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Design and Synthesis of Oxazoline-Based Scaffolds for Hybrid Lewis Acid/Lewis Base Catalysis of Carbon–Carbon Bond Formation

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Abstract: A new class of hybrid Lewis acid/Lewis base catalysts has been designed and prepared with an initial objective of promoting stereoselective direct aldol reactions. Several scaffolds were synthesized that contain amine moieties capable of enamine catalysis, connected to heterocyclic metal-chelating sections composed of an oxazole–oxazoline or thiazole–oxazoline. Early screening results have identified oxazole–oxazoline-based systems capable of promoting a highly diastereo- and enantioselective direct aldol reaction of propionaldehyde with 4-nitrobenzaldehyde, when combined with Lewis acids such as zinc triflate.

Key words: hybrid catalysis - aldol reaction - organocatalysis - Lewis acids - oxazoline - asymmetric catalysis

The use of small molecule organocatalysts to promote carbon–carbon bond formation is now an established strategy for the preparation of complex organic molecules.[1] The discoveries by Eder and co-workers[2] and Hajos and co-workers[3] that proline can catalyze highly enantioselective intramolecular aldol reactions, as well as the report by List that it can catalyze highly enantioselective intermolecular aldol reactions,[4] led to an explosion of research into the design and utility of organocatalysts. Proline is a simple and elegant example of a bifunctional organocatalyst that serves to activate a 'donor' aldehyde or ketone via enamine formation with its amine moiety, for addition to an appropriate acceptor that is activated by the carboxylic acid (Scheme 1, top).[5] There are now many related bifunctional organocatalysts incorporating various hydrogen-bond donors to activate different acceptors, but more rare are reports of hybrid catalysts containing discreet and separate metal Lewis acid/organic Lewis base moieties for carbon–carbon bond formation. Despite the intense study of organocatalysts in recent years, as a class

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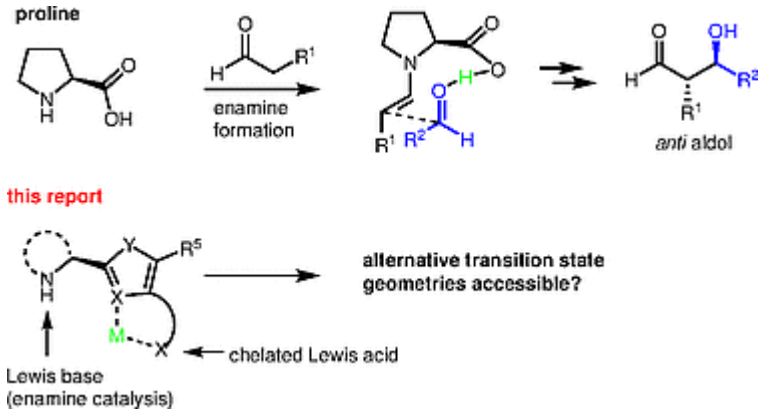
their activities continue to be significantly lower than those of enzymes and transition-metal catalysts. An additional challenge (not unique to organocatalysts) is that specific diastereomeric products may be difficult to obtain. A possible solution to some of these shortcomings may lie in the replacement of Brønsted acids or hydrogen-bond donors with chelated Lewis acids (e.g., Scheme 1, bottom). This approach offers the flexibility of using a wide range of Lewis acids, including transition and rare earth metals, as well as the ability to modulate metal and ligand geometries and electronics. A seminal example of such a hybrid Lewis acid/Lewis base catalyst is the ferrocenylphosphine–gold(I) complexes with tethered amines reported by Ito and Hayashi for asymmetric aldol reactions with isocyanoacetate substrates.[6] Other representative examples for carbon–carbon bond formation include reports from the labs of Shibasaki,[7] Kozlowski,[8] Lin,[9] Whiting,[10] Hong,[11] Dixon,[12] and Dong.[13]



Scheme 1 Design of bifunctional direct aldol catalysts

With an initial interest in identifying direct aldol reaction catalysts that could be useful for the efficient preparation of polypropionate natural product analogues, we have designed a number of hybrid Lewis acid/Lewis base catalysts with the potential to promote various carbon–carbon bond formations. This manuscript discloses our early efforts to identify novel bifunctional catalysts capable of promoting catalytic direct aldol reactions.[14] The combination of amino acid derivatives and Lewis acidic transition metals as catalysts for direct aldol reactions is an approach that has been explored previously,[15] [16] [17] [18] [19] [20] [21] but these catalysts have generally not displayed activities above those of standard organocatalysts, nor have they provided access to unique products. Therefore, we believe that

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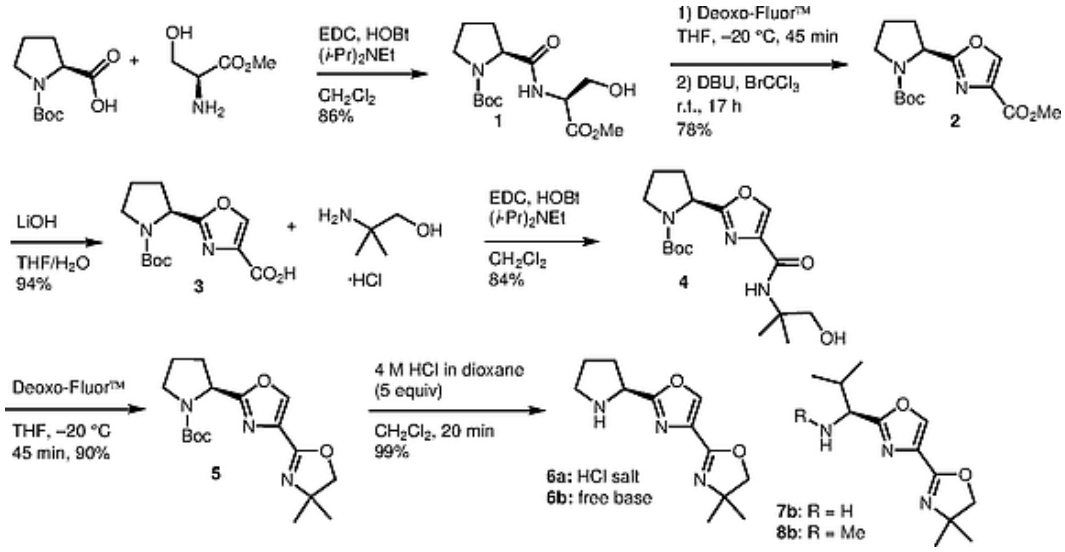
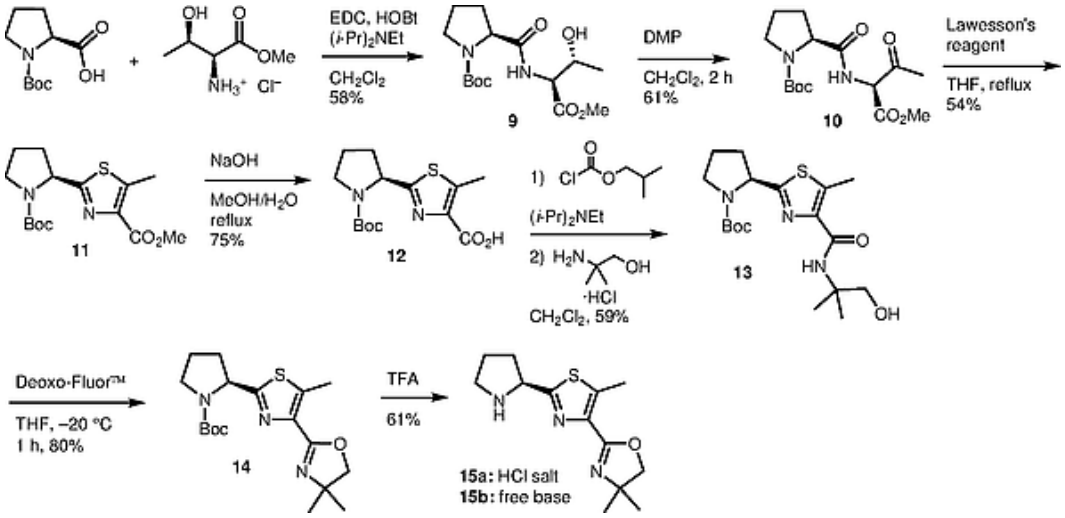
this strategy is worthy of further investigation, especially since it is an approach that has been effectively used by Nature in type-II aldolases.[22]



Scheme 2 Synthesis of oxazole–oxazoline precatalysts



Scheme 3 Synthesis of thiazole–oxazoline precatalyst

A significant challenge inherent with multifunctional catalysts is the possibility for self-quenching. It is necessary for the activating moieties to be close enough in space to bring the substrates together, but not so close as to interact negatively with each other. Our initial design (Scheme 1, bottom) utilizes 5-membered heterocycles to act as a spacer between the amine and Lewis acid, while concurrently acting

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as a multidentate ligand to hold the Lewis acid in a favorable orientation. Hybrid catalysts with pyridine-based scaffolds have been reported by Wang[18 19] and Zhao[20] for cross-aldol reactions with ketone donors.

Our desire for air- and moisture-tolerant catalysts inspired us to design oxazoline-based systems, a well-established ligand for asymmetric synthesis using a variety of Lewis acidic transition metals. The preparation of an oxazole–oxazoline precatalyst is outlined in Scheme 2. *N*-Boc-l-proline was coupled to l-serine methyl ester with EDC to form dipeptide 1. The dipeptide was reacted with Deoxo-Fluor [bis(2-methoxyethyl)aminosulfur trifluoride] according to a protocol reported by Wipf and Williams to form an intermediate oxazoline,[23] which was treated with DBU and $BrCCl_3$ and allowed to warm to room temperature to form the oxazole 2. The yield of 2 improved in our hands using an aqueous workup ($NaHCO_3$ wash) prior to forming the oxazole, rather than using a one-pot protocol. Next, the methyl ester was hydrolyzed and the resulting acid 3 was cleanly coupled with 2-amino-2-methylpropanol to obtain amide 4. This was again cyclized using Deoxo-Fluor[24] to oxazole–oxazoline 5, then the Boc group was removed to provide the desired precatalyst as its HCl salt 6a. The valine-based precatalysts 7 and 8 (Scheme 2) were prepared by a similar strategy (see Supporting Information).

Next, a thiazole analogue of precatalyst 6 was prepared (Scheme 3). Peptide coupling of *N*-Boc-l-proline and l-threonine methyl ester with EDC gave the desired amide 9. Subsequent Dess–Martin periodinane (DMP) oxidation and treatment with Lawesson's reagent[25] produced thiazole 11, followed by ester hydrolysis to yield acid 12. Peptide coupling of 12 with 2-amino-2-methylpropanol using EDC led to unsatisfactory yields, so alternatively the mixed anhydride was prepared from isobutyl chloroformate and treated with the amino alcohol, giving amide 13 in reasonable yield. Oxazoline 14 was synthesized using analogous conditions to the oxazole, and finally amine deprotection with TFA and neutralization gave the thiazole–oxazoline precatalyst 15b.

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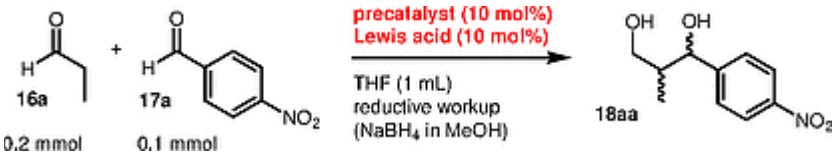
Table 1 Select Precatalyst and Metal Salt Screening Results for Direct Aldol Reaction of Propionaldehyde and 4-Nitrobenzaldehyde[a]



Entry	Precatalyst	Metal salt	*syn*-Isomer		*anti*-Isomer		Yield (%)
			%	ee (%)	%	ee (%)	
1	6b	NiI_2	–	–	–	–	–[b]
2	6b	$CuBr_2$	–	–	–	–	–[b]
3	6b	$Cu(OTf)_2$	–	–	–	–	–[b]
4	6b	AgOTf	–	–	–	–	–[b]
5	6b	$Sn(OTf)_2$	–	–	–	–	–[b]
6	6b	$InCl_3$	35	2	65	13	48
7	6b	$In(OTf)_3$	43	9	57	12	16
8	6b	$Sm(OTf)_3$	35	5	65	40	44
9	6b	$Yb(OTf)_3$	33	20	67	25	58
10	6b	$Mg(OTf)_2$	23	6	77	79	17
11	6b	$ZnBr_2$	49	28	51	10	60
12	6b	$Zn(OTf)_2$	37	55	63	58	48
13	7b	$Zn(OTf)_2$	64	30	36	49	16
14	8b	$Zn(OTf)_2$	27	1	73	14	39
15	15b	$Zn(OTf)_2$	51	4	49	24	48
16	l-proline	–	19	5	81	83	33
17	–	$Zn(OTf)_2$	–	–	–	–	–[b]
18	6b	–	46	14	54	45	8

[a] Enantiomeric excess and yield determined by chiral HPLC with 1,2-dichlorobenzene as internal standard. Reaction conditions: 4-nitrobenzaldehyde (0.10 mmol, 0.1 M final concentration), propionaldehyde (0.20 mmol), precatalyst (10 mol%), metal salt (10 mol%), THF, 24 h.
[b] No reaction observed.

With a collection of precatalysts in hand, we tested them in the direct aldol reaction of propionaldehyde (16a) and 4-nitrobenzaldehyde (17a).[26] Reactions were run with 0.1 mmol of 4-nitrobenzaldehyde (17a) as the limiting reagent, and were subsequently treated with excess $NaBH_4$ to reduce the aldehyde products and prevent any epimerization or condensation reactions that could complicate analyses. Isomer ratios and reaction yields were determined by chiral normal-phase HPLC (see Supporting Information for details).

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Each precatalyst was tested initially with 15 different metal salts in THF, with select results presented in Table 1. Optimal results were observed with the oxazole–oxazoline catalyst 6b (entries 1–12). A number of common Lewis acids yielded no reaction when combined with 6b (entries 1–5). Counterion effects were observed with some metal salts; for example $InCl_3$ (entry 6) gave superior yield to $In(OTf)_3$ (entry 7), and superior enantioselectivities were observed with $Zn(OTf)_2$ (entry 12) than with $ZnBr_2$ (entry 11). Decent anti selectivity (77%) and good enantioselectivity (79% ee) was observed with $Mg(OTf)_2$, but the yield (17%) was low (entry 10). Though our HPLC methods were unable to quantify the amount of unreacted 4-nitrobenzaldehyde precisely, low-yielding reactions corresponded to reactions with high amounts of unreacted 4-nitrobenzaldehyde, which was observed as the 4-nitrobenzyl alcohol after reductive work-up. The alternative precatalysts 7b, 8b, and 15b generally showed decreased yields and enantioselectivities; representative results with $Zn(OTf)_2$ are provided (entries 13–15). The primary amine precatalyst 7b is the only one described here with any syn selectivity (64% syn, entry 13), though we are currently exploring alternative primary amine based catalysts that may be more effective for syn-aldol reactions.[27] [28] [29] As a benchmark to our results in Table 1, l-proline, previously reported for cross-aldol reactions with aldehydes,[30] [31] gave decent anti selectivity (81%) and enantioselectivity (83% ee) under our screening conditions, but with only 33% yield. No reaction was observed with only $Zn(OTf)_2$ (entry 17) and very limited reaction was observed with only 6b in THF (entry 18); other control reactions are discussed with Table 2. An initial screen of various additives (acids, bases, Lewis bases, and halide salts) in aldol reactions with benzaldehyde and 4-nitrobenzaldehyde did not yield any improvements in diastereoselectivity, enantioselectivity, or yield with $Zn(OTf)_2$ or $InCl_3$ and several different precatalysts; the only exception was the use of certain basic additives such as DBU, which boosted the yield and destroyed all enantioselectivity, likely by promoting a background reaction as well as facilitating the retroaldol reaction to equilibrate the isomeric mixture of products.

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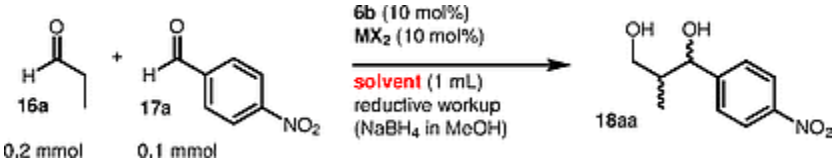
Table 2 Solvent Screen and Control Experiments[a]



Entry	Precatalyst	Metal salt	Solvent	*syn*-Isomer		*anti*-Isomer		Yield (%)
				%	ee (%)	%	ee (%)	
1	6b	$Zn(OTf)_2$	THF	37	55	63	58	48
2	6b	$Zn(OTf)_2$	DCE	29	46	71	53	4
3	6b	$Zn(OTf)_2$	i-PrOH	46	71	54	25	27
4	6b	$Zn(OTf)_2$	benzene	28	49	72	55	12
5	6b	$Zn(OTf)_2$	MeCN	45	69	55	41	43
6	6b	$Zn(OTf)_2$	MeCN/H_2O (1:1)	47	18	53	0	89
7	6b	$Zn(OTf)_2$	MeCN/H_2O (9:1)	27	79	73	92	54[b]
8	6b	$Zn(OTf)_2$	MeCN/H_2O (100:1)	47	78	53	67	51
9	6b	$Zn(OTf)_2$	MeCN/H_2O (500:1)	47	63	53	48	45
10	6b	$Zn(OTf)_2$	MeCN/H_2O (1000:1)	45	74	55	44	34
11	6b	$InCl_3$	MeCN/H_2O (9:1)	10	12	90	93	52[b]
12	6a	$Zn(OTf)_2$	MeCN/H_2O (9:1)	57	27	43	13	2
13	5	–	MeCN/H_2O (9:1)	60	20	40	9	1
14	5	$Zn(OTf)_2$	MeCN/H_2O (9:1)	84	63	16	19	1
15	(±)-2-phenylpyrrolidine (10 mol%)	–	MeCN/H_2O (9:1)	61	–	39	–	30
16	(±)-2-phenylpyrrolidine (10 mol%)	$Zn(OTf)_2$	MeCN/H_2O (9:1)	61	–	39	–	11
17	5 + (±)-2-phenylpyrrolidine (10 mol%)	$Zn(OTf)_2$	MeCN/H_2O (9:1)	56	6	44	0	29

[a] Enantiomeric excess and yield was determined by chiral HPLC with 1,2-dichlorobenzene as internal standard. Reaction conditions: 4-nitrobenzaldehyde (0.10 mmol, 0.1 M final concentration), propionaldehyde (0.20 mmol), precatalyst (10 mol%), metal salt (10 mol%), 24 h, unless otherwise noted.
[b] Isolated yield. Reactions were run for 48 h with 4-nitrobenzaldehyde (1.0 mmol), at a final concentration of 0.25 M. See Supporting Information for details.

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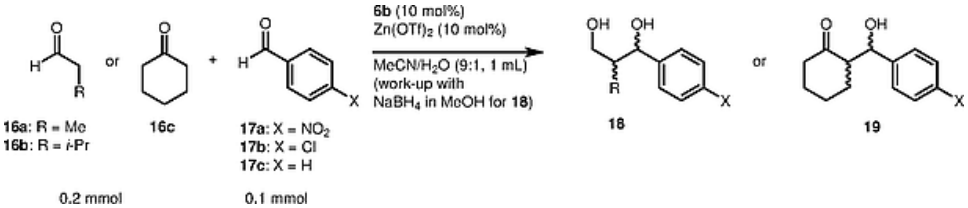
More promising results were observed in investigations of solvent effects and water concentrations (Table 2). In particular, water had a drastic effect on both diastereoselectivity and enantioselectivity. The use of MeCN/H_2O (1:1) gave a significant improvement in yield versus just MeCN, but completely abrogated the enantioselectivity for the anti product (entries 5 vs. 6). Alternatively, decreasing the amount of water by an order of magnitude (entry 7) gave excellent enantioselectivity (92% ee for the anti product) with the catalyst generated from 6b and $Zn(OTf)_2$, with moderate yield (54%). Decreasing the amount of water decreased the diastereoselectivity somewhat, and decreased the enantioselectivity of the anti product significantly (entries 8–10). The use of MeCN/H_2O (9:1) also gave excellent results with 6b and $InCl_3$ (90% anti selective, 93% ee, 52% isolated yield, entry 11).

