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Article

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Expanding the Boxmi Ligand Family: Synthesis and Application of NON and NSN Ligands

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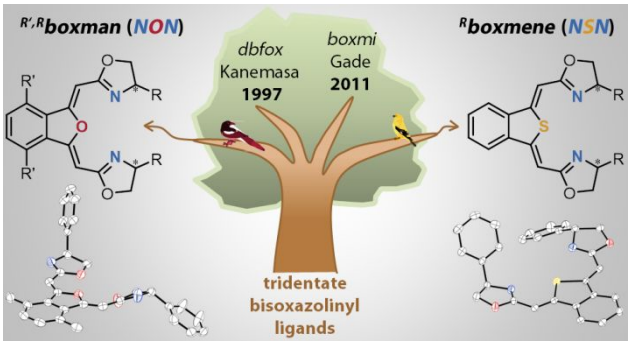
Graphical Abstract



Abstract:

Two synthetic strategies for a new family of neutral *NON* ligands featuring a "bis(oxazolinylmethylidene)isobenzofuran" framework (boxman) are reported. A Pd-mediated cyclization reaction forming the isobenzofuran core constitutes the key reaction in the eight-step

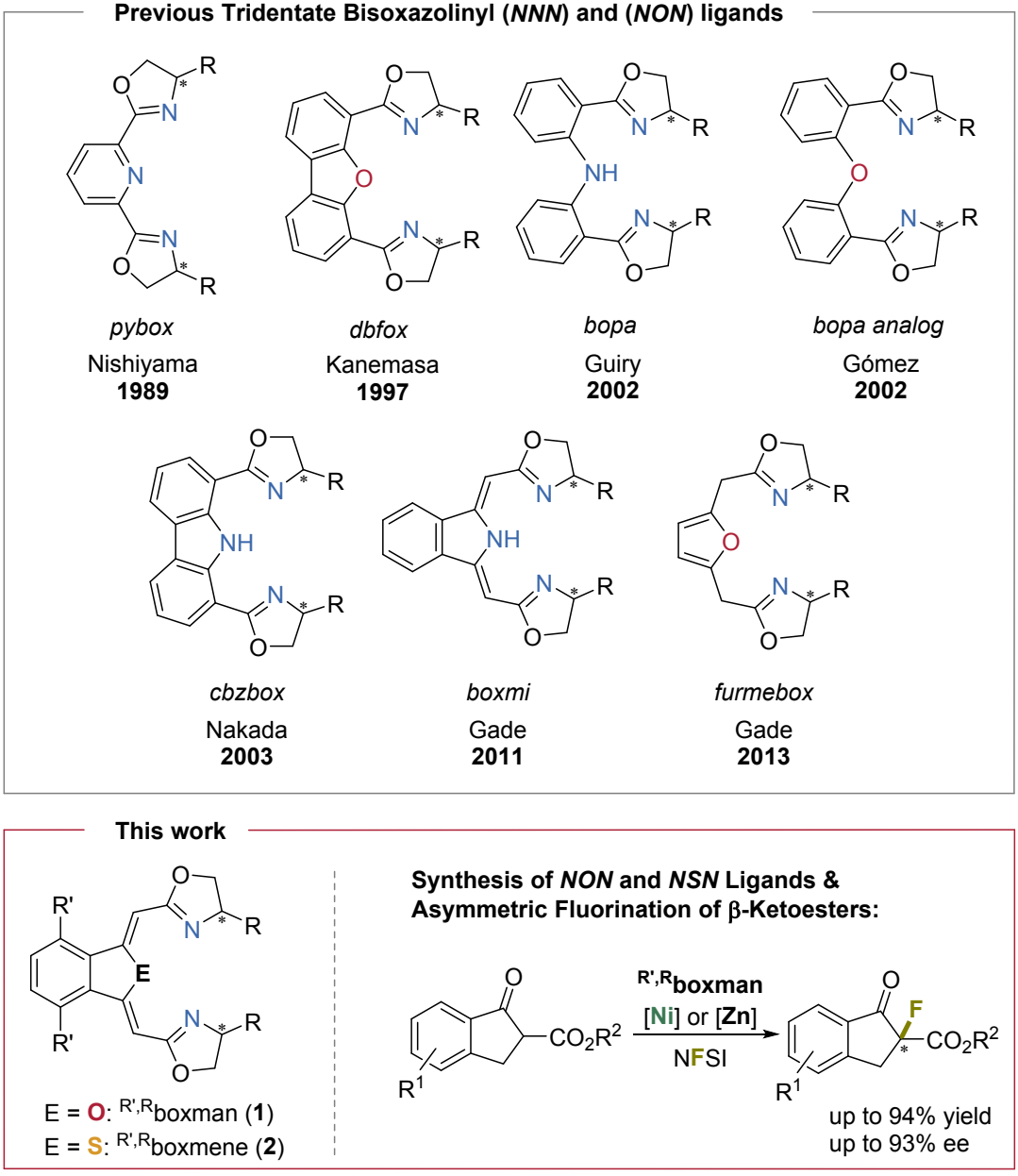
synthetic route to the non-backbone-methylated target compound ^{H,R}boxman. In contrast, introduction of two additional methyl groups provides stereochemical control during backbone construction and thereby access to the methylated derivative ^{Me,R}boxman, which was synthesized in five steps and improved yields. In addition, the synthetic sequence was transferred to the thio analogue, providing access to the *NSN* ligand ^{H,R}boxmene. Subsequent complexation experiments with iron and cobalt chloride precursors afforded the four-coordinated chlorido complexes ^{Me,R}boxmanMCl_2 (R = Ph, *i*Pr; M = Fe, Co) and established the boxman family as *trans*-chelating, bidentate bis(oxazoline) ligands. Application of the latter in the nickel(II)- and zinc(II)-catalyzed α-fluorination of β-ketoesters and oxindoles (up to 98% yield and 94% *ee*) demonstrated their suitability for enantioselective catalysis.

Introduction

The success of transition-metal catalyzed asymmetric synthesis is inherently connected to the development of stereodirecting ligands which ensure the efficient transfer of chirality. As a consequence, extensive research in this field has given rise to numerous classes of *privileged ligand structures*,[1] ranging from chiral phosphines and NHCs to alcohols and salen-derivatives.[2] However, the use of oxazolines as chiral structural units has been of particular interest due to their facile preparation from amino alcohols and their efficient stereoinduction in asymmetric transformations.[3] With notable exceptions like the phox ligand,[4] C_2-symmetric bisoxazoline ligands, in particular, emerged as a versatile class of ligands for a wide range of reactions.[5] Nowadays, this group of ligands includes prominent examples such as pybox,[6] box,[7] dbfox[8] and boxmi[9] (Figure 1). Apart from the two oxazoline cycles as common structural elements, these

ligands vary with respect to the type and length of bridging elements, resulting in polydentate stereodirecting ligands with different denticities, charges and chelating angles.

Figure 1. Recent Examples for *NNN*- and *NON*-Bisoxazolinyl Ligands and Work Presented in this Study



Whereas both aliphatic links in neutral *NN* ligands (e.g. box, spirobox[10]) and a central nitrogen donor in (monoanionic) tridentate *NNN* bisoxazoline ligands (e.g. pybox, cbzbox,[11] bopa,[12] pyrrmebox,[13] boxmi) are well established, the incorporation of an oxygen atom as central donor remains rare. In fact, to the best of our knowledge, the oxygen analog of bopa[14] as well as the ligands furmebox[15] and dbfox are the only existing examples exhibiting these structural characteristics (Figure 1). The dbfox ligand was found to induce high enantiomeric excesses in various Lewis acid-catalyzed reactions such as the α-fluorination of β-ketoesters.[16]

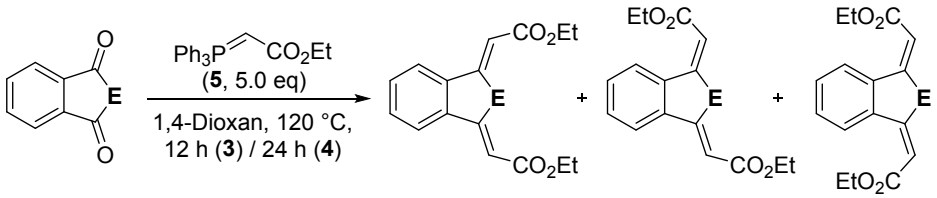
In recent studies, we reported the synthesis of "bis(oxazolinylmethylidene)isoindolines",[9] boxmi-H, and demonstrated their potential as a stereodirecting ligand platform in a range of 3*d* metal-catalyzed transformations.[17] Motivated by the success of the dbfox ligand and other neutral compounds as well as our previous boxmi-related work, we aimed at combining the structural properties of that ligand system with a neutral central donor. This led us to the preparation of the oxygen and sulfur analogues of the established boxmi framework, namely to the synthesis of the ligands bis(oxazolinylmethylidene)isobenzofuran ("boxman") and –thiophene ("boxmene"). As part of this study, we demonstrate two synthetic strategies towards boxman as well as an adapted synthetic route to boxmene, a first brief evaluation of their coordination chemistry to 3*d* metals, and their application as stereodirecting ligands in the α-fluorination of β-ketoesters and oxindoles (Chart 1).

Results and Discussion

Initial Approach for Backbone Construction of boxman.

Following our synthetic strategy for the synthesis of the monoanionic *NNN* pincer ligand boxmi-H,[9] we started our investigations by employing standard Wittig conditions for the construction of the backbone. Reacting phthalic anhydride (**3a**) and thioloanhydride (**4**) with Wittig reagent **5** resulted in isomeric mixtures of the corresponding (*Z*,*Z*)-, (*E*,*Z*)- and (*E*,*E*)-products **6a** and **7** (Scheme 1).[18] Interestingly, whereas only the synthetically useless isomers (*E*,*Z*)-**6a** and (*E*,*E*)-**6a** were formed for the oxygen derivative **6**, the selective formation of the desired diester (*Z*,*Z*)-**7** was observed when employing the sulfur analogue (for details see below). This necessitated an alternative route to the target *NON* ligand which is presented below.

Scheme 1. Initial Wittig Reaction for Backbone Preparation



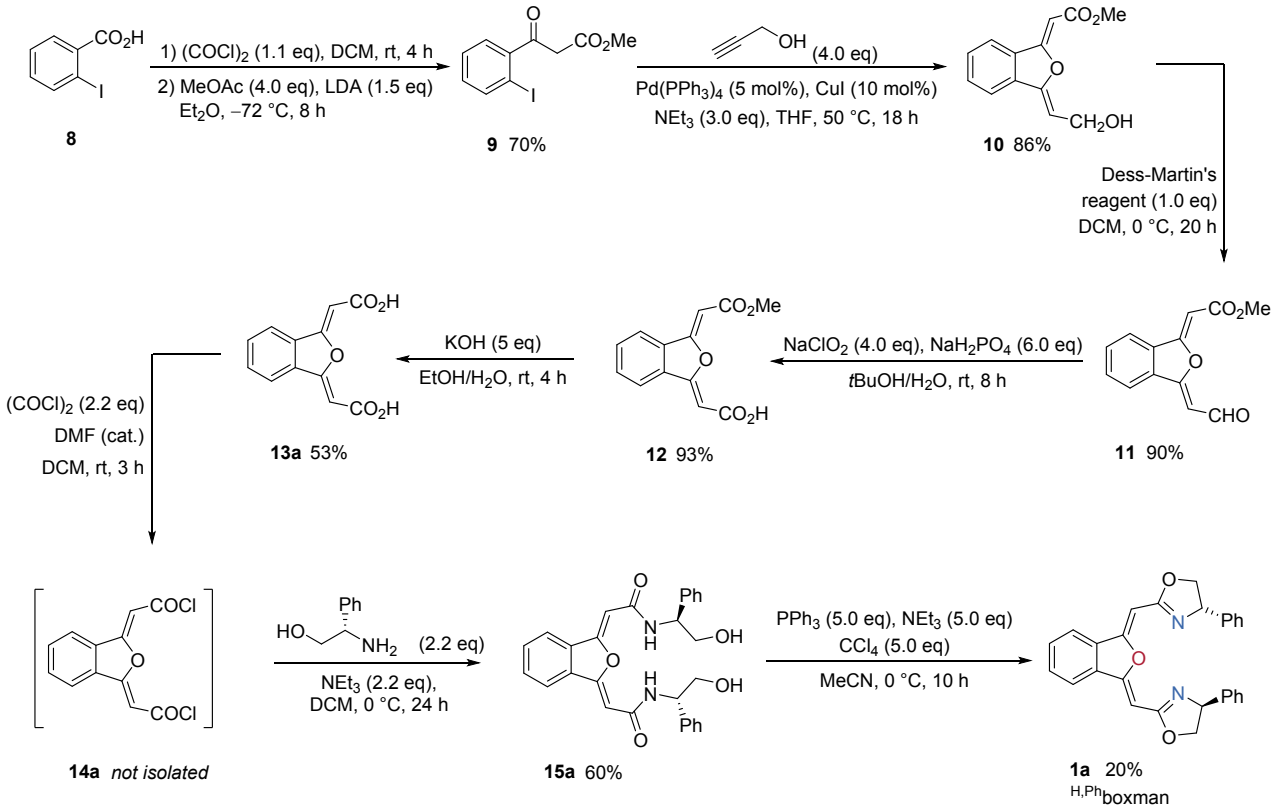
3 (E = O)
4 (E = S)

	(*Z*,*Z*)	(*E*,*Z*)	(*E*,*E*)
E = O: 6a	0%	15%	11%
E = S: 7	19%	0%	0%

Synthesis of *NON* Ligand ^{H,Ph}boxman.

