Asymmetric Synthesis of Chiral, Nonracemic Trifluoromethyl-Substituted Piperidines and Decahydroquinolines

Jinlong Jiang,*,‡ Robert J. DeVita,‡ George A. Doss,†
Mark T. Goulet,‡ and Matthew J. Wyvratt‡

Department of Medicinal Chemistry
Department of Drug Metabolism
Merck Research Laboratories, Rahway, New Jersey 07065

The synthesis of trifluoromethyl-substituted heterocycles has become an important area of pharmaceutical research owing to the unique physical and biological properties imparted by the trifluoromethyl group.[1] In many systems, the substitution of a methyl by a trifluoromethyl group results in added metabolic stability and lipophilicity ($\pi_{CF_3} = 1.07$ vs $\pi_{CH_3} = 0.5$),[2] which may improve pharmacokinetic properties of drug candidates. Although trifluoromethyl derivatives of aromatic nitrogen heterocycles are well documented, saturated analogues are much less known.[3] The synthesis of structurally complex trifluoromethyl-substituted saturated heterocycles in either racemic or enantiomerically pure forms creates significant challenges for the synthetic chemist. In this communication, we describe an efficient preparation of chiral, nonracemic trifluoromethyl-substituted piperidines and decahydroquinolines from the chiral trifluoromethyl lactam **2** via palladium-catalyzed reactions of the α-(trifluoromethanesulfonyloxy)enamine **3** (enamine triflate) and α-(diphenylphosphoryloxy)enamine **4** (enamine phosphate), as well as highly regioselective and facially selective Diels–Alder reactions of the novel, nonracemic trifluoromethyl-substituted diene **16** (Scheme 3).

Chiral lactams of type **1** (Figure 1) have been extensively studied as templates in asymmetric syntheses mainly based on the initial alkylation of the methylene group adjacent to the carbonyl group either by treatment with a base followed by reaction with an alkyl halide[4a–c] or by thio-Claisen rearrangement of the corresponding thiolactams.[5] Synthetic methods for the introduction of an alkyl group at the position where the lactam carbonyl group is situated (the 2-position of the six-membered ring) seldom have been reported.[6,7] We now report a cyclic enamine triflate or phospate route to functionalize the carbonyl group of the lactam **2**.

Palladium-catalyzed coupling reactions of the lactam-derived triflates,[8a–c] and lactone-derived cyclic ketene acetal phosphates[9] were reported only recently. All previously reported lactam-
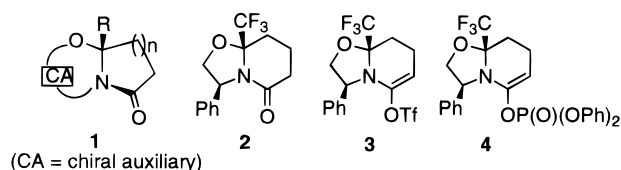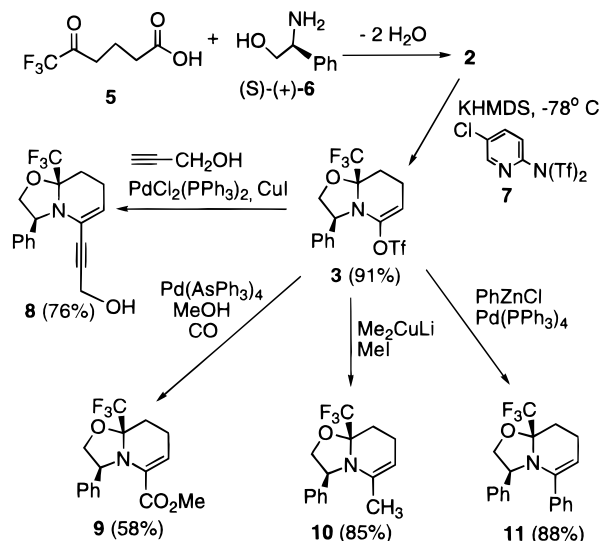

Figure 1.

Scheme 1

derived triflates invariably had a stabilizing carbonyl or sulfonyl group on the lactam-nitrogen atom. Cyclic enamine triflates without a carbonyl or sulfonyl group on the nitrogen atom and cyclic enamine phosphates were not previously reported. We now disclose the preparation of chiral, nonracemic trifluoromethyl-substituted enamine triflate **3** and enamine phosphate **4** from the lactam **2**, and the preliminary results of their Pd-catalyzed coupling reactions. The synthetic utility of the intermediates **3** and **4** is illustrated by the first asymmetric synthesis of an enantiomerically pure 2-trifluoromethyl-6-alkylpiperidine **15**, oxazoline-protected piperidines **12**–**14** (Scheme 2), and 2-trifluoromethyldecahydroquinolines **20** and **22** (Scheme 3).

