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Tetrahydropyridines via $FeCl_3$-Catalyzed Carbonyl−Olefin Metathesis

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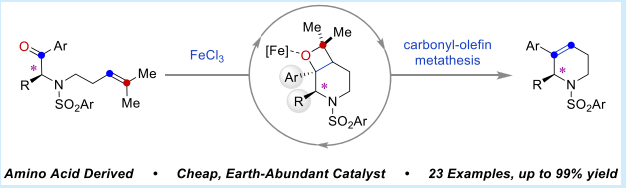
ABSTRACT: Herein we describe the application of Lewis-acid-catalyzed carbonyl−olefin metathesis toward the synthesis of substituted tetrahydropyridines from commercially available amino acids as chiral pool reagents. This strategy relies on $FeCl_3$ as an inexpensive and environmentally benign catalyst 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.



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 preclinical studies.[2] A variety of methods have been developed to access these nitrogen-containing heterocycles (**1**), including approaches that rely on olefin−olefin metathesis,[3] asymmetric multicomponent reactions,[4] aza-Diels−Alder reactions,[5] and asymmetric annulations[6] (Figure 1A). Additional strategies include the cyclization of sulfinyl dienamines,[7] the ring expansion of furan derivatives,[8] the reduction of pyridine scaffolds,[9] and transition-metal-catalyzed cyclizations.[10] Whereas these strategies provide differentially substituted tetrahydropyridines, they often require precious metal catalysts, expensive chiral ligands, and 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, indenes, polyaromatic hydrocarbons, and 3-pyrrolines.[11−13] Upon the reaction with $FeCl_3$ 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 toward tetrahydropyridines **4** (Figure 1B). Our approach relies on readily available amino acids as chiral pool reagents and $FeCl_3$ as an inexpensive and earth-abundant metal catalyst. This strategy is amenable to the gram scale and provides the desired products in up to 99% yield. Initial efforts focused on the development of a scalable, three-step sequence to convert commercially available amino acids into the corresponding aryl ketones that would function as substrates

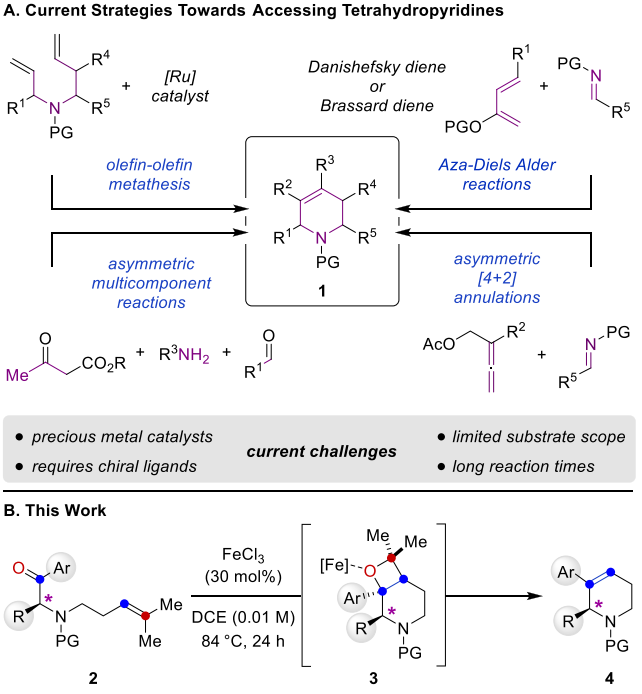


Figure 1. (A) Literature precedent for the synthesis of tetrahydropyridines. (B) This work: a strategy toward tetrahydropyridines relying on carbonyl−olefin metathesis.

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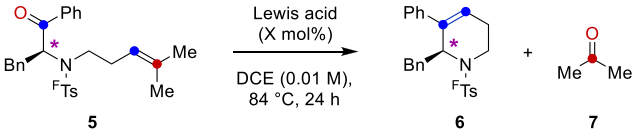
(2) for carbonyl−olefin metathesis. The best yields of **2** were obtained in a sequence relying on the initial conversion of the amino acids to the corresponding Weinreb amides,[16] followed by the addition of an aryllithium or Grignard reagent and the final alkylation of the amine functionality with either homoprenyl bromide or iodide. Importantly, this sequence was amenable to the 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 for their ability to promote the desired carbonyl−olefin metathesis reaction (Table 1). We first evaluated stronger Lewis acids as

Table 1. Evaluation of Reaction Conditions[a]



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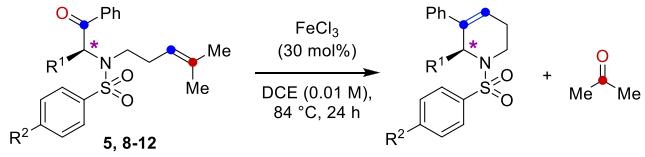
entry	Lewis acid	mol %	time (h)	yield (%)[b]	conversion (%)[b]
1	$AlCl_3$	50	24	7	45
2	$TiCl_4$	50	24	0	99
3	$SnCl_4$	50	24	43	45
4	BCl_3	50	24	48	49
5	$GaCl_3$	50	24	58	99
6	$BF_3{\cdot}OEt_2$	50	24	52	95
7	$FeBr_3$	50	24	40	97
8	$FeCl_3$	50	24[c]	68	99
9	$FeCl_3$	50	12	69	99
10	$FeCl_3$	50	24	88	99
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	$Fe(OTf)_3$	50	24	37	97