In view of the stereochemical issues accompanied with the Wittig reaction with phthalic anhydride, we first focused on the development of an alternative route to prepare the ligand backbone (Scheme 2).

Scheme 2. Synthesis of ^{H,Ph}boxman 1a



Starting with 2-iodobenzoic acid (**8**), chlorination and subsequent Claisen-type condensation with methyl acetate led to the formation of β-ketoester **9** in 70% yield. The following Pd-catalyzed, *O*-nucleophilic intramolecular heterocyclization reaction under comparatively mild conditions then provided access to the isobenzofuran core, constituting the key step for the synthesis of ^{H,Ph}boxman (**1a**): Pd-catalyzed Sonogashira coupling of propargyl alcohol and subsequent cyclization between carbonyl and alkyne moiety gave compound **10** in 86% yield. It is interesting to note that ethyl propiolate could also be used for the isobenzofuran formation, resulting immediately in desired diester **6a** (see Scheme 1). However, low activities and limited scalability of the reaction impeded the further development of this direct approach to a generally applicable

synthetic protocol. Instead, conversion of alcohol **10** to acid **12** was achieved in a stepwise fashion employing Dess-Martin and Pinnick oxidation reactions. As direct amidation attempts of the carboxylic groups turned out not to be effective, the mixed acid ester **12** was first treated with potassium hydroxide and then transformed into acid chloride **14a**. The latter could readily be converted into diamide **15a** upon reaction with 2-phenylglycinol under basic conditions. Finally, ring closure exploiting an Appel-type cyclization protocol[19] with $PPh_3/NEt_3/CCl_4$ yielded the neutral *NON* ligand ^{H,Ph}boxman (**1a**) in 20% yield.

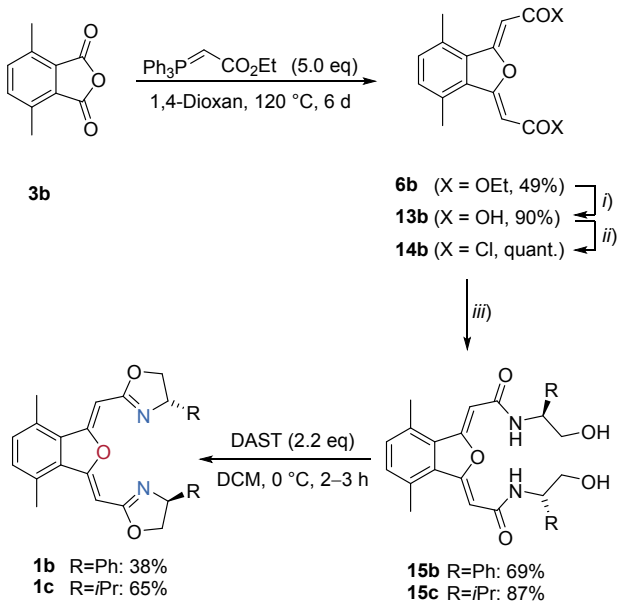
Alternative Synthesis of *NON* Ligand ^{Me,R}boxman.

With a successful synthetic route for ^{H,Ph}boxman (**1a**) in hand, we were interested in a more direct strategy towards the latter due to the great effort – 8 steps in total – associated with ligand synthesis according to Scheme 2. Reconsidering our initial approach for the construction of the ligand backbone, we envisioned that steric control through an appropriate substitution pattern in the backbone should in principle allow us to circumvent the aforementioned stereochemical problems (Scheme 3).

In fact, introduction of two methyl groups in 2,6-dimethylphthalic anhydride[20] led to the exclusive formation of (*Z,Z*)-**6b** when subjected to standard Wittig conditions. Applying the very same reaction sequence as before, we were able to convert diester **6b** into diamide **15** in three steps with significantly improved yields. As Appel-type reaction conditions for the final cyclization produced inseparable side products, we eventually employed (diethylamino)sulfur trifluoride (DAST) as cyclization reagent for the final step.[21] Contrarily, this cyclization method

turned out not to be applicable to the non-methylated derivative **1a**, illustrating the sensitivity of the given system with respect to final oxazoline synthesis.

Scheme 3. Synthesis of ^{Me,R}boxman (1b and 1c)



Reaction conditions: *i*) KOH (10 eq.), EtOH/THF/H_2O, rt, 4 h; *ii*) $(COCl)_2$ (2.2 eq.), DMF (cat.), DCM, 0 °C, 3 h; *iii*) (*S*)-amino alcohol (2.5 eq.), NEt_3 (2.5 eq.), DCM, 0 °C, 24 h.

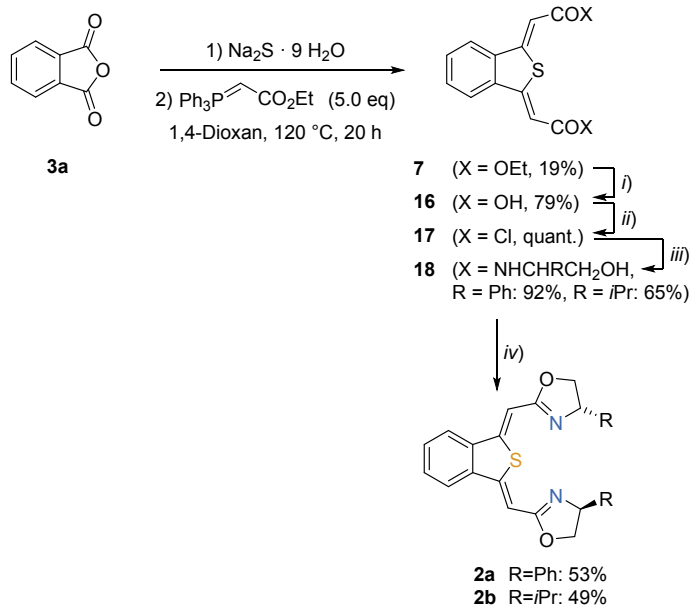
In this way, the backbone-methylated *NON* ligands ^{Me,R}boxman (**1b,c**) were readily synthesized and obtained in good yields (R = Ph: 38%, R = *i*Pr: 65%). All in all, this synthetic strategy is a considerable improvement compared to above-mentioned initial route in terms of practical feasibility and synthetic accessibility at the expense of a slight structural modification.

Synthesis of *NSN* Ligand ^{H,R}boxmene.

Having established an effective route to *NON* ligands $^{R',R}$boxman, we then aimed at extending this synthetic concept to the sulfur derivative, $^{R',R}$boxmene (**2**). Regarding the general strategy, early-stage sulfur introduction and subsequent functionalization according to the oxygen

congener **1** was chosen as reasonable approach (Scheme 4). In this context, the starting material **4** for the analogous synthesis is readily available from the reaction of phthalic anhydride with sodium sulfide.[22] Intriguingly, this initial oxygen-sulfur exchange reaction turned out to be only applicable to the synthesis of the non-methylated derivative **3a**, but not to 2,6-dimethylphthalic anhydride. However, as mentioned above, the thioloanhydride **4** surprisingly proved suitable for directly accessing (*Z,Z*)-**7** (see Scheme 1), the absolute configuration of which was additionally confirmed by X-ray diffraction (for details see SI).

Scheme 4. Synthesis of ^{H,R}boxmene (2)



Reaction conditions: *i*) KOH (10 eq.), EtOH/THF/H_2O, rt, 4 h; *ii*) $(COCl)_2$ (5.0 eq.), DMF (cat.), DCM, 0 °C, 3 h; *iii*) (*S*)-amino alcohol (2.5 eq.), NEt_3 (2.5 eq.), DCM, 0 °C, 20 h. *iv*) DAST (2.8 eq.), DCM, 0 °C, 3 h.

Interestingly, the sulfur analogue **4** displayed an increased reactivity in the Wittig coupling and required only one day at 120 °C for complete conversion, which is in notable contrast to a reaction time of 6 d at the same temperature in case of phthalic anhydride (see Scheme 3). From a practical point of view, thiophthalic anhydride (**4**) could be prepared *in situ* and subjected to the

Wittig reaction without prior purification giving compound (*Z,Z*)-**7** in an overall 19% yield. Subsequently, all previous reaction conditions found for the preparation of ^{Me,R}boxman could also be applied to the synthesis of ^{H,R}boxmene in similar yields.

Ligand Characterization.

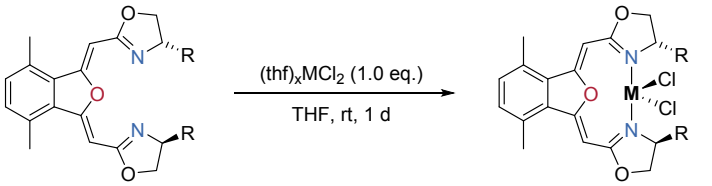
The ligands were comprehensively characterized by NMR spectroscopy and mass spectrometry. In addition, single-crystal X-ray structure analyses were carried out in order to confirm the (*Z,Z*) configuration and to determine structural details of this new ligand class (see SI). In the solid state structure of ^{Me,Ph}boxman, the *N*-donors at the oxazoline units point away from the isobenzofuran core, highlighting a certain degree of internal flexibility of these ligands. Regarding the sulfur derivative, the solid-state structure revealed a preorganized orientation of the donor atoms and the C_2-chiral character of this ligand framework. In both cases, the oxazoline rings align almost coplanar with the central isobenzofuran fragment, showing only slight torsions.

Synthesis of boxman Metal Complexes.

With these neutral *NON* and *NSN* ligands in hand, we carried out a first study of their coordination chemistry in 3*d* metal complexes. Following our previous work on earth-abundant metal-catalyzed stereoselective catalysis,[17] we chose iron and cobalt for initial complexation reactions. Moreover, the absence of stereoelectronical preferences in d^6 and d^7, respectively, *high-spin* complexes allows for an exclusive evaluation of the coordinating properties of the ligands in question. In this context, treating $(thf)_xMCl_2$ (M = Fe, Co) precursors with one

equivalent of ^{Me,R}boxman (R = Ph, *i*Pr) in tetrahydrofuran yielded the respective ^{Me,R}boxmanMCl$_2$ complexes **19-20** as colored solids in good yields (Scheme 5).

Scheme 5. Synthesis of Metal Complexes ^{Me,R}boxmanMCl$_2$ (19-20)



1b (R = Ph)
1c (R = *i*Pr)

19a (M = Fe, R = Ph, 63%)
19b (M = Fe, R = *i*Pr, 64%)
20a (M = Co, R = Ph, 91%)
20b (M = Co, R = *i*Pr, 84%)

In all cases, moderately-resolved paramagnetic ^{1}H and ^{13}C NMR spectra with comparatively small shift dispersions were observed, indicating the presence of one well-defined complex species in each case (SI). The magnetic susceptibilities in solution of these paramagnetic chlorido complexes were determined employing the Evans method,[23] and found to be in good agreement with the respective *spin-only* values (μ_{SO} = 4.90 μ_B for d^6, and 3.87 μ_B for d^7 *high-spin* complexes, respectively) for *high-spin* configurations in complexes **19** and **20**.

