Chiral Tetrahydropyridines via FeCl₃-Catalyzed Carbonyl-Olefin Metathesis

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Supporting Information Placeholder

Amino Acid Derived • Cheap, Earth-Abundant Catalyst • 24 Examples, up to 99% yield

ABSTRACT: Herein, we describe the application of Lewis acid-catalyzed carbonyl-olefin metathesis towards the synthesis of chiral, substituted tetrahydropyridines from commercially available amino acids as chiral pool reagents. This strategy relies on FeCl₃ as an inexpensive and environmentally benign catalyst and enables access to a variety of substituted tetrahydropyridines under mild reaction conditions. The reaction proceeds with complete stereoretention and is viable for a variety of natural and unnatural amino acids to provide the corresponding tetrahydropyridines in up to 99% yield.

Chiral tetrahydropyridines and piperidines represent ubiquitous structural scaffolds found in a variety of biologically active natural products and pharmaceuticals.¹ Recent estimates report that in the past decade, over 12,000 piperidine-derived compounds were included in clinical and pre-clinical studies.² A variety of methods have been developed to access these nitrogen-containing heterocycles (**1**) including approaches relying on olefin-olefin metathesis,³ asymmetric multicomponent reactions,⁴ aza-Diels Alder reactions,⁵ and asymmetric annulations⁶ (Fig. 1A). Additional strategies include the cyclization of sulfinyl dienamines,⁷ ring expansion of furan derivatives,⁸ the reduction of pyridine scaffolds,⁹ and transition metal-catalyzed cyclizations.¹⁰ While these strategies provide differentially substituted tetrahydropyridines, they often require precious metal catalysts, expensive chiral ligands, extended reaction times, or have a limited substrate scope.

We recently reported a distinct design principle for catalytic carbonyl-olefin ring-closing metathesis reactions for the synthesis of cyclic systems such as spirocyclic lactones, indenones, polyaromatic hydrocarbons and 3-pyrrolines.¹¹⁻¹³ Upon reaction with FeCl₃ as a Lewis acid catalyst, aryl ketones bearing prenyl or styrenyl fragments undergo a concerted, asynchronous [2+2]-cycloaddition to form intermediate oxetanes. A subsequent Lewis acid-catalyzed retro [2+2]-cycloreversion results in the desired ring-closing metathesis product.^{14,15} Herein we report the expansion of this robust synthetic strategy towards chiral tetrahydropyridines **4**. Our approach relies on readily available amino acids as chiral pool reagents and FeCl₃ as an inexpensive and earth-abundant metal catalyst. This strategy is amenable to gram-scale and provides

A. Current Strategies Towards Accessing Tetrahydropyridines

B. This Work

Figure 1. A. Literature precedent for the synthesis of chiral tetrahydropyridines. **B. This work:** a strategy towards chiral tetrahydropyridines relying on carbonyl-olefin metathesis.

the desired products in up to 99% yield with complete retention of enantiopurity.

Table 1. Evaluation of Reaction Conditions.

entry	Lewis acid	mol %	time (h) ^a	yield (%) ^b	conversion (%) ^b
1	AlCl ₃	50	24	7	45
2	TiCl ₄	50	24	0	99
3	SnCl ₄	50	24	43	45
4	BiCl ₃	50	24	48	49
5	GaCl ₃	50	24	58	99
6	BF ₃ ·OEt ₂	50	24	52	95
7	FeBr ₃	50	24	40	97
8	FeCl ₃	50	24 ^c	68	99
9	FeCl ₃	50	12	69	99
10	FeCl ₃	50	24	88	99
11	FeCl ₃	30	24	89	99
12	FeCl ₃	10	24	6	10
13	FeCl ₃	10	72	39	40
14	Fe(OTf) ₃	50	24	30	91
15	Sc(OTf) ₃	50	24	37	97

Conditions: All reactions were performed using 0.02 mmol of substrate in DCE (0.01 M) at 84 °C for the indicated time. ^bYield and conversion determined by ¹H-NMR using dimethyl terephthalate as an internal standard. ^cThe Lewis acid was added at 0 °C and the reaction was allowed to warm to room temperature.

