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3-Aryl-2,5-Dihydropyrroles via Catalytic Carbonyl-Olefin Metathesis

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Abstract

Herein, we describe the development of a synthetic strategy towards chiral 3-pyrrolines based on the design principle of iron(III)-catalyzed carbonyl-olefin metathesis. This approach takes advantage of commercially available amino acids as chiral pool reagents and FeCl₃ as a Lewis acid catalyst. Our strategy is characterized by its operational simplicity, mild reaction conditions and functional group tolerance. Investigations show that an electron-deficient nitrogen protecting group overcomes limitations arising from competitive binding of the Lewis acid catalyst to unfavorable Lewis basic sites, which ultimately enables catalytic turnover.

Keywords

carbonyl-olefin metathesis; pyrrolines; iron(III) chloride; amino acids; Lewis acid catalysis

Chiral pyrrolidine and pyrrole derivatives represent ubiquitous structural motifs in biologically active natural products¹ and serve as important templates in drug discovery.² Chiral pyrrolidines also function as ligands in asymmetric catalysis³ and are crucial components of hydrogen-bond donor catalysts.⁴ As a result of these wide-ranging implications, the development of synthetic strategies to access chiral nitrogen-containing heterocycles constitutes an active area of research. Among the currently available synthetic strategies are the reductive cyclization of *N*-tert-banesulfinyl ketimines^{5,6} to access chiral pyrrolidines **1**, and enantioselective hydroamination approaches^{7–10} to α -substituted pyrrolidines **2** (Fig. 1). Additional strategies rely on transition-metal catalyzed asymmetric α -arylation and alkylation procedures^{11–14} (**3** and **4**, Fig. 1).

Recently, we reported the development of an efficient iron(III)-catalyzed carbonyl-olefin metathesis reaction^{15,16} that enables the direct formation of alkenes from carbonyls and olefins via intermediate oxetanes.^{16a} We recognized the potential of this carbonyl-olefin metathesis approach to access 3-pyrrolines **5** from secondary amines **6a**, however, initial

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ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at <http://pubs.acs.org>. The Supporting Information includes experimental details and spectroscopic data for all new reactants and products.

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investigations showed that the reaction was hampered by low yields and required super-stoichiometric amounts of FeCl₃ to proceed (Fig. 2a).^{16b} As part of their studies on iron-catalyzed carbonyl-olefin metathesis of styrenes **6b**, Li and coworkers¹⁷ reported the synthesis of pyrrolines **7** using super-stoichiometric allyl-TMS (5.0 equiv) for efficient conversion. The authors suggested this additive was necessary to curtail catalyst inhibition by the benzaldehyde byproduct (Fig. 2A). In our case, we hypothesized that the need for super-stoichiometric FeCl₃ was a consequence of competitive binding to the sulfonamide (product and starting material) resulting in the inhibition of efficient catalyst turnover.^{16a,17}

In this report, we provide experimental support for this hypothesis which identifies the sulfonamide as a competitive binding site for the FeCl₃ catalyst and prevents the desired metathesis reaction (Fig. 2C). Based on these mechanistic insights, we show that attenuating the Lewis basicity of the sulfonamide moiety is a viable strategy to overcome this limitation due to substrate inhibition of the catalyst. Our approach now allows for synthetic access to the desired enantioenriched 3-pyrrolines and their corresponding 6-membered analogs in high yields, enables catalyst turnover and avoids the formation of stoichiometric amounts of waste byproducts. Importantly, our strategy favors substrates bearing prenyl substitution so the metathesis reaction forms acetone as byproduct which is easily removed from the reaction mixture. Notably, carbonyl-olefin metathesis reactions of the corresponding styrenes were previously shown to proceed following a distinct oxetane fragmentation pathway via intermediate carbocations.^{16c} Consequently, the potential for undesired byproduct formation is increased and lower yields of the desired products are often observed compared to the corresponding prenyl derivatives, which form oxetanes that undergo a concerted, asynchronous fragmentation.^{16c}

