Synthesis and Reactions of α-(Trifluromethanesulfonyloxy) Enecarbamates Prepared from *N*-Acyllactams

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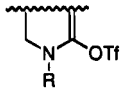
Since their discovery twenty years ago,[1] vinyl trifluoromethanesulfonates (vinyl triflates) have been widely used as synthetic intermediates.[2–6] Cross coupling of vinyl triflates with various organometallic compounds like organocopper, -aluminum, -stannane, -zinc, and -boron reagents under mild conditions and with high chemo- and stereoselectivity is an effective way to construct many organic molecules.[2] These versatile intermediates can be easily prepared from the corresponding carbonyl compounds or enolates by treatment with triflic anhydride,[7] *N,N*-bis(trifluoromethanesulfonyl)aniline,[8] or *N*-pyridyltriflimides.[9] The preparation and reactivity of vinyl triflates from enolates of ketones, aldehydes, and lactones have been studied,[2] while vinyl triflates **1** formed from enolates of *N*-substituted lactams have received little attention.[10] These functionalized vinyl triflates have considerable potential as precursors to piperidines and pipecolic acids (i.e. **2**), as well as other nitrogen-containing heterocycles.



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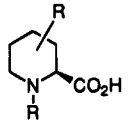

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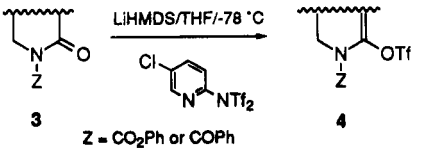
Substituted piperidines are present in many pharmaceuticals possessing neuroleptic, antihypertensive, anti-inflammatory, antitumor, anti-HIV, and anticonvulsant activities.[11] The related nonproteinogenic amino acid (*S*)-pipecolic acid (**2**, R = H) is widely distributed in plants.[11] Recently, pipecolic acid has attracted attention[12] as a component and starting material for a variety of synthetic peptides,[13] potential enzyme inhibitors,[14] synthetic drugs,[15] immunosuppressant natural product FK506,[16] and antifungal antibiotic demethoxyrapamycin.[17] There have been several enantioselective syntheses reported for pipecolic acid and its derivatives using chiral auxiliaries to effect asymmetric induction, or by using amino acids as chiral starting materials;[12] however, no catalytic asymmetric method has been previously described.

Scheme 1



3 Z = CO_2Ph or COPh **4**

Table 1. Conversion of *N*-Acyllactams to Vinyl Triflates[a]

entry	*N*-acyllactams[b]	yield[c], %	vinyl triflate[d]	yield[c], %
1	**3a** Z = CO_2Ph	72	**4a** Z = CO_2Ph	90
2	**3b** Z = COPh	80	**4b** Z = COPh	87
3	**3c**	71	**4c**	71
4	**3d**	79	**4d**	54

[a] Satisfactory IR, ^1H and ^{13}C NMR, and microanalysis data were obtained for all new compounds. [b] The product was obtained by treating the corresponding lactam with 1.1 equiv of *n*-BuLi, and quenching with the appropriate acyl chloride at −78 °C. [c] Yield of product obtained from radial preparative-layer chromatography. [d] Obtained by treating **3a–d** with 1.5 equiv of LiHMDS and enolate trapping with 2.5 equiv of *N*-(5-chloro-2-pyridyl)triflimide at −78 °C in THF.

In this communication we report the synthesis of vinyl triflates **4** from *N*-acyllactams **3** (Scheme 1), their coupling reactions with various organometallic reagents, and the results of a study on the asymmetric hydrogenation of α-substituted 1-acyl-1,2,3,4-tetrahydropyridines. This methodology was used in a catalytic asymmetric synthesis of (*S*)-pipecolic acid.

Vinyl triflates **4a–d** were prepared from *N*-acyllactams[18] **3a–d** in good to high yield by enolate formation and trapping with one of our recently developed pyridine-derived triflating reagents[9] (Table 1). In a comparison study, enolate trapping of **4a** under identical conditions was not as efficient (29%) using *N*-phenyltriflimide.[8]

In a typical experiment, an *N*-acyllactam was treated with LiHMDS at −78 °C, and the resulting enolate was treated with *N*-(5-chloro-2-pyridyl)triflimide.[9] The reac-

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(18) These *N*-acyllactams were prepared by treating the corresponding lactam with *n*-BuLi at −78 °C and then quenching the reaction with the acyl chloride.

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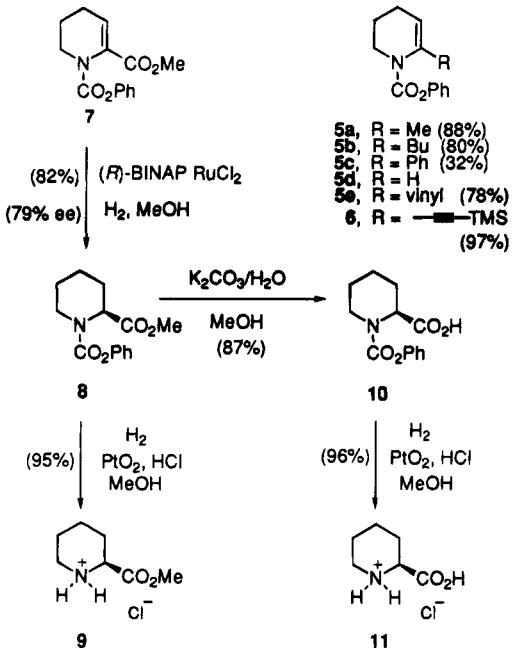
Scheme 2