In addition to these characteristic features in solution, the molecular structures in the solid-state were established by X-ray diffraction (Figure 2). Interestingly, the metal centers were found to be four-coordinate in both cases, exhibiting a distorted tetrahedral coordination sphere with the metal atoms positioned significantly above the plane of the donor atoms of the boxman ligand ($d_{M–plane}$ = 0.969(3) to 1.042(1) Å). Whereas the M–N bond lengths for the oxazoline groups are in accordance with similar compounds reported in literature, the M–O distances in the range of $d_{M–O}$ = 2.442(2) to 2.557(3) Å indicate the absence of significant bonding interactions between the central oxygen donor and the metal atom, thus establishing the boxman framework as a *trans*-chelating bidentate ligand in the given context. These structural characteristics demonstrate

distinct difference between boxman complexes and comparable boxmi based compounds,[9, 17e, 17g, 24] in which a meridional coordinating and structurally rigid ligand was observed in all cases.

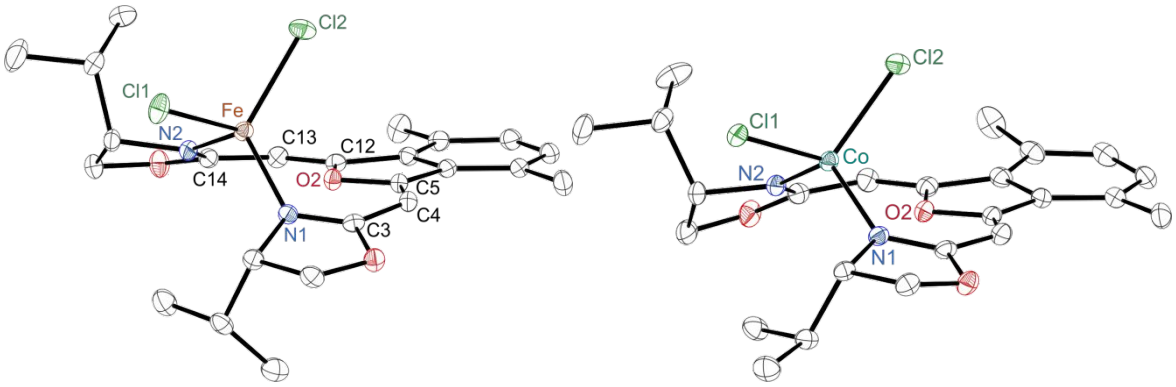
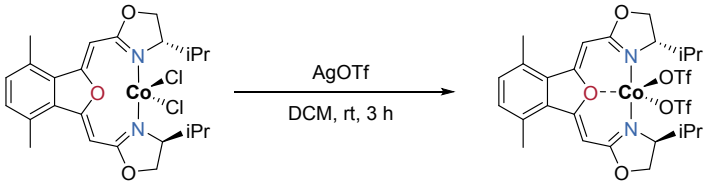


Figure 2. Molecular structures of iron and cobalt complexes **19b** (left) and **20b** (right) in the solid state. Hydrogen atoms have been omitted for clarity; displacements ellipsoids are set at 50% (**19b**) and 30% (**20b**) probability level; only one of the two independent molecules is shown for **20b**. Selected bond lengths [Å] and angles [°], values for the second independent molecules are given in square brackets: **19b**: Fe–N1 2.0832(18); Fe–N2 2.0995(18); Fe–Cl1 2.3427(6); Fe–Cl2 2.2923(6); Fe-O2 2.4423(15); N1–Fe–N2 120.14(7); Cl1–Fe–Cl2 107.56(2); N1–C3–C4–C5 15.8(4); C12–C13–C14–N2 –17.1(4); **20b**: Co–N1 2.062(4) [2.063(3)]; Co–N2 2.051(4) [2.055(4)]; Co–Cl1 2.2911(12) [2.2928(12)]; Co–Cl2 2.2814(12) [2.2811(13)]; Co-O2 2.515(3) [2.521(3)]; N1–Co–N2 121.92(15) [122.93(14)]; Cl1–M–Cl2 108.04(5) [110.61(5)]; N1–C3–C4–C5 –18.5(8) [–16.3(8)]; C12–C13–C14–N2 27.3(9) [31.2(8)].

In a next step, we focused on investigating further binding modes of the neutral *NON* ligands $^{R',R}$boxman. In this context, we treated chlorido complex **20b** with the chloride abstracting agent AgOTf (silver triflate), leading to a change of color from cyan to purple-blue (Scheme 6).

Scheme 6. Generation of Ditriflato Complexe ^{Me,iPr}boxmanCo(OTf)$_2$ (21)



20b **21**

The isolation of the reaction product turned out to be difficult due to the formation of unknown impurities and concomitant ligand dissociation. We were, however, able to obtain single crystals of a methylene chloride solvate of the product which was identified by X-ray diffraction as the ditriflato complex **21** (Figure 3). Due to mediocre crystal quality, disorder and the presence of no less than eight independent molecules only the salient features of the structure are discussed. A distorted trigonal-bipyramidal coordination sphere around the cobalt center is observed for complex **21**. The Co–O distance is significantly shortened ($d_{Co–O}$ = 2.316(9)-2.362(8) Å) and the cobalt atom is located in closer proximity to the plane of the donor atoms of the boxman ligand ($d_{Co–plane}$ = 0.803(8)-0.885(8) Å) compared to the respective chlorido complex (for **20b**: $d_{Co–O}$ = 2.515(3) [2.521(3)] Å, $d_{Co–plane}$ = 0.991(3) [0.975(3)] Å). In view of an averaged Co–O bond length of $\bar{d}_{Co–O(thf)}$ = 2.117(6) Å in Co·(thf) complexes,[25] these findings demonstrate only a relatively weak interaction between the cobalt center and the central isobenzofuran core.

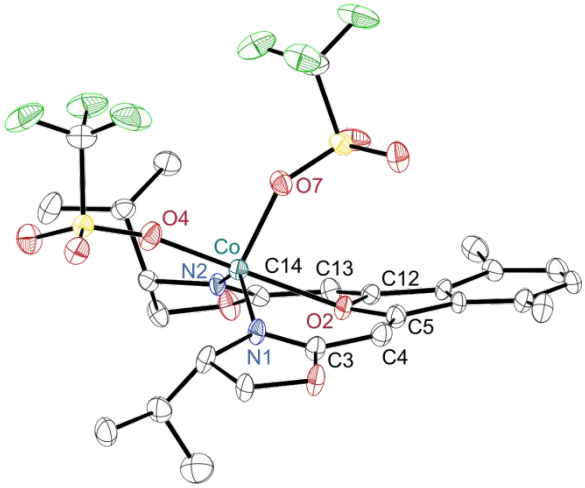


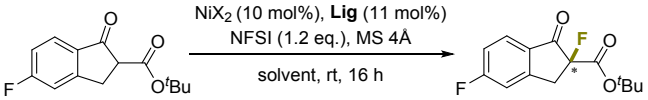
Figure 3. Molecular structure of the ditriflato complex **21** in the solid state. Hydrogen atoms have been omitted for clarity; displacements ellipsoids are set at 50% probability level; only one of the eight independent molecules in **21**·0.25 CH_2Cl_2 is shown. Selected bond lengths [Å] and angles [°], given as range for all independent molecules: Co–N1 1.978(11)-2.005(11); Co–N2 1.964(12)-2.016(12); Co–O2 2.316(9)-2.362(8); Co–O4 1.992(10)-2.032(10); Co–O7 1.963(10)-

2.002(9); N1–Co–N2 127.3(5)-132.4(5); O2–Co–O4 172.6(4)-178.7(4); O2–Co–O7 79.8(4)-89.0(4); N1–C3–C4–C5 –10(3)-(–24(3)); C12–C13–C14–N2 15(3)-21(3).

Ni- and Zn-Catalyzed Fluorination of Ketoesters and Oxindoles.

Having established the coordination chemistry of boxman ligands in iron and cobalt metal complexes, we then aimed at evaluating their stereodirecting performance in catalytic transformations. With the appearance of **1** in metal complexes as *trans*-chelating, bidentate ligand, we envisioned the application of preferably square-planar coordinated metals as prerequisite for this objective. Therefore, we chose the Lewis acid catalyzed asymmetric fluorination of β-ketoesters and oxindoles with *N*-fluorobenzenesulfonimide (NFSI) as test reaction,[16] for which we previously observed excellent yields and enantioselectivities when employing the related boxmi ligand (Table 1).[9]

Table 1. Optimization of Reaction Conditions for the Nickel-Catalyzed Fluorination of Ketoester 22a



22a *standard conditions*[a] **23a**

#	varied condition[b]	% yield[c]	% *ee*[d]
1	*none*	>95	93
2	salt: $Ni(OTf)_2$	>95	90
3	salt: $Ni(NTf_2)_2$	>95	89
4	salt: $Ni(dme)Cl_2$	>95	88
5	salt: $Ni(OAc)_2$	n.d.[e]	41
6	salt: $Ni(ClO_4)_2 \cdot 6\ H_2O$	>95	76
7	ligand: ^{Me,iPr}boxman	>95	59

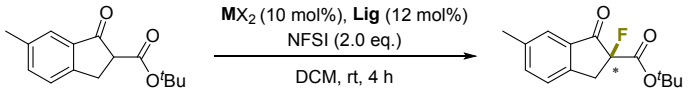
8	solvent: *n*-pentane	n.d.	15
9	solvent: toluene	>95	91
10	solvent: Et_2O	n.d.	41
11	solvent: THF	n.d.	20
12	solvent: MeCN	n.d.	22

[a] standard conditions: substrate **22a** (40 µmol, 1.0 eq.), *N*-fluorobenzenesulfonimide (1.2 eq.), $Ni(ClO_4)_2$ (10 mol%), ^{Me,Ph}boxman (11 mol%), molecular sieve 4 Å, dichloromethane, room temperature, 16 h.
[b] deviation from standard condition; unless indicated otherwise.
[c] determined by ^{19}F NMR spectroscopy of the reaction mixture.
[d] determined by HPLC analysis.
[e] not determined.

Starting with the previously reported standard conditions and the readily available ligands ^{Me,R}boxman **1b,c**, nickel perchlorate in combination with ^{Me,Ph}boxman gave near-quantitative conversion of test substrate **22a** and an excellent enantiomeric excess of 93% *ee* (entry 1). The use of (dimethoxyethane) nickel dichloride ((dme)$NiCl_2$) as well as other anhydrous nickel salts with weakly coordinating anions resulted in similar stereoinduction (entries 2-6). In contrast, substantial differences in stereoselectivity were obtained when modifying the oxazoline substituent as a change from Ph to *i*Pr led to a dramatically reduced enantiomeric excess (entry 7). In addition, solvent screening indicated only toluene and dichloromethane as suitable solvents (entries 8-12). Monitoring the reaction progress by ^{19}F NMR spectroscopy, we found that reducing the reaction temperature below room temperature or the catalyst loading below 10 mol% would lead to impractically long reaction times.

In a next step, we focused both on extending the scope of the reaction and on a comparison of the ligand structures developed in this work (Table 2). Regarding further metal salts, the use of copper salts led to racemic mixtures (entry 2), whereas zinc bistriflimide was found to provide similarly high stereoselectivities as nickel salts (entry 3).