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

catalysts for the metathesis reaction of substrate **5**. When aryl ketone **5** was converted with 50 mol % of $AlCl_3$, the desired tetrahydropyridine **6** was formed in only 7% yield (entry 1, Table 1). Similarly, $TiCl_4$ did not provide the desired heterocycle **6**, albeit the complete conversion of aryl ketone **5** was observed (entry 2, Table 1). In comparison, the use of 50 mol % $SnCl_4$ or $BiCl_3$ provided the desired product **6** in 43 and 48% yield, respectively (entries 3 and 4, Table 1). Improved yields of **6** in 58% were observed with $GaCl_3$, whereas utilizing $BF_3{\cdot}OEt_2$ resulted in 52% yield. The complete consumption of substrate **5** was observed in both cases (entries 5 and 6, Table 1). Diminished yields of tetrahydropyridine **6** were obtained when $FeBr_3$ was selected as the Lewis acid catalyst, whereas $FeCl_3$ (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 h led to lower yields of tetrahydropyridine **6** of 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, catalyst loadings of 30 mol % $FeCl_3$ 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 the Supporting Information for details.)

Electronically differentiated sulfonamides were then examined as nitrogen protecting groups in the carbonyl−olefin metathesis, respectively (Table 2). Our previous efforts toward

Table 2. Evaluation of Protecting Groups[a]



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entry	substrate	R^1	R^2	σp	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	**12**	H	OMe	−0.27	78[b]
7	**5**	Bn	CF_3	0.54	89

[a]Conditions: All reactions were performed using 0.1 mmol of substrate and $FeCl_3$ (30 mol %) in DCE (0.01 M) at 84 °C for 24 h. [b]Reaction was stirred for 48 h.

the development of a synthetic approach toward 3-pyrrolines revealed that sulfonamides can function as competitive binders to $FeCl_3$, 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 excellent yield.[15b] Similar observations were made in the present study toward tetrahydropyridines, in which electron-deficient sulfonamides resulted in the desired metathesis products in yields of up to 89% (entries 1, 2, and 7, Table 2). However, more electron-rich sulfonamides also proved to be viable substrates and resulted in good yields of up to 78% of the desired tetrahydropyridines, albeit requiring prolonged reaction times of 48 h (entries 4−6, Table 2).[17] This is in stark contrast with observations made in our previous studies toward 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). Whereas 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 2, 3, 5, and 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, the addition of 5.0 equiv of allytrimethylsilane[15a] to **18** under otherwise identical

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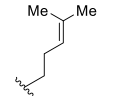
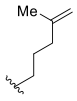
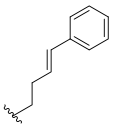
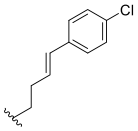
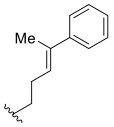
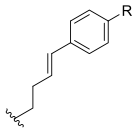
Table 3. Evaluation of the Olefin Subunit[a]

entry	substrate	yield (%)	entry	substrate	yield (%)
1		**5** 89	4		**15** 29
2		**13** 0	5		**16** 0
3		**14** 3	6		**17** R = Me 10 **18** R = OMe 0

[a]Conditions: All reactions were performed using 0.1 mmol of substrate and $FeCl_3$ (30 mol %) in DCE (0.01 M) at 84 °C for 24 h.

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 (Figure 2). 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 **8**, provided the metathesis product in up to 89% yield.[15a] The reaction also proceeds in good yield with more electron-rich sulfonamide protecting groups such as **20** and **21**. 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 **22**–**26** including para and meta substituents. We next investigated the electronic effects on the aromatic ring. The reaction was tolerant of biaryl systems as well as electron-withdrawing substituents, providing products **25**, **26**, and **27** in good yield. Alternatively an electron-rich aryl ether formed the desired carbonyl–olefin metathesis product **28** in 56% yield. The *ortho*-anisole derivative was also found to provide the desired product **29** in 22% yield; however, stoichiometric quantities of iron were required for the transformation to proceed. Other electron-rich systems including heteroaromatics were well tolerated. The desired product **31** derived from thienylalanine was provided in 64% yield, whereas product **32** from the corresponding thienyl ketone was obtained in 57% yield. The unnatural amino acids **30** and **33** also proceeded in good yield, providing functional handles for further elaboration. Importantly, this reaction proceeded with complete stereoretention and established catalytic carbonyl–olefin metathesis reactions as a viable approach for the

