyl Iminium Ions

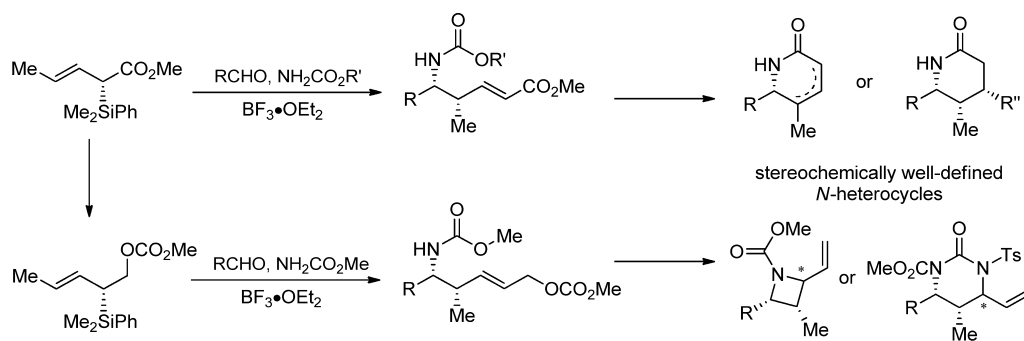
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Received May 23, 2012

ABSTRACT



Homoallylic carbamates bearing an α,β -unsaturated ester or an allylic carbonate were generated respectively utilizing novel chiral silanes through Lewis acid promoted asymmetric aminocrotylation. Those bifunctional building blocks could further undergo Michael addition or cyclization to selectively form functionalized lactams, azetidines, and tetrahydropyrimidinones.

Highly functionalized vinylogous Mannich products are valuable synthetic intermediates in organic synthesis and have been frequently employed in natural product synthesis.¹ In this regard, δ -amino- γ -methyl- α,β -unsaturated carbonyl compounds, behaving as bifunctional synthons, have been utilized to prepare iminosugar derivatives² and Tyr-Gly CH₃-ADI (an alkene dipeptide isostere),³ as well as key intermediates in the synthesis of the natural product nupharamine.⁴ These materials promise to give access to molecules of pharmacological and biological interest. Established approaches to such subunits include the Mannich reaction² and S_N2' aziridine

opening⁵ followed by Wittig homologation and further functional group manipulation. Direct access of homoallylic amines bearing an unsaturated carbonyl group can be realized by the vinylogous Mukaiyama–Mannich reaction using ketene acetals.⁶ However, the corresponding asymmetric versions⁷ are rare and remain underdeveloped.

Due to the prevalence of medicinally important compounds bearing stereodefined C–N bonds, the asymmetric addition of allyl metal and related reagents to C=N Pi-bonds has attracted the attention of the synthetic community.⁸ Well-documented studies from our laboratory have established chiral crotylsilanes of type-2 as carbon nucleophiles in highly diastereo- and enantioselective reactions with in situ generated *N*-acyl iminium ions to construct

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Scheme 1. Extension of Chiral Silane **1** to Homoallylic Carbamates