Table 2. Optimization of Reaction Conditions for the Fluorination of Ketoester 22b



22b **23b**

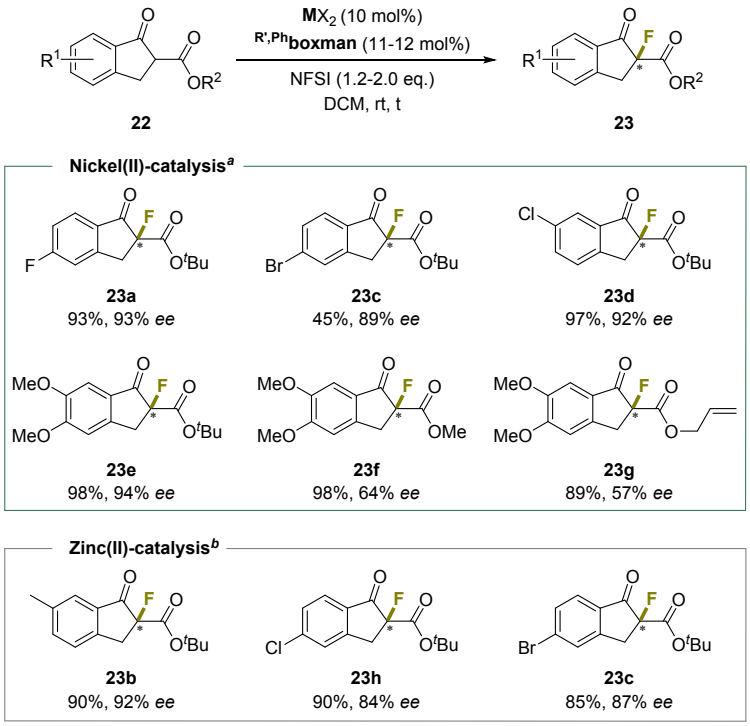
#	Metal salt	Ligand	% yield	% *ee*[b]
1[c]	$Ni(ClO_4)_2 \cdot 6\ H_2O$	^{H,Ph}boxman	93	82
2[c]	$Cu(OTf)_2$	^{H,Ph}boxman	96	1
3	$Zn(NTf_2)_2$	^{H,Ph}boxman	90	92
4	$Zn(NTf_2)_2$	^{Me,Ph}boxman	60	90
5	$Zn(NTf_2)_2$	^{H,Ph}boxmene	36	9

[a] reaction conditions: substrate **22b** (0.10 mmol), *N*-fluorobenzenesulfonimide (2 eq.), metal salt (10 mol%), ligand (12 mol%), dichloromethane (1.0 mL), room temperature, 4 h.
[b] determined by HPLC analysis.
[c] 5 h reaction time.

Upon altering the ligand from ^{H,Ph}boxman to the backbone methylated derivative ^{Me,Ph}boxman, only subtle changes in enantiodiscrimination were observed (entry 4) for the Zn-catalyzed fluorination. On the other hand, employment of the sulfur analogue ^{H,Ph}boxmene rendered the fluorinated reaction product with only a marginal enantiomeric excess.

Having determined the ideal conditions for the catalytic systems, we proceeded to screen a range of suitable substrates for both the nickel(II)- and zinc(II)-catalyzed enantioselective fluorination (Scheme 7). Generally high yields and stereoselectivities demonstrated the applicability of our catalytic system.

Scheme 7. Substrate Scopes for the Nickel(II) and Zinc(II)-catalyzed Fluorination of β-Ketoesters

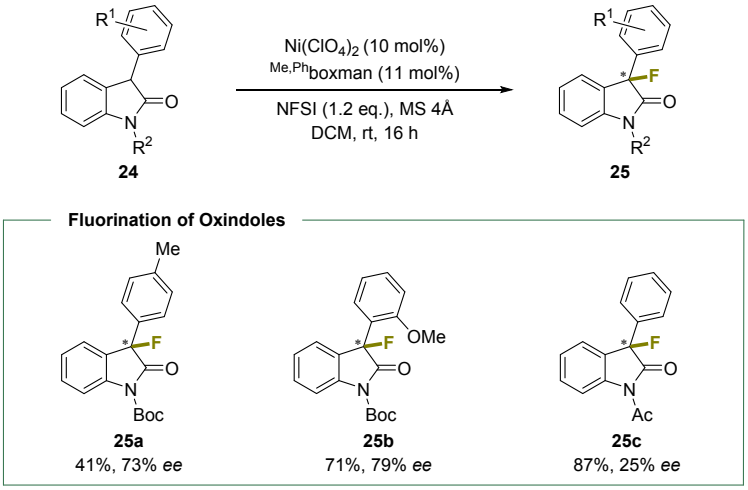


[a] reaction conditions: substrate **22** (0.1 mmol), *N*-fluorobenzenesulfonimide (1.2 eq.), $Ni(ClO_4)_2$ (10 mol%), ^{Me,Ph}boxman (11 mol%), molecular sieves (4 Å), dichloromethane (1.0 mL), room temperature, 16 h.
[b] reaction conditions: substrate **22** (0.1 mmol), *N*-fluorobenzenesulfonimide (2.0 eq.), $Zn(NTf)_2$ (10 mol%), ^{H,Ph}boxman (12 mol%), dichloromethane (1.0 mL), room temperature, 5 h.
[c] enantiomeric excess determined by HPLC analysis.

Whereas backbone substitution of the ketoester appeared to have only moderate influence on the reaction outcome (R^1 = F, Cl, Br, Me, MeO), the steric bulk of the ester group turned out to be a key prerequisite for a successful functionalization: exchanging the *tert*-butyl moiety for ethyl and allyl groups resulted in high conversions, but significantly reduced enantioselectivities. Given the structural resemblance of oxindoles and β-ketoesters, we also applied our standard protocol to three derivatives of this class of substrates. Overall, inferior results in terms of yield and stereoselectivity were obtained for oxindoles compared to β-ketoesters (Scheme 8) whereas

the same general trends were found: backbone substitution had no major influence on the enantioselectivity, while steric bulk of the protecting group (boc *versus* acetyl) was vital.

Scheme 8. Substrate Scope for the Nickel-catalyzed Fluorination of Oxindoles[a]



[a] enantiomeric excess determined by HPLC analysis.

Conclusions

In conclusion, the class of stereodirecting bis(oxazoline) ligands has been extended by two further representatives, namely the *NON* ligand "bis(oxazolinylmethylidene)isobenzofuran", $^{R',R}$boxman, and its thio derivative ^{R}boxmene. In case of $^{R',R}$boxman, the stereochemial issues accompanied with initial backbone construction were either resolved by a Pd-catalyzed heterocyclisation reaction (R' = H, 8 steps in total) or by means of the introduction of stereodirecting methyl groups (R' = Me, 5 steps overall). The effective use of these *trans*-chelating ligands in the nickel(II)- or zinc(II)-catalyzed α-fluorination of carbonyl substrates has provided first evidence of their potential in stereoselective catalysis and prompts further applications in 3*d* metal catalysis.

Experimental Section

Unless stated otherwise, all manipulations were performed under dried argon in standard Schlenk glassware, which was flame-dried prior to use. Solvents were dried according to standard procedures. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance (400 MHz, 600 MHz) instruments. Mass spectra were recorded by the mass spectrometry service of Shanghai Institute of Organic Chemistry or at the mass spectrometry facility of the Institute of Organic Chemistry. 2,6-Dimethyl phthalic anhydride (**3b**)[20] and ketoesters[26] were synthesized according to literature procedures. All other starting materials were obtained commercially and used without further purification.

Preparation of compound 9:

To a solution of 2-iodobenzoic acid (4.96 g, 20.0 mol, 1.0 eq.) in anhydrous DCM (80 mL) was added oxalyl chloride (1.86 mL, 22.0 mol, 1.1 eq.) and 100 μL DMF *via* syringe at room temperature. After stirring the reaction mixture at room temperature for 4 h, all volatiles were removed *in vacuo* to afford the raw product, which can be used without any further operation. In a separate flask was added methyl acetate (6.36 mL, 80.0 mol, 4.0 eq.) to a solution of lithium diisopropylamide (15 mL, 2 M in THF, 1.5 eq.) in anhydrous Et_2O (100 mL) slowly at –72 °C. The mixture was stirred for 20 min at this temperature, before a suspension of the acyl chloride in Et_2O (15 mL) was added very slowly. After stirring the mixture at –72 °C for 30 min, the reaction was stopped by adding aqueous HCl (1 M, 100 mL). The product was extracted with Et_2O (2 x 100 mL) and the combined organic phases were washed with brine (50 mL) and dried over sodium sulfate. Subsequently, the solvent was removed *in vacuo* and the crude product was purified by column chromatography (petroleum ether/ethyl acetate = 35:1), affording the product

as yellow oil (4.26 g, 14 mol, 70%). The product exists as a 1.7:1.0 mixture of ketone and enol tautomers. Spectroscopic Data have been reported previously.[27] ^{1}H NMR (400.20 MHz, $CDCl_3$, 295 K): δ (ppm) = 12.27 (s, 0.5 H, enol), 7.94 (dd, *J* = 17.8, 7.9 Hz, 1 H, ketone), 7.91 (d, *J* = 7.8 Hz, 0.5 H, enol), 7.47 (ddd, *J* = 8.2, 7.5, 1.2 Hz, 2 H, ketone and enol), 7.40 (dd, *J* = 9.0, 2.0 Hz, 2 H, ketone and enol), 7.16 (td, *J* = 7.7, 1.7 Hz, 2 H, ketone), 7.14–7.06 (m, 0.5 H, enol), 5.36 (s, 0.5H, enol), 4.00 (s, 2 H, ketone), 3.82 (s, 1.7 H, enol), 3.74 (s, 3 H, ketone).

Preparation of compound 10:

To a solution of compound **9** (6.08 g, 20.0 mmol, 1.0 eq.) in anhydrous THF (400 mL) were added propargyl alcohol (4.6 mL, 80.0 mmol, 4.0 eq.), $Pd(PPh_3)_4$ (1.16 g, 1.0 mol, 5 mol%), CuI (381 mg, 2.0 mol, 10 mol%) and Et_3N (8 mL, 60.0 mmol, 3.0 eq.). The reaction mixture was stirred at 50 °C for 8 h. Subsequently, the solvent was removed under reduced pressure and the residue was purified by column chromatography (petroleum ether/ethyl acetate = 1:1) to afford the product as yellow solid in (3.99 g, 17.2 mol, 86%). ^{1}H NMR (400.20 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.62 (d, *J* = 3.8 Hz, 1 H), 7.60 (d, *J* = 3.4 Hz, 1 H), 7.54 (t, *J* = 7.4 Hz, 1 H), 7.46 (t, *J* = 7.4 Hz, 1 H), 5.70 (t, *J* = 6.8 Hz, 1 H), 5.62 (s, 1 H), 4.66 (d, *J* = 6.8 Hz, 2 H), 3.80 (s, 3 H). ^{13}C{^{1}H} NMR (100.63 MHz, $CDCl_3$, 295 K): δ (ppm) = 166.1, 162.0, 152.5, 134.1, 132.7, 131.7, 129.8, 121.2, 120.3, 103.5, 87.8, 57.2, 51.4. HRMS (EI^+): calcd. for $C_{13}H_{12}NaO_4^+$ $[M+Na]^+$: 255.0628; found: 255.0627.

Preparation of compound 11:

To a solution of compound **10** (4.64 g, 20.0 mmol, 1.0 eq.) in anhydrous DCM (180 mL) at 0 °C was added Dess–Martin periodinane (8.48 g, 20.0 mmol, 1.0 eq.). The reaction mixture was stirred at 0 °C overnight, before aqueous $Na_2S_2O_3$ (10%, 50 mL) and saturated $NaHCO_3$ (50 mL)

solutions were added. After 30 min, the suspension was filtered and the organic phase was washed successively with a saturated $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic phase was then dried over sodium sulfate and freed from any volatiles *in vacuo*. The crude product was recrystallized from DCM/PE, affording the product as white solid (4.14 g, 18.0 mmol, 90%). ^{1}H NMR (400.20 MHz, $CDCl_3$, 295 K): δ (ppm) = 10.39 (d, *J* = 8.0 Hz, 1 H), 7.75-7.69 (m, 2 H), 7.64 (m, *J* = 7.2 Hz, 2 H), 5.94 (d, *J* = 8.0 Hz, 1 H), 5.82 (s, 1 H), 3.81 (s, 3 H). ^{13}C{^{1}H} NMR (100.63 MHz, $CDCl_3$, 295 K): δ (ppm) = 189.0, 165.2, 164.8, 160.0, 133.5, 133.0, 132.8, 132.3, 122.5, 121.6, 102.4, 92.7, 51.8. HRMS (ESI$^+$): calcd. for $C_{13}H_{10}NaO_4^+$ $[M+Na]^+$: 253.0483; found: 253.0471.

