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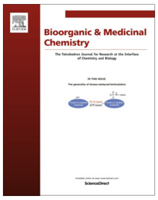

Synthesis and evaluation of phenylalanine-derived trifluoromethyl ketones for peptide-based oxidation catalysis

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This manuscript is dedicated to Professor William L. Jorgensen on the occasion of his receiving the Tetrahedron Prize

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ABSTRACT

We report the synthesis of phenylalanine-derived trifluoromethyl ketones for the in situ generation of dioxiranes for the purpose of oxidation catalysis. The key features of this synthesis include the use of a masked ketone strategy and a Negishi cross-coupling to access the parent amino acid. The derivatives can be readily incorporated into a peptide for use in oxidation chemistry and exhibit good stability and reactivity.

1. Introduction

Since oxidation remains a fundamental maneuver in organic synthesis, the development of new approaches to oxidation catalysis remains an intensely pursued research area. In the area of olefin epoxidation catalysis, an impressive list of biocatalysts,[1] metal-based catalysts,[2] and organocatalysts[3] seems to be growing without any indication of ebb. Among the most widely employed epoxidation catalysts is the remarkable carbohydrate-derived Shi ketone,[4] which has proven to be a seminal contribution (Fig. 1a). We recently explored the possibility that peptide-based ketones[5,6] might also be effective catalysts for oxidation, perhaps for both epoxidation and C–H hydroxylation reactions.[7,8] In an earlier study, for example, we found that a peptide-based trifluoromethyl ketone exhibited good catalytic properties, such that certain olefins could undergo epoxidation with enantiomeric ratios of up to 91:9 and good yields with use of 10 mol% of the catalyst (Fig. 1b).[6] However, certain limitations were encountered, including the compatibility of an *N*-terminal amino acid residue as the moiety carrying the trifluormethyl ketone as the catalytic side chain. These tribulations led us to speculate about potential advantages of new ketones, such as arene-substituted trifluoromethyl ketones[9] as possible replacements for the aliphatic ketones we had studied previously. Tuning of the arene was a particular advantage we coveted, and, thus, we set our sights on catalysts of type **1** (Fig. 1c). We imagined, for example, that arene substitution could modulate reaction rates. *p*-Fluoroarene substitution, for example, had been demonstrated by Hilinski to be advantageous in ketone-catalyzed C–H hydroxylation reactions.[7] The successful synthesis of these unusual compounds, and the demonstration of their suitability as competent catalysts for olefin epoxidation is the subject of this report.

2. Results and discussion

The synthesis of phenylalanine derivatives has been studied extensively, culminating in numerous methods to access a wide variety of analogues.[10] Our retrosynthetic analysis of our proposed catalyst culminated in a projected Negishi cross-coupling of a prefunctionalized aryl bromide and a suitably protected β-iodoalanine as the key step (Scheme 1). Our synthesis thus began with the nucleophilic trifluoromethylation of commercial 2-bromo-4-fluorobenzaldehyde **3** using $CF_3Si(CH_3)_3$.[11] Oxidation of trifluorocarbinol **4a** to ketone **5** using IBX, followed by a Wittig olefination provided trifluoromethyl styrene derivative **6** in 76% yield, which was designed to serve as a masked ketone precursor.[12] Notably, our initial attempts at direct Negishi cross-coupling of **4a** and Boc-β-iodoalanine methyl ester were unsuccessful, resulting in