Table 3 Exploration of Substrate Scope



0.2 mmol 0.1 mmol

Entry	Donor	Acceptor	Product	*syn*-Isomer		*anti*-Isomer		Yield (%)
				%	ee (%)	%	ee (%)	
1	16a	17a	18aa	27	79	73	92	54[b]
2	16a	17b	18ab	57	34	43	49	9
3	16a	17c	18ac	–	–	–	–	–[c]
4	16b	17a	18ba	–	–	–	–	–[c]
5	16b	17b	18bb	–	–	–	–	–[c]
6	16b	17c	18bc	–	–	–	–	–[c]
7	16c	17a	19ca	5	58	95	29	18
8	16c	17b	19cb	–	–	–	–	–[c]
9	16c	17c	19cc	–	–	–	–	–[c]

[a] Enantiomeric excess and yield was determined by chiral HPLC with 1,2-dichlorobenzene as internal standard. Reaction conditions: acceptor (0.4 mmol), donor (0.8 mmol), 6b (10 mol%), $Zn(OTf)_2$ (10 mol%), MeCN/H_2O (9:1), 20 °C, 24 h (with 17a) or 70 °C, 48 h (with 17b and 17c), unless otherwise noted. Reductive work-ups were performed for reactions with aldehyde donors (16a, 16b).
[b] Isolated yield after 48 h with 4-nitrobenzaldehyde (1.0 mmol) and propionaldehyde (2.0 mmol), at a final concentration of 0.25 M. See Supporting Information for details.
[c] No reaction observed.

Data from several control experiments are also included in Table 2. To demonstrate that optimal results are observed with a bifunctional

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catalyst over dual catalysis using a discrete organocatalyst and Lewis acid catalyst, we studied the use of several catalyst combinations for the addition of propionaldehyde (16a) to 4-nitrobenzaldehyde (17a) under our optimal conditions. First, the Boc-protected precursor 5 to the bifunctional precatalyst 6b gave only trace reaction on its own (entry 13), and also trace reaction when combined with $Zn(OTf)_2$ (entry 14); at most compound 5 could act as a ligand for $Zn(OTf)_2$. Racemic 2-phenylpyrrolidine was used as a surrogate for the strictly Lewis or Brønsted basic aspects of our hybrid catalyst; it gave a fairly significant background reaction (30% yield, entry 15), but this was attenuated when it was combined with $Zn(OTf)_2$ (11% yield, entry 16). With the combination of 5 and $Zn(OTf)_2$ (10 mol% each) plus 2-phenylpyrrolidine (entry 17), no improvement in yield is obtained compared to simply 2-phenylpyrrolidine, which suggests that a dual catalysis mechanism may not be operative, and 6b and $Zn(OTf)_2$ (entry 7) may indeed act as a hybrid catalyst.

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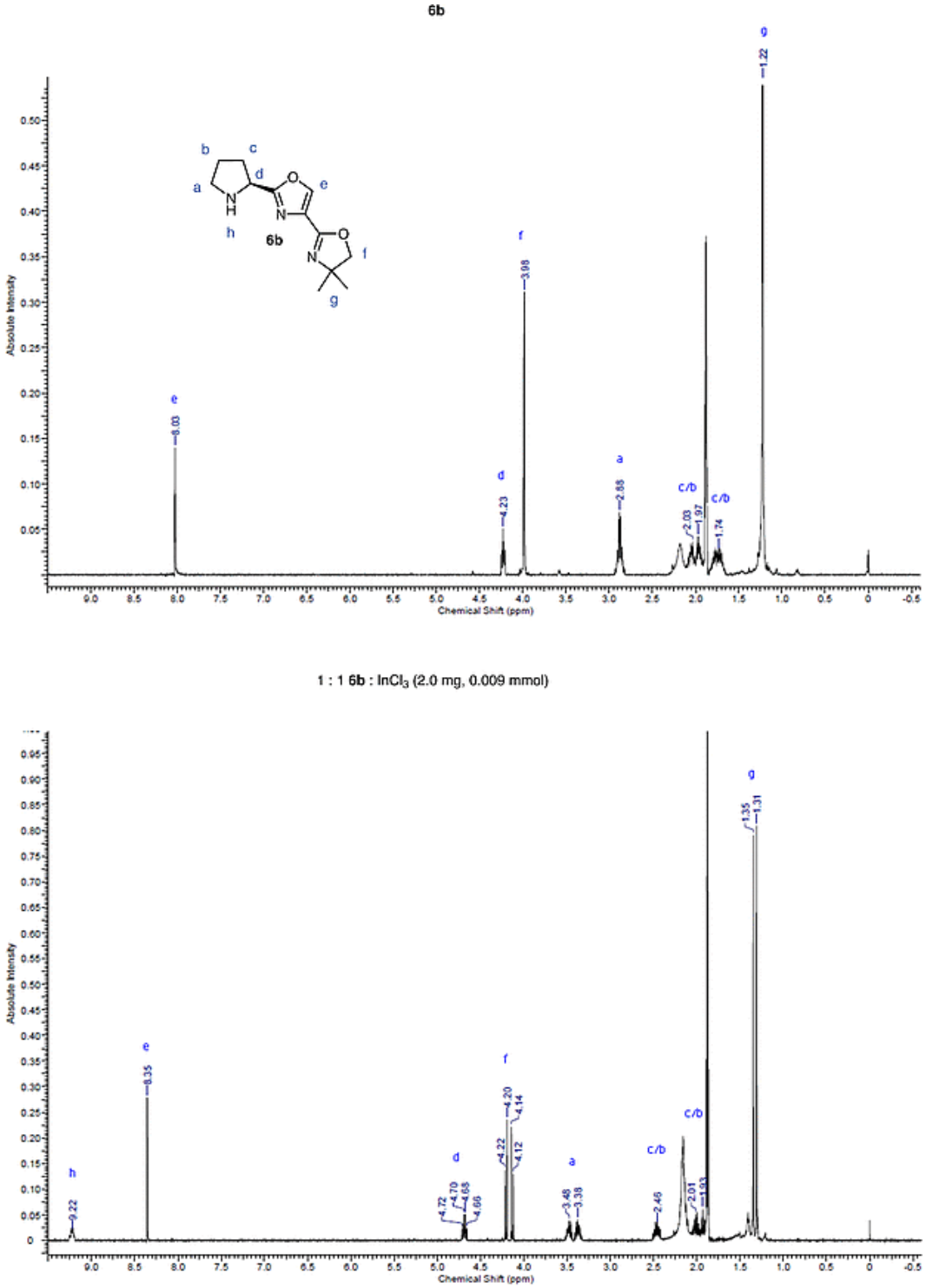

Figure 1 ^{1}H NMR spectra in CD_3CN of 6b (top) and 6b + $InCl_3$ (1 equiv) (bottom)

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We selected $Zn(OTf)_2$ over $InCl_3$ for further study because of the possibility for $InCl_3$ to promote a background reaction via a non-hybrid catalyst pathway; we had observed that pyrrolidine and $InCl_3$ (10 mol% each) promoted the addition of propionaldehyde (16a) to 4-nitrobenzaldehyde (17a) in THF at room temperature in 48% yield, though no reaction was observed with benzaldehyde under these circumstances. The combination of 6b and $Zn(OTf)_2$ was tested with several alternative donor and acceptor combinations (Table 3). A sluggish reaction of propionaldehyde (16a) with 4-chlorobenzaldehyde (17b) (entry 2) was observed, and no reaction was observed between benzaldehyde (17c) and several different donors. A low-yielding reaction was observed between cyclohexanone (16c) and 4-nitrobenzaldehyde (17a) (entry 7).

In order to potentially shed some light on the nature of our active catalysts and the factors that may govern their reactivities, we performed some simple NMR studies examining the interactions between precatalyst 6b and several metal salts giving catalysts with good activity, including $Zn(OTf)_2$ and $InCl_3$. With zinc salts, highly broad peaks were observed, suggesting that a variety of coordination states are present that interchange on the NMR timescale. Spectra with $InCl_3$ were more directly informative. The combination of 6b and 1 equivalent of $InCl_3$ led to downfield shifts in all of the signals in the spectrum of 6b (Figure 1), suggesting that the metal may coordinate to both the oxazole–oxazoline as well as the pyrrolidine moieties. Interestingly, the diastereotopic oxazoline methylene and methyl protons become separate signals only after metal coordination. The substantial shift of the protons at both the 2- and the 5-positions of the pyrrolidine (labeled a and d in the Figure 1) after addition of $InCl_3$ is additional evidence that coordination to the pyrrolidine nitrogen is occurring, and 6b is certainly capable of bridging two metal centers. We hypothesize that the lack of obvious improvement in catalytic activity of our and other bifunctional catalysts versus simple amine-based organocatalysts may be due to the fact that the amine is at least partially tied up by the metal, even if it may be in a reversible manner. When excess 6b (up to 2.5 equiv) is mixed with $InCl_3$, there is no evidence for the combination of free ligand in solution together with a ligand–metal complex. This suggests a dynamic binding process where the ligand is coming on and off the metal rapidly, giving a spectrum that represents the average of each ligand species. There is

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also no change in these spectra upon cooling to –20 °C, which is evidence that any exchange process is very rapid on the NMR timescale. Our current efforts are directed towards the synthesis of alternative systems that will be less prone to potential intermolecular coordination of catalyst Lewis acid/Lewis base functionality.

In conclusion, we have designed and prepared several heterocyclic scaffolds capable of supporting bifunctional Lewis acid/Lewis base catalysis. Proof of concept was obtained for the bifunctional catalysis of a direct aldehyde cross-aldol reaction using a proline-derived oxazole–oxazoline scaffold 6b with a number of Lewis acids, though the substrate scope is presently limited. Additional investigations with related scaffolds are underway to identify efficient catalysts capable of promoting carbon–carbon bond formations between aldehyde/ketone donors and less activated acceptors, which continues to be a general challenge in this field.

All reagents and solvents were purchased from commercial vendors and used as received. NMR spectra were recorded on Varian 300 MHz or 400 MHz spectrometers as indicated relative to TMS, $CDCl_3$ solvent, or DMSO-d_6 (^{1}H δ = 0, ^{13}C δ = 77.16, or ^{13}C δ = 39.5, respectively). Unless otherwise indicated, NMR data were collected at 25 °C. Flash chromatography was performed using Biotage SNAP cartridges filled with 40–60 μm silica gel, or C18 reverse phase columns (Biotage® SNAP Ultra C18 or Isco Redisep® Gold C18Aq) on Biotage Isolera systems, with photodiode array UV detectors. Analytical TLC was performed on Agela Technologies 0.25-mm glass plates with 0.25-mm silica gel. Visualization was accomplished with UV light (254 nm) and aq $KMnO_4$ stain followed by heating, unless otherwise noted. Tandem liquid chromatography/mass spectrometry (LC-MS) was performed on a Shimadzu LCMS-2020 with autosampler, photodiode array detector, and single-quadrupole MS with ESI and APCI dual ionization, using a Peak Scientific nitrogen generator. Unless otherwise noted, a standard LC-MS method was used to analyze reactions and reaction products: Phenomenex Gemini C18 column (100 × 4.6 mm, 3 μm particle size, 110 A pore size); column temperature 40 °C; 5 μL of sample in MeOH at a nominal concentration of 1 mg/mL was injected, and peaks were eluted with a gradient of 25–95% MeOH/H_2O (both with 0.1% formic acid) over 5 min, then 95% MeOH/H_2O for 2 min. Purity was measured by UV

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absorbance at 210 or 254 nm. HRMS were obtained at the University of Wisconsin-Milwaukee Mass Spectrometry Laboratory with a Shimadzu LCMS-IT-TOF with ESI and APCI ionization. Gas chromatography/mass spectrometry (GC-MS) was performed with Agilent Technologies 6850 GC with 5973 MS detector, and Agilent HP-5S or Phenomenex Zebron ZB-5MSi Guardian columns (30 m, 0.25 mm ID, 0.25 μm film thickness). IR spectra were obtained as a thin film on NaCl or KBr plates using a Thermo Scientific Nicolet iS5 spectrophotometer. Optical rotations were measured with a Perkin Elmer 341 polarimeter at 589 nm, with a 10-mL cell with 10-cm path length. Specific rotations are reported as follows: $[\alpha]_D^{T\,^\circ C}$ (c = g/100 mL, solvent).

Spectral data for Boc-protected proline derivatives may be complicated by rotamers.

tert-Butyl (2S)-2-{[(2S)-3-Hydroxy-1-methoxy-1-oxopropan-2-yl]carbamoyl}pyrrolidine-1-carboxylate (1)

[CAS Reg. No. 7535-76-4]

N-Boc-l-proline (4.00 g, 18.6 mmol), l-serine methyl ester (3.18 g, 20.4 mmol), and HOBt (4.27 g, 27.9 mmol) were added to a 500-mL round-bottom flask with a stir bar and dissolved in CH_2Cl_2 (150 mL). DIPEA (7.95 mL, 46.5 mmol) was then added by syringe, followed by EDC·HCl (5.34 g, 27.9 mmol). The mixture was stirred at r.t. for 48 h, then it was transferred to a separatory funnel and washed with water (~125 mL), 1 M HCl (~125 mL), and then sat. $NaHCO_3$ (~125 mL). The organic portion was dried (Na_2SO_4), filtered, and concentrated to a white foam. The crude compound was dissolved in CH_2Cl_2 (~10 mL) and purified by flash chromatography (100 g silica gel cartridge; 0–10% MeOH/CH_2Cl_2 gradient) to yield the product (5.08 g, 86%) as a white foam. This compound has been previously reported and characterized.[32]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 1.68 (s, 1 H), 1.89 (br), 2.06 (br), 2.18 (br), 3.47 (br), 3.80 (s, 3 H), 3.89 (br), 4.03 (br), 4.18 (br), 4.62 (br m, 1 H), 7.06 (br).

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Methyl 2-[(2S)-1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]oxazole-4-carboxylate (2)

[CAS Reg. No. 955401-52-2]

Dipeptide 1 (3.42 g, 10.8 mmol) was added to a 250-mL flask with stir bar and sealed under N_2, then THF (120 mL) was added, and the solution was cooled to –20 °C. Deoxo-Fluor (2.12 mL, 11.9 mmol) was added via syringe, and the mixture was stirred for 45 min at –20 °C. The reaction was then quenched with sat. aq $NaHCO_3$ (~30 mL). The organic portion was dried (Na_2SO_4), filtered, and concentrated and dried under high vacuum. The crude material was redissolved in THF (120 mL) and cooled to 0 °C in an ice bath. $BrCCl_3$ (3.94 mL, 40.0 mmol) was added via syringe, followed by DBU (5.16 mL, 40.0 mmol), which was added dropwise over ~5 min. The mixture was removed from the ice bath and allowed to warm to r.t. while stirring for 17 h. Water (100 mL) was added to the solution, then the mixture was extracted with EtOAc (3 ×) in a separatory funnel. The combined organics were dried (Na_2SO_4), filtered, and concentrated to a dark brown oil. The crude was purified by flash chromatography (100 g silica gel cartridge; 0–100% EtOAc/hexanes gradient) to yield the product (2.51 g, 78%) as a white solid. This compound has been previously reported and characterized.[33]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.29 (Boc peak, rotamer 1), 1.44 (Boc peak, rotamer 2) (9 H), 1.86–2.01 (m, 1 H), 2.03–2.20 (comp, 2 H), 2.24–2.45 (m, 1 H), 3.44–3.68 (comp, 2 H), 3.84–3.98 (comp, 3 H), 4.89–5.07 (comp, 1 H), 8.18 (s, 1 H).

2-[(2S)-1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]oxazole-4-carboxylic Acid (3)

[CAS Reg. No. 1511857-57-0]

Ester 2 (2.48 g, 8.37 mmol) was added to a 50-mL flask with stir bar along with THF (25 mL) and water (8 mL). LiOH (261 mg, 17.6 mmol) was added and the flask was stirred for 24 h, after which time TLC analysis (10% MeOH/CH_2Cl_2) indicated that the reaction was complete. The mixture was diluted with CH_2Cl_2 (~75 mL) and water (~75 mL), then the pH was adjusted to 4 with 2 M aq HCl. The layers

were separated and the aqueous phase was re-extracted with CH_2Cl_2 (2 × 50 mL). The combined organics were then dried (Na_2SO_4), filtered, and concentrated to yield the product (1.23 g, 94%) as an off-white foam. This compound has been previously reported and characterized.[34]

IR (thin film): 3435, 2978, 2537, 1685, 1585, 1406, 1250, 1611, 1113, 982 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 1.27 (rotamer 1), 1.44 (rotamer 2) (9 H), 1.90–2.16 (comp, 3 H), 2.37 (m, 1 H), 3.49 (m, 1 H), 3.59 (m, 1 H), 4.94 (m, 2 H), 8.47 (s, 1 H).

tert-Butyl (2S)-2-{4-[(1-Hydroxy-2-methylpropan-2-yl)carbamoyl]oxazol-2-yl}pyrrolidine-1-carboxylate (4)

Carboxylic acid 3 (2.00 g, 7.09 mmol) was dissolved in CH_2Cl_2 (100 mL). HOBt (1.30 g, 8.50 mmol, 1.5 equiv), DIPEA (5.46 mL, 31.9 mmol), and 2-amino-2-methylpropanol hydrochloride (2.67 g, 21.3 mmol) were added, followed by EDC·HCl (1.63 g, 8.27 mmol). The mixture was stirred for 48 h, then it was washed with water (75 mL), 0.1 M HCl (75 mL), and sat. $NaHCO_3$ (75 mL). The organic phase was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was redissolved in CH_2Cl_2 and purified by flash chromatography (50 g silica gel cartridge; 0–100% EtOAc/hexanes gradient) to yield the product (2.10 g, 84%) as an off-white foam, which was used in the subsequent step.

$[\alpha]_D^{25}$ –58 (0.203, CH_2Cl_2).

IR (thin film): 3391.9, 2976.8, 2246.1, 1683.8, 1598.1, 1517.6, 1394.3, 1160.8, 1119.8, 918.7 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 0.79 (s, 1 H), 0.89 (s, 5 H), 0.99 (br, 6 H), 1.05 (br, 3 H), 1.56 (br, 1 H), 1.67 (br, 2 H), 1.90 (br, 1 H), 3.11 (br, 2 H), 3.27 (br, 2 H), 4.52 (br, 2 H), 6.62 (s, 1 H), 7.70 (br, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.5, 24.5, 26.9, 28.1, 31.2, 32.3, 46.3, 46.7, 49.4, 54.6, 56.2, 70.1, 72.7, 80.0, 136.2, 140.5, 140.9, 153.7, 154.3, 161.0, 164.7, 165.2.

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tert-Butyl (2S)-2-[4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)oxazol-2-yl]pyrrolidine-1-carboxylate (5)

Amido alcohol 4 (2.00 g, 5.66 mmol) was added to a 250-mL flask with stir bar and sealed under N_2. THF (75 mL) was added and the flask was cooled to –20 °C. Deoxo-Fluor (3.10 mL, 6.23 mmol) was added by syringe, and the mixture for stirred for 45 min at –20 °C. The reaction was quenched by the addition of sat. $NaHCO_3$ (30 mL) and water (75 mL), then extracted with EtOAc (3 × 35 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated to give the product (1.71 g, 90%) as an off-white solid; mp 94–97 °C.