Preparation of compound 12:

Under ambient conditions, compound **11** (4.60 g, 20.0 mmol, 1.0 eq.) was dissolved in *tert*-BuOH (200 mL) and H_2O (40 mL) and a solution of $NaClO_2$ (7.40 g, 80.0 mmol, 4.0 eq.) and NaH_2PO_4 (14.0 g, 120 mmol, 6.0 eq.) in 40 mL H_2O was added very slowly at room temperature. After stirring the mixture for 8 h, all volatiles were removed under reduced pressure. The residue was diluted in 100 mL DCM and treated with 50 mL hydrochloric acid (1 M). The organic phase was washed with water (200 mL) and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure afforded the raw product **12**, which purified by recrystallization from DCM/PE. The product was obtained as white solid (4.61 g, 18.7 mmol, 93%). ^{1}H NMR (400.20 MHz, DMSO- d_6, 295 K): δ (ppm) = 12.31 (s, 1 H), 8.10 (dd, *J* = 8.5, 5.1 Hz, 2 H), 7.68 (dd, *J* = 8.5, 5.1 Hz, 2 H), 6.15 (s, 1 H), 6.07 (s, 1 H), 3.69 (s, 3 H). ^{13}C{^{1}H} NMR (100.63 MHz, DMSO-d_6, 295 K): δ (ppm) = 165.2, 164.1, 160.4, 159.4, 133.3, 133.0, 132.3, 132.1, 122.2,

122.1, 93.4, 91.4, 51.1. HRMS (ESI$^+$): calcd. for $C_{13}H_{10}NaO_5^+$ $[M+Na]^+$: 269.0420; found: 269.0419.

Preparation of compound 13a:

Under ambient conditions, compound **12** (2.46 g, 10.0 mmol, 1.0 eq.) and KOH (2.80 g, 50.0 mmol, 5.0 eq.) were dissolved in a solution of ethanol (50 mL) and H_2O (30 mL). The reaction mixture was then stirred at room temperature for 4 h. After removing ethanol under reduced pressure, hydrochloric acid (1 M) was added, until large amount of solid precipitated. The suspension was filtered and the filter cake was dried *in vacuo*, affording the product as white solid (1.24 g, 5.34 mol, 53%). ^{1}H NMR (400.20 MHz, DMSO-d_6, 295 K): δ (ppm) = 8.07 (dd, J = 5.8, 3.0 Hz, 2 H), 7.67 (dd, J = 5.8, 3.0 Hz, 2 H), 6.02 (s, 1 H). ^{13}C{^{1}H} NMR (100.63 MHz, DMSO-d_6, 295 K): δ (ppm) = 165.2, 159.5, 133.2, 132.0, 122.0, 92.9. HRMS (ESI$^+$): calcd. for $C_{12}H_9O_5^+$ $[M+H]^+$: 233.0444; found: 233.0447.

Preparation of compounds 15a:

To a solution of compound **13a** (2.32 g, 10.0 mmol, 1.0 eq.) in anhydrous DCM (50 mL) was added oxalyl chloride (1.27 mL, 22.0 mmol, 2.2 eq.) and 100 µl DMF *via* syringe at room temperature. The mixture was stirred at room temperature for 3 h. Subsequently, all volatiles were removed *in vacuo*, affording the raw acyl chloride as brown solid. The residue was redissolved in 15 mL anhydrous DCM and treated subsequently with triethylamine (3.06 mL, 22.0 mmol, 2.2 eq.) and 2-phenylglycinol (3.02 g, 22.0 mmol, 2.2 eq.) at 0 °C. After stirring the reaction mixture at 0 °C for 24 h, water (20 mL) was added. The resulting mixture was extracted with DCM (3 x 50 mL) and the combined organic phases were dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash

chromatography (petroleum ether/ethyl acetate = 4:1 to dichloromethane/ethanol = 10:1) to afford the product as white solid (2.82 g, 6.0 mmol, 60%). ^{1}H NMR (400.20 MHz, DMSO-d_6, 295 K): δ (ppm) = 8.72 (d, J = 8.2 Hz, 2 H), 7.95 (dd, J = 5.7, 3.0 Hz, 2 H), 7.68 (dd, J = 5.7, 3.0 Hz, 2 H), 7.49–7.27 (m, 4 H), 7.29–7.08 (m, 6 H), 6.14 (s, 2 H), 5.02 (dd, J = 13.7, 8.0 Hz, 4 H), 3.70 (td, J = 11.3, 4.8 Hz, 4 H). ^{13}C{^{1}H} NMR (100.63 MHz, DMSO-d_6, 295 K): δ (ppm) = 163.5, 156.2, 141.3, 132.5, 132.0, 128.2, 127.2, 126.8, 121.8, 95.9, 64.7, 55.5. HRMS (ESI$^+$): calcd. for $C_{28}H_{26}N_2NaO_5^+$ [M+Na]$^+$: 493.1734; found: 493.1737.

Preparation of compounds 1a:

To a solution of compound **15a** (940 mg, 2.00 mmol, 1.0 eq.) in MeCN (50 mL) were added PPh_3 (2.62 g, 10.0 mol, 5.0 eq.), Et_3N (1.39 mL, 10.0 mol, 5.0 eq.) and CCl_4 (966 µl, 10.0 mmol, 5.0 eq.). The reaction mixture was stirred at 0 °C. After completion of the reaction (monitored by TLC, about 10 h), water (100 mL) was added and the resulting mixture was extracted with DCM (5 x 50 mL). The combined organic phases were dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (petroleum ether/ethyl acetate = 1:1), affording the product as white solid (172 mg, 0.40 mmol, 20%). ^{1}H NMR (400.20 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.69 (s, 2 H), 7.57 (s, 2 H), 7.33 (s, 10H), 6.06 (s, 2 H), 5.33 (t, J = 9.2 Hz, 2 H), 4.82 (t, J = 9.1 Hz, 2 H), 4.29 (t, J = 8.3 Hz, 2 H). ^{13}C{^{1}H} NMR (100.63 MHz, $CDCl_3$, 295 K): δ (ppm) = 162.8, 157.7, 142.4, 133.6, 131.5, 128.8, 127.6, 126.9, 121.3, 88.9, 75.0, 69.7. HRMS (ESI$^+$): calcd. for $C_{28}H_{22}N_2NaO_3^+$ [M+Na]$^+$: 457.1523; found: 457.1522.

Preparation of compound 6b:

A mixture of 2,5-dimethylphthalic anhydride (5.14 g, 29.2 mmol, 1.0 eq.) and (carbethoxymethylene)triphenylphosphorane (50.8 g, 146 mmol, 5.0 eq.) was suspended in 150 mL absolute 1,4-dioxane. After heating the reaction mixture to 120 °C for 6 d, the solvent was removed *in vacuo*. The dark brown residue was purified by column chromatography (petroleum ether/ethyl acetate = 5:1 → 3:1), yielding the product as a yellow solid (4.50 g, 14.2 mmol, 49%). ^{1}H NMR (600.13 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.22 (s, 2 H), 5.79 (s, 2 H), 4.30 (q, J = 7.1 Hz, 4 H), 2.52 (s, 6 H), 1.37 (t, J = 7.1 Hz, 6 H). ^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 295 K): δ [ppm] = 164.7, 161.2, 133.9, 132.7, 132.2, 95.8, 60.5, 20.5, 14.5. HRMS (EI^+): calcd. for $C_{18}H_{20}O_5^+$ $[M]^+$: 316.1311; found: 316.12908.

Preparation of compound 13b:

Under ambient conditions, a solution of KOH (4.26 g, 75.9 mmol, 10.0 eq.) in 30 mL water was added dropwise to a suspension of compound **6b** (2.40 g, 7.59 mmol, 1.0 eq.) in 100 mL ethanol, 60 mL tetrahydrofuran and 30 mL water. The reaction mixture was stirred at room temperature for 3-4 h forming a brown solution. Subsequently, the solvent was removed under reduced pressure and the residue was redissolved in 300 mL water. The solution was acidified with aqueous HCl (2M, about 30 mL), until a pH value of 2-3 was reached. The resulting precipitate was filtered, washed with water and distilled azeotropically with toluene, affording the product as an off-white solid (1.78 g, 6.84 mmol, 90%). ^{1}H NMR (600.13 MHz, DMSO-d_6, 295 K): δ (ppm) = 12.13 (s, 2 H), 7.36 (s, 2 H), 5.69 (s, 2 H), 2.47 (s, 6 H). ^{13}C{^{1}H} NMR (150.90 MHz, DMSO-d_6, 295 K): δ [ppm] = 165.1, 159.5, 134.1, 132.5, 131.2, 96.0, 19.8. HRMS (EI^+): calcd. for $C_{14}H_{12}O_5^+$ $[M]^+$: 260.0685; found: 260.06694.

Preparation of compound 14b:

Carbonic acid **13b** (1.50 g, 5.77 mmol, 1.0 eq.) was suspended in 250 mL dichloromethane. Subsequently, oxalylchloride (1.61 g, 1.09 mL, 12.7 mmol, 2.2 eq.) and a catalytic amount of *N,N*-dimethylformamide were added dropwise at 0 °C. The suspension was warmed to room temperature over a period of 2-3 h, giving a dark red solution. The reaction mixture was freed from any volatiles *in vacuo* to obtain the crude product in quantitative yield, which was used for subsequent reactions without further purification. ^{1}H NMR (600.13 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.40 (s, 2 H), 6.19 (s, 2 H), 2.59 (s, 6 H). $^{13}C\{^{1}H\}$ NMR (150.90 MHz, $CDCl_3$, 295 K): δ (ppm) = 161.7, 159.9, 135.8, 131.8, 102.0, 20.5. HRMS (EI^+): calcd. for $C_{14}H_{10}ClO_3^+$ $[M\text{-}Cl]^+$: 261.0313; found: 261.03019.

Preparation of compound 15b:

Acid chloride **14b** (1.15 g, 3.84 mmol, 1.0 eq) was dissolved in 120 mL dichloromethane and a solution of triethylamine (971 mg, 1.34 mL, 9.59 mmol, 2.5 eq.) and (*S*)-2-phenylglycinol (1.32 g, 9.59 mmol, 2.5 eq.) in 10 mL dichloromethane was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 24 h. Approximately 2/3 of the solvent volume was then removed under reduced pressure and the reaction was quenched by the addition of 80 mL water. The resulting precipitate was filtered, washed with water and little dichloromethane, and dried *in vacuo*, yielding the product as a colorless solid (1.31 g, 2.63 mmol, 69%). ^{1}H NMR (600.13 MHz, DMSO- d_6, 295 K): δ (ppm) = 8.91 (d, J = 8.2 Hz, 2 H), 7.37 (s, 2 H), 7.36-7.33 (m, 4 H), 7.23-7.18 (m, 6 H), 5.94 (s, 2 H), 5.05-5.01 (m, 2 H), 5.00 (t, J = 5.8 Hz, 2 H), 3.80-3.70 (m, 2 H), 3.74-3.68 (m, 2 H), 2.49 (s, 6 H). $^{13}C\{^{1}H\}$ NMR (150.90 MHz, DMSO- d_6, 295 K): δ (ppm)

= 163.8, 156.3, 141.5, 133.6, 132.3, 130.8, 128.1, 127.3, 126.8, 99.1, 64.6, 55.6, 19.6. HRMS (EI$^+$): calcd. for $C_{30}H_{31}N_2O_5^+$ $[M+H]^+$: 499.2227; found: 499.2237.

Preparation of compound 15c:

A solution of L-valinol (790 mg, 7.66 mmol, 2.5 eq.) and triethylamine (1.07 mL, 7.66 mmol, 2.5 eq.) in 10 mL dichloromethane was added dropwise to a solution of acid chloride **14b** (910 mg, 30.6 mmol, 1.0 eq.) in 100 mL dichloromethane at 0 °C. The red solution was then stirred at 0 °C for 20 h, before it was concentrated to 1/5 of its volume and quenched with 70 mL water. The reaction mixture was extracted with dichloromethane and the combined organic phases were washed with water (3 x 50 mL) and dried over sodium sulfate. The solvent was reduced *in vacuo* to 3-4 mL and treated with *n*-pentane, yielding a brown oil. The supernatant was removed and the residue was purified by column chromatography (dichloromethane/methanol = 19:1). The product was obtained as an off-white solid (1.15 g, 2.67 mmol, 87%). ^{1}H NMR (600.13 MHz, DMSO-d_6, 295 K): δ (ppm) = 8.16 (d, J = 9.0 Hz, 2 H), 7.38 (s, 2 H), 5.92 (s, 2 H), 4.63 (t, J = 5.5 Hz, 2 H), 3.83-3.79 (m, 2 H), 3.54-3.52 (m, 4 H), 2.50 (s, 6 H), 1.97-1.89 (m, 2 H), 0.89-0.85 (m, 12 H). ^{13}C{^{1}H} NMR (150.90 MHz, DMSO-d_6, 295 K): δ (ppm) = 163.9, 155.8, 133.3, 132.0, 130.8, 99.4, 61.5, 55.8, 28.6, 19.7, 19.6, 18.2. HRMS (ESI$^-$): calcd. for $C_{24}H_{33}N_2O_5^+$ $[M-H]^+$: 429.2395; found: 429.2397.