At the outset of our investigations, we developed a concise and modular synthetic strategy to access metathesis substrates **12** from commercially available amino acids which enables distinct variations of the α -amino and aryl ketone substituents (Fig. 3).¹⁸ When metathesis precursor *N*-tosyl amine **18a** was reacted with 20 mol% of weak Lewis acids (e.g. ZnCl₂, FeCl₂), no formation of the desired metathesis product **19a** was observed. Similarly, catalytic amounts of the strong Lewis acid AlCl₃ resulted in exclusive re-isolation of unreacted starting material **18a**. Notably, the use of SnCl₄ and GaCl₃ under otherwise identical reaction conditions resulted in the formation of desired metathesis product **19a**, albeit in low yields while significant amounts of dealkylated starting material were observed (entries 1 and 2, Table 1). Subsequent experiments identified FeCl₃ as a superior Lewis acid generating **19a** in 19% yield while no competing substrate dealkylation was observed (entry 3, Table 1). These results are consistent with our previous studies of catalytic carbonyl-olefin metathesis reactions which illustrated that a fine-tuned combination of Lewis acidity and oxophilicity was essential for an efficient Lewis acid catalyst.^{16b,19} Longer reaction times did not improve the yield, however, higher catalyst loadings of up to 50 mol% resulted in increased yields of metathesis product **19a** in 72% (entries 4–6, Table 1). Importantly, no erosion in enantioselectivity was observed in the carbonyl-olefin metathesis of **18a**, resulting in the formation of the desired product in 98% *ee*. During our initial investigations into the synthesis of highly valuable heterocyclic compounds using carbonyl-olefin metathesis, we observed the need for stoichiometric amounts of FeCl₃ or additional nucleophilic reagents

and hypothesized that competitive Lewis acid binding to the tosyl protecting group was preventing effective catalysis. We postulated that the presence of Lewis basic sites other than the carbonyl oxygen in **18a** could sequester FeCl₃, thus requiring higher catalyst loadings.

Subsequent efforts focused on the evaluation of electronically distinct nitrogen-protecting groups (e.g. Boc, Cbz, Ns) in the carbonyl-olefin metathesis of **18a** which resulted in increased substrate dealkylation and provided diminished yields of the desired metathesis products. We hypothesized that attenuating the electronic properties of the sulfonamide functionality in **18a** by adding electron-withdrawing substituents to the aromatic ring would disfavor sequestering of FeCl₃ and prevent stalling of the carbonyl-olefin metathesis reaction. When the tosyl group was replaced with 4-chlorobenzenesulfonamide (^{Cl}Ts) **18b** and subjected to carbonyl-olefin metathesis, the desired product was obtained in increased yields of 96% (entry 7, Table 1). *N*-tosyl amine **18c** bearing a trifluoromethyl group (4-trifluoromethyl-benzene sulfonyl; ^FTs) was selected to further probe this hypothesis and prepared using commercial 4-(trifluoromethyl)benzene-sulfonyl-chloride.^{20,21} When aryl ketone **18c** was subjected to the optimized reaction conditions, the desired metathesis product **19c** was obtained in increased yields of 99% (entry 8, Table 1). Importantly, the desired carbonyl-olefin metathesis product **19c** is now obtainable in up to 80% yield with as low as 5 mol% FeCl₃ (entry 10, Table 1). In comparison, Brønsted acids such as *p*TsOH and anhydrous HCl did not promote the desired carbonyl-olefin metathesis reaction (entries 12 and 13, Table 1). Subsequent theoretical investigations supported our initial hypothesis that an electron-deficient sulfonamide moiety enables turnover of the Lewis acid catalyst (Fig. 4 A). Unproductive binding of FeCl₃ to the sulfonamide oxygen in **18c** was found to be 1.9 kcal/mol higher in energy compared to *N*-tosyl amine **18a** leading to preferential binding of FeCl₃ to the carbonyl oxygen in the electron-deficient substrate which is productive for catalysis. Additional competition experiments of amines **18a** and **18c** provided further support for this hypothesis (Fig. 4B). When **18c** was subjected to attenuated reaction conditions, metathesis product **19c** was formed in 83% yield (entry 1, Fig. 4). However, when the reaction of **18c** was conducted in the presence of 0.3 equiv. of *N*-tosyl amine **18a**, **19c** was formed in decreased yield of 76% (entry 2, Fig. 4). The yield is further reduced to 53% of **19c** when equimolar amounts of both amines **18a** and **18c** are converted under the carbonyl-olefin metathesis conditions (entry 3).