$[\alpha]_D^{25}$ –82 (0.168, CH_2Cl_2).

IR (thin film): 2974, 2890, 1700, 1582, 1478, 1393, 1366, 1249, 1160, 1097, 986 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 6 H), 1.38 (rotamer 1), 1.44 (rotamer 2) (9 H), 1.94 (m, 1 H), 2.00–2.37 (comp, 3 H), 3.39–3.68 (comp, 2 H), 4.10 (rotamer s, 2 H), 4.84–5.11 (m, 1 H), 8.01 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.6, 24.3, 28.3, 31.3, 32.6, 46.4, 46.7, 49.2, 54.3, 54.8, 58.8, 67.7, 71.6, 79.1, 79.9, 139.7, 140.3.

4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2-[(2S)-pyrrolidin-2-yl]oxazole Hydrochloride (6a)

N-Boc pyrrolidine 5 (1.65 g, 4.92 mmol) was added to a 5-mL flask with stir bar and dissolved in CH_2Cl_2 (5 mL). 4 M HCl in dioxane (8 mL) was added and the mixture was stirred overnight. The resulting suspension was filtered by gravity and rinsed with hexane, then dried under vacuum to give the product (1.33 g, 99%) as a sticky white foam.

$[\alpha]_D^{25}$ –76 (0.136, CH_2Cl_2).

IR (thin film): 2971, 2497, 1673, 1599, 1464, 1151, 1113, 1030, 988, 933 cm^{-1}.

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^{1}H NMR (300 MHz, CD_3OD): δ = 1.66 (s, 6 H), 2.15–2.38 (m, 2 H), 2.50 (m, 1 H), 2.62 (m, 1 H), 3.47–3.63 (comp, 2 H), 4.96 (s, 2 H), 5.13 (app t, J = 7.8 Hz, 1 H), 9.20 (s, 1 H).

^{13}C NMR (101 MHz, CD_3OD): δ = 23.2, 25.1, 28.5, 45.9, 54.8, 63.5, 84.3, 125.7, 149.7, 161.2, 164.2.

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{12}H_{17}N_3O_2$: 236.1394; found: 236.1388.

tert-Butyl (2S)-2-{[(2S)-3-Hydroxy-1-methoxy-1-oxobutan-2-yl]carbamoyl}pyrrolidine-1-carboxylate (9)

[CAS Reg. No. 955401-36-2]

N-Boc-l-proline (3.75 g, 17.4 mmol), l-threonine methyl ester HCl (2.96 g, 17.4 mmol), and HOBt (2.94 g, 19.2 mmol) were added to a 250-mL round-bottom flask equipped with a magnetic stir bar. CH_2Cl_2 (100 mL) was then added followed by DIPEA (6.76 g, 52.3 mmol). The mixture was stirred for 5 min then EDC·HCl (3.67 g, 19.2 mmol) was added. The flask was sealed with a septum and stirred at r.t. for 24 h, after which time the starting material had been consumed (LC-MS). The mixture was diluted with CH_2Cl_2 (200 mL), and the organic layer was separated and washed with 0.1 M HCl, deionized water, sat. $NaHCO_3$, and finally brine. The combined organics were dried (Na_2SO_4) and concentrated under vacuum to afford a pale yellow oil. The crude oil was taken up in minimal CH_2Cl_2 and purified by flash chromatography (100 g silica gel column, 0–11% MeOH/CH_2Cl_2 gradient) to yield 9 (4.1 g, 58%) as a clear colorless oil. The ^{1}H NMR data obtained were in agreement with that reported in the literature.[35]

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (d, J = 1.0 Hz, 3 H), 1.47 (s, 9 H), 1.84–1.98 (m, 2 H), 2.10–2.49 (m, 2 H), 2.76 (br, 1 H), 3.30–3.58 (m, 2 H), 3.77 (s, 3 H), 4.27–4.33 (m, 1 H), 4.58 (dd, J = 9.0, 2.86 Hz, 1 H).

Methyl [(2S)-1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-5-methylthiazole-4-carboxylate (11)

[CAS Reg. No. 347191-33-7]

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Alcohol 9 (3.60 g, 10.9 mmol) was added to a 250-mL round-bottom flask containing CH_2Cl_2 (150 mL) and DMP (5.08 g, 12.0 mmol). The mixture was stirred at r.t. for 1 h before water was added (0.816 g, 45.3 mmol), then stirred for a further 1 h before the consumption of the starting material was observed (LC-MS). The crude was filtered through basic alumina to remove precipitated salts and concentrated to afford 10 (2.20 g, 61%) as a colorless oil. The product was taken directly on to the next step without further purification.

Keto ester 10 (2.50 g, 7.61 mmol) was taken up in dry THF (40 mL). Lawesson's reagent (6.16 g, 15.2 mmol) was added and the flask was fitted with a condenser and sealed with a rubber septum. The apparatus was purged with N_2 and placed under positive N_2 pressure then refluxed for 24 h, after which time TLC indicated the consumption of starting material. The mixture was cooled to r.t. and diluted with CH_2Cl_2 (100 mL), then the organic layer was washed with sat. $NaHCO_3$, water, and brine, dried (Na_2SO_4), and concentrated. The crude was purified via flash chromatography (50 g silica gel, 0–78% EtOAc/hexanes gradient) to yield 11 (1.34 g, 54%) as an orange oil. The ^{1}H NMR data obtained were in agreement with that reported in the literature.[36]

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.31 (s, 6 H), 1.47 (s, 3 H), 1.92 (br, 2 H), 2.13–2.42 (m, 2 H), 2.75 (s, 3 H), 3.29–3.68 (m, 2 H), 3.93 (s, 3 H), 5.08–5.21 (m, 1 H).

2-[(2S)-1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl]-5-methylthiazole-4-carboxylic Acid (12)

Thiazole 11 (1.34 g, 4.00 mmol) was added to a 500-mL round-bottom flask followed by MeOH (150 mL) and H_2O (40 mL), along with NaOH pellets (0.82 g, 20.5 mmol). The mixture was stirred at reflux for 48 h, after which time the starting material had been consumed (LC-MS). The mixture was brought to neutral pH using 2 M HCl, and the solvent was removed to afford an oily orange solid. Deionized water was added, and the solution was extracted with CH_2Cl_2 (3 ×). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated to afford an orange foam. The crude material was taken up into CH_2Cl_2 and purified via flash chromatography (50 g silica

gel column, 0–100% EtOAc/hexanes gradient) to yield 12 (0.97 g, 75%) as a tan oil; R_f = 0.31 (EtOAc/hexanes, 50:50).

$[\alpha]_D^{25}$ –97 (0.156, CH_2Cl_2).

IR (thin film): 3411, 2976, 1700, 1394, 1166, 729 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): δ = 1.31 (rotamer 1), 1.49 (rotamer 2) (9 H), 1.96 (br, 2 H), 2.29 (br, 2 H), 2.78 (br, 3 H), 3.57 (br, 2 H), 5.09 (br, 1 H).

^{13}C NMR is complicated due to rotamers.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 13.2, 14.2, 21.0, 23.2, 24.0, 28.3, 28.4, 32.6, 34.0, 46.6, 47.0, 58.7, 59.3, 80.6, 128.5, 131.7, 141.7, 145.5, 154.2, 163.9, 164.4, 170.6, 171.3, 171.6.

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{14}H_{21}N_2O_4S$: 313.1217; found: 313.1210.

tert-Butyl (2S)-2-{4-[(2-Hydroxy-2-methylpropan-2-yl)carbamoyl]-5-methylthiazol-2-yl}pyrrolidine-1-carboxylate (13)

Carboxylic acid 12 (1.01 g, 3.22 mmol) was added to a 100-mL round-bottom flask with CH_2Cl_2 (20 mL), followed by DIPEA (0.833 g, 6.45 mmol). Isobutyl chloroformate (0.484 g, 3.55 mmol) was added dropwise then the mixture was stirred at r.t. After 2 h, consumption of the carboxylic acid and the formation of the mixed anhydride were observed (LC-MS). During the mixed anhydride formation, 2-amino-2-methylpropanol (0.486 g. 3.87 mmol) and DIPEA (0.417 g, 3.22 mmol) were stirred at r.t. in CH_2Cl_2 (20 mL) in a separate flask. After the formation of the mixed anhydride was complete, the 2-amino-2-methylpropanol/DIPEA mixture was added and the mixture was stirred overnight, after which time LC-MS indicated complete consumption of the mixed anhydride. The mixture was washed with 0.1 M HCl, sat. $NaHCO_3$, and brine. Acid and base washes were each back extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a yellow oil, then dissolved in CH_2Cl_2 and purified via flash chromatography (25 g silica gel column,

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0–100% EtOAc/hexanes gradient) to yield 13 (0.73 g, 59%); R_f = 0.50 (EtOAc/hexanes, 50:50).

$[\alpha]_D^{25}$ –52 (0.217, CH_2Cl_2).

IR (thin film): 3350, 2975, 2250, 1690, 1400, 1050, 725 cm^{-1}

^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 6 H), 1.36 (rotamer 1), 1.45 (rotamer 2) (9 H), 1.94 (br, 2 H), 2.14 (br, 1 H), 2.24 (br s, 1 H), 2.65–2.78 (m, 3 H), 3.41 (m, J = 9.2, 8.1 Hz, 1 H), 3.54 (br, 1 H), 3.61–3.73 (m, 2 H), 4.87–5.34 (m, 1 H), 7.51 (s, 1 H).

Carbon NMR is complicated due to rotamers.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 12.8, 14.2, 23.1, 23.9, 24.8, 28.4, 32.7, 33.8, 46.4, 46.9, 56.0, 58.8, 59.0, 70.9, 80.2, 140.6, 142.0, 142.1, 154.1, 154.6, 163.6, 169.4, 169.8, 171.1.

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{18}H_{29}N_3O_4S$: 384.1952; found: 384.1942.

tert-Butyl (2S)-2-[4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-5-methylthiazol-2-yl]pyrrolidine-1-carboxylate (14)

Amino alcohol 13 (0.730 g, 1.90 mmol) was added to a 15-mL round-bottom flask. The flask was sealed under N_2 and dry THF (5 mL) was added and cooled to –20 °C. Deoxo-fluor (0.463 g, 2.09 mmol) was added dropwise over 5 min. The mixture was stirred at –20 °C for 1 h, after which time LC-MS indicated the consumption of the starting material. The mixture was allowed to warm to 5 °C and then quenched with sat. aq $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated to give an orange oil. The crude oil was dissolved in CH_2Cl_2 and purified via flash chromatography (10 g silica gel column, 0–100% EtOAc/hexanes gradient) to yield 14 (0.56 g, 80%) as a pale yellow oil; R_f = 0.80 (EtOAc/hexanes, 50:50).

$[\alpha]_D^{25}$ –63 (0.270, CH_2Cl_2).

IR (thin film): 2975, 1690, 1375, 1150 cm^{-1}

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^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (s, 6 H), 1.26 (rotamer 1), 1.36 (rotamer 2) (9 H), 1.67–1.90 (m, 2 H), 1.99–2.29 (m, 2 H), 2.58 (br, 2 H), 3.24–3.40 (m, 1 H), 3.42 (br, 1 H), 3.98 (br, 2 H), 5.01 (br, 1 H).

^{13}C NMR is complicated due to rotamers.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 12.9, 22.9, 23.7, 28.2, 28.3, 28.4, 32.8, 34.1, 43.3, 46.5, 46.9, 59.0, 59.4, 67.5, 71.3, 78.7, 80.1, 138.4, 139.2, 154.1, 157.9, 172.2.

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{18}H_{27}N_3O_3S$: 366.1846; found: 366.1841.

4-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-5-methyl-2-[(2S)-pyrrolidin-2-yl]thiazole (15b)

Compound 14 (0.278 g, 0.761 mmol) was placed in a 4-mL vial followed by TFA (0.173 g, 1.52 mmol) and was allowed to stir overnight at r.t.. The mixture was diluted with water (2 mL), and the pH was brought to 11 using 7.4 M aq NH_4OH. The aqueous layers were extracted with EtOAc (3 ×), dried (Na_2SO_4), and concentrated to afford an orange oil. The crude oil was taken up into CH_2Cl_2 and purified via flash chromatography (5 g silica gel column). The column was flushed with 5 column volumes of EtOAc, then the desired product was eluted with MeOH and concentrated to yield the product (0.124 g, 61%) as a yellow oil; R_f = 0.40 (5% MeOH/CH_2Cl_2).

$[\alpha]_D^{25}$ –32 (0.165, CH_2Cl_2).

IR (thin film): 3300, 2980, 2210, 1650, 725 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 6 H), 1.65–1.82 (m, 2 H), 1.82–1.93 (m, 1 H), 2.05–2.27 (m, 1 H), 2.61 (s, 3 H), 2.92–3.07 (m, 2 H), 3.11 (br, 1 H), 4.01 (s, 2 H), 4.48 (t, J = 1.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 12.9, 25.4, 28.4, 33.9, 46.8, 59.4, 67.4, 78.8, 139.0, 158.2, 175.0.

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HRMS (ESI$^+$): *m/z* [M + H]$^+$ calcd for $C_{13}H_{19}N_3OS$: 266.1320; found: 266.1322.

Acknowledgment

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Supporting Information

Author contributions, general reaction screening protocol and HPLC data, representative aldol protocol with 6b, synthetic protocols for synthesis of precatalysts 7 and 8, and NMR spectra, are available online at: http://dx.doi.org/10.1055/s-0035-1560436.

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Supporting Information

Design and Synthesis of Oxazoline-based Scaffolds for Hybrid Lewis Acid/Lewis Base Catalysis of Carbon–Carbon Bond Formation

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Contents

1. Author contributions

Dennis Wiedenhoeft: Assisted with catalyst design; designed, investigated, and optimized precatalyst syntheses; characterized products; screened reactions; analyzed data; designed experiments; wrote supporting information; supervised research.

Adam Benoit: Assisted with catalyst design; designed, investigated, and optimized precatalyst syntheses; characterized products; developed HPLC methods; screened reactions; analyzed data; designed experiments; wrote supporting information; edited the manuscript; supervised research.

Yibiao Wu: Resynthesized precatalysts; screened reactions; characterized products.

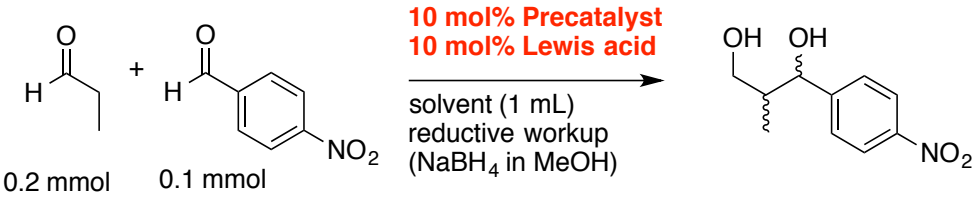
Jacob Porter: Investigated precatalyst synthetic routes; prepared precatalysts; characterized products; screened reactions; performed NMR studies.

Rajdeep Virdi: Investigated precatalyst synthetic routes; prepared precatalysts; characterized products.

Alaa Shanaa: Screened reactions.

Chris Dockendorff: Designed catalysts; designed synthetic routes; analyzed data; designed experiments; wrote and edited the manuscript; edited supporting information; supervised research.

2. General reaction screening protocol and HPLC data



Stock solutions of **precatalyst (**0.02 M), **4-nitrobenzaldehyde** (0.40 M), and **propionaldehyde** (0.80 M) were prepared. All precatalysts were used as free bases (or zwitterions) by neutralizing HCl salts with aqueous ammonium hydroxide and extracting with DCM prior to use.

1) **Metal salts** (0.01 mmol) were weighed into separate 1.5 mL HPLC vials.

2) If solid additives were included, they were added to the vials at this time.

3) **Precatalyst** solutions (500 μL of 0.02 M stock solution, 0.01 mmol) were added to each vial.

4) If additive solutions were included, they were added to the vials next.

5) **4-Nitrobenzaldehyde** solution (250 μL of 0.40 M solution, 0.1 mmol), was added to each vial.

6) **Propionaldehyde** (250 μL of 0.80 M solution, 0.2 mmol) was added to each vial.

After addition of all reagents, the vials were capped (PTFE septa) and placed in a cardboard vial box attached to a vortex shaker. Vials were shaken for 24 hours on the lowest speed to avoid leakage from the vials. 9 mL glass test tubes were labeled to correspond to each of the reaction vials and sodium borohydride (~75 mg, 2 mmol, 20 eq.) was added to each tube and cooled on ice. 4:1 DCM:MeOH (1 mL) was added, then the reaction solutions were pipeted dropwise (over ~30 s) to the test tubes. The tubes were removed the ice bath and warmed to room temperature over thirty minutes, with periodic mixing. Saturated aqueous ammonium chloride solution (1 mL) was then added via pipet dropwise (~ 1 min.) to each tube to quench the reduction reaction, followed by 1 M aqueous HCl (1 mL) added via pipet dropwise (~1 min.) to further neutralize the solutions and to help dissolve solid precipitates. DCM (~1 mL) was added to each tube to resolve the phases. The organic phases were separated to fresh 9 mL tubes, then the remaining solutions were extracted with additional DCM (2 x 2 mL). The combined organic solutions were concentrated via Speedvac (initially at 400 torr with low heating, then 25 torr). A stock solution

of LC-MS grade isopropanol with 5 mg/mL of *o*-dichlorobenzene as an internal standard was made. Each crude sample was dissolved in 1 mL of this stock solution and filtered through a 0.22 micron nylon syringe filter into a 1.5 mL HPLC vial. The samples were analyzed by HPLC using 5 uL injections and 13:87 IPA:hexane isocratic method (1 mL/min.) for 20 min., with a Phenomenex Lux 5 μm Cellulose-2 column (250 x 4.6 mm) and UV detection at λ = 254 nm. Representative retention times: 3.3 min: *o*-dichlorobenzene; 9.3 min: benzyl alcohol; 10.7 min., *syn* enantiomer 1; 12.0 min., *syn* enantiomer 2; 14.5 min., *anti* enantiomer 1; 15.6 min., *anti* enantiomer 2.