Preparation of compound 1b:

A suspension of amide **15b** (1.65 g, 3.31 mmol, 1.0 eq.) in 50 mL dichloromethane was treated dropwise at 0 °C with diethylaminosulfur trifluoride (1.31 mL, 1.60 g, 9.93 mmol, 3.0 eq.). The solution was stirred at 0 °C for 2.5 h and then quenched by adding 4 N aqueous ammonium hydroxide solution (20 mL). The reaction mixture was extracted with dichloromethane and the

combined organic phases were dried over sodium sulfate and purified by column chromatography (silica gel was deactivated with triethylamine prior to use, petroleum ether/ethyl acetate = 2:1 → 0:1). The product is obtained as a yellow solid (575 mg, 1.24 mmol, 38%). Single crystals suitable for X-ray diffraction analysis were obtained by layering a solution of the compound in dichloromethane with toluene and *n*-pentane. ^{1}H NMR (600.13 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.35-7.34 (m, 8 H), 7.29- 7.25 (m, 2 H), 7.23 (s, 2 H), 6.09 (s, 2 H), 5.32 (dd, *J* = 10.1 Hz, *J* = 8.9 Hz, 2 H), 4.80 (dd, *J* = 10.1 Hz, *J* = 8.3 Hz, 2 H), 4.27 (t, *J* = 8.6 Hz, 2 H), 2.57 (s, 6 H). ^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 295 K): δ (ppm) = 163.5, 158.4, 142.5, 133.5, 132.3, 132.1, 128.8, 127.7, 127.0, 92.3, 74.9, 69.7, 20.6. HRMS (ESI^+): calcd. for $C_{30}H_{27}N_2O_3^+$ $[M+H]^+$: 463.2016; found: 463.2020.

Preparation of compound 1c:

Diethylaminosulfur trifluoride (1.78 mL, 2.17 g, 13.5 mmol, 4.0 eq.) was added dropwise at 0 °C to a suspension of compound **15c** (1.45 g, 3.36 mmol, 1.0 eq.) in 50 mL dichloromethane. After stirring the mixture at 0 °C for 4 h, the reaction was stopped by adding aqueous ammonium hydroxide solution (4 N, 20 mL). The product was purified by column chromatography (silica gel was deactivated with triethylamine prior to use, petroleum ether/ethyl acetate/dichloromethane/triethylamine = 4:1:1, 1% → 3:2:3, 1% → 0:2:5, 2% → 0:1:1, 2%) and obtained as a beige solid (868 mg, 2.20 mmol, 65%). Single crystals suitable for X-ray diffraction analysis were obtained from a hot saturated solution of the compound in ethyl acetate / *n*-hexane. ^{1}H NMR (600.13 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.17 (s, 2 H), 5.97 (s, 2 H), 4.51 (dd, *J* = 9.7 Hz, *J* = 8.3 Hz, 2 H), 4.12 (*t*, J = 8.6 Hz, 2 H), 4.01-3.96 (m, 2 H), 2.53 (s, 6 H), 1.85-1.77 (m, 2 H), 1.09 (d, *J* = 6.7 Hz, 6 H), 0.95 (d, *J* = 6.7 Hz, 6 H). ^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 295

K): δ (ppm) = 162.3, 157.9, 133.2, 132.1, 92.4, 72.6, 70.8, 33.2, 20.6, 19.6, 18.8. HRMS (ESI^+): calcd. for $C_{24}H_{31}N_2O_3^+$ $[M+H]^+$: 395.2329; found: 395.2333.

Preparation of compound 7:

Under ambient conditions, phthalic anhydride (7.39 g, 49.9 mmol, 1.0 eq.) and sodium sulfide (16.8 g, 69.8 mmol, 1.4 eq.) nonahydrate were stirred at room temperature, which led to liquefaction. After three days, the clear, orange liquid was quenched with 10% hydrochloric acid. The resulting white solid was filtered, washed with water and dried by azeotropic distillation with benzene. This product and ethyl 2-(triphenyl-λ^5-phosphaneylidene)acetate (74.3 g, 213 mmol, 5 eq.) were suspended in 100 mL dry 1,4-dioxane and stirred overnight at 110 °C until NMR analysis of the raw product showed complete conversion. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (deactivated silica; petroleum ether/ethyl acetate 3:1). The product was obtained as an orange-colored solid (2.82 g, 9.27 mmol, 19%). Single crystals suitable for X-ray diffraction analysis were obtained by layering a solution of the compound in dichloromethane with *n*-pentane. ^1H NMR (600.13 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.79-7.78 (m, 2 H), 7.53-7.52 (m, 2 H), 6.63 (s, 2 H), 4.32 (q, ^3J = 7.1 Hz, 4 H), 1.36 (t, ^3J = 7.1 Hz, 6 H). $^{13}C\{^1H\}$ NMR (150.90 MHz, $CDCl_3$, 295 K): δ (ppm) = 166.7, 155.8, 139.0, 130.9, 121.1, 107.2, 60.9, 14.6. HRMS (ESI^+): calcd. for $C_{16}H_{16}NaO_4S^+$ $[M+Na]^+$: 327.0662; found: 327.0663.

Preparation of compound 16:

Under ambient conditions, diethyl ester **7** (2.16 g, 7.10 mmol, 1.0 eq.) was suspended in a mixture of 100 mL ethanol, 30 mL tetrahydrofuran and 30 mL water. A solution of sodium hydroxide (2.84 g, 71.0 mmol, 10 eq.) in 30 mL water was added and the mixture was stirred at

room temperature for 3 hours. Subsequently, the organic solvents were removed *in vacuo*, the residue dissolved in water and filtrated. The filtrate was acidified with 60 mL 10% hydrochloric acid and stirred for 30 min. The resulting precipitate was filtered, washed with water and dried by azeotropic distillation with benzene. The product was obtained as a yellow solid (1.39 g, 5.62 mmol, 79%). ^{1}H NMR (600.13 MHz, DMSO-d_6, 295 K): δ (ppm) = 12.76 (s, 2 H), 8.17-8.15 (m, 2 H), 7.62-7.60 (m, 2 H), 6.90 (s, 2 H). ^{13}C{^{1}H} NMR (150.90 MHz, DMSO-d_6, 295 K): δ (ppm) = 167.8, 155.1, 138.2, 131.2, 122.6, 108.2. HRMS (ESI$^-$): calcd. for $C_{12}H_7O_4S^-$ [M–H]$^-$: 247.0071; found: 247.0069.

Preparation of compound 18a:

Diacid **16** (750 mg, 3.02 mmol, 1.0 eq.) was suspended in 120 mL dry dichloromethane. In an ice bath, a catalytic amount of *N,N*-dimethyl formamide and oxalyl chloride (1.50 mL, 2.22 g, 17.5 mmol, 5.8 eq.) were added dropwise. The suspension was allowed to warm up to room temperature. After 20 h, all volatiles were removed *in vacuo* to yield a brown–green solid. This crude dichloride was resuspended in 150 mL dry dichloromethane. *(S)*-2-Phenylglycinol (980 mg, 7.14 mmol, 2.4 eq.) and dry triethylamine (1.10 mL, 763 mg, 7.54 mmol, 2.5 eq.) were dissolved in 5 mL dry dichloromethane and added dropwise at 0 °C. After 20 h, the reaction was stopped by addition of water and stirred for 30 min. The resulting gum-like brown precipitate was separated, washed with dichloromethane and water, dried by azeotropic distillation with benzene and used without further purification. The product was obtained as a light brown solid (1.35 g, 2.77 mmol, 92%). ^{1}H NMR (600.13 MHz, DMSO-d_6, 295 K): δ (ppm) = 8.68 (d, ^{3}J = 8.2 Hz, 2 H), 7.84-7.83 (m, H), 7.62-7.61 (m, 2 H), 7.36-7.31 (m, 8 H), 7.25-7.23 (m, 2 H), 7.02 (s, 2 H), 5.00-4.94 (m, 4 H), 3.64-3.61 (m, 4 H). ^{13}C{^{1}H} NMR (150.90 MHz, DMSO-d_6, 295 K): δ (ppm)

= 165.0, 150.3, 141.3, 138.3, 130.6, 128.2, 127.0, 126.9, 121.4, 109.9, 64.7, 55.2. HRMS (ESI$^-$): calcd. for $C_{28}H_{25}N_2O_4S^-$ [M–H]$^-$: 485.1541; found: 485.1541.

Preparation of compound 18b:

Diacid **16** (1.18 g, 4.75 mmol, 1.0 eq.) was suspended in 100 mL dry dichloromethane. In an ice bath, catalytic amounts of *N,N*-dimethyl formamide and oxalyl chloride (1.5 mL, 2.22 g, 17.5 mmol, 3.7 eq.) were added dropwise. The suspension was allowed to warm to room temperature. After 20 h, all volatiles were removed *in vacuo* to yield a brown–green solid. This crude dichloride was resuspended in 100 mL dry dichloromethane. *(S)*-Valinol (1.33 mL, 1.23 g, 11.9 mmol, 2.5 eq.) and triethylamine (1.66 mL 1.21 g, 11.9 mmol, 2.5 eq.) were dissolved in 10 mL dry dichloromethane and added dropwise at 0 °C. After 20 h, the reaction was stopped by addition of water and stirred for 30 min. The resulting gum-like precipitate was separated, washed with dichloromethane and water and dried by azeotropic distillation with benzene. The product was obtained as a light brown solid (1.31 g, 3.12 mmol, 65%). ^{1}H NMR (600.13 MHz, DMSO-d_6, 295 K): δ (ppm) = 7.90 (d, ^3J = 9.1 Hz, H), 7.81-7.80 (m, 2 H), 7.60-7.59 (m, 2 H), 6.99 (s, 2 H), 4.68 (s, 2 H), 3.70-3.69 (m, 2 H), 3.48-3.42 (m, 4 H), 1.91-1.88 (m, 2 H), 0.89 (d, ^3J = 6.8 Hz, 6 H), 0.87 (d, ^3J = 6.8 Hz, 6 H). ^{13}C{^{1}H} NMR (150.90 MHz, DMSO-d_6, 295 K): δ (ppm) = 165.4, 149.8, 138.4, 130.4, 121.3, 110.2, 61.3, 55.8, 28.3, 19.7, 18.1. HRMS (ESI$^-$): calcd. for $C_{22}H_{29}N_2O_4S^-$ [M–H]$^-$: 417.1854; found: 417.1855.

Preparation of compound 2a:

To a suspension of diamide **18a** (1.32 g, 2.71 mmol, 1.0 eq.) in 100 mL dry dichloromethane at 0 °C, diethylaminosulfur trichloride (1.00 mL 1.22 g, 7.57 mmol, 2.8 eq.) was added dropwise. After stirring for 3 h at 0 °C, the reaction was quenched by addition of 4 N aqueous ammonium

hydroxide and extracted with dichloromethane. The organic phase was dried over sodium sulfate, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel was deactivated with triethylamine prior to use; petroleum ether/ethyl acetate 4:1 → 1:1). The product was obtained as a yellow solid (651 mg, 1.44 mmol, 53%). Single crystals suitable for X-ray diffraction analysis were obtained by layering a solution of the compound in dichloromethane with toluene and *n*-pentane. ^{1}H NMR (600.13 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.80-7.78 (m, 2 H), 7.51-7.50 (m, 2 H), 7.36-7.32 (m, 8 H), 7.29-7.26 (m, 2 H), 6.85 (s, 2 H), 5.42-5.39 (m, 2 H), 4.79-4.76 (m, 2 H), 4.25 (t, ^{3}J = 8.2 Hz, 2 H). ^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 295 K): δ (ppm) = 164.2, 150.2, 142.6, 139.2, 130.3, 128.8, 127.6, 121.6, 103.8, 75.1, 70.1. HRMS (EI^+): calcd. for $C_{28}H_{21}N_2O_2S^+$ $[M–H]^+$: 449.1318; found: 449.1316.