Lactam **2** was prepared by condensation of acid **5**[3] with (S)-(+)-phenylglycinol **6** in the presence of *p*-toluenesulfonic acid with a Dean–Stark trap. Purification by column chromatography afforded a single diastereomer **2** in 70% yield (Scheme 1). Treatment of the lactam **2** with potassium bis(trimethylsilyl)amide (KHMDS) at −78 °C followed by reaction with *N*-(5-chloro-2-pyridinyl)triflimide (**7**) gave triflate **3** in 91% yield. Triflate **3** is stable under basic conditions and was purified by filtration through a basic aluminum oxide pad, but it was readily hydrolyzed under acidic conditions. The new triflate **3** was subjected to the typical organometallic coupling reactions as previously reported for α-(trifluoromethanesulfonyloxy)encarbamates.[8a,b] Reaction of the triflate **3** with methyl cuprate and palladium-catalyzed coupling reactions with propargyl alcohol, phenylzinc chloride, and carbon monoxide/methanol gave enamines **8**–**11** in good to excellent yield.

Cleavage of the oxazoline ring of oxazoline-protected piperidines such as **12** (Scheme 2) by hydrogenation to generate *cis*-

‡ Department of Medicinal Chemistry.

† Department of Drug Metabolism.

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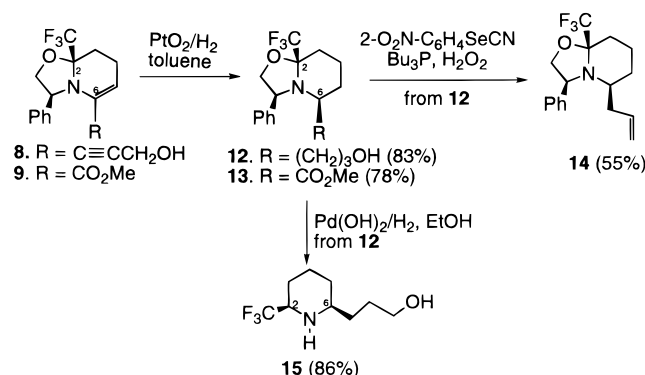
(6) Meyers *et al.*[7] recently reported the synthesis of chiral, nonracemic piperidines from the chiral lactam **1** (*n* = 2) via Eschenmoser sulfide contraction followed by hydrogenation of the enamine. Our attempts to use this method for the synthesis of chiral 2-trifluoromethyl-6-alkylpiperidines were, however, unsuccessful. Treatment of the CF₃ version of chiral thiolactam derived from **2** with an excess of methyl α-bromoacetate led exclusively to the recovery of lactam **2** probably via hydrolysis of a labile thioiminium intermediate.

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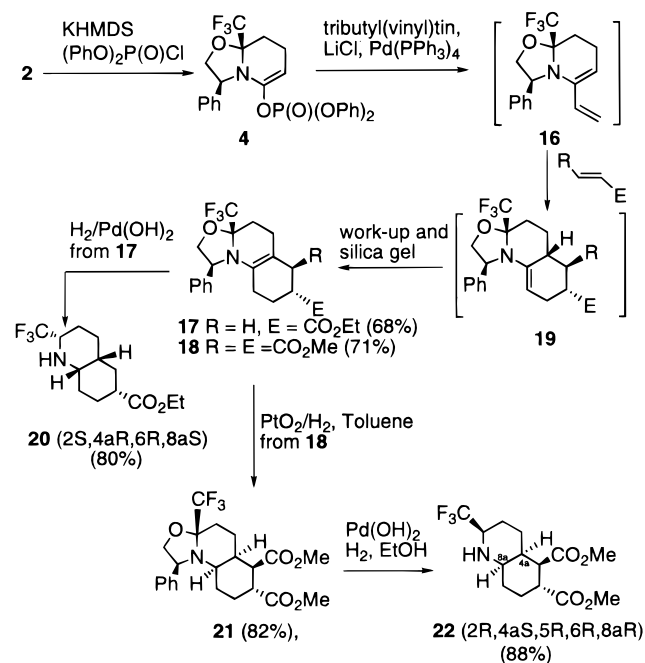
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Scheme 2

8. R = C≡CCH₂OH
9. R = CO₂Me

12. R = (CH₂)₃OH (83%)
13. R = CO₂Me (78%)

14 (55%)

15 (86%)

Scheme 3

17 R = H, E = CO₂Et (68%)
18 R = E = CO₂Me (71%)

20 (2S,4aR,6R,8aS)
(80%)

21 (82%),

22 (2R,4aS,5R,6R,8aR)
(88%)

2,6-disubstituted piperidines is well documented.[10] The mechanism involves cleavage of the PhCH−N bond, formation of an imine intermediate, and reduction of the C=N bond. Therefore, formation of the enantiomerically pure piperidines by hydrogenation of compounds **8** and **9** requires the enamine C=C bond to be reduced prior to the oxazoline ring. We found that the enamine double bond of compounds **8** and **9** was selectively reduced by hydrogen (45 psi) over PtO₂ in toluene to give the oxazoline-protected piperidine **12** and CF₃-pipecolic ester **13**, respectively. Hydrogenation of **12** over Pd(OH)₂ in ethanol gave piperidine **15** in 86% yield. One-step hydrogenation of compound **8** over Pd(OH)₂ in ethanol gave the piperidine **15** with lower optical rotation indicating a portion of **15** was generated via an achiral imine intermediate (formed by initial cleavage of the PhCH−N bond). The oxazoline ring of compounds **12** and **13** can be visualized as a NH protecting group during side chain transformations such as that needed to convert the alcohol **12** to olefin **14**[11] or to make further transformations of the C=C bond of the olefin **14** before the oxazoline ring was cleaved.[12]