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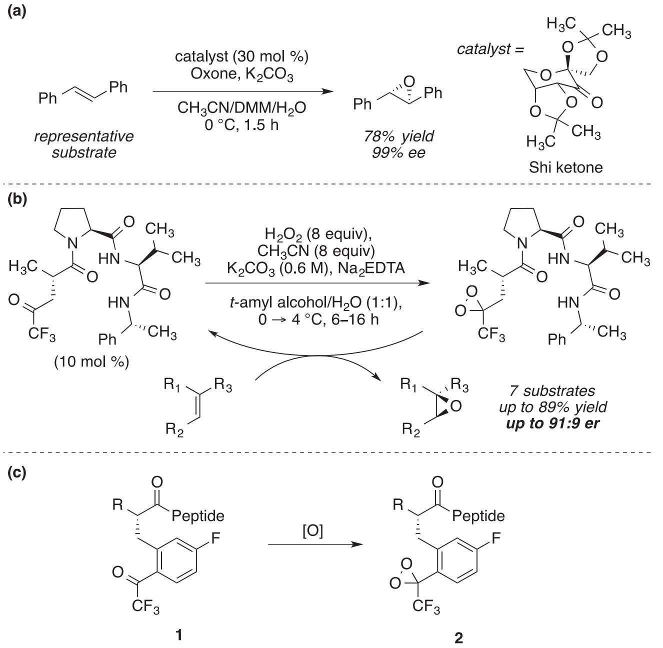
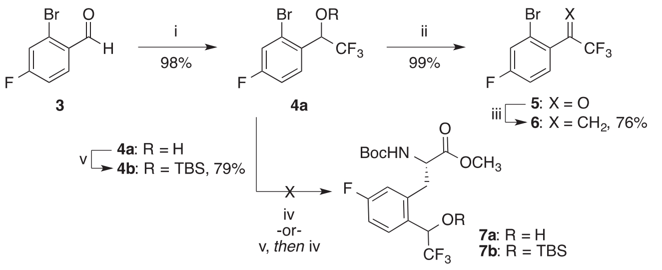


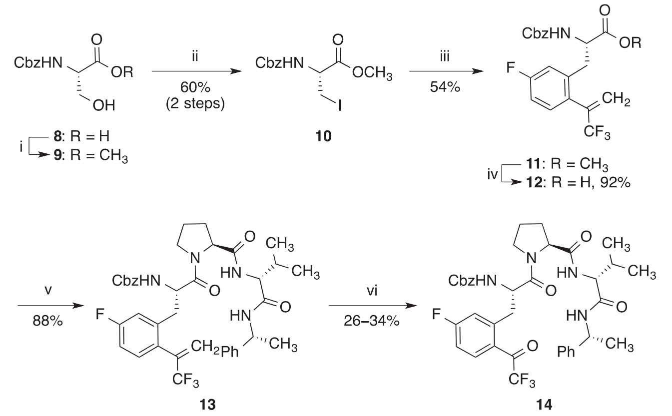
Figure 1. (a) Asymmetric olefin epoxidation with the fructose-derived ketone catalyst of Shi. (b) Previous alkyl trifluoromethyl ketone peptide-based catalyst for enantioselective olefin epoxidation. (c) Proposed second-generation phenylalanine derived trifluoromethyl ketones as potential oxidation catalysts. DMM, dimethoxymethane; EDTA, ethylenediaminetetraacetic acid.

only recovered starting material and proto-dehalogenation, leading to alanine derivatives. Moreover, when TBS ether derivative **4b** was subjected to the Negishi cross-coupling conditions, product **7b** was not observed, which may be attributed to the steric bulk of the silyl group inhibiting oxidative addition. However, when the ketone was masked as the olefin (as in compound **6**), *ortho* cross-coupling was successful (*vide infra*), perhaps due to the decrease in size relative to **4b**.

Thus, the revised monomer synthesis began with esterification of Cbz-Ser-OH (**8**) and subsequent Appel iodination to afford the requisite β-iodoalanine methyl ester **10** (Scheme 2).[13] Subsequent Negishi cross-coupling of bromide **6** with iodide **10** gave the fully protected monomer **11** in 54% yield. Saponification of methyl ester **11** provided the free carboxylic acid **12**, which was then efficiently incorporated into a peptide scaffold through standard EDC/HOBt coupling methods to give the ketone precursor **13**. Lastly, the styrene moiety was converted to the ketone through ozonolysis providing the desired catalyst **14** in 26–34% yield.