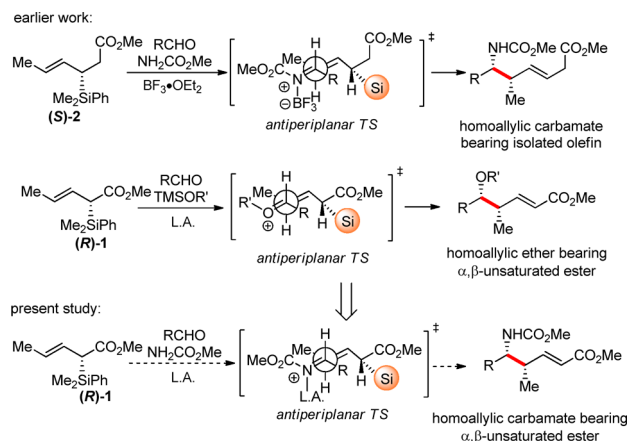


Table 1. Optimization of the Three-Component Aminocrotylation

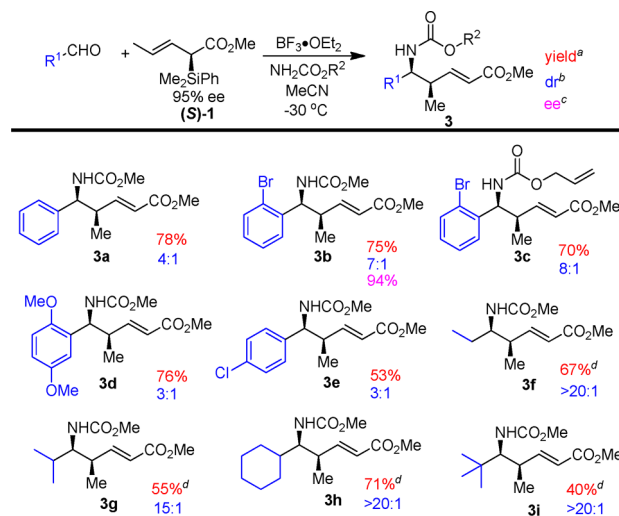
entry	Lewis acid (equiv)	solvent	temperature (°C)	yield (%) ^{a,e}	dr ^{b,e}
1	<i>p</i> -toluenesulfonic acid (0.5 equiv)	MeCN	rt	0 ^d	NA
2	PS-TsOH (0.3 equiv)	MeCN	rt	0 ^d	NA
3	TMSOTf (1 equiv)	CH ₂ Cl ₂	-50	80	2:1
4	TiCl ₄ (1 equiv)	CH ₂ Cl ₂	-78	NR	NA
5	BF ₃ ·OEt ₂ (2 equiv)	MeCN	-30	75	7:1
6 ^c	BF ₃ ·OEt ₂ (2 equiv)	EtCN	-50	20%	2:1
7 ^c	BF ₃ ·OEt ₂ (2 equiv)	CH ₂ Cl ₂	-30	30%	4:1
8	BF ₃ ·OEt ₂ (2 equiv)	toluene	-30	NR	NA
9	BF ₃ ·OEt ₂ (2 equiv)	DMF	-10	NR	NA

^a Isolated yield. ^b Dr based on analysis of crude ¹H NMR spectra. ^c Less than 50% conversion after 48 h. ^d Only observed silane decomposition. ^e NR = no reaction. NA = not available.

homoallylic carbamates with an isolated olefin.⁹ We have recently demonstrated that vinylogous aldol products can be effectively generated with high levels of diastereo- and enantioselectivity utilizing crotylsilanes obtained by

asymmetric Rh(II) and Cu(I) carbenoid Si–H insertion.¹⁰ In line with this work, we expected that extension of these silane reagents to asymmetric aminocrotylation processes could directly access homoallylic carbamates containing an α,β-unsaturated ester, thereby extending our silane-based bond construction methods (Scheme 1). Herein, we describe an efficient procedure for the aminocrotylation and [3 + 2] annulation of novel crotylsilanes using in situ generated *N*-acyl iminium ions as reaction intermediates.¹¹ The generated vinylogous Mannich products can undergo further diversification by taking advantage of their rich functionality.

Scheme 2. Aminocrotylation Using Silane (S)-1



^a Yield based on the purified product. ^b Dr based on the crude ¹H NMR spectra. ^c Ee based on chiral HPLC analysis. ^d Reactions were conducted at –10 °C.

Initial experiments were focused on the three-component crotylation of 2-bromobenzaldehyde, organosilane (**S**)-**1**, and methylcarbamate by evaluating selected Lewis acids and solvents. Optimization studies (Table 1, entries 1–5) indicated that BF₃·OEt₂ was the optimal promoter. Further evaluation (entries 5–9) identified MeCN as the most efficient solvent in terms of reactivity and selectivity. Under the optimal conditions, crotylation product **3b** was obtained with 75% yield and 7:1 diastereoselectivity.

A range of aldehydes were evaluated under the optimized conditions to test the reaction scope (Scheme 2). Similar to the crotylation with aldehydes, the three-component aminocrotylation between silane (**S**)-**1** and aryl imines afforded homoallylic carbamates in good yield, but only moderate diastereoselectivity, with the best level of selectivity being achieved with 2-bromobenzaldehyde (**3b** and **3c**). The allylcarbamate (**3c**) also functioned as

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efficiently as the methylcarbamate. On the other hand, the reaction generally delivered products in excellent selectivity with aliphatic imines. Notably, for the cases examined, the straight chain aliphatic substrate afforded very high *syn/anti* selectivity with only one diastereomer (**3f**) being observed. *Syn* products were formed which was consistent with the well-established *anti*-S_{E'} mechanism. Select examples were carried through ee analysis using chiral HPLC and showed that the enantioenrichment of the silane reagent was completely transferred into the homoallylic carbamate products (**3b** and **3g**).