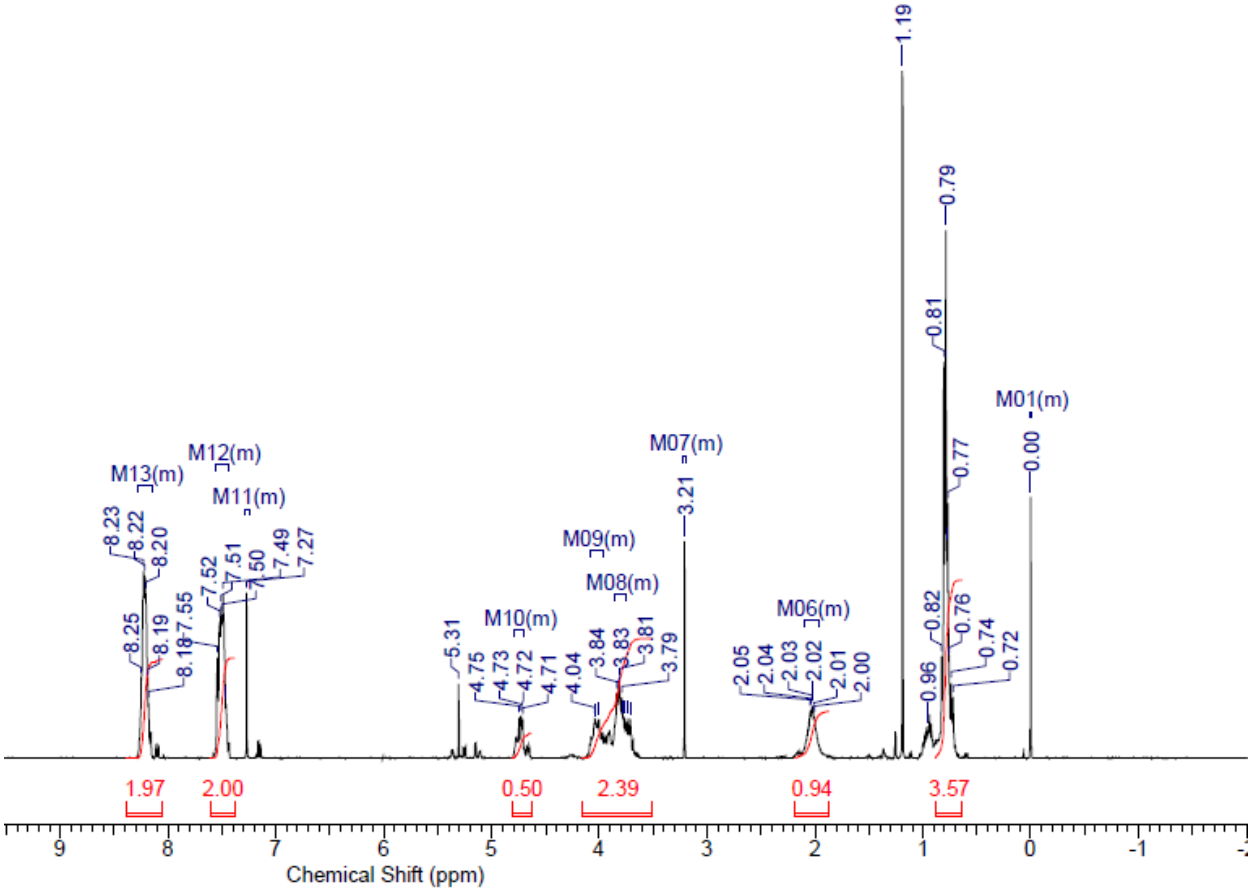
3. Representative aldol protocol with 6b

(Table 2, entries 7 and 11)

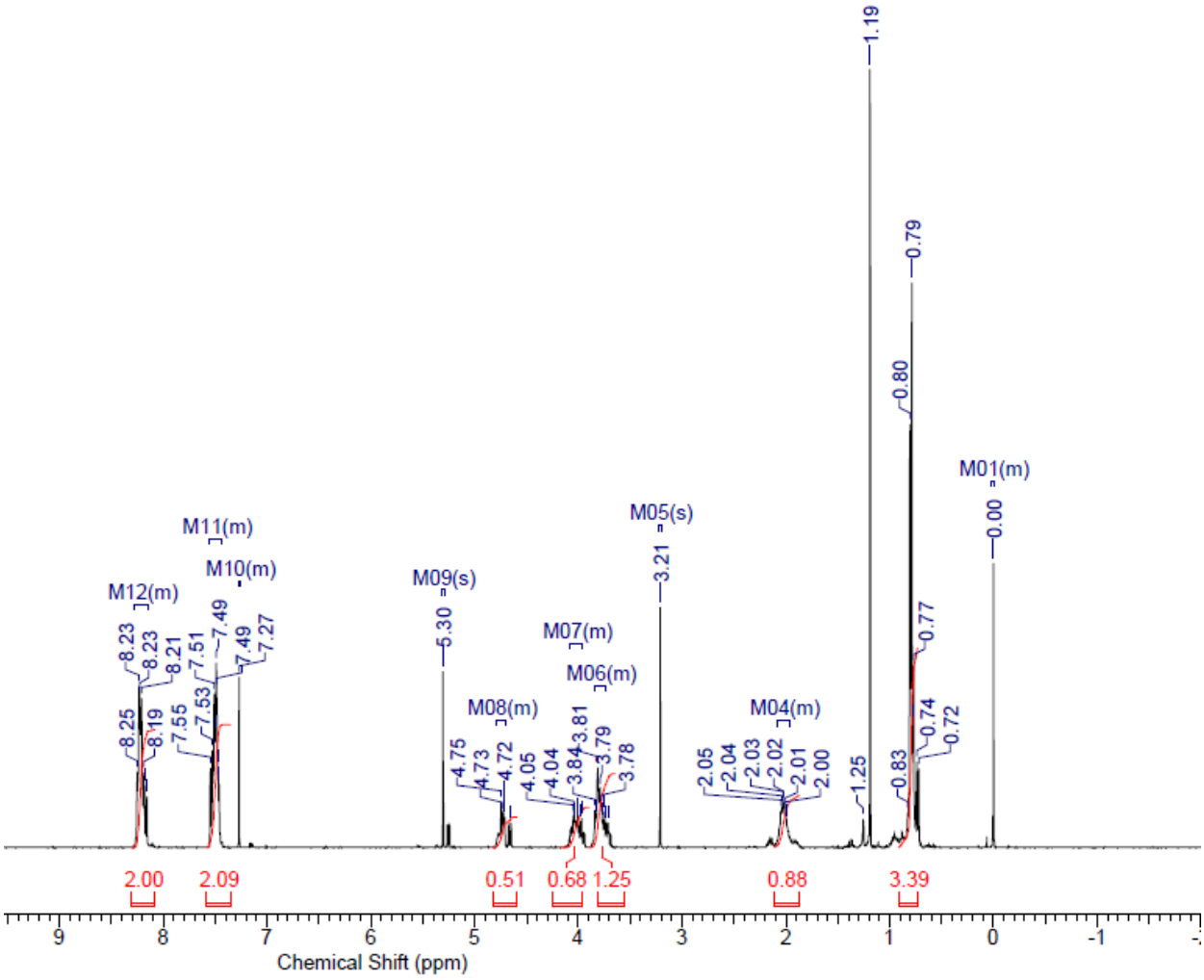
The precatalyst hydrochloride salt **6a** (0.264 g, 0.971 mmol) was added to a 2 dram reaction vial followed by THF (2.5 mL) and conc. ammonium hydroxide (7.44 M, 0.65 mL, 4.84 mmol). The solution was stirred for 10 min. before being diluted with DCM (5.0 mL) and deionized water (3.0 mL). The aqueous layer was separated and re-extracted with DCM (5 mL). The combined organic layers were washed with brine, dried over sodium sulfate, and condensed to afford the neutral precatalyst **6b** as a yellow oil which was used without purification (0.144 g, 64%).

Metal salt (10 mol%) was added to a 2 dram reaction vial followed by **6b** (10 mol%) added as a solution in 9:1 MeCN/H_2O (2.5 mL). After addition of **6b**, an additional 2.5 mL 9:1 MeCN/H_2O was added followed by 4-nitrobenzaldehyde (0.150 g , 1.00 mmol) as a solid. Lastly, propionaldehyde (0.36 mL, 5.0 mmol) was added via syringe, and reactions were stirred at room temperature for 48 hours. The reactions were quenched by pipetting them into a solution of sodium borohydride (0.19 g, 5.0 mmol) in 25% MeOH in DCM (5 mL) in test tubes cooled to 0° C. After 5 min. the reactions were brought to room temperature and allowed to react for an additional 30 min. Lastly, saturated aqueous ammonium chloride (5 mL) was added and the reactions quenched for 20 min. before being diluted with DCM (5 mL). The organic layers were separated and the aqueous layers were re-extracted DCM (5 mL). The combined organic layers were concentrated under reduced pressure to give dark yellow oils. The crude materials were dissolved in minimal DCM and loaded onto a 10 g SiO_2 column and purified via a 0 to 75% MTBE : hexanes gradient to yield the desired products **18aa** (isomeric mixtures) as pale yellow oils: $Zn(OTf)_2$ (0.113 g, 54%); $InCl_3$ (0.108 g, 52%).

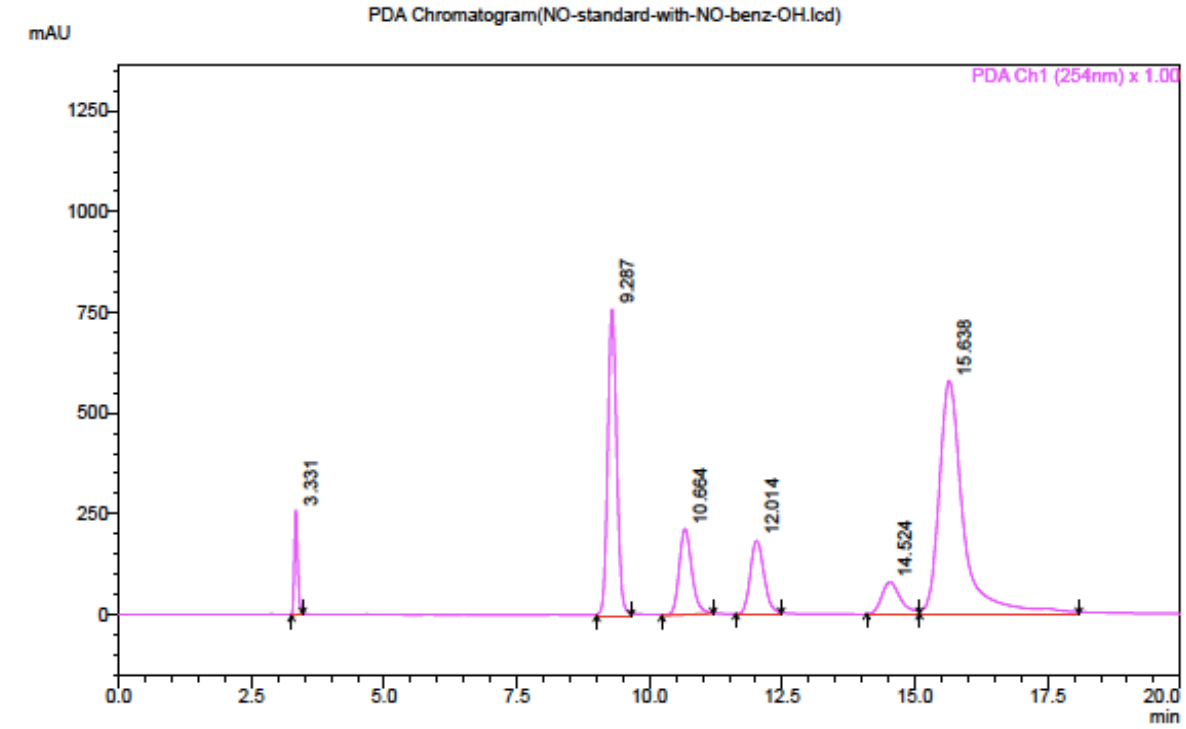
Aldol product 18aa (Table 2, entry 7: $Zn(OTf)_2$)



Aldol product 18aa (Table 2, entry 11: $InCl_3$)



Standard HPLC chromatogram (isomeric mixture of 18aa plus 1,2-dichlorobenzene (vide infra)

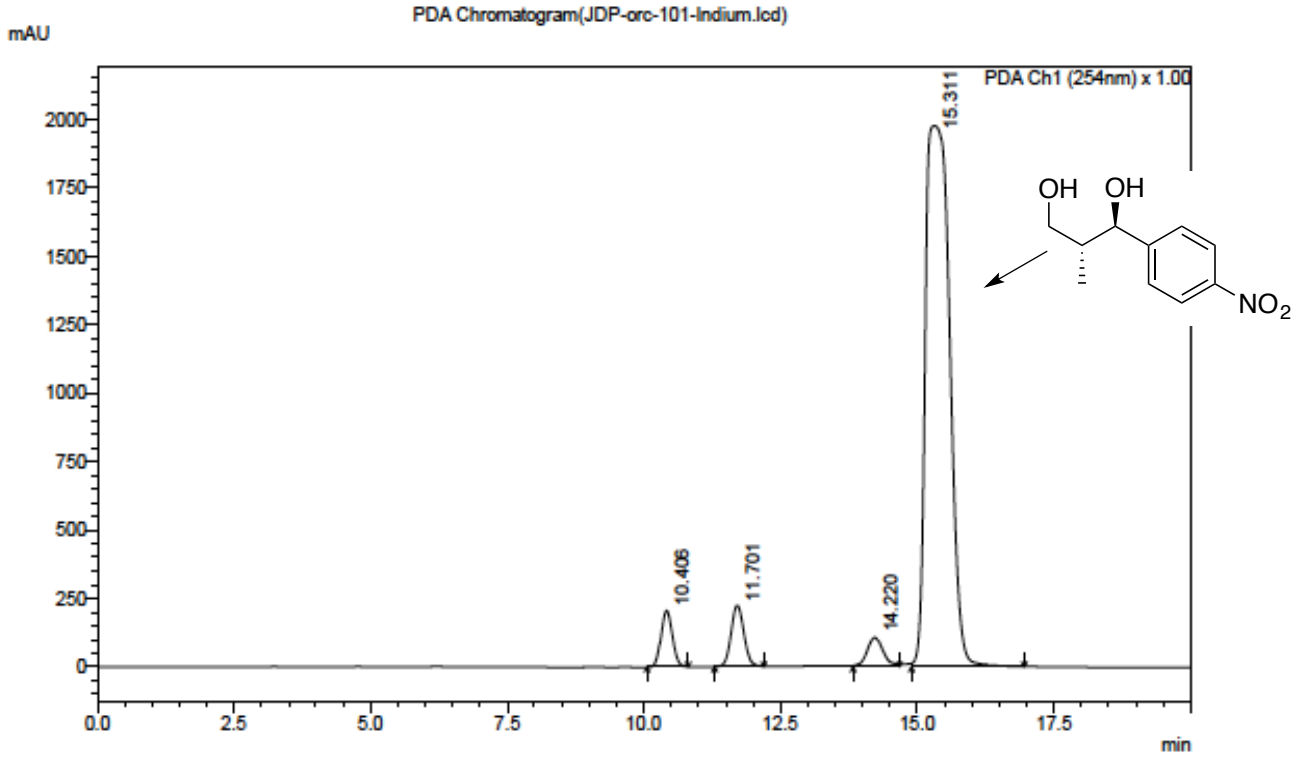


PDA Peak Table(NO-standard-with-NO-benz-OH.lcd)

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%	Peak Start	Peak End	Lambda max	USP Width
1	3.331	1181072	259852	3.187	3.253	3.467	215/270/327	0.137
2	9.287	8966891	760488	24.199	9.003	9.653		0.320
3	10.664	3564545	213525	9.620	10.229	11.200	271/214/486	0.439
4	12.014	3254557	181954	8.783	11.627	12.480		0.475
5	14.524	1880477	78783	5.075	14.091	15.083	268/492	0.621
6	15.638	18207019	578443	49.136	15.083	18.091	194/268/486	0.722
Total		37054561	2073045	100.000				

HPLC chromatogram from aldol reaction with 10 mol% 6b + $InCl_3$ (Table 2, entry 11):

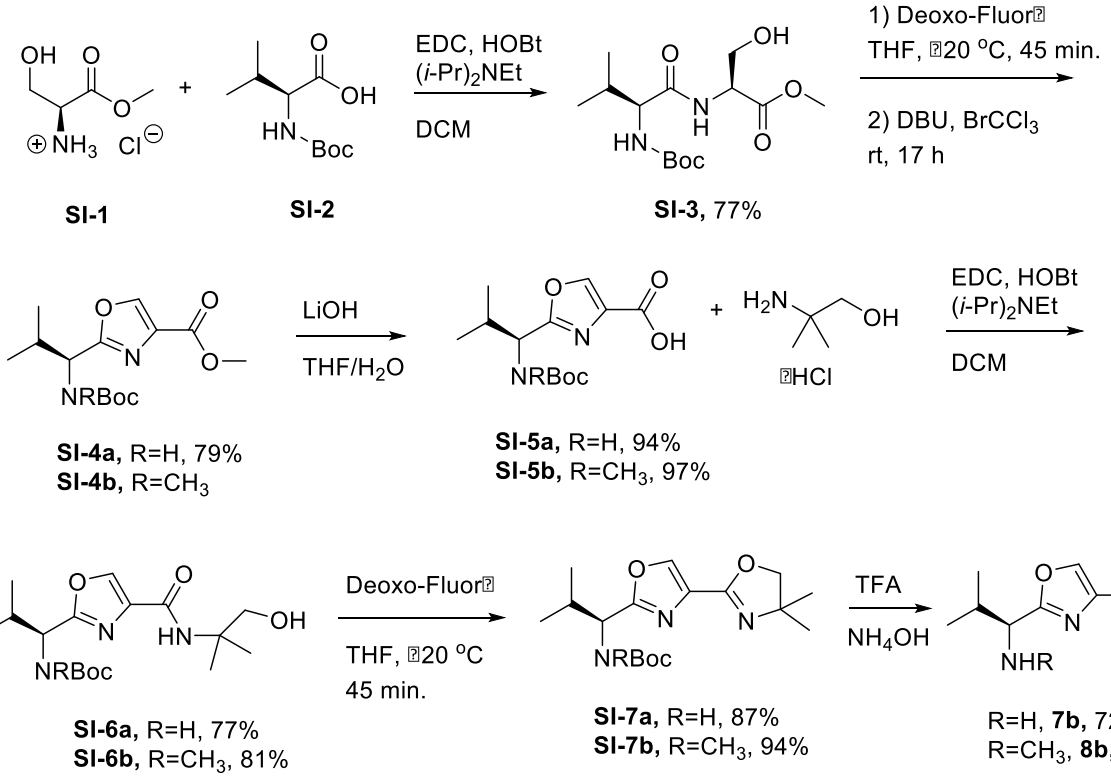


PDA Peak Table(JDP-orc-101-Indium.lcd)

PDA Ch1 254nm

Peak#	Ret. Time	Area	Height	Area%	Peak Start	Peak End
1	10.406	2974905	205526	4.272	10.059	10.816
2	11.701	3768825	223494	5.412	11.296	12.192
3	14.220	2229374	107117	3.201	13.824	14.677
4	15.311	60663966	1976233	87.114	14.891	16.960
Total		69637070	2512370	100.000		

4. Synthetic protocols for synthesis of precatalysts 7 and 8



SI-1 **SI-2** **SI-3,** 77%

SI-4a, R=H, 79%
SI-4b, R=CH_3

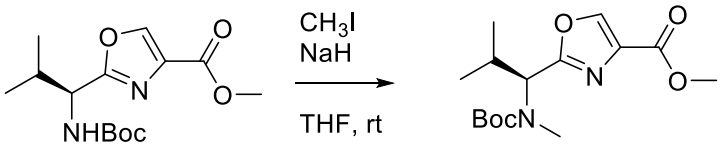
SI-5a, R=H, 94%
SI-5b, R=CH_3, 97%

SI-6a, R=H, 77%
SI-6b, R=CH_3, 81%

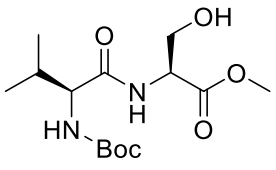
SI-7a, R=H, 87%
SI-7b, R=CH_3, 94%

R=H, **7b,** 72%
R=CH_3, **8b,** 97%

N-Methylation of the carbamate SI-4a



SI-4a **SI4b,** 71%

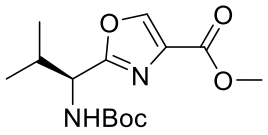


SI-3

Methyl (2S)-2-[(2S)-2-{[(tert-butoxy)carbonyl]amino}-3-methylbutanamido]-3-hydroxypropanoate (SI-3)

N-Boc-L-valine **SI-1** (5.80 g, 26.7 mmol), L-serine methyl ester **SI-2** (4.36 g, 28.0 mmol) and HOBt (5.32 g, 34.7 mmol) were added to a 500 mL round bottom flask with stir bar and dissolved in DCM (250 mL). DIPEA (11.0 mL, 64.1 mmol) was then added by syringe, followed by EDC-HCl (6.65 g, 34.7 mmol). The reaction was stirred at room temperature for 48 h, then the reaction was transferred to a separatory funnel and washed with water (~125 mL), 1M HCl (~125 mL), then saturated sodium bicarbonate (~125 mL). The organic portion was dried with sodium sulfate, filtered, and concentrated to a white solid. The crude compound was dissolved in DCM (~10 mL) and purified by flash chromatography (100 g SiO_2 cartridge; 0 to 10% MeOH/DCM gradient) to yield the title compound as a white solid (6.5 g, 77%). This compound has been previously reported and characterized (CAS# 71017-98-6).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 - 1.03 (m, 6 H), 1.44 (s, 9 H), 1.67 (s, 1 H), 2.01 - 2.20 (m, 1 H), 3.02 (t, *J*=6.1 Hz, 1 H), 3.80 (s, 3 H), 3.82 - 3.91 (m, 1 H), 3.96 (s, 2 H), 4.67 (dt, *J*=7.3, 3.5 Hz, 1 H), 5.10 (d, *J*=8.3 Hz, 1 H), 6.82 (d, *J*=8.0 Hz, 1 H).