Initial efforts focused on the development of a scalable, 3-step sequence to convert commercially available amino acids into the corresponding aryl ketones that would function as substrates **2** for carbonyl-olefin metathesis. The best yields of **2** were obtained in a sequence relying on initial conversion of the amino acids to the corresponding Weinreb amides,¹⁶ followed by addition of an aryllithium or Grignard reagent and final alkylation of the amine functionality with either homoprenylbromide or -iodide. Importantly, this sequence was amenable to gram-scale and proved viable for all natural and unnatural amino acids evaluated in the course of this work. With a robust substrate synthesis in hand, we turned our attention to the evaluation of distinct Lewis acids upon their ability to promote the desired carbonyl-olefin metathesis reaction (Table 1). We first evaluated stronger Lewis acids as catalysts for the metathesis reaction of chiral substrate **5**. When aryl ketone **5**

Table 2. Evaluation of Protecting Groups.

entry	substrate	R ¹	R ²	σ _p	yield (%)
1	8	H	CF ₃	0.54	84
2	9	H	Cl	0.37	80
3	10	H	H	0.0	78
4	11	H	Me	-0.17	72
5	12	H	OMe	-0.27	47
6	13	H	OMe	-0.27	78 ^a
7	5	Bn	CF ₃	0.54	89

Conditions: All reactions were performed using 0.1 mmol of substrate and FeCl₃ (30 mol%) in DCE (0.01 M) at 84 °C for 24 h. ^aReaction was stirred for 48 h.

was converted with 50 mol% of AlCl₃, the desired tetrahydropyridine **6** was formed in only 7% yield (entry 1, Table 1). Similarly, TiCl₄ did not provide the desired heterocycle **6**, albeit complete conversion of aryl ketone **5** was observed (entry 2, Table 1). In comparison, the use of 50 mol% SnCl₄ or BiCl₃ provided the desired product **6** in 43% yield and 48% yield, respectively (entries 3 and 4, Table 1). Improved yields of **6** in 58% were observed with GaCl₃, while utilizing BF₃·OEt₂ resulted in 52% yield. Complete consumption of substrate **5** was observed in both cases (entries 5 and 6, Table 1). Diminished yields of tetrahydropyridine **6** were obtained when FeBr₃ was selected as the Lewis acid catalyst whereas FeCl₃ (50 mol%) proved superior and resulted in 88% yield (entries 7 and 10, Table 1). Attempts to lower the reaction temperature to ambient conditions or shorten the reaction time to 12 hours led to lower yields of tetrahydropyridine **6** in 68% and 69%, respectively (entries 8 and 9, Table 1). Iron- and scandium-based metal triflates similarly resulted in the formation of the desired carbonyl-olefin metathesis products, albeit in diminished yields of 30% and 37%, respectively (entries 14 and 15, Table 1). However, lower catalyst loadings of 30 mol% FeCl₃ were tolerated well and resulted in the formation of **6** in 89% yield with 99% conversion of starting material, which was ultimately established as the optimal set of reaction conditions (entry 11, Table 1). When the reaction was conducted relying on toluene as the solvent under otherwise optimal reaction conditions, the desired tetrahydropyridine **6** was obtained in 75% yield (see Supplemental Information for details). Electronically differentiated sulfonamides were then examined as nitrogen protecting groups in the carbonyl-olefin metathesis reaction towards tetrahydropyridines (Table 2). Our previous efforts towards the development of a synthetic approach towards 3-pyrrolines revealed that sulfonamides can function as competitive binders to FeCl₃, which sequesters the catalyst and results in lower overall yields.^{15b} By utilizing more electron-deficient protecting groups, the reactivity of the Lewis basic site was attenuated and the carbonyl-olefin metathesis reaction was able to proceed in

Table 3. Evaluation of the Olefin Subunit.

entry	substrate	yield (%)	entry	substrate	yield (%)
1	5	89%	2	16	29%
3	14	0%	4	17	0%
5	15	3%	6	18 R = Me 10% 19 R = OMe 0%	

Conditions: All reactions were performed using 0.1 mmol of substrate and FeCl₃ (30 mol%) in DCE (0.01 M) at 84 °C for 24 h.

Table 4. Evaluation of Substrate Scope.