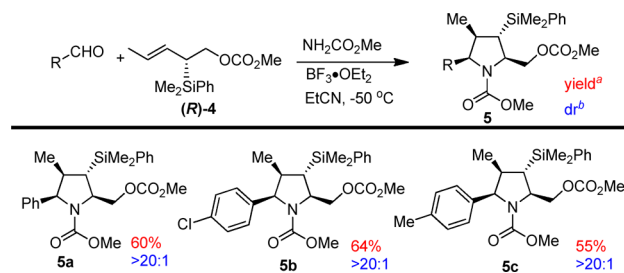
In anticipation of achieving enhanced selectivity for aminocrotylation with aromatic substrates, the parent unsaturated ester (**R**)-**1** was converted to allylic carbonate (**R**)-**4** by reduction and subsequent acylation of the primary alcohol. In contrast to silane **1**, homoallylic carbamates **6** and pyrrolidine products **5** were isolated in certain instances using reagent (**R**)-**4**. At reaction temperatures lower than $-50\text{ }^{\circ}\text{C}$, the *N*-carbamoyl pyrrolidines **5** were produced in good yield and excellent selectivity with three *in situ* generated arylimines (Scheme 3). On the other hand, acyclic homoallylic carbamates **5** were solely detected and isolated when the reactions were warmed to $-15\text{ }^{\circ}\text{C}$ (Scheme 4). For the cases studied, only the arylimines were effective in the formation of pyrrolidine products. Alkyl or branched aldehydes required higher temperatures in the initial condensation and did not produce the kinetically favored [3 + 2] annulation product. Interestingly, the imine derived from 2-bromobenzaldehyde afforded the homoallylic carbamate **6b** without the annulated pyrrolidine detected even when the reaction was carried out at low temperature ($-50\text{ }^{\circ}\text{C}$), behaving differently than the arylimines illustrated in Scheme 3. Homoallylic carbamates of type **5** were generally obtained in high yield and with good to excellent diastereoselectivity employing silane (**R**)-**4**. Chiral HPLC traces of selected examples (**6b** and **6h**) showed that the chirality of the crotylsilane was transferred into the homoallylic carbamate products which were obtained in $>92\%$ ee.

The resulting homoallylic carbamates **3** and **6** are potentially useful chiral building blocks that possess both electrophilic and nucleophilic sites available for further manipulation. Nitrogen-containing heterocycles, such as lactams, azetidines, and tetrahydropyrimidinones, are found in a large number of natural products and compounds of biological significance. We envisioned that the carbamate-unsaturated ester and carbamate-allylic carbonate subunits could be applied as synthetic platforms that were capable of delivering lactams, azetidines, and tetrahydropyrimidinones with different substitution patterns.

Treatment of allylcarbamate **3c** with the polymer-bound Pd(0) reagent (PS-Ph₃-Pd) afforded homoallylic amine **7**,¹² which cyclized effectively when mediated by microwave irradiation to give the unsaturated lactam **8** with concomitant *E/Z* olefin isomerization (Scheme 5). Cyclization of amine **7** using Zr(O*t*Bu)₂-2-hydroxypyridine as the catalyst

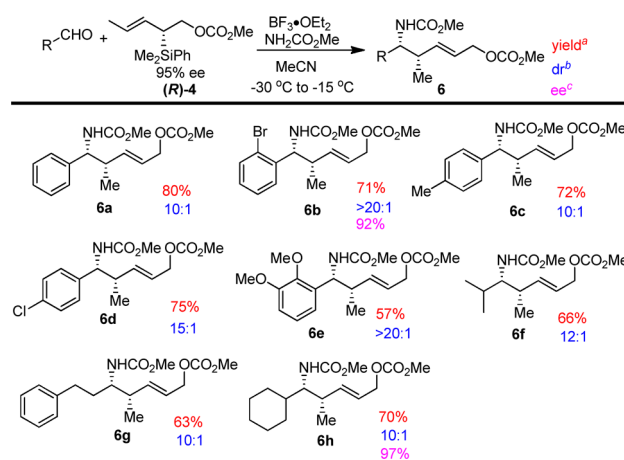
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Scheme 3. [3 + 2] Annulations Using Silane (**R**)-**4**



^aYield based on the purified material after chromatography over silica gel. ^bDr based on the crude ¹H NMR analysis.

Scheme 4. Aminocrotylation Using Silane (**R**)-**4**



^aYield based on purified materials. ^bDr based on crude ¹H NMR analysis. ^cEe based on chiral HPLC analysis.

afforded the unexpected lactam **9** accompanied by an olefin migration to the trisubstituted system. On the other hand, conjugate addition of *in situ* generated lithium dimethylcuprate¹³ to unsaturated ester **3c** led to the acyclic carbamate **10** with moderate diastereoselectivity, which cyclized during Alloc deprotection to deliver the saturated lactam **11**. The structure of the major diastereomer **11** was secured by X-ray crystal structural analysis and indicated that the conjugate addition followed the “modified” Felkin–Anh model for chiral Michael acceptors.¹⁴