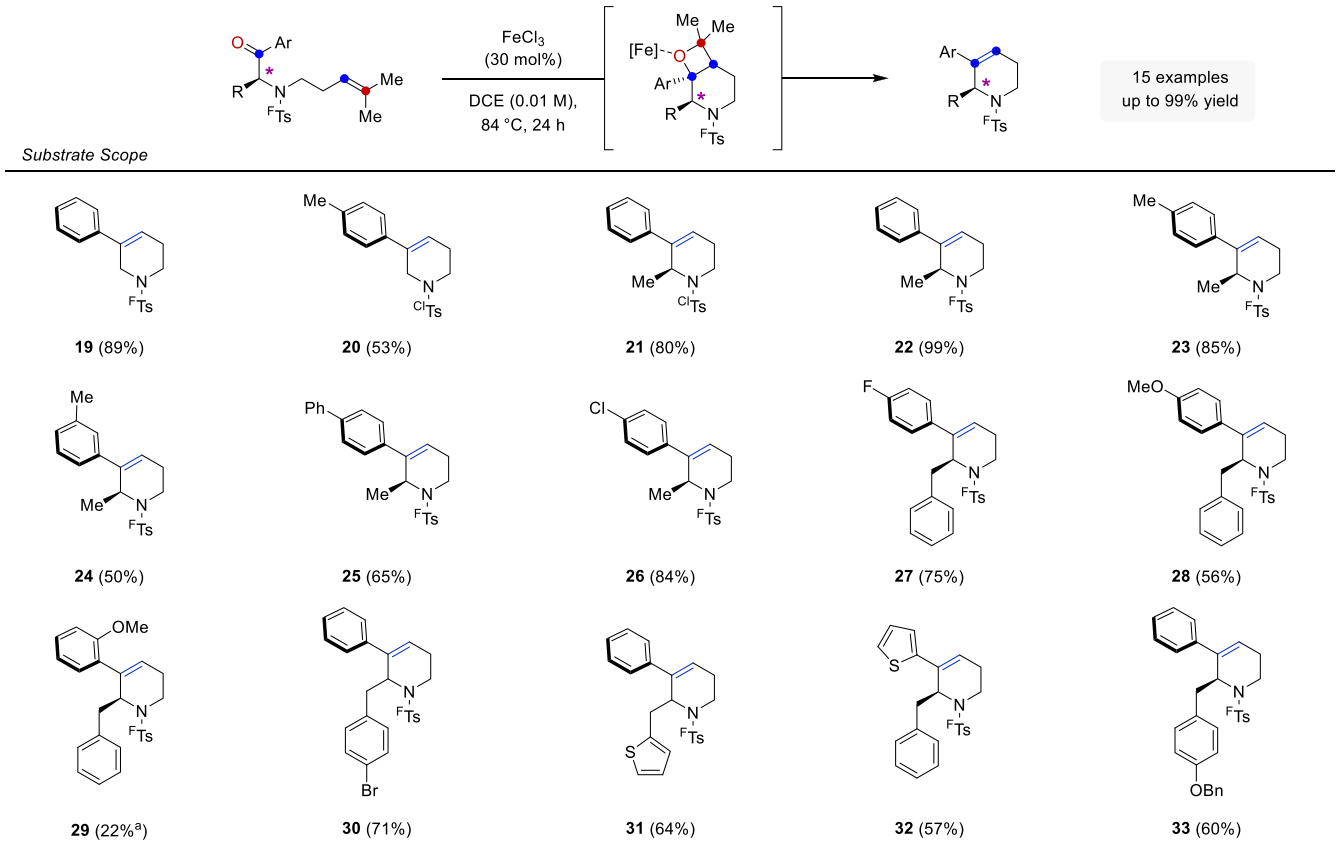


Figure 2. Evaluation of the substrate scope. Conditions: All reactions were performed using 0.1 mmol of substrate and $FeCl_3$ (30 mol %) in DCE (0.01 M) at 84 °C for 24 h. [a]With 1.0 equiv of $FeCl_3$ for 48 h.

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synthesis of tetrahydropyridines from amino acids as chiral pool reagents. (See the Supporting Information for more information.)

Subsequent efforts focused on developing an efficient protocol for sulfonamide deprotection of the tetrahydropyridine products obtained (Figure 3). Reductive conditions[18] relying on SmI_2 resulted in the facile deprotection of **22** to form the corresponding secondary amine **34**, which, upon exposure to Boc_2O at 50 °C, afforded the corresponding carbamate **35** in 92% yield over this two-step sequence. The oxidation of the amine or aromatization to the corresponding pyridine was not observed under the optimized deprotection conditions.

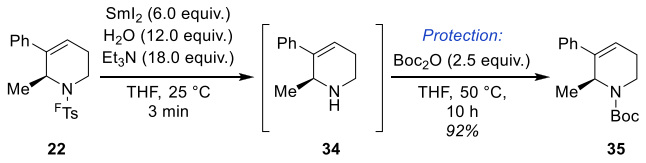

Figure 3. Derivatization of ^{F}Ts-protected products.

In this Letter, we demonstrate the development of a novel approach toward functionalized 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 is amenable to the gram scale. Sulfonamide protecting groups proved to be essential in the carbonyl−olefin metathesis reactions that underwent facile deprotection under reductive conditions in excellent yield, highlighting that the catalytic carbonyl−olefin metathesis is a feasible approach for the synthesis of tetrahydropyridines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00918.

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

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Notes

The authors declare no competing financial interest.

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