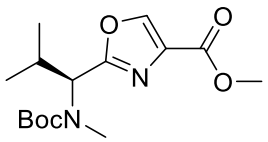


SI-4a

Methyl 2-[(1S)-1-{[(tert-butoxy)carbonyl]amino}-2-methylpropyl]-1,3-oxazole-4-carboxylate (SI-4a)

Dipeptide **SI-3** (6.50 g, 20.5 mmol) was added to a 500 mL flask with stir bar and sealed under nitrogen, then DCM (200 mL) was added, and the solution was cooled to -20 °C. Deoxo-Fluor (4.14 mL, 22.5 mmol) was added via syringe, and the reactions was stirred for 45 min. at -20 °C. The reaction was then quenched with saturated aqueous sodium bicarbonate (~70 mL). The organic portion was dried with sodium sulfate, filtered, and concentrated and dried under hivacuum. The crude material was redissolved in DCM (200 mL) and cooled to 0 ^{o}C in an ice bath. Bromotrichloromethane (7.44 mL, 75.5 mmol) was added via syringe, followed by DBU (9.75 mL, 75.5 mmol), which was added dropwise over ~5 min. The reaction was removed from the ice bath and allowed to warm to room temperature while stirring overnight. Water (200 mL) was added to the solution, then the mixture was extracted with EtOAc (x 3) in a separatory funnel. The combined organics were dried with sodium sulfate, filtered, and concentrated to a dark brown oil. The crude was purified by flash chromatography (100 g SiO_2 cartridge; 0 to 100% EtOAc/hexanes gradient) to yield the title compound as a white solid (6.09 g, 79%). This compound has been previously reported and characterized (CAS# 158068-97-4).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.87 - 0.98 (m, 6 H), 1.44 (s, 9 H), 2.10 - 2.29 (m, 1 H), 3.92 (s, 3 H), 4.74 - 4.88 (m, 1 H), 5.28 (d, J=7.2 Hz, 1 H), 8.19 (s, 1 H).

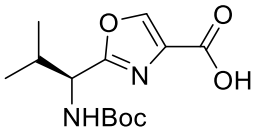


SI-4b

Methyl 2-[(1S)-1-{[(tert-butoxy)carbonyl](methyl)amino}-2-methylpropyl]-1,3-oxazole-4-carboxylate (SI-4b)

Ester **SI-4a** (2.63 g, 8.82 mmol) was placed in an oven dried 250 mL flask and sealed under nitrogen. Iodomethane (0.58 mL, 9.26 mmol) was added, followed by THF (75 mL). NaH (60% dispersion on paraffin oil, (0.529 g, 13.2 mmol) was added and allowed to react under nitrogen at room temperature overnight. The solution was diluted with DCM (100 mL) and washed with water. The aqueous portion was back extracted with two additional portions of DCM. The combined organics were concentrated and redissolved in DCM (~10 mL), then purified by flash chromatography (100 g SiO_2 cartridge; 0 to 100% EtOAc/hexanes gradient) to yield the title compound as a dark yellow oil (1.94 g, 71%). This compound has been previously reported and characterized (CAS# 137008-30-0).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 0.89 - 1.00 (d, 6 H), 1.47 (s, 9 H), 2.50 (dq, J=17.7, 6.6 Hz, 1 H), 2.77 (s, 3 H), 3.92 (s, 3 H), 4.83 - 5.23 (dd, 1 H), 8.21 (s, 1 H).

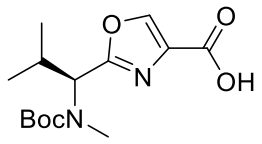


SI-5a

2-[(1S)-1-{[(tert-butoxy)carbonyl]amino}-2-methylpropyl]-1,3-oxazole-4-carboxylic acid (SI-5a)

Ester **SI-4a** (4.50 g, 15.1 mmol) was added to a 250 mL flask with stir bar along with THF (50 mL) and water (15 mL). LiOH (759 mg, 31.7 mmol) was added and the reaction was stirred for 24 h, after which time TLC analysis (10% MeOH/DCM) indicated that the reaction was complete. The reaction was diluted with DCM (~75 mL) and water (~50 mL), then the pH was adjusted to 4 with 2 M aq. HCl. The layers were separated and the aqueous phase was re-extracted with DCM (2 x 50 mL). The combined organics were then dried with sodium sulfate, filtered, and concentrated to yield the title compound as a white solid (4.03 g, 94%). This compound has been previously reported and characterized (CAS# 220717-54-4).

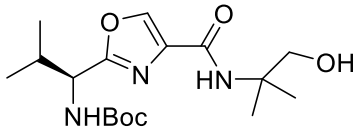
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (dd, J=13.5, 6.7 Hz, 6 H), 1.42 (s, 9 H), 1.86 (dt, J=6.8, 3.2 Hz, 1 H), 2.17 - 2.27 (m, 1 H), 3.76 (s, 1 H), 4.83 (dd, J=9.7, 6.2 Hz, 1 H), 5.92 (br, 1 H), 8.29 (s, 1 H).



SI-5b

2-[(1S)-1-{[(tert-butoxy)carbonyl](methyl)amino}-2-methylpropyl]-1,3-oxazole-4-carboxylic acid (SI-5b)

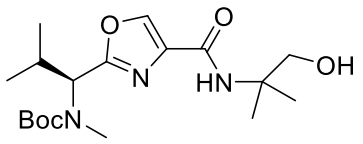
Ester **SI-4b** (1.90 g, 6.13 mmol) was added to a 250 mL flask with stir bar along with THF (60 mL) and water 5.6 mL). LiOH (306 mg, 12.3 mmol) was added and the flask was stirred for 24 h, after which time TLC analysis (10% MeOH/DCM) indicated that the reaction was complete. The reaction was diluted with DCM (~75 mL) and water (~50 mL), then the pH was adjusted to 4 with 2 M aq. HCl. The layers were separated and the aqueous phase was re-extracted with DCM (2 x 50 mL). The combined organics were then dried with sodium sulfate, filtered, and concentrated to yield the title compound as a pale yellow solid (1.76 g, 97%). The compound was advanced without further purification.



SI-6a

Tert-butyl N-[(1S)-1-{4-[(1-hydroxy-2-methylpropan-2-yl)carbamoyl]-1,3-oxazol-2-yl}-2-methylpropyl]carbamate (SI-6a)

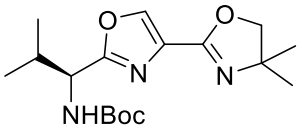
Carboxylic acid **SI-5a** (2.25 g, 7.93 mmol) was dissolved in DCM (100 mL). HOBt (1.28 g, 9.50 mmol), DIPEA (4.82 mL, 27.7 mmol), and 2,2-dimethyl-2-amimoethanol hydrochloride (1.03 g, 7.92 mmol) were added, followed by EDC-HCl (1.82 g, 9.52 mmol). The reaction was stirred for 48 h, then the mixture was washed with water (75 mL), 0.1 M aqueous HCl (75 mL), and saturated aqueous sodium bicarbonate (75 mL). The organic phase was dried with sodium sulfate, filtered, and concentrated. The resulting crude oil was redissolved with DCM and purified by flash chromatography (100 g SiO_2 cartridge; 0 to 100% EtOAc/hexanes gradient) to yield a white solid (2.16 g, 77%), which was used in the subsequent step.



SI-6b

Tert-butyl N-[(1S)-1-{4-[(1-hydroxy-2-methylpropan-2-yl)carbamoyl]-1,3-oxazol-2-yl}-2-methylpropyl]-N-methylcarbamate (SI-6b)

Carboxylic acid **SI-5b** (1.71 g, 5.74 mmol) was dissolved in DCM (100 mL). HOBt (0.93 g, 6.91 mmol), DIPEA (3.50 mL, 20.1 mmol), and 2,2-dimethyl-2-amimoethanol hydrochloride (0.72 g, 5.74 mmol) were added, followed by EDC-HCl (1.32 g, 6.9 mmol). The reaction was stirred for 24 h, then the mixture was washed with water (75 mL), 0.1 M HCl (75 mL), and saturated sodium bicarbonate (75 mL). The organic phase was dried with sodium sulfate, filtered, and concentrated. The resulting crude oil was redissolved with DCM and purified by flash chromatography (100 g SiO_2 cartridge; 0 to 100% EtOAc/hexanes gradient) to yield a yellow oil (1.72 g, 82%), which was used in the subsequent step.



SI-7a

Tert-butyl N-[(1S)-1-[4-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1,3-oxazol-2-yl]-2-methylpropyl]carbamate (SI-7a)

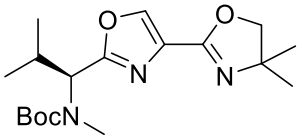
Amido alcohol **SI-6a** (1.90 g, 5.34 mmol) was added to a 250 mL flask with stir bar and sealed under nitrogen. DCM (60 mL) was added and the flask was cooled to -20 °C. Deoxo-Fluor (1.19 mL, 5.92 mmol) was added by syringe, and the reaction for stirred for 45 min. at -20 °C. The reaction was quenched by addition of saturated sodium bicarbonate (75 mL) and water (75 mL), then extracted with EtOAc (3 x 35 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated. The resulting crude oil was redissolved with DCM and purified by flash chromatography (100 g SiO_2 cartridge; 0 to 100% EtOAc/hexanes gradient) to yield a white solid, m.p. 76–78 °C, (1.9 g, 87%).

$[\alpha]_D^{25}$ –54° (0.255, DCM)

IR (thin film): 2970, 2934, 1716, 1684, 1521, 1365, 1247, 1172, 1095, 987, 876 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.85 (dd, J=6.5, 3.7 Hz, 6 H), 1.16 - 1.23 (m, 1 H), 1.33 (s, 6 H), 1.37 (s, 9 H), 2.14 (dq, J=13.1, 6.5 Hz, 1 H), 4.04 (s, 2 H), 4.75 (dd, J=9.1, 5.8 Hz, 1 H), 5.40 (d, J=9.2 Hz, 1 H), 7.99 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 18.1, 18.8, 28.5, 28.5, 33.4, 54.4, 67.9, 79.5, 80.0, 130.8, 140.7, 155.5, 156.0, 165.3.



SI-7b

Tert-butyl N-[(1S)-1-[4-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1,3-oxazol-2-yl]-2-methylpropyl]-N-methylcarbamate (SI-7b)

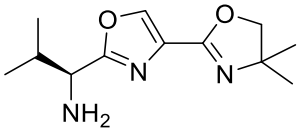
Amido alcohol **SI-6b** (1.45 g, 3.94 mmol) was added to a 250 mL flask with stir bar and sealed under nitrogen. DCM (60 mL) was added and the flask was cooled to -20 °C. Deoxo-Fluor (0.802 mL, 4.38 mmol) was added by syringe, and the reaction for stirred for 45 min. at -20 °C. The reaction was quenched by addition of saturated sodium bicarbonate (75 mL) and water (75 mL), then extracted with EtOAc (3 x 35 mL). The combined organics were dried with sodium sulfate, filtered, and concentrated. The resulting crude oil was redissolved with DCM and purified by flash chromatography (100 g SiO_2 cartridge; 0 to 100% EtOAc/hexanes gradient) to yield a white solid, m.p. 80–82°C, (1.3 g, 94% yield).

$[\alpha]_D^{25}$ –164 (0.236, DCM)

IR (thin film): 2968, 2932, 1692, 1582, 1390, 1366, 1301, 1256, 1150, 1093, 990, 882 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 - 0.94 (m, 6 H), 1.33 (s, 6 H), 1.41 (d, J=5.6 Hz, 9 H), 2.38 - 2.52 (m, 1 H), 2.71 (s, 2 H), 4.04 (s, 2 H), 4.86 (d, rotomer 1, *J*=11.2 Hz, 0.45 H) 5.09 (d, rotomer 2, *J*=11.2 Hz, 0.55 H), 8.03 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8, 20.2, 28.5, 28.6, 29.4, 29.7, 58.3, 68.0, 79.4, 131.0, 140.8.



7b

(1S)-1-[4-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1,3-oxazol-2-yl]-2-methylpropan-1-amine (7b)

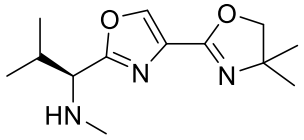
N-Boc pyrrolidine **SI-7a** (0.130 g, 3.93 mmol) was added to a 4 mL vial with stir bar and dissolved with TFA (0.06 mL, 0.77 mmol) was added and the reaction was stirred overnight. 2 mL of water was added to the vial, and adjusted the pH to 11 with aqueous ammonium hydroxide. The aqueous layer was extracted 3 x ~5 mL (5% MeOH in DCM). The organic layer was washed with brine, dried over sodium sulfate and condensed. The resulting crude oil was redissolved with DCM and purified by flash chromatography (5 g SiO_2 cartridge; 0 to 10% MeOH/DCM gradient) to yield a light yellow oil, (0.67 g, 72% yield).

$[\alpha]_D^{25}$ +5 (0.139, DCM)

IR (thin film): 2965, 2932, 1684, 1583, 1464, 1388, 1366, 1190, 1097, 989, 916, 854 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (dd, *J*=6.8, 5.5 Hz, 6 H), 1.38 (s, 6 H), 1.39 - 1.43 (m, 1 H), 2.15 (dq, *J*=13.1, 6.7 Hz, 1 H), 3.85 (d, *J*=6.0 Hz, 1 H), 4.09 (s, 2 H), 8.03 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 17.8, 17.9, 19.0 19.10, 24.7, 28.3, 33.3, 33.4, 55.8, 55.9, 67.7, 70.4, 76.8, 77.1, 77.4, 79.2, 130.5, 140.2, 155.8, 168.4.



8b

[(1S)-1-[4-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1,3-oxazol-2-yl]-2-methylpropyl](methyl)amine (8b)

N-Boc pyrrolidine **SI-7b** (0.130 g, 3.74 mmol) was added to a 4 mL vial with stir bar and dissolved with TFA (0.06 mL, 0.74 mmol), then stirred overnight. Water (2 mL) was added to the vial, and the pH was adjusted to 11 with aqueous ammonium hydroxide. The aqueous layer was extracted with 5% MeOH in DCM (3 x 5 mL), then the organic layer was washed with brine, dried over sodium sulfate, and concentrated. The resulting crude oil was redissolved with DCM and purified by flash chromatography (5 g SiO_2 cartridge; 0 to 10% MeOH/DCM gradient) to yield a light yellow oil (0.90 g, 97% yield).

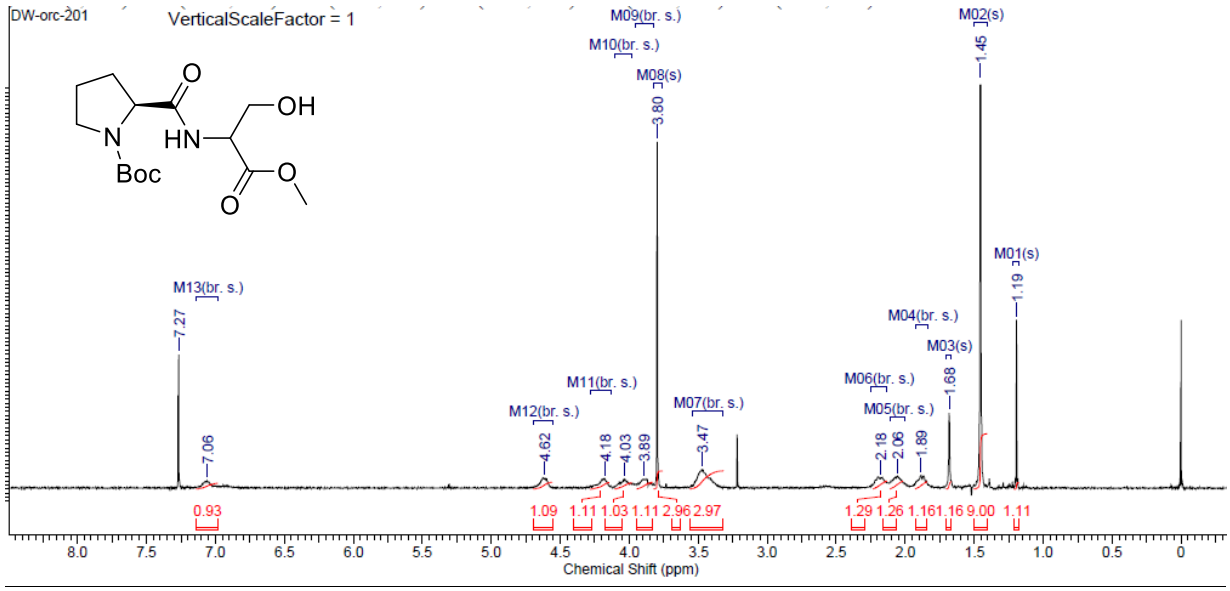
$[\alpha]_D^{25}$ –38 (0.102, DCM)

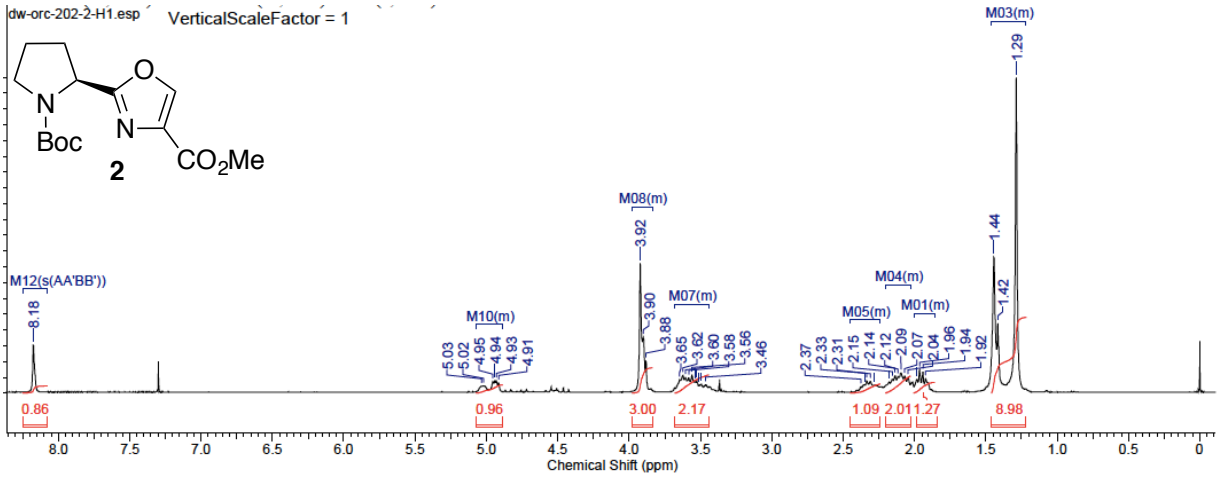
IR (thin film): 2966, 2933, 1684, 1653, 1558, 1457, 1364, 1095, 987, 815 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 - 0.83 (m, 3 H), 0.96 (d, *J*=6.8 Hz, 3 H), 1.31 - 1.37 (m, 6 H), 2.01 (dq, *J*=13.7, 6.8 Hz, 1 H), 2.24 - 2.30 (m, 3 H), 3.45 (d, *J*=7.1 Hz, 1 H), 4.04 (s, 2 H) 8.01 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 19.0, 19.3, 28.2, 32.8, 35.0, 64.7, 67.7, 79.1, 130.4, 140.3, 155.8, 166.9.