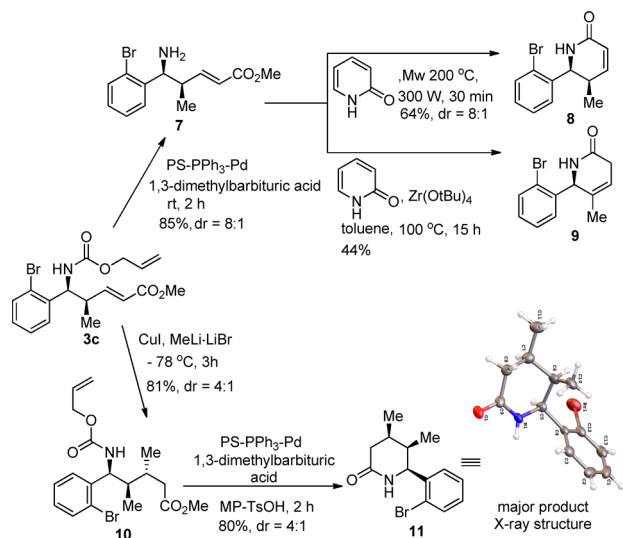
Palladium- and iridium-catalyzed intramolecular amidation of allylic carbonates represents an effective method for preparing pyrrolidine and piperidine heterocycles.¹⁵

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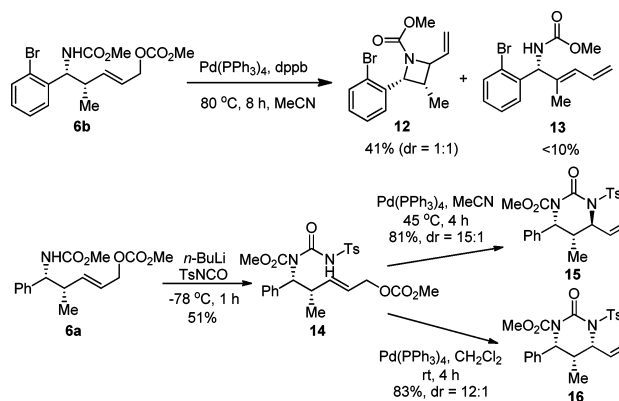
Scheme 5. Lactam Formation Using Homoallylic Carbamates 3



In that context, we anticipated that we could extend this transformation to the synthesis of functionalized azetidines. Indeed, our initial experiments indicated that the palladium-catalyzed allylic amidation of homoallylic carbamate **6b** produced the azetidine product **12** in 41% yield as a mixture of 1:1 ratio diastereomers along with a linear diene **13** as a byproduct (Scheme 6). However, with other homoallylic carbamates **6**, only the diene byproduct was observed, thus indicating that the elimination of a π -allyl intermediate predominated over our desired azetidine formation. Even though we were not quite clear with the reason why the *ortho* bromo substituent helped the formation of the azetidine product at this stage, we did show that those homoallylic carbamates of type **6** had the potential as platforms for the generation of functionalized azetidines. Further investigations following this line of experiments are presently underway in our laboratory.

The aminocrotylation products **6** are well suited to the use of Menche's method for the conversion into 1,3-*syn*- and 1,3-*anti*-tetrahydropyrimidinones, which can be further converted to the free diamines.¹⁶ When the allylic substitution of urea **14** derived from carbamate **6a** was carried out in MeCN, the *anti*-tetrahydropyrimidinone **15** was obtained with good selectivity. Conversely, when the reaction was

Scheme 6. Diversification of Homoallylic Carbamates 6



conducted in CH_2Cl_2 , it afforded the *syn*-tetrahydropyrimidinone product **16** as the major product, in contrast to the *anti*-selective reaction described by Menche. In this way, both the *syn* and *anti* diastereomers can be accessed by a simple change in solvents.

In summary, novel silanes of type **1** and **4**, generated from asymmetric metal catalyzed carbenoid Si–H insertion,^{10a} have been applied in three-component aminocrotylation to give direct access to homoallylic carbamates bearing an unsaturated ester or allylic carbonate, in good yield and selectivity. In some cases, the [3 + 2] annulation product through a [1,2]-silyl shift pathway was observed. The chirality is transferred completely from the enantioenriched silane reagents to the products according to chiral HPLC analysis. Application of this methodology in the preparation of complex, biologically active molecules is currently underway in our laboratory.

Acknowledgment. Financial support was obtained from NIH CA 53604 and NIGMS CMLD initiative (P50-GM067041). The authors are grateful to Prof. John A. Porco, Jr. and Prof. Aaron B. Beeler (Boston University) for helpful discussions and Dr. Paul Ralifo, Dr. Norman Lee, and Dr. Jeffrey Bacon (Boston University) for assistance with NMR, HRMS, and X-ray measurements.

Supporting Information Available. Experimental details and selected spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.