The cyclic enamine phosphate **4** was prepared from the lactam **2** by using the procedure of Nicolaou *et al.*[9] for the preparation

of lactone-derived ketene acetal phosphates (Scheme 3). Thus, treating lactam **2** with KHMDS, HMPA, and diphenyl chlorophosphate gave the cyclic enamine phosphate **4**, which was stable under neutral and basic conditions, but partially hydrolyzed to the lactam **2** on silica gel column chromatography. In practice, phosphate **4** was used without purification.

Reaction of the phosphate **4** with tributyl(vinyl)tin in the presence of catalytic Pd(PPh₃)₄ and anhydrous LiCl in refluxing THF for 2 h gave diene **16**, which was trapped *in situ* by ethyl acrylate or methyl fumarate to give adducts **19**. The initially formed adducts **19** were partially isomerized to adducts **17** and **18** during workup and column chromatography on silica gel, and complete isomerization was accomplished by stirring with silica gel for 1 h. Both adducts **17** and **18** were obtained as single isomers in 65−71% yield (overall isolated yields based on the lactam **2**). The exclusive endo facial selectivity from the α-face can be accounted for by the Diels−Alder transition state model of diene **16** in which the bulky phenyl and trifluoromethyl groups block the endo entry of dienophiles from the β-face. The exo compounds were not detected by ¹H NMR.

The asymmetric Diels−Alder reaction is a very powerful tool to build complex molecules with absolute stereocontrol. However, as previously noted,[13] there are few examples of the use of enantiomerically pure dienes for Diels−Alder reactions. The present diene **16**[14] represents a novel example of the chiral, nonracemic trifluoromethyl-substituted dienes. The chiral auxiliary oxazoline is readily cleaved by hydrogenation. Thus, adduct **17** was transformed in high yield by hydrogenation over Pd(OH)₂ catalyst[7] into the decahydroquinoline **20** with (*S*)-configuration at the 2-position. The oxazoline ring appears to be reduced prior to the C=C bond during the H₂/Pd(OH)₂ process (via a chiral, nonracemic imine intermediate). Compound **22** with (*R*)-configuration at the 2-position was obtained by a two-step hydrogenation from compound **18** in which the C=C bond was reduced prior to cleavage of the oxazoline ring.

In summary, we have developed an efficient method to functionalize the carbonyl group of lactam **2** via the palladium-catalyzed coupling reaction of the cyclic enamine triflate **3** and phosphate **4**. Reactions of triflate **3** with a variety of organometallic reagents afforded chiral, nonracemic trifluoromethyl-substituted piperidine derivatives.[15] Conversion of phosphate **4** to the chiral, nonracemic diene **16**, followed by highly facially selective Diels−Alder reactions and hydrogenation, gave chiral, nonracemic trifluoromethyl-substituted decahydroquinolines.[15] Other reactions and applications of triflate **3** and phosphate **4** are currently under investigation.

Supporting Information Available: Experimental procedures and characterization data for compounds **2**, **3**, **8**−**18**, and **20**−**22** and their ¹H NMR (including ¹H NMR spectrum of the crude phosphate **4**) and ¹³C NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For example, we prepared 2-trifluoromethyl-6-(2-hydroxyethyl)-piperidine in high yield by ozolysis of the olefin **14** followed by hydrogenation over Pd(OH)₂.

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(14) The Diels−Alder reactions of racemic 2-(*N*-acylamino)-1,3-diene (**23**) and 2-(*N*-tosylamino)-1,3-diene (**24**) were recently reported by Cha *et al.* (Ha, J. D.; Kang, C. H.; Belmore, K. A.; Cha, J. K. *J. Org. Chem.* **1998**, *63*, 3810−3811) and by Speckamp *et al.*,[8b] respectively.

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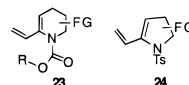
(15) [a]²⁰_D: **2**, +144.3° (CHCl₃, *c* 0.6); **3**, +122.3° (CHCl₃, *c* 2.3); **8**, +184.9° (CHCl₃, *c* 0.35); **9**, +151.0° (CHCl₃, *c* 0.9); **10**, +161.3° (CHCl₃, *c* 0.7); **11**, +204.0° (CHCl₃, *c* 1.5); **12**, +89.2° (CHCl₃, *c* 0.9); **13**, +62.5° (CHCl₃, *c* 0.5); **14**, +89.7° (CHCl₃, *c* 1.7); **15**, +19.7° (CHCl₃, *c* 1.7); **17**, +147.8° (CHCl₃, *c* 0.8); **18**, +92.0° (CHCl₃, *c* 1.1); **20**, −6.0° (CHCl₃, *c* 1.0); **21**, +153.5° (CHCl₃, *c* 1.3); **22**, +4.2° (CHCl₃, *c* 1.0).