Graphical Abstract

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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.

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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 organocatalysts³ seems to be growing without any indication of ebb. Among the most widely employed epoxidation catalysts is the remarkable carbohydrate-derived ketone of Shi,⁴ which has proven to be a seminal contribution (Figure 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 (Figure 1b).⁶ However, certain limitations were encountered, including the compatibility of an *N*-terminal amino acid residue as the moiety carrying the trifluoromethyl ketone as the catalytic side chain. These tribulations led us to speculate about potential advantages of new ketones, for example arene-substituted trifluoromethyl ketones⁹ as possible replacements for the aliphatic ketones we had studied previously. Tuning of the arene was a particular advantage we coveted, and we thus set our sights on catalysts of type **1** (Figure 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-

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.

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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 $\text{CF}_3\text{Si}(\text{CH}_3)_3$.¹¹ Oxidation of trifluorocarbonol **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 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**.

Scheme 1. Synthesis of aryl bromide **5**

Scheme 1: i) $\text{CF}_3\text{Si}(\text{CH}_3)_3$, K_2CO_3 (1 mol%), DMF, RT then Bu_4NF ; ii) IBX, EtOAc, 77 °C; iii) *n*-BuLi, $\text{CH}_3\text{PPh}_3\text{Br}$, THF, 0 °C to RT; iv) Boc- β -iodoalanine methyl ester, Zn dust, I_2 (30 mol%), SPhos (7.5 mol%), $\text{Pd}_2(\text{dba})_3$ (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.

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.

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** (Equation 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 species¹⁴ as a result of the electrophilic nature of the trifluoromethyl ketone (Figure 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), with the Cbz-deprotected. Based on these findings, we concluded that the catalyst would not be suitable for our intended applications.

Scheme 2. Synthesis of trifluoromethyl ketone catalyst **14**

Scheme 2: 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%), $\text{Pd}_2(\text{dba})_3$ (5 mol%), DMF, 55 °C; iv) LiOH, $\text{H}_2\text{O}/\text{THF}$, 0 °C to RT; v) H-Pro-D-Val-(*R*)- α -Mba-HCl, EDC-HCl, HOBt-H₂O, *i*-Pr₂EtN, CH_2Cl_2 , 0 °C to RT; vi) O_3 , CH_2Cl_2 , -78 °C then $(\text{CH}_3)_2\text{S}$, -78 °C to RT. Cbz, carboxybenzyl; Mba, methylbenzylamine; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; HOBt, hydroxybenzotriazole.

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 grams of carboxylic acid **22** and >250 mg of catalyst **24** in a single batch.

Figure 2. ^{19}F NMR analysis of **13–14** and **17–18** (A) Pure compound **13**. (B) Mixture of compounds **13**, **14** and **14·H₂O** obtained after first round of purification (see supplementary information). (C) Mixture of compounds **14** and **17** obtained after second round of purification (see supplementary information). (D) Products from C with activated 4Å molecular sieves overnight. No disappearance of ^{19}F signals at δ –80.27 and –80.51 ppm suggests that the peaks are not related to a hydrated species. (E) Crude analysis of catalyst decomposition under the oxidation reaction conditions in the absence of substrate demonstrating appearance of **17** and **18** during the course of the reaction as a part of the catalyst decomposition pathway. Similar results were also obtained in the presence of substrate.

With a robust synthesis of the monomer and the ability to incorporate the catalytic residue into a suitable peptide scaffold, the stage was set for investigating its potential utility and reactivity. As a benchmark for reactivity, we turned our attention to low reactivity olefins, such as substituted styrene derivatives, using previously developed reaction conditions.^{6,9} The aryl trifluoromethylketone catalyst **24** was able to catalyze the epoxidation of substrate **25** to **26** in >99% conversion with no apparent catalyst degradation (Equation 2). Minimal enantioselectivity was observed in this experiment, although the stage is now set to explore incorporation of this catalytic ketone into an expanded library of peptides. Importantly, in the absence of the ketone catalyst, <5% conversion was observed, suggesting

that the ketone is indeed generating a dioxirane *in situ* as the active catalyst species, in analogy to many other reports.¹⁶ It is also interesting to note that while the ketone catalyst is obtained as a mixture of the ketone and hydrated species, there appear to be no negative effects observed on the reactivity and turnover of the catalyst, presumably since either may enter into the necessary catalytic cycle. For example, when purified *via* reversed-phase chromatography, the catalyst is obtained as a 1:2 mixture of the ketone and hydrate. However, when purified *via* normal phase chromatography, the catalyst was isolated as a >20:1 ketone:hydrate mixture. Both mixtures performed equally well under the reaction conditions.

Scheme 3. Synthesis of methyl analogue **24**.