We next evaluated the effect of varying the olefin substitution on the iron(III)-catalyzed carbonyl-olefin metathesis reaction (Table 2). Prenylated moieties proved to be superior and led to efficient formation of the desired metathesis products in up to 99% yield (entry 1, Table 2). Styrene derivatives **21-27** resulted in overall decreased yields of 3-pyrroline **19c** (entries 2–6, Table 2). Importantly, *para*-methoxystyrene **23b** failed to undergo carbonyl-olefin metathesis and resulted in complete dealkylation of the starting material.¹⁹ In comparison, no formation of the desired metathesis products was observed when crotyl alkene **26b** or terminal alkene **27b** were subjected to the optimized reaction conditions, which is consistent with previous reports.^{16,19}

These results support our previous findings which establish prenyl-derived alkenes as superior substrates for catalytic carbonyl-olefin metathesis.^{16c} While prenyl-derived alkenes undergo the desired transformation in an asynchronous, concerted fashion, the

corresponding styrenyl-derivatives proceed via a distinct reaction pathway.^{16c} For these substrates, oxetane fragmentation occurs in a stepwise fashion via intermediate carbocations. This does explain the lower yields obtained for these substrates as a result of competing reaction paths (entries 2–6, Table 2).

The optimized reaction conditions developed for the iron(III)-catalyzed carbonyl-olefin metathesis reaction proved efficient to access a wide range of commercially available, natural and unnatural amino acid-derived 3-pyrrolines (Table 3). Importantly, toluene was established as a viable alternative solvent (**19c** and **31**, Table 3) resulting in up to 94% yield of the desired metathesis product. Substrates stemming from alanine resulted in the desired metathesis products in good to excellent yields (**29–32**, Table 3). Similarly, phenylalanine-derived starting materials proved efficient in the carbonyl-olefin metathesis reaction and resulted in the corresponding 3-pyrrolines in excellent yields (**19**, **36**, **43** and **47**, Table 3). Substrates incorporating heteroatoms were also compatible with the optimal reaction conditions for carbonyl-olefin metathesis. Methionine-derived 3-pyrroline **37** is obtained in 64% yield while the metathesis product **41** stemming from thienyl-alanine is obtained in 84% yield. This method is amendable to heteroaromatic ketones as well – the thienyl derivative **36** provided 70% of the desired product. Additional unnatural amino acid analogs of phenylalanine bearing naphthyl substituents provided the desired metathesis products in good to excellent yields of up to 91% (**46**, **51**, **52** and **53**, Table 3). It is interesting to note that glycine-derived 3-pyrroline **28** was formed in diminished yield of 50% while lower yields are also observed for the valine-derived substrate **33**. In comparison, the leucine-derived 3-pyrroline **34** is obtained in good yields of 67%. We suspect that a methylene-substituent in α -position to the nitrogen-heteroatom is beneficial for the formation of an intermediate oxetane (Fig. 2C) whereas additional steric bulk at the β -position leads to more sterically constrained oxetane intermediates. Furthermore, 2-amino isobutyric acid-derived 3-pyrrolines bearing a gem-dimethyl substituent in the α -positions are formed in excellent yields (**38–40**, Table 3). Further evaluation revealed that the carbonyl-olefin metathesis reaction is well tolerated by both electron deficient and electron-rich aryl ketone substrates (**30–32**, **39–40**, **42**, **43**, **50**, and **53** Table 3).

Additionally, the substrates bearing the electron-deficient sulfonamide protecting groups unanimously resulted in higher yields than their corresponding *N*-tosylated analogs, providing further support for our design principle for iron-catalyzed carbonyl-olefin metathesis reactions (**19**, **46–49** Table 3).

Moreover, the carbonyl-olefin metathesis reaction was amenable to the synthesis of six-membered analogs (**45**, **54**) in up to 89% yield.