5. NMR spectra

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5.02
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4.94
4.93
4.91
M08(m)
3.92
3.90
3.88
M07(m)
3.65
3.62
3.60
3.58
3.56
3.46
M04(m)
M05(m)
M01(m)
2.37
2.33
2.31
2.15
2.14
2.12
2.09
2.07
2.04
1.96
1.94
1.92
M03(m)
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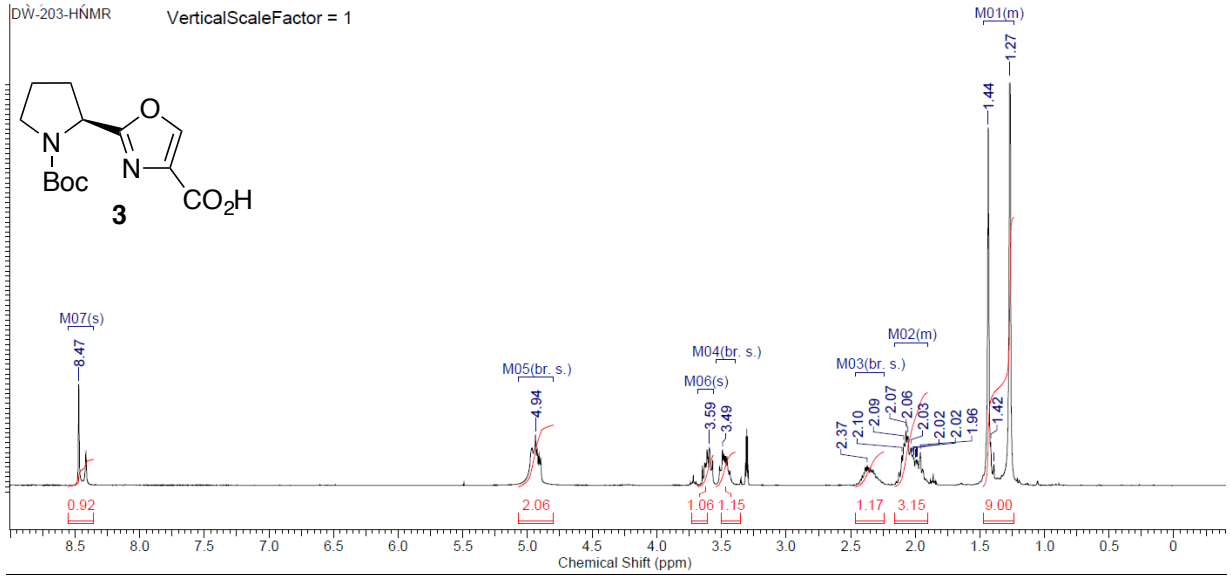
1.09
2.01
1.27
8.98
Chemical Shift (ppm)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CO2H
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M04(br. s.)
M06(s)
3.59
3.49
M02(m)
M03(br. s.)
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2.10
2.09
2.07
2.06
2.03
2.02
2.02
1.96
M01(m)
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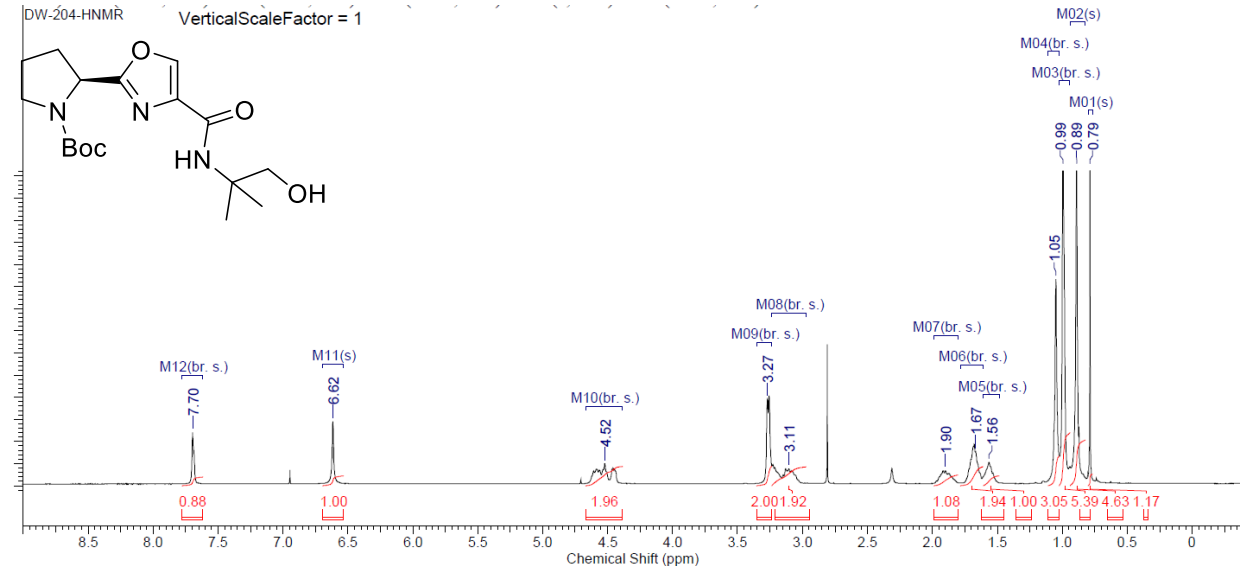
0.92
2.06
1.06
1.15
1.17
3.15
9.00
Chemical Shift (ppm)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N
N
O
Boc
HN
OH
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M03(br. s.)
M01(s)
0.99
0.89
0.79
1.05
M08(br. s.)
M09(br. s.)
M07(br. s.)
M06(br. s.)
M05(br. s.)
M12(br. s.)
M11(s)
M10(br. s.)
3.27
3.11
1.90
1.67
1.56
7.70
6.62
4.52
0.88
1.00
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1.92
1.08
1.94
1.00
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5.39
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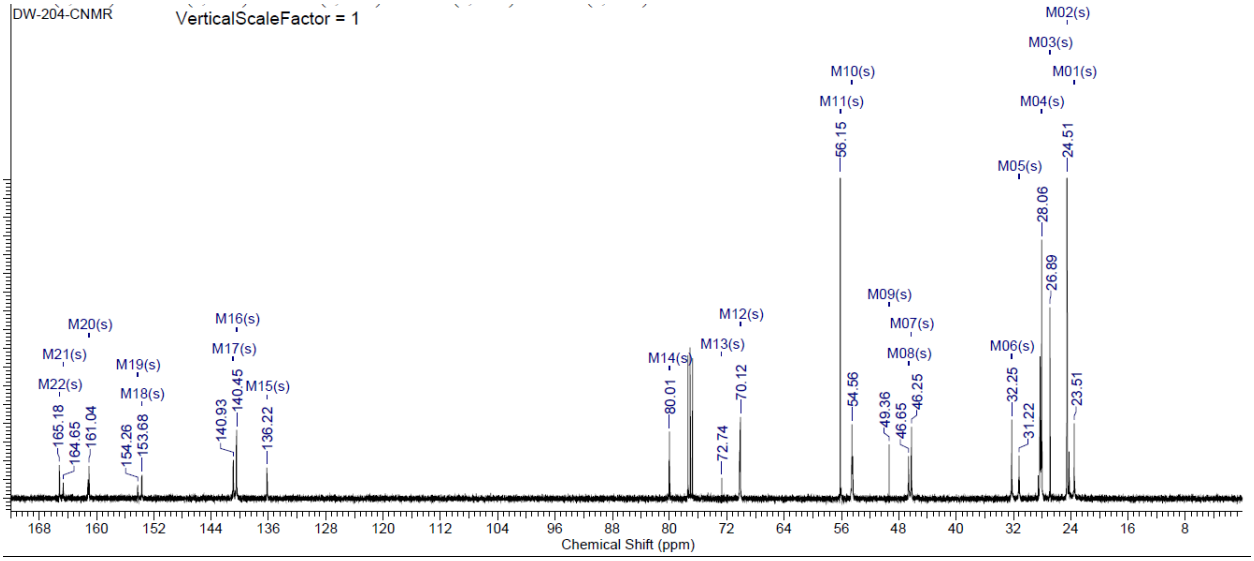
1.17
Chemical Shift (ppm)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M10(s)
M11(s)
M04(s)
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24.51
M05(s)
28.06
26.89
M09(s)
M07(s)
M08(s)
M06(s)
M20(s)
M21(s)
M22(s)
M19(s)
M18(s)
M16(s)
M17(s)
M15(s)
M14(s)
M13(s)
M12(s)
165.18
164.65
161.04
154.26
153.68
140.93
140.45
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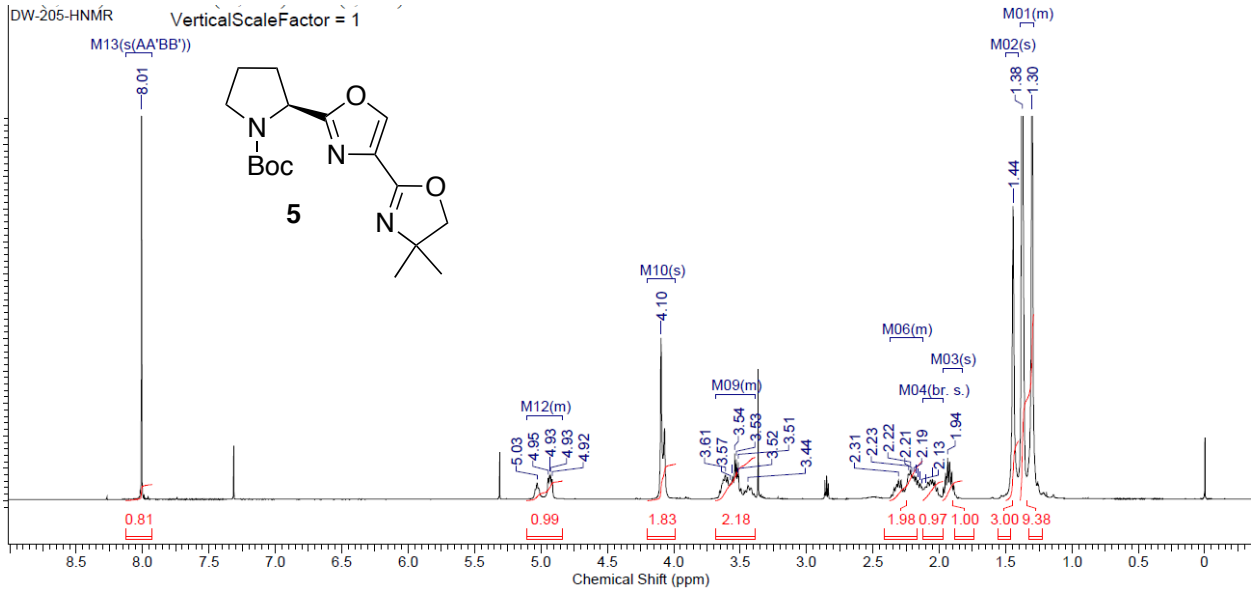
46.65
46.25
32.25
31.22
23.51
Chemical Shift (ppm)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Boc
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N
O
N
5
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M02(s)
1.38
1.30
1.44
M10(s)
4.10
M06(m)
M03(s)
M04(br. s.)
M09(m)
M12(m)
5.03
4.95
4.93
4.92
3.61
3.57
3.54
3.53
3.52
3.51
3.44
2.31
2.23
2.22
2.21
2.19
2.13
1.94
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0.99