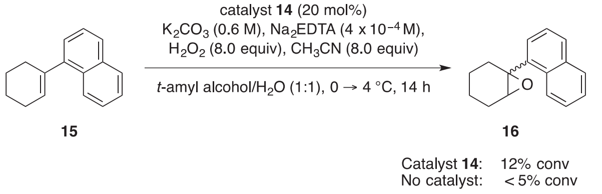
Scheme 1. Synthesis of aryl bromide **5**. Reagents and conditions: (i) $CF_3Si(CH_3)_3$, K_2CO_3 (1 mol %), DMF, rt *then* Bu_4NF; (ii) IBX, EtOAc, 77 °C; (iii) *n*-BuLi, CH_3PPh_3Br, THF, 0 °C to rt; (iv) Boc-β-iodoalanine methyl ester, Zn dust, I_2 (30 mol %), SPhos (7.5 mol %), $Pd_2(dba)_3$ (3.75 mol %), DMF, 60 °C; (v) TBSCl, imidazole, DMAP, DMF, rt. IBX, 2-iodoxybenzoic acid; SPhos, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; dba, dibenzylideneacetone; TBSCl, *tert*-butyldimethylsilyl chloride; DMAP, 4-dimethylaminopyridine.



Scheme 2. Synthesis of trifluoromethyl ketone catalyst **14**. (i) CH_3I, K_2CO_3, DMF, rt; (ii) I_2, imidazole, PPh_3, CH_2Cl_2, 0 °C to rt; (iii) **6** (1.3 equiv), Zn dust, I_2 (30 mol %), SPhos (10 mol %), $Pd_2(dba)_3$ (5 mol %), DMF, 55 °C; (iv) LiOH, H_2O/THF, 0 °C to rt; (v) H-Pro-D-Val-(*R*)-α-Mba·HCl, EDC·HCl, HOBt·H_2O, *i*-Pr_2EtN, CH_2Cl_2, 0 °C to rt; (vi) O_3, CH_2Cl_2, −78 °C *then* $(CH_3)_2S$, −78 °C to rt. Cbz, carboxybenzyl; Mba, methylbenzylamine; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HOBt, hydroxybenzotriazole.

Initial studies with the *N*-protected peptide catalyst as a dioxirane precursor for olefin epoxidation showed low catalyst turnover, leading to only 12% conversion of **15** to the desired epoxide **16** (Eq. 1). These modest results led to an investigation into the stability of catalyst **14**. Intriguingly, ^{19}F NMR studies revealed the formation of **17** (4:1 dr) wherein the nitrogen of the carbamate had undergone cyclization with the ketone to generate a proposed hemiaminal species[14] as a result of the electrophilic nature of the trifluoromethyl ketone (Fig. 2). In an attempt to reverse the cyclization reaction, the mixture obtained after reversed phase purifications was suspended in $CHCl_3$ with 4 Å molecular sieves; yet, no change in the relative amounts of **14** and **17** was observed. We had previously observed that trifluoromethyl ketone hydrates may revert to the ketone form under these conditions.[6] Additionally, ^{19}F NMR analysis performed after the catalyst was subjected to the reaction conditions, in the presence or absence of substrate, revealed a mixture of **17** (4:1 dr) and **18** (2:1 dr). Based on these findings, we concluded that the catalyst would not be suitable for our intended applications.

In order to circumvent this issue, we sought to synthesize a new analogue wherein the *N*-terminus was replaced with a simple methyl group, in analogy to the strategy we had used in previous catalyst designs with no deleterious effects.[6,15] The synthesis began with an Appel iodination of methyl (*S*)-(+)-3-hydroxy-2-methylpropionate ester **19** to afford iodide **20**. Negishi cross-coupling with bromide **6** and subsequent saponification provided the free acid **22** in 65% yield over three steps (Scheme 3). In a departure from our previous synthetic strategy, we hypothesized that ozonolysis prior to peptide coupling would be preferable, as it would provide the fully deprotected residue in turn reducing the number of manipulations to the catalyst. Thus we found that ozonolysis of olefin **22** provided the trifluoromethyl ketone monomer **23** in 55% yield. The phenylalanine analogue was then incorporated into a peptide scaffold using HCTU as the coupling reagent to afford **24** in good yield. Additionally, each step of the synthesis has been demonstrated to be scalable, providing access to >6 g of carboxylic acid **22** and >250 mg of catalyst **24** in a single batch.



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