tion was quenched with 10% NaOH, and standard workup gave the vinyl triflates **4a–d** in 54–90% yield as shown in Table 1. Both six- and seven-membered cyclic lactams **3a–d** provided the vinyl triflates in good yield. Isolation of the corresponding five-membered vinyl triflate derived from 2-pyrrolidone was problematical due to its rapid decomposition. The structure of the acyl group on nitrogen appears to have little effect on vinyl triflate formation as shown in entries 1–3.

To test the reactivity of this new class of triflates, they were subjected to various organometallic coupling reactions.[19] Reaction of **4a** with alkyl(aryl)organocuprates (R_2CuLi) gave α-substituted enecarbamates **5a–c** (Scheme 2) along with some α-unsubstituted tetrahydropyridine **5d** (see supplementary material, Table 2). When these reactions were quenched with the corresponding alkyl iodide prior to workup, the yield of the product improved where R is methyl and *n*-butyl, and none of the α-unsubstituted tetrahydropyridine derivative **5d** was isolated. This result strongly suggests the presence of a vinyl organocopper intermediate possibly formed by metal–TfO exchange. (Trimethylsilyl)acetylene underwent palladium-mediated coupling with triflates **4a** and **4d** to provide the desired products (e.g. **6**) in 97% and 95% yields, respectively. In a similar manner, vinyltributyltin coupled with vinyl triflate **4a** to give 78% yield of the 6-vinyl-1,2,3,4-tetrahydropyridine **5e**. When tributyltin hydride was used as the organotin reagent, reduction of **4a** to the α-unsubstituted tetrahydropyridine **5d** occurred.

We could successfully carbonylate the vinyl triflate **4a** to provide the methyl ester **7** using Cacchi's procedure.[20] Having the α-substituted enecarbamates **5a–c** and **7** in hand, we examined their reduction via catalytic asymmetric hydrogenation using various catalysts (Scheme 2).

Even though there are several reports on the catalytic asymmetric hydrogenation of open chain enamides,[21] to our knowledge there is only one report on the catalytic asymmetric hydrogenation of an enamide where the enamide double bond is endocyclic.[22]

Poor enantioselectivity (<15% ee) was observed for the hydrogenation of enecarbamates **5a–c** using chiral ruthenium and rhodium complexes. Reduction of α,β-unsaturated ester **7** with chiral rhodium complexes[23,24] [(COD)Rh((*R*,*R*)-Me-DuPHOS)]$^+$ and [(COD)Rh(*R*)-BINAP]$^+$ gave low enantiomeric excess (3–20%), while hydrogenation of **7** with Noyori's ruthenium catalyst,[25] (*R*)-BINAP $RuCl_2$, provided **8** with a good enantiomeric excess (80% ee) in moderate yield (52%) at 50 °C. A study was done on the temperature and pressure dependency of the reaction (see supplementary material, Table 3). Higher temperature (80 °C) was used to obtain a good yield of the product (83%) without significantly decreasing the ee (78%).

The *N*-phenoxycarbonyl group of **8** was cleaved[26] by hydrogenation (PtO_2, MeOH, HCl) under balloon pressure to give the corresponding hydrochloride salt of the methyl ester of (*S*)-pipecolic acid (**9**). By comparing the optical rotation [$[\alpha]^{25}_D$ −6.2 (*c* 0.74, H_2O)] of the product with the literature value [$[\alpha]^{25}_D$ −9.1 (*c* 3.6, H_2O)],[27] the absolute configuration of **9** was determined to be *S*. In two steps from the methyl ester **8** (79% ee by HPLC), (*S*)-pipecolic acid hydrochloride was synthesized in high yield. The methyl ester **8** was hydrolyzed to its carboxylic acid **10** in 87% yield using aqueous K_2CO_3 in methanol, and cleavage of the *N*-phenoxycarbonyl group (H_2, PtO_2, HCl) gave a 96% yield of (*S*)-pipecolic acid hydrochloride (**11**) [$[\alpha]^{23}_D$ −8.48 (*c* 0.5, H_2O); lit.[28] $[\alpha]^{23}_D$ −10.3 (*c* 0.98, H_2O)].

In summary, we have successfully prepared novel vinyl triflates from cyclic *N*-acyllactams and studied their coupling reactions with various organometallic reagents. This methodology can be used for the synthesis of α-substituted 1,2,3,4-tetrahydropyridines and other azaheterocycles and provides an alternative to the α-lithiation/alkylation procedure.[29] The palladium-mediated carbonylation of vinyl triflate **4a** and subsequent catalytic asymmetric hydrogenation allowed a synthesis of (*S*)-pipecolic acid to be accomplished in high yield and high ee.

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Supplementary Material Available: Tables 2 and 3, ^1H and ^{13}C NMR spectra (300 and 75 MHz) of compounds lacking analyses, and experimental details and characterization data for **3–11** (54 pages).

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