1.83
2.18
1.98
0.97
1.00
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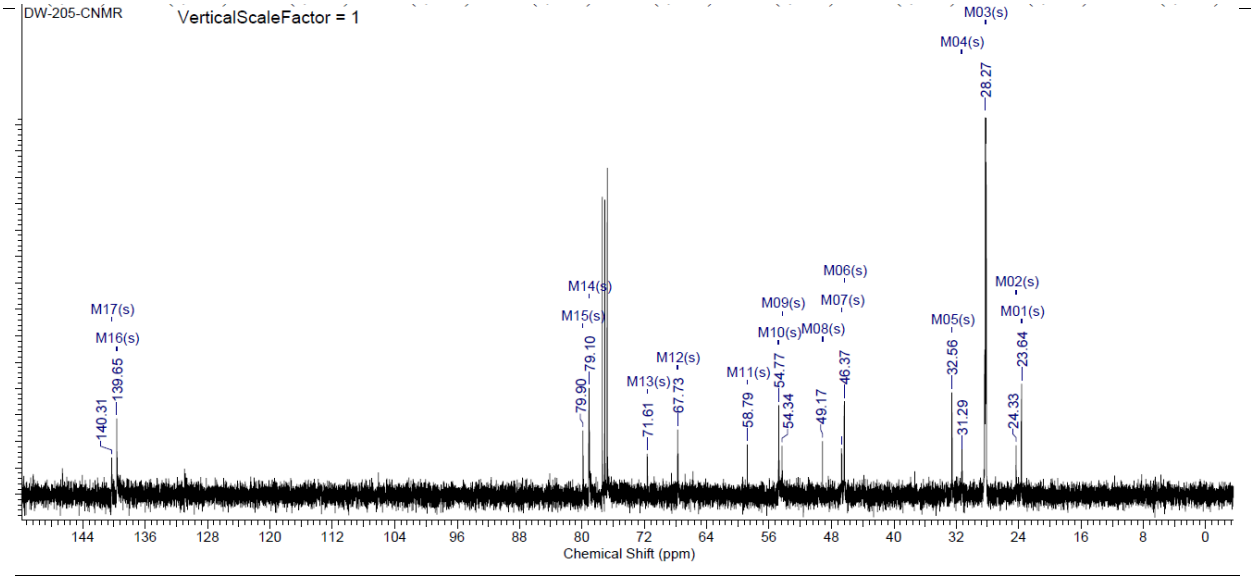
Chemical Shift (ppm)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M04(s)
28.27
M14(s)
M15(s)
M06(s)
M09(s)
M07(s)
M10(s)
M08(s)
M12(s)
M13(s)
M11(s)
M05(s)
M02(s)
M01(s)
M17(s)
M16(s)
140.31
139.65
79.90
79.10
71.61
67.73
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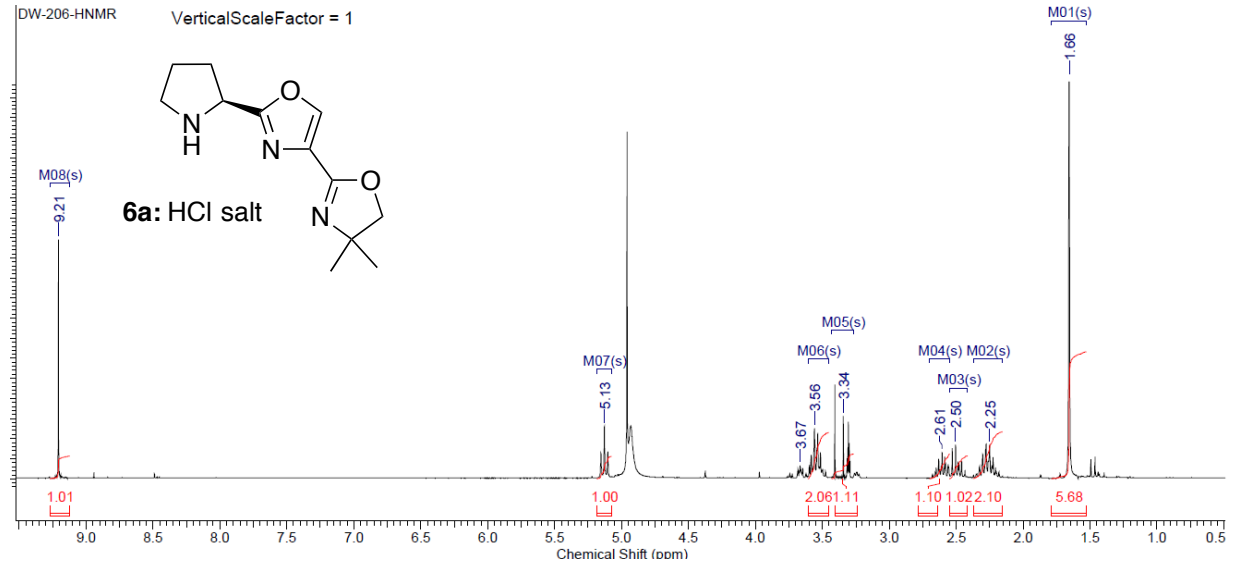
54.77
54.34
49.17
46.37
32.56
31.29
24.33
23.64
Chemical Shift (ppm)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6a: HCl salt
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M01(s)
1.66
M07(s)
5.13
M05(s)
M06(s)
3.56
3.34
3.67
M04(s)
M02(s)
M03(s)
2.61
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1.00
2.06
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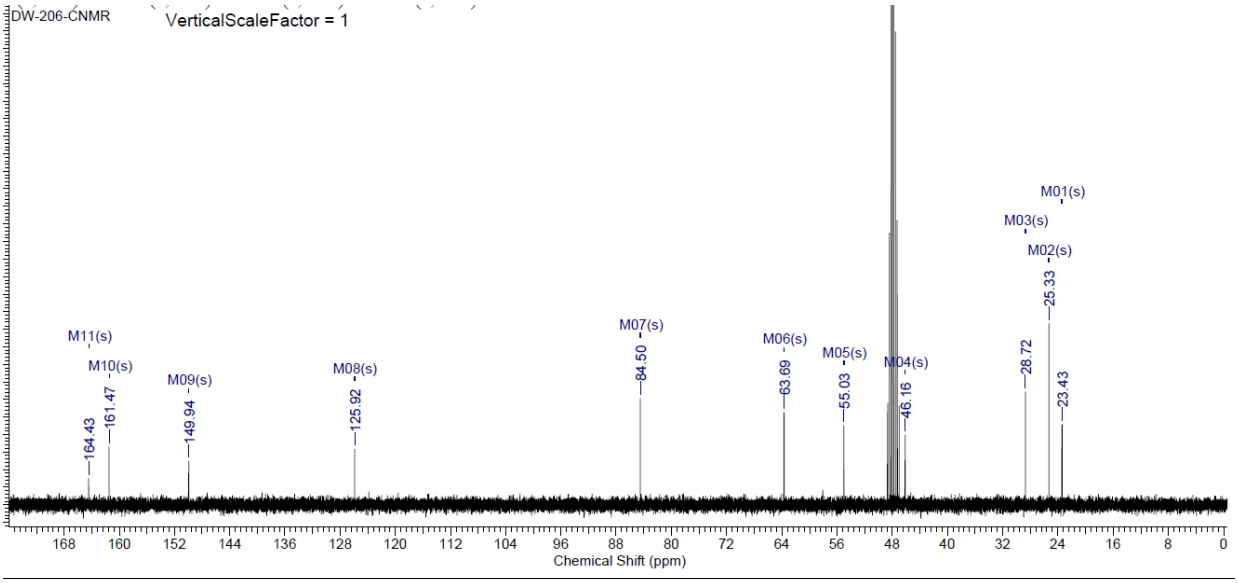
1.02
2.10
5.68
Chemical Shift (ppm)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M10(s)
M09(s)
M08(s)
M07(s)
M06(s)
M05(s)
M04(s)
M01(s)
M03(s)
M02(s)
164.43
161.47
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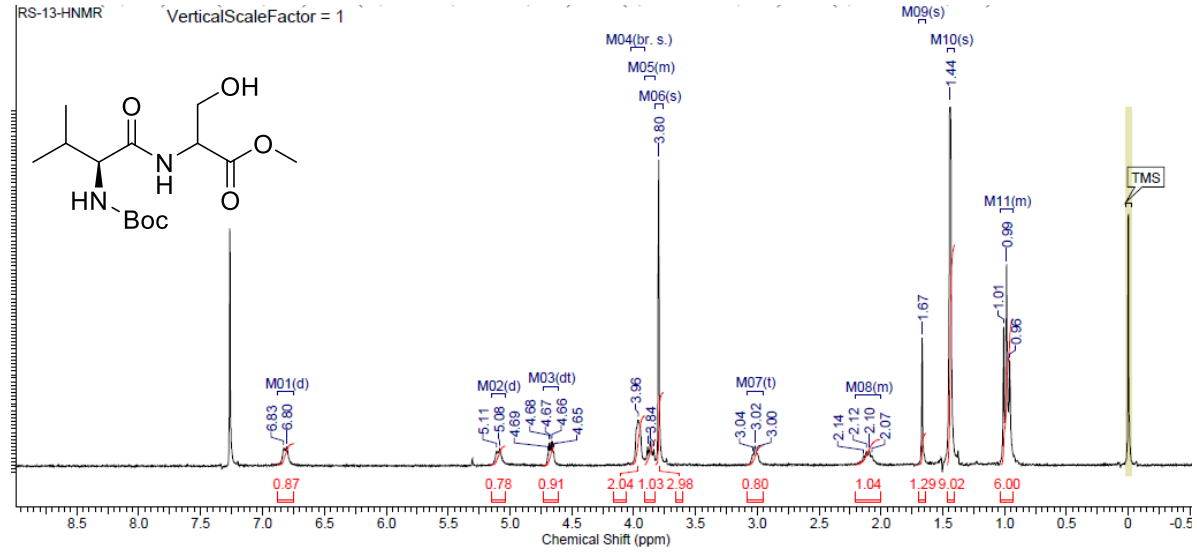
125.92
84.50
63.69
55.03
46.16
28.72
25.33
23.43
Chemical Shift (ppm)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O
N
H
O
O
HN
Boc
M09(s)
M04(br. s.)
M10(s)
M05(m)
M06(s)
1.44
3.80
TMS
M11(m)
M01(d)
M02(d)
M03(dt)
M07(t)
M08(m)
1.67
1.01
0.99
0.96
6.83
6.80
5.11
5.08
4.69
4.68
4.67
4.66
4.65
3.96
3.84
3.04
3.02
3.00
2.14
2.12
2.10
2.07
0.87
0.78
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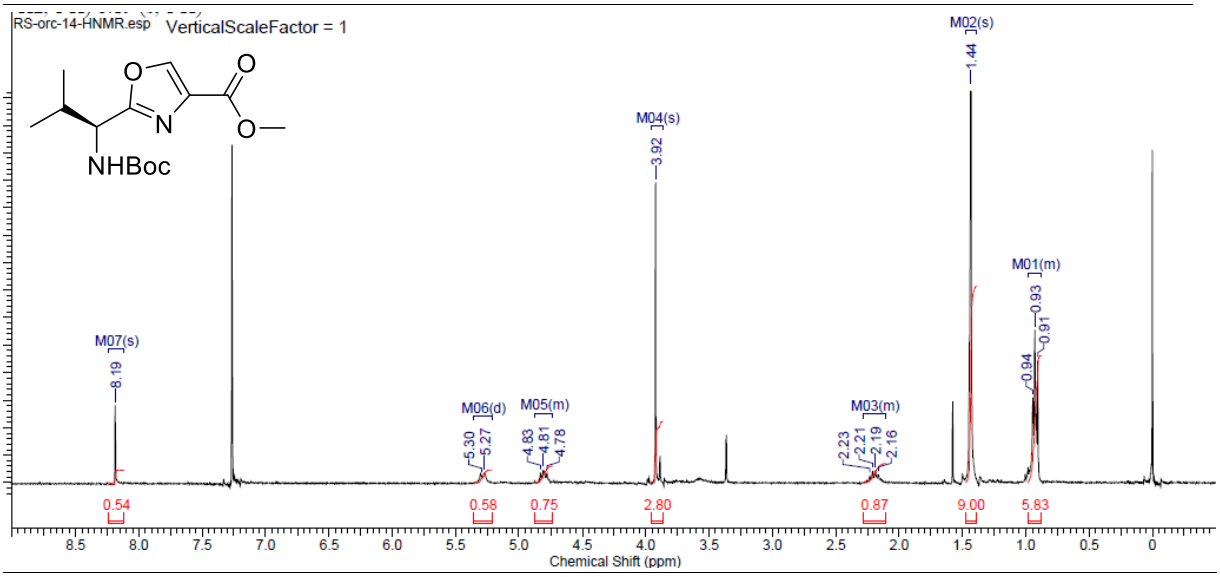
2.04
1.03
2.98
0.80
1.04
1.29
9.02
6.00
Chemical Shift (ppm)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O
O
N
O
NHBoc
M02(s)
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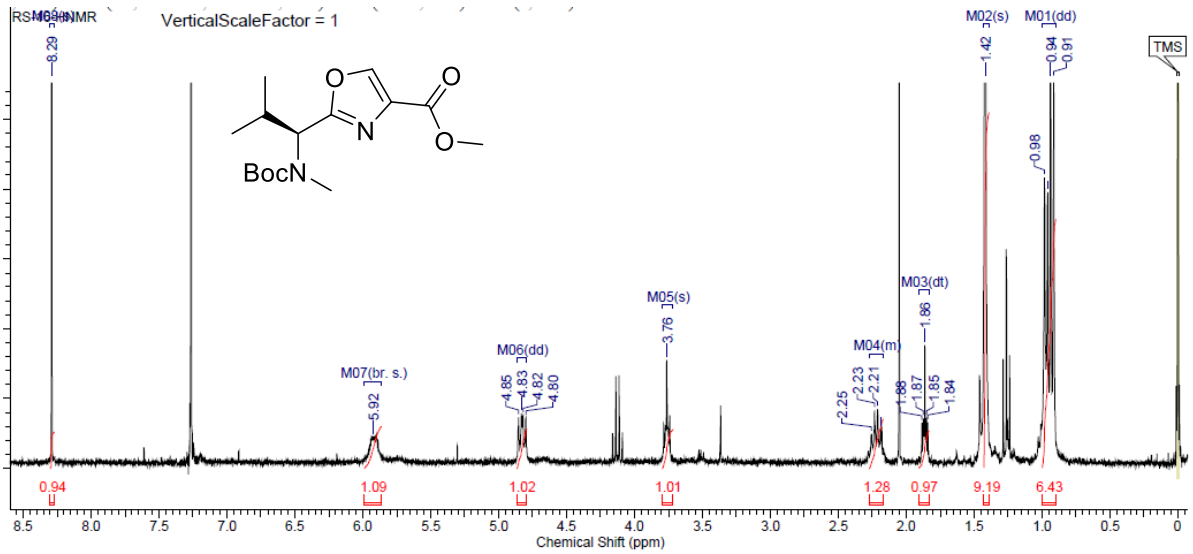
M04(s)
3.92
M01(m)
0.93
0.91
0.94
M07(s)
8.19
M06(d)
M05(m)
M03(m)
5.30
5.27
4.83
4.81
4.78
2.23
2.21
2.19
2.16
0.54
0.58
0.75
2.80
0.87
9.00
5.83
Chemical Shift (ppm)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8.29
O
O
N
O
BocN
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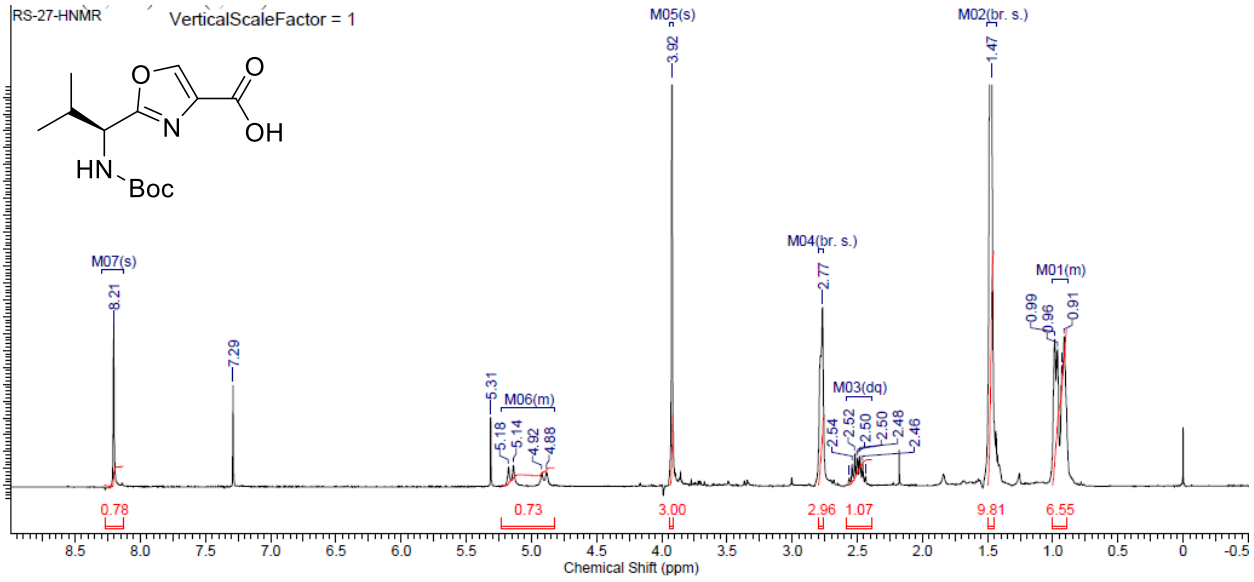
M01(dd)
1.42
0.94
0.91
TMS
0.98
M05(s)
3.76
M03(dt)
1.86
M06(dd)
M04(m)