Finally, the resulting chiral 3-pyrroline building blocks can undergo facile subsequent modifications to result in valuable chiral building blocks. Cleavage of the protecting group is facile with SmI_2 to generate the free amines **55** (Fig. 5).²² Importantly, the reaction proceeds with complete stereoretention (98% *ee*) and proceeds in up to 97% yield (over two steps). Furthermore, these building blocks can be used to access epoxides **57** bearing three contiguous stereocenters, as well as pyrrolidin-3-ones **58** (Fig. 6). Additionally,

hydrogenation reaction of substituted 3-pyrrolines are known and have been reported to proceed in up to 99% yield.²³

The development of a new strategy for the synthesis of chiral 3-pyrrolines is reported relying on the design principle of an iron(III)-catalyzed carbonyl-olefin metathesis reaction. Importantly, the carbonyl-olefin metathesis reaction described herein is operationally facile, relies on commercially available chiral pool reagents and proceeds under mild reaction conditions with complete stereoretention to result in the desired 3-pyrrolines in up to 98% *ee*. We expect that our strategy of attenuating the Lewis basicity of the sulfonamide to enable the desired mode of Lewis acid-activation for carbonyl-olefin metathesis can serve as a general strategy for other reactions in which sequestering of the active Lewis acid catalyst is observed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Selected strategies to access chiral α -arylated and -alkylated pyrrolidines

R = aryl, alkyl; PG = Boc, Bn; R' = aryl, alkyl

Figure 1.
Current approaches towards accessing chiral pyrrolidines.

A. Carbonyl-Olefin Metathesis for the Synthesis of 3-Pyrrolines

Our group:

Li (2016):

B. This Work: enantioenriched 3-pyrrolines

advantages:

- enantioenriched 3-pyrrolines
- **8** is non-competitive byproduct
- no additive required
- facile deprotection of **11**

C. Our revised design:

Figure 2.
Synthesis of chiral 3-pyrrolines via carbonyl olefin metathesis.

Figure 3.
Flexible 3-step substrate synthesis from chiral pool reagents.

Figure 4.
Competitive binding between Lewis basic substrate sites.

Figure 5.
Selected modifications of chiral 3-pyrroline *N*-protecting group.

Figure 6.
Selected modifications of chiral 3-pyrroline products.

Table 1.

Reaction optimization of carbonyl-olefin metathesis.

18a: R = Ts (98% ee)
18b: R = 4-ClPhSO₂ (^{Cl}Ts)
18c: R = 4-CF₃PhSO₂ (^FTs)

19a: R = Ts (98% ee)
19b: R = 4-ClPhSO₂ (^{Cl}Ts)
19c: R = 4-CF₃PhSO₂ (^FTs)

entry	Lewis acid	mol %	R	yield (%)	conversion (%)
1	SnCl ₄	20	Ts	3	26
2	GaCl ₃	20	Ts	8	59
3	FeCl ₃	20	Ts	19	19
4	FeCl ₃	30	Ts	24	24
5	FeCl ₃	40	Ts	53	91
6	FeCl ₃	50	Ts	72	100
7	FeCl ₃	50	ClTs	96	100
8	FeCl ₃	50	FTs	99	100
9	FeCl ₃	30	FTs	96	100
10	FeCl ₃	20	FTs	90	100
11	FeCl ₃	5	FTs	80	100
12	pTsOH	20	Ts	0	0
13	HCl(in DCE)	20	Ts	0	0

Table 2.

Evaluation of the influence of alkene substituents.

entry	substrate	yield(%)	entry	substrate	yield(%)
1	18a 18c	72 95	5	24b	49
2	21b	39	6	25b	34
3	22b	58	7	26b	0

entry	substrate	yield(%)	entry	substrate	yield(%)
4		0	8		0
	23b			27b	

Conditions: all reactions were performed using 0.1 mmol of substrate and FeCl_3 (50 mol%) in DCE (0.01M). The reactions were stirred for 1h at 0°C and 23h at rt.

Table 3.

Evaluation of substrate scope.