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Enantioselective Cobalt-Catalyzed Sequential Nazarov Cyclization/Electrophilic Fluorination: Access to Chiral α-Fluorocyclopentenones

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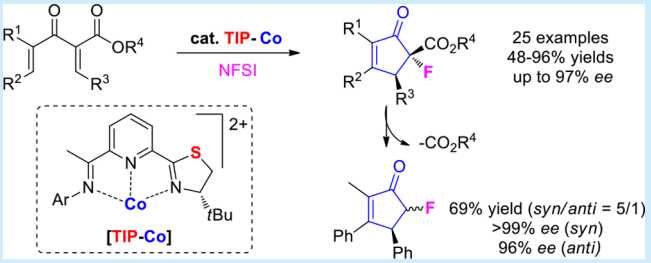
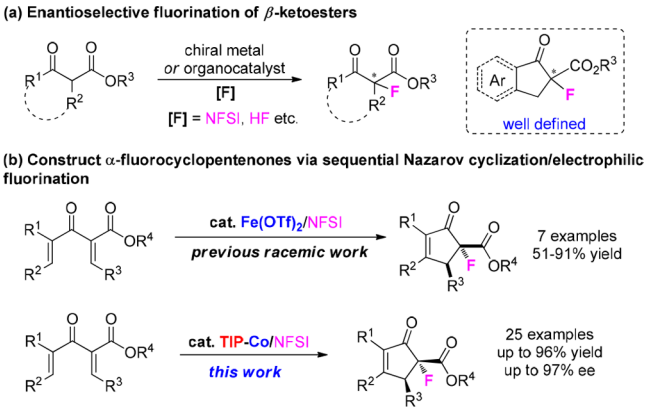
Supporting Information

ABSTRACT: A newly designed thiazoline iminopyridine ligand for enantioselective cobalt-catalyzed sequential Nazarov cyclization/electrophilic fluorination was developed. Various chiral α-fluorocyclopentenones were prepared with good yields and diastereo- and enantioselectivities. Further derivatizations could be easily carried out to provide chiral cyclopentenols with three contiguous stereocenters. Furthermore, a direct deesterification of fluorinated products could afford chiral α-single fluorine-substituted cyclopentenones.



Organic fluorine compounds currently play an increasingly important role in pharmaceuticals, agrochemicals, and materials science[1] due to the unique properties of the carbon−fluorine bond.[2] The development of efficient methods for synthesis of chiral fluorinated molecules has become increasingly attractive in recent years.[3] In particular, the construction of chiral carbon−fluorine quaternary stereocenters is not only fascinating but also still challenging.[4] Since the first example was reported by Togni and co-workers,[5] enantioselective fluorination of β-ketoesters, as one of the most efficient strategies for the construction of carbon−fluorine quaternary stereocenters, has been successfully achieved in both chiral metal catalysis and organocatalysis[4,6] (Scheme 1a). Although asymmetric fluorinations of indanone and cyclopentanone derivatives were widely investigated, to the best of our knowledge, asymmetric fluorination of cyclopentenone derivatives has not been reported.

Scheme 1. Construction of Chiral Carbon−Fluorine Quaternary Stereocenters through Fluorination of β-Ketoesters



Chiral cyclopentenone derivatives are extensively present in many bioactive compounds and also used as key intermediates in asymmetric synthesis.[7] Asymmetric Nazarov cyclization is one of the most efficient methods for the construction of chiral cyclopentenones.[8] A sequential Nazarov cyclization/electrophilic fluorination, reported by Ma and co-workers[9] in 2007, has been demonstrated as an efficient strategy to construct α-fluoroindanones as well as three chiral examples. Later, Itoh and co-workers[10] developed a racemic iron-catalyzed sequential Nazarov cyclization/electrophilic fluorination to afford α-fluorocyclopentenones in moderate to good yields (Scheme 1b). Recently, a direct strategy for synthesis of α-fluorocyclopentenones without a carbon−fluorine stereocenter, via a fluorine-directed and activated Nazarov cyclization, was reported by Ichikawa and co-workers.[11] Based on previously reported works, the development of asymmetric sequential Nazarov cyclization/electrophilic fluorination for the synthesis of chiral α-fluorocyclopentenones is still highly desirable. Herein, we report an efficient enantioselective cobalt-catalyzed sequential Nazarov cyclization/electrophilic fluorination to deliver chiral α-fluorocyclopentenones with adjacent carbon- and fluorine-substituted quaternary and tertiary stereocenters (Scheme 1b).