Scheme 3. i) I_2 , imidazole, PPh_3 , CH_2Cl_2 , 0 °C to RT; ii) **6** (1.0 equiv), Zn dust, I_2 (30 mol%), SPhos (10 mol%), $\text{Pd}_2(\text{dba})_3$ (5 mol%), DMF, 55 °C; iii) KOH, $\text{H}_2\text{O}/\text{EtOH}$, 0 °C to RT; iv) O_3 , CH_2Cl_2 , –78 °C then $(\text{CH}_3)_2\text{S}$, –78 °C to RT; v) H-D-Pro-Aic-D-Phe- $\text{N}(\text{CH}_3)_2\cdot\text{HCl}$, HCTU, NMM, CH_2Cl_2 , –10 °C to RT. HCTU, 2-(6-Chloro-1H-benzotriazole-1-yl)-1,1,3,3-tetramethylammonium hexafluorophosphate; NMM, *N*-methylmorpholine.

Finally, during the course of our studies, we were able to obtain an X-ray crystal structure of ketone **24** (Figure 3).¹⁷ The catalyst presents a folded secondary structure in the solid state, wherein the methyl group of the catalytic residue adopts a conformation driven by minimization of allylic strain.¹⁸ The X-ray structure also shows that the trifluoromethyl ketone is orientated away from the peptide scaffold, which signals a ground state conformer that may not be favorable for intermolecular interactions that could lead to highly enantioselective epoxidations. Second-generation catalysts that include the possibility for enhanced interactions, either through catalyst dynamics, or explicit targeting of preferred conformations in solution, could be the paths to achieve stereoselectivity in the future.

Conclusions

Figure 3. The X-ray crystal structure of **24**.¹⁹

We have developed a robust and scalable route to access trifluoromethyl ketone-functionalized phenylalanine derivatives and analogues for studies in dioxirane-mediated oxidations. With the broad applicability of trifluoromethyl ketones within medicinal chemistry and chemical biology, it is our hope that the methodology developed herein could be of value beyond the context of our specific goals.²⁰ Nevertheless, for our local objectives, preliminary studies have shown that the catalysts in which the amino functionality of the catalytic residue is replaced with a methyl group are both highly reactive towards olefin epoxidation and demonstrate increased stability. We are currently optimizing the catalyst designs further with hopes of developing an improved peptide-based catalyst.

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References and notes:

- (a) de Vries, E. J.; Janssen, D. B. *Curr. Opin. Biotechnol.* **2003**, *14*, 414–420. (b) Archelas, A.; Furstoss, R. *Annu. Rev. Microbio.* **1997**, *51*, 491–525.
- (a) Jørgensen, K. A. *Chem. Rev.* **1989**, *89*, 431–458. (b) Xia, Q.; Ge, H.; Ye, C.; Liu, Z. M.; Su, K. *Chem. Rev.* **2005**, *105*, 1603–1662.
- (a) Davis, R. L.; Stiller, J.; Naicker, T.; Jiang, H.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 7406–7426. (b) Zhu, Y.; Wang, O.; Cornwall, R. G.; Shi, Y. *Chem. Rev.* **2014**, *114*, 8199–8256.
- (a) Wang, Z. X.; Tu, Y.; Frohn, M.; Zhang, J. R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235. (b) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488–496.
- Blank, J. T.; Miller, S. J. *Biopolymers (Pept. Sci.)* **2006**, *84*, 38–47.
- Romney, D. K.; Miller, S. J. *Org. Lett.* **2012**, *14*, 1138–1141.
- Pierce, C. J.; Hilinski, M. K. *Org. Lett.* **2014**, *16*, 6504–6507 and references therein.
- Newhouse, T.; Baran, P. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 3362–3374.
- Limnios, D.; Kokotos, C. G. *J. Org. Chem.*, **2014**, *79*, 4270–4276.
- (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415. (b) Jackson, R. F. W.; Perez-Gonzalez, M. *Org. Synth.* **2005**, *81*, 77. (c) Ross, A. J.; Lang, H. L.; Jackson, R. F. W. *J. Org. Chem.*, **2010**, *75*, 245–248.
- Prakash, G. K. S.; Panja, C.; Vaghoo, H.; Surampudi, V.; Kultyshev, R.; Mandal, M.; Rasul, G.; Mathew, T.; Olah, G. A. *J. Org. Chem.*, **2006**, *71*, 6806–6813.
- Cheng, H.; Pei, Y.; Leng, F.; Li, J.; Liang, A.; Zou, D.; Wu, Y.; Wu, Y. *Tetrahedron Lett.* **2013**, *54*, 4483–4486.
- Hattori, Y.; Asano, T.; Kiriata, M.; Yamaguchi, Y.; Wakamiya, T.; *Tetrahedron Lett.* **2008**, *49*, 4977–4980.
- Billar, T.; Langlois, B. R.; Blond, G. *Eur. J. Org. Chem.* **2001**, 1467–1471.
- Jakobsche, C. E.; Peris, G.; Miller, S. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 6707–6711.
- (a) Shu, L.; Shi, Y. *Tetrahedron Lett.* **1999**, *40*, 8721–8724. (b) Burke, C. P.; Shu, L.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 6320–6323.
- Crystallographic data are deposited with the Cambridge Crystallographic Data Centre under the accession number CCDC 1490745 (**24**).
- Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.
- CYLview, 1.0b; C. Y. Legault, Université de Sherbrooke, 2009, <http://www.cylview.org>.
- Kelly, C. B.; Mercadante, M. A.; Leadbeater, N. E. *Chem. Commun.* **2013**, *49*, 11133–11148.