Preparation of compound 2b:

To a suspension of diamide **18b** (1.31 g, 3.12 mmol, 1.0 eq.) in 100 mL dry dichloromethane at 0 °C, diethylaminosulfur trifluoride (1.24 mL, 1.51 g, 9.35 mmol, 3.0 eq.) were added. After stirring for 3 h at 0 °C, the reaction was quenched by addition of 4 N aqueous ammonium hydrochloride and extracted with dichloromethane. The organic phase was dried over sodium sulfate, the solvent was removed *in vacuo* and the residue was purified by flash column chromatography (silica gel was deactivated with triethylamine prior to use; petroleum ether/ethyl acetate 2:1 → 1:1). The product was obtained as an orange-colored solid (589 mg, 1.54 mmol, 49%). ^{1}H NMR (600.13 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.74-7.73 (m, 2 H), 7.46-7.45 (m, 2 H), 6.73 (s, 2 H), 4.43-4.40 (m, 2 H), 4.12-4.05 (m, 4 H), 1.83-1.77 (m, 2 H), 1.06 (d, ^{3}J = 6.7 Hz, 6 H), 0.95 (d, ^{3}J = 6.7 Hz, 6 H). ^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 295 K): δ (ppm) = 163.0,

149.9, 139.2, 130.1, 121.5, 103.8, 72.9, 70.9, 33.3, 19.1, 18.7. HRMS (ESI^+): calcd. for $C_{22}H_{27}N_2O_2S^+$ $[M+H]^+$: 383.1788; found: 383.1794.

Preparation of compounds ^{Me,R}boxmanMCl$_2$ (General Procedure GP1):

A solution of the respective ligand (**1b** or **1c**, 1.0 eq.) in tetrahydrofuran (approximately 5 ml) was added to a solution of $MCl_2(thf)_x$ (M = Fe, Co; 1.0 eq.) in tetrahydrofuran (5-10 ml). The reaction mixture was stirred at room temperature for 1-2 d, turning into a colored suspension. The solvent was reduced to 1/2 of its volume *in vacuo* and treated with *n*-pentane for complete precipitation. The solid was separated by filtration, washed consecutively with little tetrahydrofuran and *n*-pentane, and dried in vacuo. Single crystals suitable for X-ray diffraction analysis were obtained by layering a solution of the respective compound in dichloromethane with toluene and *n*-pentane.

Preparation of compound 19a:

Employing **GP1**, ligand **1b** (46.7 mg, 101 µmol) was reacted with $FeCl_2$ (12.8 mg, 101 µmol). The product was obtained as a green beige solid (37.4 mg, 63.5 µmol, 63%).^{1}H NMR (600.13 MHz, CD_2Cl_2, 295 K,): δ (ppm) = 10.88 (s, 2 H), 8.06 (bs, 2 H) 5.60 (s, 2 H), 4.89 (s, 4 H), 0.62 (s, 4 H). ^{13}C NMR (150.90 MHz, CD_2Cl_2, 295 K,): δ (ppm) = 303.9 (s), 230.4 (s), 208.3 (s), 161.9 (s), 153.5 (s), 144.2 (d, J = 162.2 Hz), 127.4 (d, J = 153.8 Hz), 122.4 (d, J = 162.1 Hz), 120.9 (s), 111.7 (s), 14.7 (q, J = 128.4 Hz), –7.9 (s). μ_{eff} = 5.25 μ_B (Evans, CD_2Cl_2, 295 K). Anal. Calcd for $C_{30}H_{26}FeN_2O_3$: C, 61.15; H, 4.45; N, 4.75. Found: C, 60.96; H, 4.76; N, 4.82.

Preparation of compound 19b:

Complexation of $FeCl_2$ (64.4 mg, 508 µmol) with ligand **1c** (200.5 mg, 508 µmol) following method **GP1** yielded the product as green beige solid (170.1 mg, 326 µmol, 64%). ^{1}H NMR

(600.13 MHz, CD_2Cl_2, 295 K,): δ (ppm) = 10.64 (s, 2 H), 8.41 (bs, 2 H), 7.29 (s, 2 H), 3.65 (s, 6 H), 2.55 (s, 2 H), 1.61 (s, 6 H), –12.30 (*b*s, 2 H). ^{13}C NMR (150.90 MHz, CD_2Cl_2, 295 K,): δ (ppm) = 279.8 (s), 253.2 (s), 224.9 (s), 159.5 (s), 146.7 (d, J = 162.6 Hz), 85.5 (s), 19.7 (s), 15.2 (q, J = 124.3 Hz), 10.3 (s), –25.4 (s), –28.0 (s). μ_{eff} = 5.14 μ_B (Evans, CD_2Cl_2, 295 K). Anal. Calcd for $C_{24}H_{30}Cl_2FeN_2O_3$: C, 55.30; H, 5.80; N, 5.37. Found: C, 55.55; H, 6.09; N, 5.13.

Preparation of compound 20a:

Employing **GP1**, ligand **1b** (130 mg, 281 µmol) was reacted with $CoCl_2(thf)_{1.2}$ (60.8 mg, 281 µmol). The product was obtained as a bright green solid (152 mg, 256 µmol, 91%). ^{1}H NMR (600.13 MHz, CD_2Cl_2, 295 K,): δ (ppm) = 16.73 (s, 2 H), 8.44 (s, 4 H), 6.88 (s, 2 H), 6.53 (s, 2 H), 3.49 (s, 6 H). ^{13}C NMR (150.90 MHz, CD_2Cl_2, 295 K,): δ (ppm) = 184.5 (s), 150.4 (s), 143.6 (d, J = 159.8 Hz), 131.2 (d, J = 159.8 Hz), 125.0 (d, J = 163.5 Hz), 112.4 (s), 62.6 (s), 18.7 (q, J = 132.6 Hz). μ_{eff} = 4.36 μ_B (Evans, CD_2Cl_2, 295 K). Anal. Calcd for $C_{30}H_{26}Cl_2CoN_2O_3$: C, 60.83; H, 4.42; N, 4.73. Found: C, 60.53; H, 4.74; N, 4.55.

Preparation of compound 20b:

Synthesis according to **GP1** with ligand **1c** (200 mg, 507 µmol) and $CoCl_2(thf)_{1.2}$ (101 mg, 507 µmol) yielded the product as bright green solid (222 mg, 423 µmol, 84%). ^{1}H NMR (600.13 MHz, CD_2Cl_2, 295 K,): δ (ppm) = 39.94 (s, 2 H), 21.41 (s, 2 H), 12.38 (s, 4 H), 10.16 (s, 2 H), 6.61 (s, 12 H), 5.94 (s, 2), 2.87 (s, 6 H). ^{13}C NMR (150.90 MHz, CD_2Cl_2, 295 K,): δ (ppm) = 198.6 (s), 186.7 (s), 150.1 (s), 142.7 (d, J = 158.6 Hz), 45.7 (m), 19.5 (m), 17.3 (q, J = 128.0 Hz), 7.8 (m), −4.8 (s). μ_{eff} = 4.14 μ_B (Evans, CD_2Cl_2, 295 K). Anal. Calcd for $C_{24}H_{30}Cl_2CoN_2O_3$: C, 54.98; H, 5.77; N, 5.34. Found: C, 55.41; H, 6.18; N, 5.06.

Preparation of compound 21:

To a solution of complex **20b** (40.0 mg, 76.3 µmol, 1.0 eq.) in 3 mL dichloromethane was added Ag(OTf) (19.6 mg, 76.3 µmol, 1.0 eq.). After stirring the reaction mixture at room temperature for 3 h, the purple-blue suspension was filtered through a plug of Celite. The filtrate was freed from any volatiles *in vacuo,* yielding the purple-blue crude product. Although further purification was hampered by the formation of inseparable side products, single crystals suitable for X-ray diffraction analysis were obtained layering a solution of the respective compound in dichloromethane with toluene and *n*-pentane..

Nickel(II)-catalyzed Enantioselective Fluorination of β-Ketoesters and Oxindoles (General Procedure GP2):

Approximately 70 mg of pestle molecular sieve 4 Å were activated by heating under vacuum. When the flask had cooled down, anhydrous nickel(II)perchlorate (2.6 mg, 10 µmol, 10 mol%,) and ^{Me,Ph}boxman (**1b**) (5.1 mg, 11 µmol, 11 mol%) were added. Under Argon atmosphere, the mixture was suspended in 5 mL dry dichloromethane. After stirring for 30 min, 100 µmol of the respective ketoester (**21**) or oxindole (**23**) were added to the suspension. After another 30 min, *N*-fluorobenzenesulfonimide (NFSI) (47.8 mg, 120 µmol, 1.2 eq.) was added. The reaction was stirred for 16 h and subsequently quenched by addition of water. The mixture was extracted with dichloromethane and the organic phases were dried over sodium sulfate and filtrated over a pad of celite. The raw product was purified by flash column chromatography over silica with the indicated eluents. Notably, to avoid the possibility of enantioenrichment/depletion of the products influenced by self-disproportionation of enantiomers (SDE),[28] the ee values of products were determined by testing the *ee* value of the total eluents after chromatography.

Zinc(II)-catalyzed Asymmetric Fluorination of β-Ketoesters (General Procedure GP3):

After stirring a mixture of $Zn(NTf_2)_2$ (0.01 mmol, 10 mol%) and ligand (**1** or **2**) (0.012 mmol, 12 mol%) in dry dichloromethane (1 ml) at room temperature for 2 h, substrate **21** (0.10 mmol, 1 eq.) was added. After stirring the reaction mixture for 30 min, NFSI (0.2 mmol, 2 eq.) was added and the reaction mixture was stirred at room temperature under argon atmosphere. After the disappearance of substrate **21** (monitored by TLC, usually 5 h), the crude product was purified by silica gel flash chromatography to afford the desired product.

Characterization of catalysis products

Compound 23a

Synthesis according to GP2. Eluent: petroleum ether/ethyl acetate 10:1. 25 mg (93.2 µmol, 93%) of a yellow oil. Spectroscopic data have been reported elsewhere.[29] ^{1}H NMR (399.89 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.86-7.82 (m, 1 H), 7.17-7.13 (m, 2 H), 3.71 (dd, $^2J_{HH}$ = 17.7 Hz, $^3J_{HF}$ = 10.6 Hz, 1 3.38 (dd, $^2J_{HH}$ = 17.9 Hz, $^3J_{HF}$ = 22.4 Hz, 1 H), 1.43 (s, 9 H). ^{19}F{^{1}H} NMR (376.27 MHz, $CDCl_3$, 295 K): δ (ppm) = –98.8 (d, $^6J_{FF}$ = 1.1 Hz, 1 F), –163.2 (d, $^6J_{FF}$ = 1.3 Hz, 1 F). HPLC (AD-H, *n*-hexane/2-propanol 95:5, 0.75 ml/min, 254 nm): $t_{R,\ minor}$ = 10.8 min, $t_{R,\ major}$ = 12.4 min, 93% *ee*.

Compound 23c

Method 1: Synthesis according to GP2. Eluent: petroleum ether/ethyl acetate 10:1. 14.9 mg (45.3 µmol, 45%) of a white solid. Method 2: Synthesis according to GP3. 28.1 mg (87.8 µmol, 85%) of a slightly white solid Spectroscopic data have been reported elsewhere.[9] ^{1}H NMR (399.89 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.70-7.68 (m, 2 H), 7.61-7.59 (m, 1 H), 3.70 (dd, $^2J_{HH}$ = 17.5 Hz, $^3J_{HF}$ = 10.7 Hz, 1 3.38 (dd, $^2J_{HH}$ = 17.5 Hz, $^3J_{HF}$ = 22.6 Hz, 1 H), 1.43 (s, 9 H). ^{19}F{^{1}H} NMR

(376.27 MHz, $CDCl_3$, 295 K): δ (ppm) = –163.4 (s, 1 F). HPLC (AD-H, *n*-hexane/2-propanol 95:5, 0.75 ml/min, 254 nm): $t_{R,\ minor}$ = 10.8 min, $t_{R,\ major}$ = 13.3 min, 89% *ee*. Method 2: HPLC (OD-H, *n*-hexane/2-propanol 99:1, 1.0 ml/min, 254 nm): $t_{R,\ minor}$ = 11.8 min, $t_{R,\ major}$ = 13.5 min, 87% *ee*.