At the beginning of our investigation, we employed α-methyl ester divinyl ketone **1a** as a model substrate and NFSI as the fluorinating agent for sequential Nazarov cyclization/electrophilic fluorination in the presence of OIP·Ni$(ClO_4)_2$·$3H_2O$ which was the best catalyst for our previous asymmetric sequential Nazarov reaction.[12] To our delight, the reaction proceeded quantitatively to afford desired product **2a**, albeit with moderate enantioselectivity (72% ee) (Table 1, entry 1). We envisioned that a more electron-rich ligand might display unusual catalytic selectivities and thiazoline could be an

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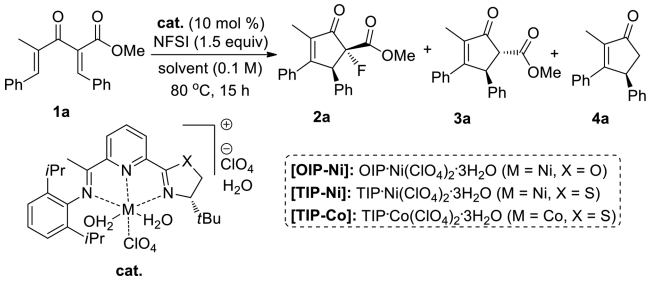
Table 1. Optimizations[a]

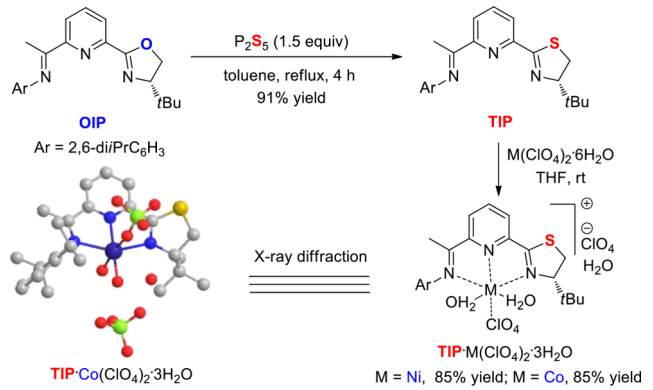


entry	cat.	2a[b] (%)	3a/4a/1[b] (%)	ee of 2a[c] (%)
1	[OIP-Ni]	>99	−/−/−	72
2	[TIP-Ni]	93	2/3/−	94
3	[TIP-Co]	98	−/2/−	94
4[d]	[TIP-Co]	96	−/4/−	92
5[e]	[TIP-Co]	77	15/−/6	92
6[f]	[TIP-Co]	97	−/2/−	82
7[g]	[TIP-Co]	94(93)	2/4/−	96

[a]Reaction conditions: **1a** (0.2 mmol), NFSI (0.3 mmol), and cat. (10 mol %) were dissolved in solvent and stirred for 15 h at 80 °C. Compound **2a** was obtained with excellent diastereoselectivity (>20/1). [b]Determined by ^{1}H NMR analysis using TMSPh as an internal standard. Isolated yield in the parentheses. [c]Determined by chiral HPLC analysis. [d]Toluene. [e]CH_2Cl_2 at 60 °C. [f]1,2-DCE. [g]7.5 mol % cat. and 1.1 equiv of NFSI with 0.5 mmol scale.

alternative of oxazoline to form a more electron-rich thiazoline iminopyridine (TIP) ligand. The TIP ligand could be conveniently synthesized using a one-step reaction of OIP ligand with P_2S_5 (Scheme 2).[13] In addition, the corresponding