Conditions: All reactions were performed using 0.1 mmol of substrate and FeCl₃ (30 mol %) in DCE (0.01 M) at 84 °C for 24 h.^aWith 1.0 equiv. of FeCl₃ for 48 h.

excellent yields.^{15b} Similar observations were made in the present study towards chiral tetrahydropyridines in which electron-deficient sulfonamides resulted in the desired metathesis products in yields of up to 89% (entries 1, 2, 7, Table 2). However, more electron-rich sulfonamides also proved viable substrates and resulted in good yields of up to 78% of the desired tetrahydropyridines, albeit requiring prolonged reaction times of 48 hours (entries 4–6, Table 2).¹⁷ This is in stark contrast to observations made in our previous studies towards chiral 3-pyrrolines in which electron-deficient sulfonamides were essential to obtain high yields of the carbonyl-olefin metathesis product.

Next, we evaluated the effect of olefin substitution (Table 3). While both prenyl- or styrenyl-derived olefins were previously shown to be suitable reaction partners for catalytic carbonyl-olefin ring-closing metathesis reactions,¹² aryl ketones bearing a prenyl substituent were found to be superior in the synthesis of tetrahydropyridines resulting in up to 89% yield of the desired product (entry 1, Table 3). Importantly, the corresponding styrenyl-derivatives either failed or provided the desired tetrahydropyridines in low yields (entries 3–6, Table 3). The addition of superstoichiometric allyltrimethylsilane to the carbonyl-olefin metathesis reactions of styrene-derivatives was previously shown to be beneficial for high yields and conversions.^{15b} However, addition of 5.0 equivalents of allyltrimethylsilane^{15a} to **19** under otherwise identical reaction conditions, did not improve the reaction as no product formation was observed. With these results in hand, we investigated the scope of this transformation (Table 4). The

reaction proceeded with a variety of aryl ketones derived from natural and unnatural amino acids bearing sterically and electronically distinct substitution. Previously challenging substrates, such as unsubstituted glycine-derived aryl ketone **20**, provided the metathesis product in up to 89% yield.^{15a} The reaction also proceeds in good yields with more electron-rich sulfonamide protecting groups such as **21** and **22**. However, the 4-(trifluoromethyl)benzenesulfonyl protecting group consistently provided the highest yield of the desired products. The reaction gave good yields of the alanine-derived products **23**, **24**, and **25** including para- and meta-substituents. We next investigated the electronic effects on the aromatic ring with phenylalanine-based substrates. The reaction was tolerant of biaryl systems as well as electron-withdrawing substituents, providing products **26**, **27** and **28** in good yields. Alternatively an electron-rich aryl ether formed the desired carbonyl-olefin metathesis product **29** in 56% yield. Additionally, the ortho anisole derivative was found to provide the desired product **30** in 22% yield, however stoichiometric quantities of iron were required for the transfor-

Figure 2. Derivatization of FTs protected products.

mation to proceed. Other electron-rich systems including heteroaromatics were well tolerated. The desired product **32** derived from thienylalanine was provided in 64% yield, while the

product **33** from the corresponding thienyl ketone was synthesized in 57% yield. The unnatural amino acids **31** and **34** also proceeded in good yield, providing functional handles for further functionalization. Importantly, this reaction proceeded with complete stereoretention and established catalytic carbonyl-olefin metathesis reactions as a viable approach for the synthesis of chiral tetrahydropyridines from amino acids as chiral pool reagents (see Supplemental Information for more information).

Subsequent efforts focused on developing an efficient protocol for sulfonamide deprotection of the tetrahydropyridine products obtained (Fig. 2). Reductive conditions^{15b,18} relying on SmI₂ resulted in facile deprotection of **23** to form the corresponding secondary amine **35** which upon exposure to Boc₂O at 50 °C afforded the corresponding carbamate **36** in 92% yield over this two-step sequence. Oxidation of the amine or aromatization to the corresponding pyridine was not observed under the optimized deprotection conditions.

In this report, we demonstrate the development of a novel approach towards chiral tetrahydropyridines from commercially available amino acids based on catalytic carbonyl-olefin metathesis as the key transformation. This sequence proved viable for a variety of readily accessible amino acids and provides the desired nitrogen-containing heterocycles in up to 99% yield. Importantly, the reaction proceeds with complete stereoretention and is amenable to gram scale. Sulfonamide protecting groups proved to be essential in the carbonyl-olefin metathesis reactions which underwent facile deprotection under reductive conditions in excellent yields, highlighting that catalytic carbonyl-olefin metathesis is a feasible approach for the synthesis of chiral tetrahydropyridines.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and spectroscopic data for all new reactants and products (PDF)

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