Compound 23d

Synthesis according to GP2. Eluent: petroleum ether/ethyl acetate 5:1. 27.5 mg (96.6 µmol, 97%) of a colorless oil. Spectroscopic data have been reported elsewhere.[30] ^{1}H NMR (399.89 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.78-7.77 (m, 1 H), 7.65-7.64 (m, 1 H), 7.45-7.43 (m, 1 H), 3.69 (dd, $^2J_{HH}$ = 17.6 Hz, $^3J_{HF}$ = 10.4 Hz, 1 3.35 (dd, $^2J_{HH}$ = 17.7 Hz, $^3J_{HF}$ = 22.6 Hz, 1 H), 1.42 (s, 9 H). ^{19}F{^{1}H} NMR (376.27 MHz, $CDCl_3$, 295 K): δ (ppm) = –163.4 (s, 1 F). HPLC (OD-H, *n*-hexane/2-propanol 90:10, 0.75 ml/min, 254 nm): $t_{R,\ minor}$ = 8.9 min, $t_{R,\ major}$ = 9.4 min, 92% *ee*.

Compound 23e

Synthesis according to GP2. Eluent: petroleum ether/ethyl acetate 3:1. 30.4 mg (98.0 µmol, 98%) of a colorless oil. Spectroscopic data have been reported elsewhere.[31] ^{1}H NMR (399.89 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.20 (s, 1 H), 6.88 (s, 1 H), 3.98 (s, 3 H), 3.90 (s, 3 H), 3.62 (dd, $^2J_{HH}$ = 17.2 Hz, $^3J_{HF}$ = 10.2 Hz, 1 3.28 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HF}$ = 22.1 Hz, 1 H), 1.44 (s, 9 H). ^{19}F{^{1}H} NMR (376.27 MHz, $CDCl_3$, 295 K): δ (ppm) = –163.1 (s, 1 F). HPLC (AD-H, *n*-hexane/2-propanol 93:7, 0.75 ml/min, 254 nm): $t_{R,\ major}$ = 19.8 min, $t_{R,\ minor}$ = 22.8 min, 94% *ee*.

Compound 23f

Synthesis according to GP2. Eluent: petroleum ether/ethyl acetate 3:1. 26.4 mg (98.4 µmol, 98%) of a yellow oil. Spectroscopic data have been reported elsewhere.[32] ^{1}H NMR (399.89 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.20 (s, 1 H), 6.89 (s, 1 H), 3.99 (s, 3 H), 3.90 (s, 3 H), 3.80 (s, 3 H),

3.69 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HF}$ = 10.4 Hz, 1 3.33 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HF}$ = 22.4 Hz, 1 H), 1.44 (s, 9 H). $^{19}F\{^1H\}$ NMR (376.27 MHz, $CDCl_3$, 295 K): δ (ppm) = –163.9 (s, 1 F). HPLC (OD-H, *n*-hexane/2-propanol 90:10, 0.75 ml/min, 254 nm): $t_{R, major}$ = 34.6 min, $t_{R, minor}$ = 41.7 min, 64% *ee*.

Compound 23g

Synthesis according to GP2. Eluent: petroleum ether/ethyl acetate 3:1. 26.4 mg (88.7 µmol, 89%) of a yellow oil. ^1H NMR (600.13 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.20 (s, 1 H), 6.89 (s, 1 H), 5.88-5.82 (m, 1 H), 5.27-5.21 (m, 2 H), 4.72-4.66 (m, 2 H), 3.98 (s, 3 H), 3.90 (s, 3 H), 3.69 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HF}$ = 10.5 Hz, 1 3.33 (dd, $^2J_{HH}$ = 17.3 Hz, $^3J_{HF}$ = 22.4 Hz, 1 H). $^{13}C\{^1H\}$ NMR (150.90 MHz, $CDCl_3$, 295 K): δ (ppm) = 193.5 (d, $^2J_{CF}$ = 18.6 Hz), 167.4 (d, $^2J_{CF}$ = 23.2 Hz), 157.3 (s), 150.4 (s), 147.0 (d, $^3J_{CF}$ = 4.1 Hz), 130.9 (s), 126.1 (d, $^3J_{CF}$ = 1.3 Hz), 119.3 (s), 107.4 (d, $^4J_{CF}$ = 1.3 Hz), 105.6 (s), 95.1 (d, $^1J_{CF}$ = 201.4 Hz), 66.8 (d, $^4J_{CF}$ = 0.8 Hz), 56.6 (s), 56.3 (s), 38.1 (d, $^2J_{CF}$ = 24.1 Hz). $^{19}F\{^1H\}$ NMR (376.27 MHz, $CDCl_3$, 295 K): δ (ppm) = –163.8 (s, 1 F). HRMS ($DART^+$): calcd. for $C_{15}H_{16}FO_5$ $[M+H]^+$: 295.0976; found: 295.0979. HPLC (OD-H, *n*-hexane/2-propanol 90:10, 0.75 ml/min, 254 nm): $t_{R, major}$ = 27.4 min, $t_{R, minor}$ = 30.4 min, 57% *ee*.

Compound 23b

Synthesis according to GP3. Eluent: petroleum ether/ethyl acetate 20:1. 23.8 mg (90.2 µmol, 90%) of a slightly yellow solid. Spectroscopic data have been reported elsewhere.[29] ^1H NMR (400.20 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.62 (s, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 3.67 (dd, *J* = 17.2 Hz, 10.8 Hz, 1 H), 3.33 (dd, *J* = 22.8 Hz, 17.2 Hz, 1 H), 1.43 (s, 9 H). HPLC (AD-H, *n*-hexane/2-propanol 99:1, 1.0 ml/min, 254 nm): $t_{R, major}$ = 11.1 min, $t_{R, minor}$ = 18.4 min, 92% *ee*.

Compound 23h

Synthesis according to GP3. Eluent: petroleum ether/ethyl acetate 20:1. 25.6 mg (90.0 µmol, 90%) of a slightly white solid. Spectroscopic data have been reported elsewhere.[29] ^{1}H NMR (400.20 MHz, $CDCl_3$, 295 K): δ (ppm) = 7.75 (d, J = 8.0 Hz, 1 H), 7.42-7.50 (m, 2 H), 3.71 (dd, J = 17.2 Hz, 10.4 Hz, 1 H), 3.37 (dd, J = 22.4 Hz, 17.2 Hz, 1 H), 1.43 (s, 9 H). HPLC (AD-H, *n*-hexane/2-propanol 95:5, 1.0 ml/min, 254 nm): $t_{R,\,major}$ = 13.2 min, $t_{R,\,minor}$ = 17.9 min, 84% *ee*.

Compound 25a

Synthesis according to GP2. Eluent: pentane/ethyl acetate 5:1 → 3:1. 13.9 mg (40.7 µmol, 41%) of a colorless oil. Spectroscopic data have been reported elsewhere.[9] ^{1}H NMR (399.89 MHz, $CDCl_3$, 295 K): δ (ppm) = 8.00 (d, ^{3}J = 8.2 Hz, 1 H), 7.53-7.48 (m, 1 H), 7.38-7.36 (m, 1 H), 7.29-7.24 (m, 3 H), 7.19 (d, ^{3}J = 8.4 Hz, 2 H), 2.35 (s, 3 H), 1.61 (s, 9 H). ^{19}F{^{1}H} NMR (376.27 MHz, $CDCl_3$, 295 K): δ (ppm) = –144.5 (s, 1 F). HPLC (OD-H, *n*-hexane/2-propanol 99:1, 0.75 ml/min, 254 nm): $t_{R,\,minor}$ = 7.8 min, $t_{R,\,major}$ = 9.3 min, 73% *ee*.

Compound 25b

Synthesis according to GP2. Eluent: pentane/ethyl acetate 10:1. 25.3 mg (70.8 µmol, 71%) of a colorless oil. ^{1}H NMR (600.13 MHz, $CDCl_3$, 295 K): δ (ppm) = 8.00 (d, ^{3}J = 8.3 Hz, 1 H), 7.52-7.49 (m, 1 H), 7.38-7.36 (m, 1 H), 7.29-7.25 (m, 2 H), 6.98-6.98 (m, 1 H), 6.93-6.91 (m, 1 H), 6.83-6.83 (m, 1 H) 3.81 (s, 3 H), 1.62 (s, 9 H). ^{13}C{^{1}H} NMR (150.90 MHz, $CDCl_3$, 295 K): δ (ppm) = 170.1 (d, $^{2}J_{CF}$ = 25.0 Hz), 159.9 (s), 149.0 (d, $^{4}J_{CF}$ = 0.9 Hz), 141.1 (d, $^{3}J_{CF}$ = 5.2 Hz), 137.2 (d, $^{2}J_{CF}$ = 27.6 Hz), 132.0 (d, J_{CF} = 3.1 Hz), 129.8 (s), 126.3 (d, J_{CF} = 0.9 Hz), 125.7 (d, $^{2}J_{CF}$ = 17.9 Hz), 125.5 (d, J_{CF} = 2.8 Hz), 118.6 (d, J_{CF} = 5.6 Hz), 115.8 (d, J_{CF} = 1.4 Hz), 115.2

(d, J_{CF} = 1.7 Hz), 112.0 (d, J_{CF} = 6.6 Hz), 92.7 (d, $^{1}J_{CF}$ = 188.3 Hz), 85.2 (s), 55.5 (s), 28.1 (s). $^{19}F\{^{1}H\}$ NMR (376.27 MHz, $CDCl_3$, 295 K): δ (ppm) = –146.0 (s, 1 F). HRMS ($DART^+$): calcd. for $C_{20}H_{24}FN_2O_4$ $[M+NH_4]^+$: 375.1715; found: 375.1713. HPLC (OD-H, *n*-hexane/2-propanol 99:1, 0.75 ml/min, 254 nm): $t_{R, minor}$ = 10.3 min, $t_{R, major}$ = 11.1 min, 79% *ee*.

Compound 25c

Synthesis according to GP2. Eluent: pentane/ethyl acetate 10:1. 23.4 mg (86.9 µmol, 87%) of a colorless oil. ^{1}H NMR (600.13 MHz, $CDCl_3$, 295 K): δ (ppm) = 8.34 (d, ^{3}J = 8.3 Hz, 1 H), 7.55-7.52 (m, 1 H), 7.43-7.39 (m, 4 H), 7.36-7.35 (m, 2 H), 7.34-7.32 (m, 1 H), 2.65 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (150.90 MHz, $CDCl_3$, 295 K): δ (ppm) = 172.8 (d, $^{2}J_{CF}$ = 25.2 Hz), 170.6 (d, $^{4}J_{CF}$ = 0.9 Hz), 141.4 (d, $^{3}J_{CF}$ = 5.3 Hz), 135.5 (d, $^{2}J_{CF}$ = 27.8 Hz), 132.1 (d, J_{CF} = 3.1 Hz), 129.9 (d, $^{5}J_{CF}$ = 1.9 Hz), 128.9 (s), 126.3 (d, $^{3}J_{CF}$ = 5.8 Hz), 126.3 (d, J_{CF} = 8.3 Hz), 126.2 (d, J_{CF} = 6.4 Hz), 125.9 (d, $^{2}J_{CF}$ = 17.8 Hz), 117.3 (d, J_{CF} = 1.3 Hz), 93.1 (d, $^{1}J_{CF}$ = 188.5 Hz), 26.6 (s). $^{19}F\{^{1}H\}$ NMR (376.27 MHz, $CDCl_3$, 295 K): δ (ppm) = –146.1 (s, 1 F). HRMS (ESI^+): calcd. for $C_{17}H_{16}FNNaO_3$ $[M+MeOH+Na]^+$: 324.1006; found: 324.1006. HPLC (OD-H, *n*-hexane/2-propanol 97:3, 0.75 ml/min, 254 nm): $t_{R, major}$ = 10.8 min, $t_{R, minor}$ = 15.6 min, 25% *ee*.

ASSOCIATED CONTENT

Supporting Information

The supporting Information is available free of charge on the ACS Publication website at DOI: xxx

- NMR spectra, chromatographic data, molecular structures in the solid-state of compounds **7**, **1b**, **1c**, **2a**, **19a**, **19b**, **20a**, **20b**, **21** (PDF)

- X ray diffraction studies of compounds **7**, **1b**, **1c**, **2a**, **19a**, **19b**, **20a**, **20b**, **21** (CIF)

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Notes

The authors declare no competing financial interest.

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