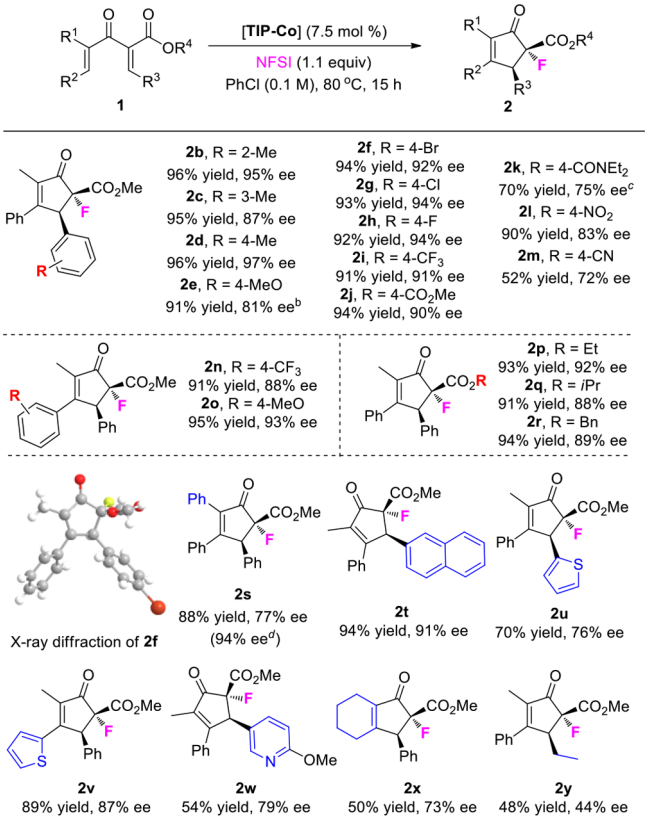
Scheme 2. Synthesis and Structure Analysis of Thiazoline Iminopyridine Complexes



metal perchlorate complexes were prepared easily and determined by X-ray diffraction analysis (TIP·$M(ClO_4)_2\cdot 3H_2O$: CCDC 1812597 for [Ni] and CCDC 1817973 for [Co]) (Scheme 2). When using the TIP·$Ni(ClO_4)_2\cdot 3H_2O$ instead of OIP-nickel complex, fortunately, the reaction afforded **2a** in 93% yield with 94% ee (Table 1, entry 2). The cobalt catalyst displayed higher reactivity than the nickel catalyst (entry 3). Further screening of other solvents gave no better results (entries 4−6). It is noteworthy that the fluorinated product **2a** could be obtained in 93% isolated yield with 96% ee using a 7.5% loading of catalyst and 1.1 equiv of NFSI when scaled up to 0.5 mmol (entry 7).

Under the optimal reaction conditions, we evaluated divinyl ketones with various substituents (Scheme 3). Various aryl

Scheme 3. Substrate Scope[a]



[a]Standard conditions: **1** (0.50 mmol), NFSI (0.55 mmol), and [TIP-Co] (7.5 mol %) were dissolved in PhCl and heated to 80 °C for 15 h; products **2** were obtained with excellent diastereoselectivity (>20/1); isolated yields after column chromatography; *ee* was determined by chiral HPLC analysis. [b]**1** (0.55 mmol) and NFSI (0.50 mmol) were used. [c]24 h. [d]After recrystallization.

substituents on the R^3 position were well tolerated regardless of the position of the substituents (*ortho*, *meta*, or *para*) and their electronic properties to furnish the corresponding products **2b−j** in 91−96% yields and 81−97% ee. Notably, electron-withdrawing groups on aryl groups, such as amide, nitro, and cyano, delivered **2k−m** with slightly lower ee values. Next, the substituents on R^2 were explored and the results demonstrated that an aryl ring with an electron-donating group (**2o**) was more suitable for this asymmetric transformation than one with an electron-withdrawing group (**2n**). When compared with **2a**, other alkyl esters substituted substrates had no effect on yield. However, a deleterious effect on the enantioselectivity was observed (**2p−r**) especially with the more bulky isopropyl ester (**2q**). In the case of phenyl substitution on the R^1 position, both yield and enantioselectivity were reduced (**2s**). Interestingly, **2s** with 94% ee could be obtained after recrystallization from petroleum ether and dichloromethane. In addition, polycycle and heterocycles, such as 2-naphthyl, 2-thienyl, and 3-pyridyl groups, were also well tolerated (**2t−w**). It is worth noting that substrates bearing cyclohexyl and ethyl groups could afford **2x** and **2y** in moderate yields with 73% ee and 44% ee, respectively. The absolute configuration of the fluorinated products was determined by the X-ray diffraction analysis of **2f** (CCDC 1832033).

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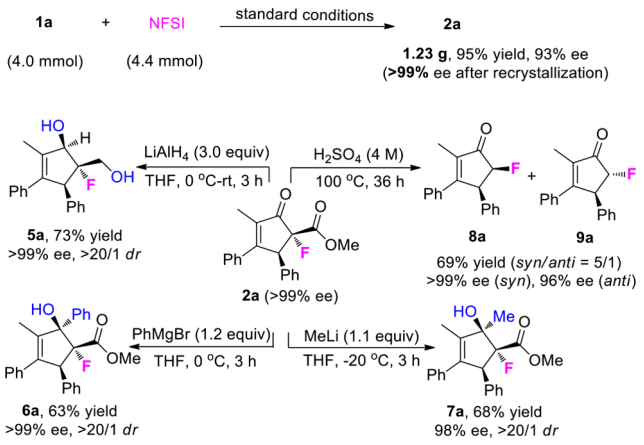
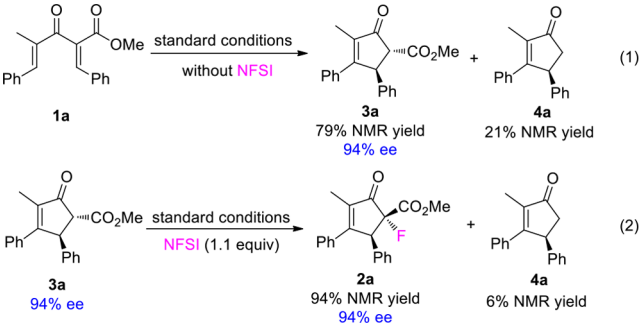
To demonstrate the synthetic potential of this asymmetric sequential reaction, gram scale reaction of **1a** was carried out to afford **2a** in 95% yield with 93% ee (Scheme 4). The more

Scheme 4. Gram Scale Reaction and Further Derivatizations of 2a



enantioenriched (>99% ee) **2a** can be obtained after recrystallization. Next, the chiral fluorinated product **2a** could undergo direct reduction of the β-ketone ester group and nucleophilic addition of a carbonyl group to construct chiral cyclopentenols **5**−**7a** with three contiguous stereocenters (Scheme 4). Although a direct highly enantioselective α-fluorination of cyclic ketones has been achieved by MacMillan and co-workers,[14] the highly enantioselective α-fluorination of cyclopentanone (88% ee) is still a challenge. Under reflux in a solution of sulfuric acid, α-fluorocyclopentenones **8a** and **9a** were obtained from **2a** in two separable diastereoisomers with excellent enantioselectivity (Scheme 4).

To elucidate the stereochemical course of this sequential process, the reaction of **1a** without NFSI under the standard reaction conditions was first conducted (eq 1). Compound **3a**



could be generated in 79% NMR yield with 94% ee (eq 1). When **3a** (94% ee) was treated with NFSI under the standard reaction conditions, the corresponding fluorinated product **2a** was obtained in 94% NMR yield with comparable ee (94% ee) (eq 2).

In summary, a new thiazoline iminopyridine ligand was developed and applied to enantioselective cobalt-catalyzed sequential Nazarov cyclization/electrophilic fluorination. Various substituted chiral α-fluorocyclopentenones were obtained with good yields and diastereo- and enantioselectivities. Further derivatizations were easily carried out to construct chiral cyclopentenols with three contiguous stereocenters. Notably, a direct deesterification of fluorinated products could deliver chiral α-single fluorine substituted cyclopentenones. Further studies on newly designed ligands for asymmetric sequential reactions are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01597.

Experimental details, characterization data of all compounds, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1812597, 1817973, and 1832033 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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