M07(br. s.)
5.92
4.85
4.83
4.82
4.80
2.25
2.23
2.21
1.88
1.87
1.85
1.84
0.94
1.09
1.02
1.01
1.28
0.97
9.19
6.43
Chemical Shift (ppm)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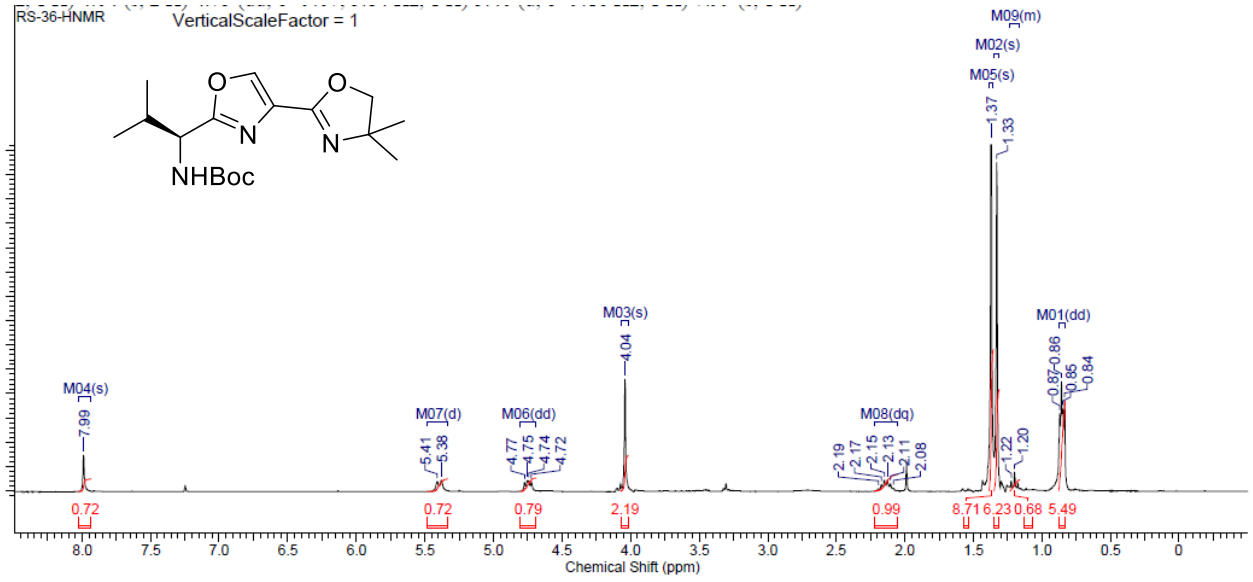
O
O
N
OH
HN
Boc
M07(s)
8.21
7.29
5.31
M06(m)
5.18
5.14
4.92
4.88
M05(s)
3.92
M04(br. s.)
2.77
M03(dq)
2.54
2.52
2.50
2.50
2.48
2.46
M02(br. s.)
1.47
M01(m)
0.99
0.96
0.91
0.78
0.73
3.00
2.96
1.07
9.81
6.55
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
-0.5
Chemical Shift (ppm)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NHBoc
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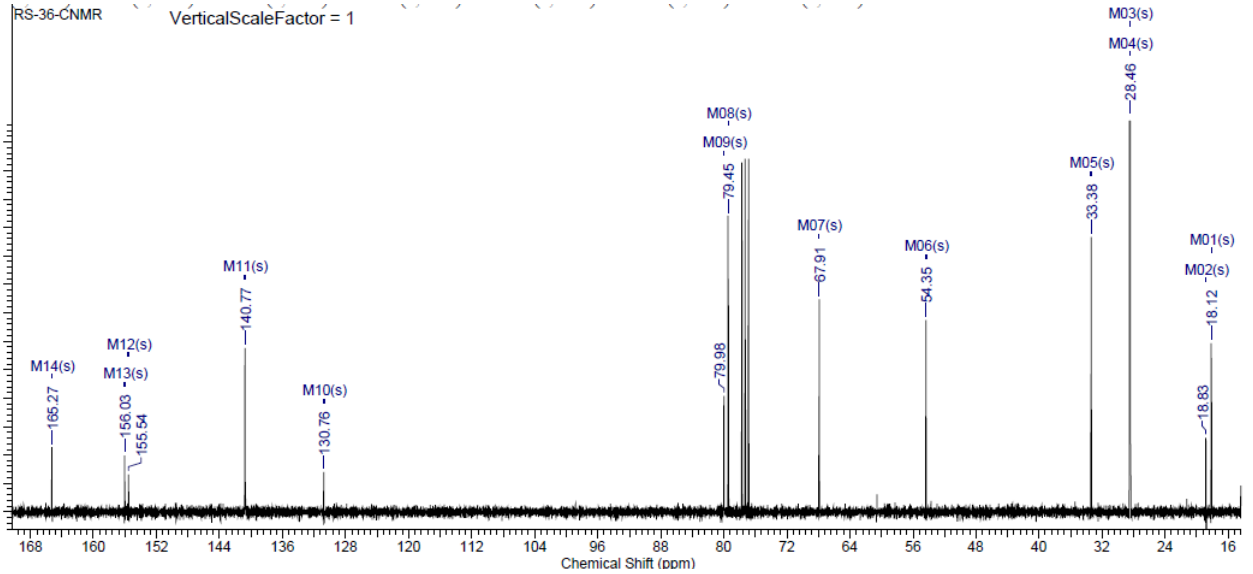
M02(s)
M05(s)
M03(s)
M01(dd)
M04(s)
M07(d)
M06(dd)
M08(dq)
Chemical Shift (ppm)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M08(s)
M09(s)
M05(s)
M07(s)
M06(s)
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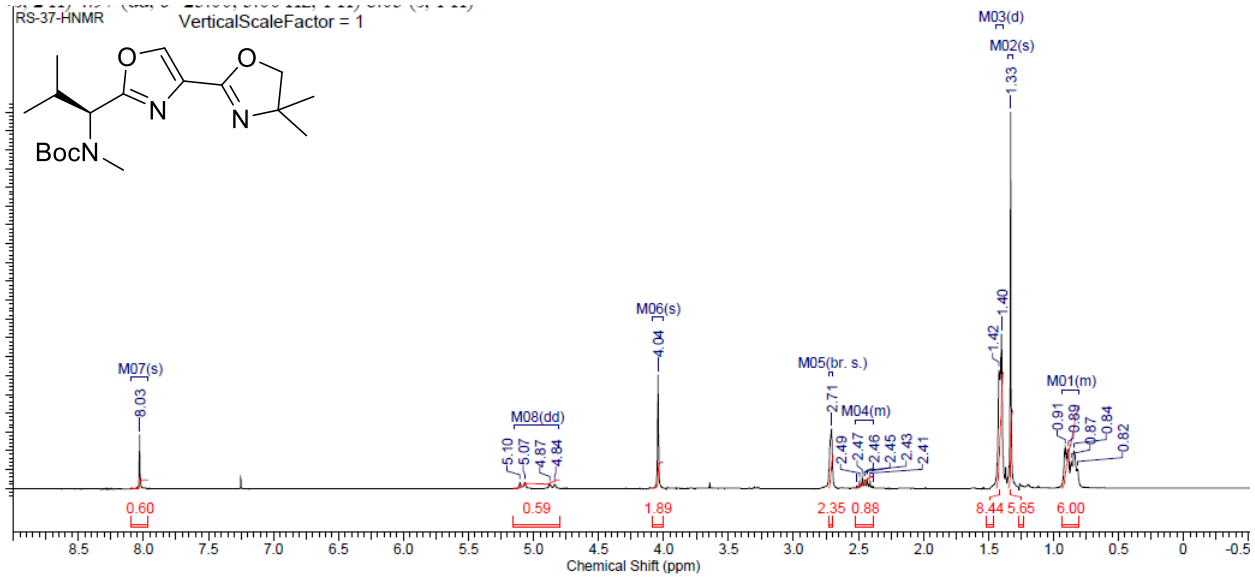
M01(s)
M02(s)
M12(s)
M13(s)
M14(s)
M10(s)
Chemical Shift (ppm)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8.03
M08(dd)
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5.07
4.87
4.84
M06(s)
4.04
M05(br. s.)
2.71
M04(m)
2.49
2.47
2.46
2.45
2.43
2.41
M03(d)
M02(s)
1.33
1.42
1.40
M01(m)
0.91
0.89
0.87
0.84
0.82
0.60
0.59
1.89
2.35
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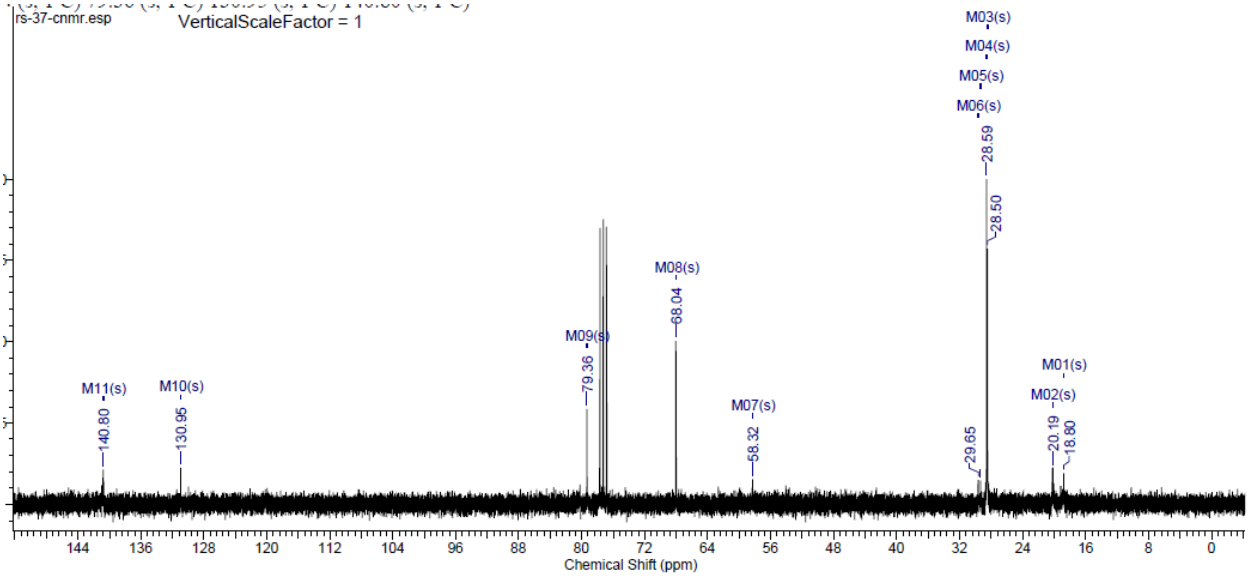
8.44
5.65
6.00
Chemical Shift (ppm)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130.95
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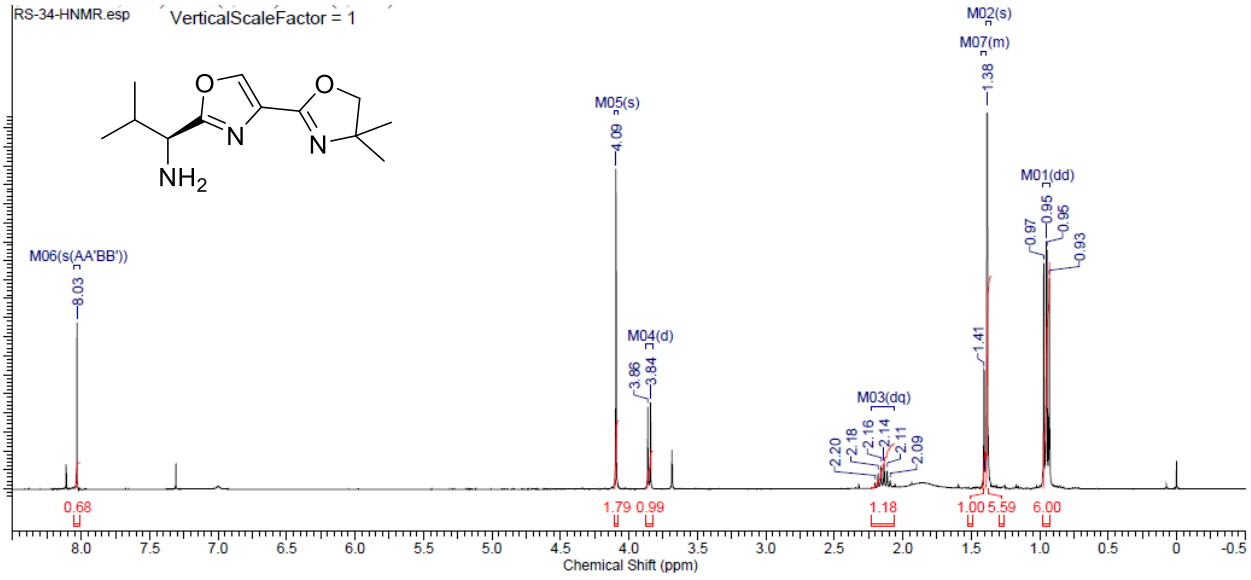
M08(s)
68.04
M07(s)
58.32
M03(s)
M04(s)
M05(s)
M06(s)
28.59
28.50
29.65
M01(s)
M02(s)
20.19
18.80
Chemical Shift (ppm)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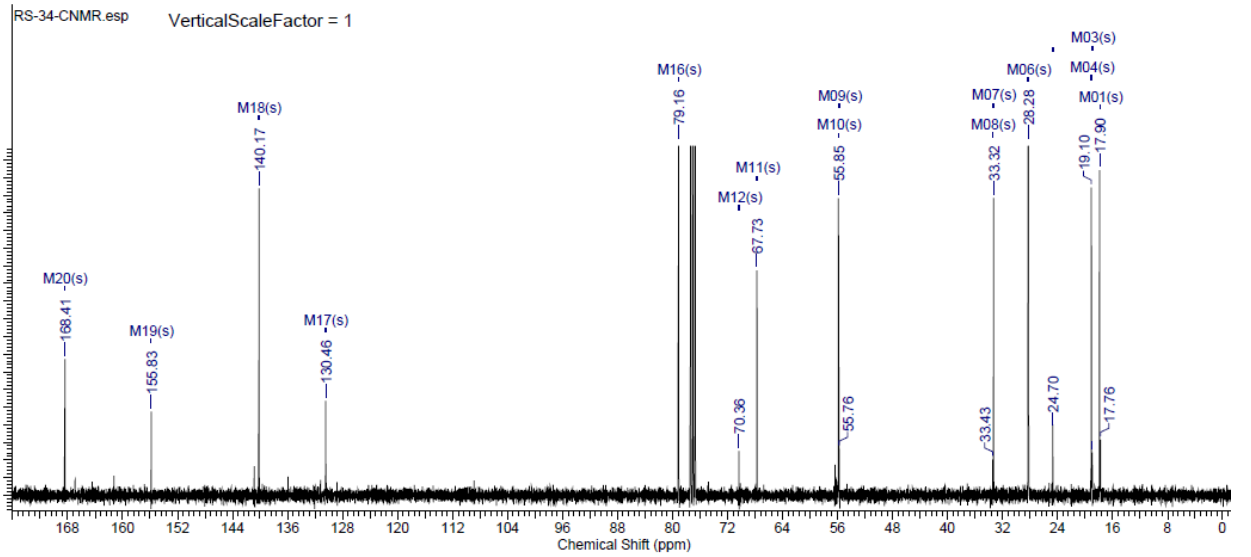
M05(s)
M01(dd)
M06(s(AA'BB'))
M04(d)
M03(dq)
Chemical Shift (ppm)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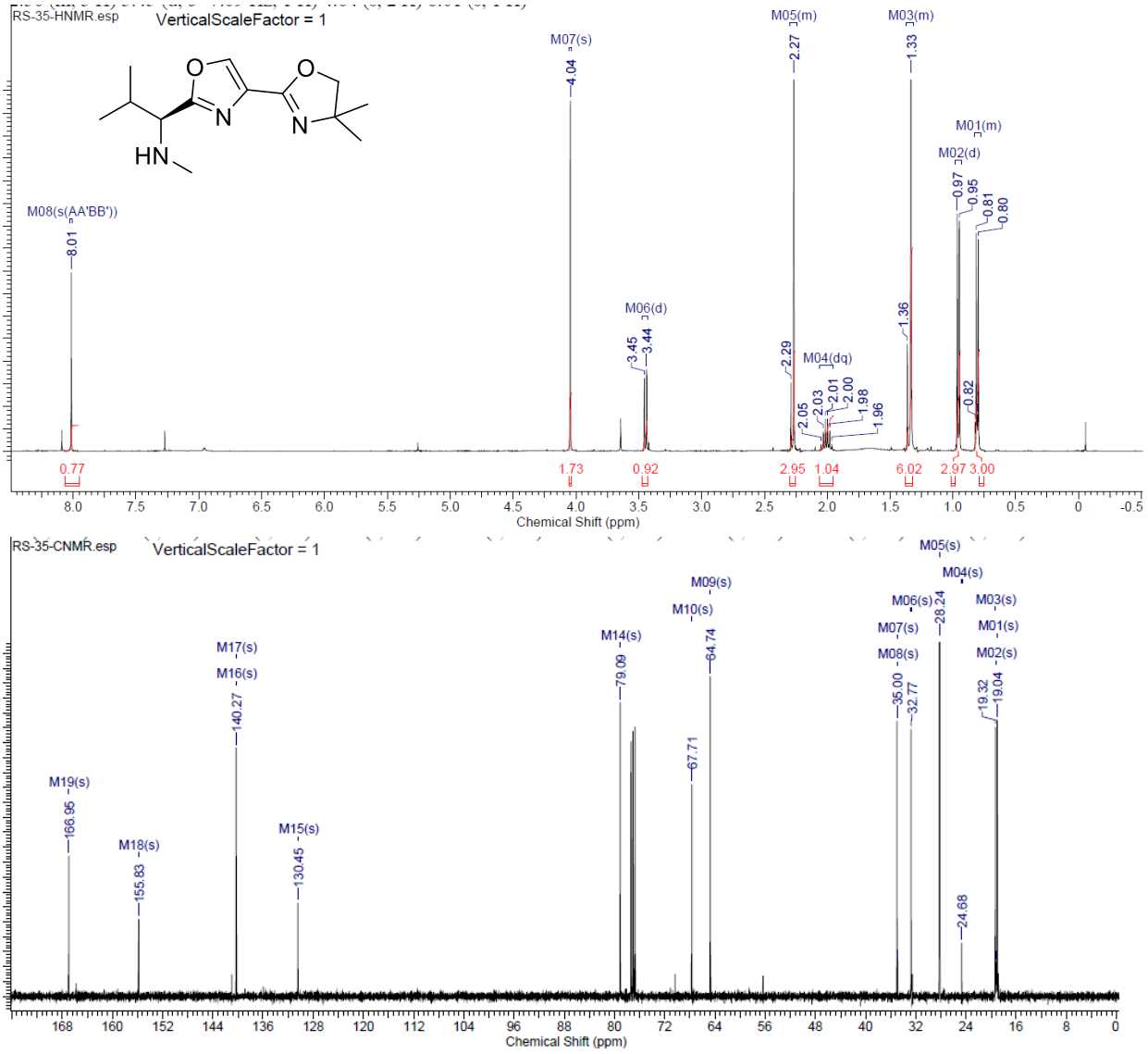
M16(s)
M06(s)
M04(s)
M18(s)
M09(s)
M07(s)
M01(s)
M10(s)
M08(s)
M11(s)
M12(s)
M20(s)
M19(s)
M17(s)
Chemical Shift (ppm)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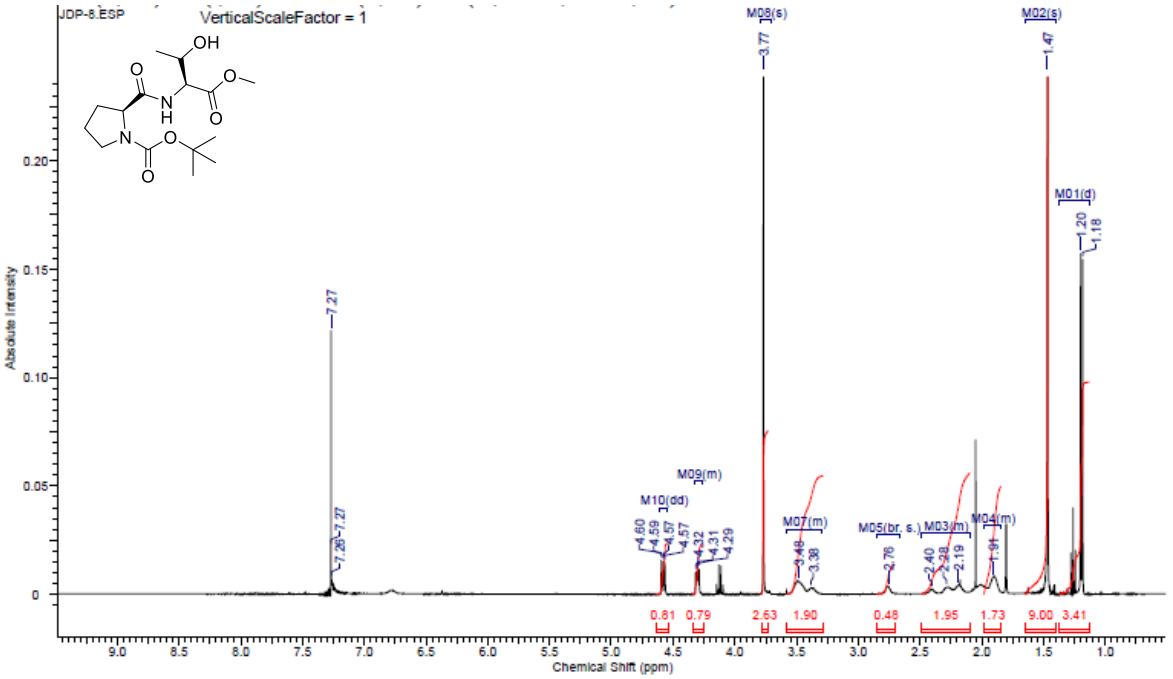
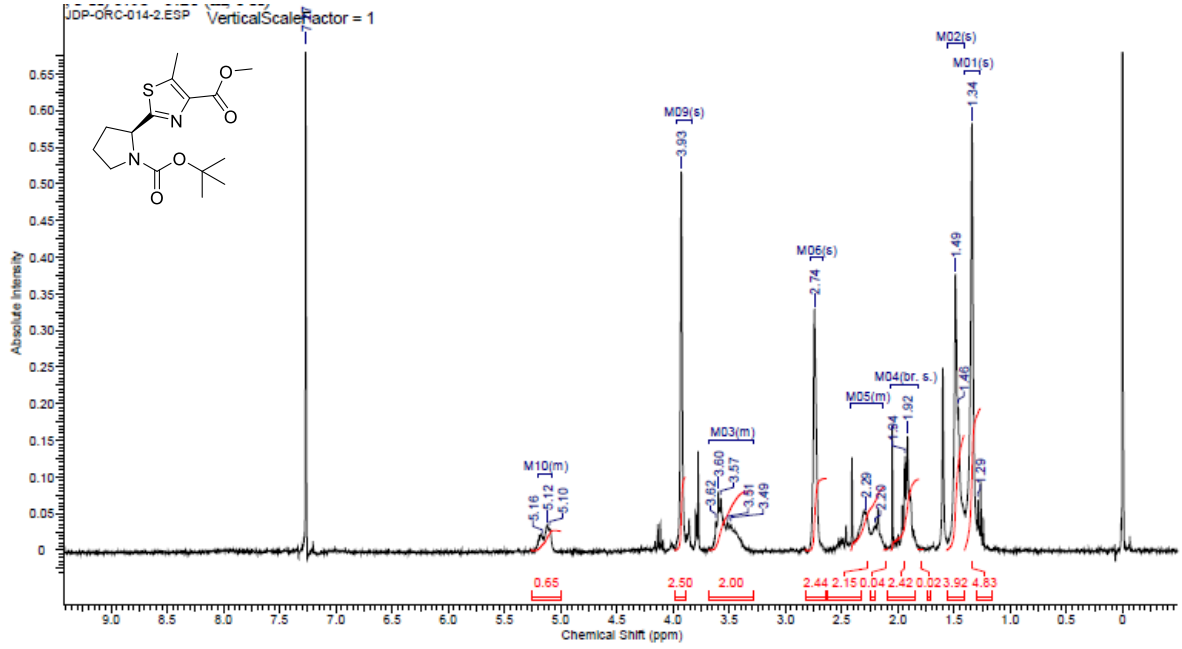
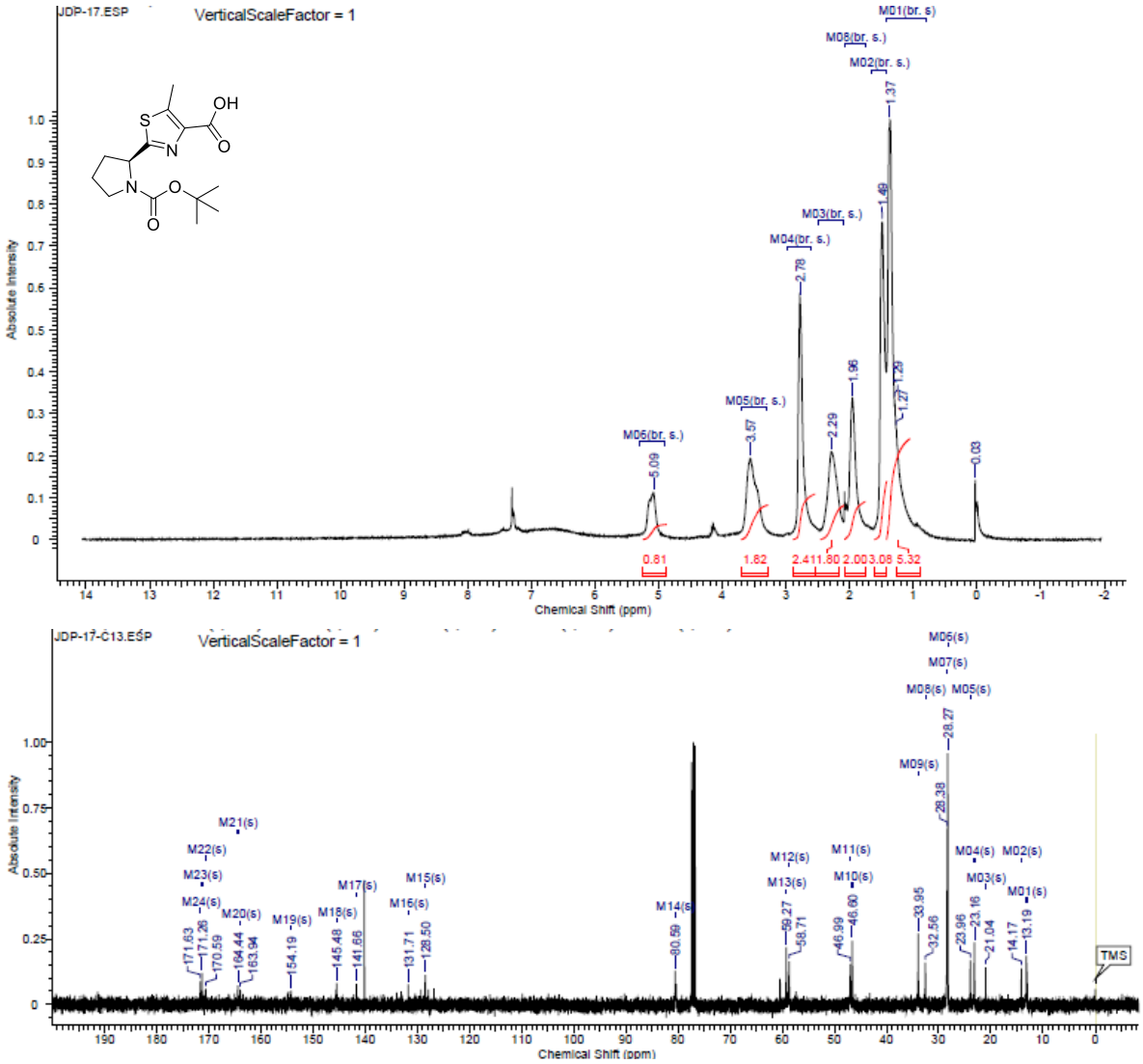
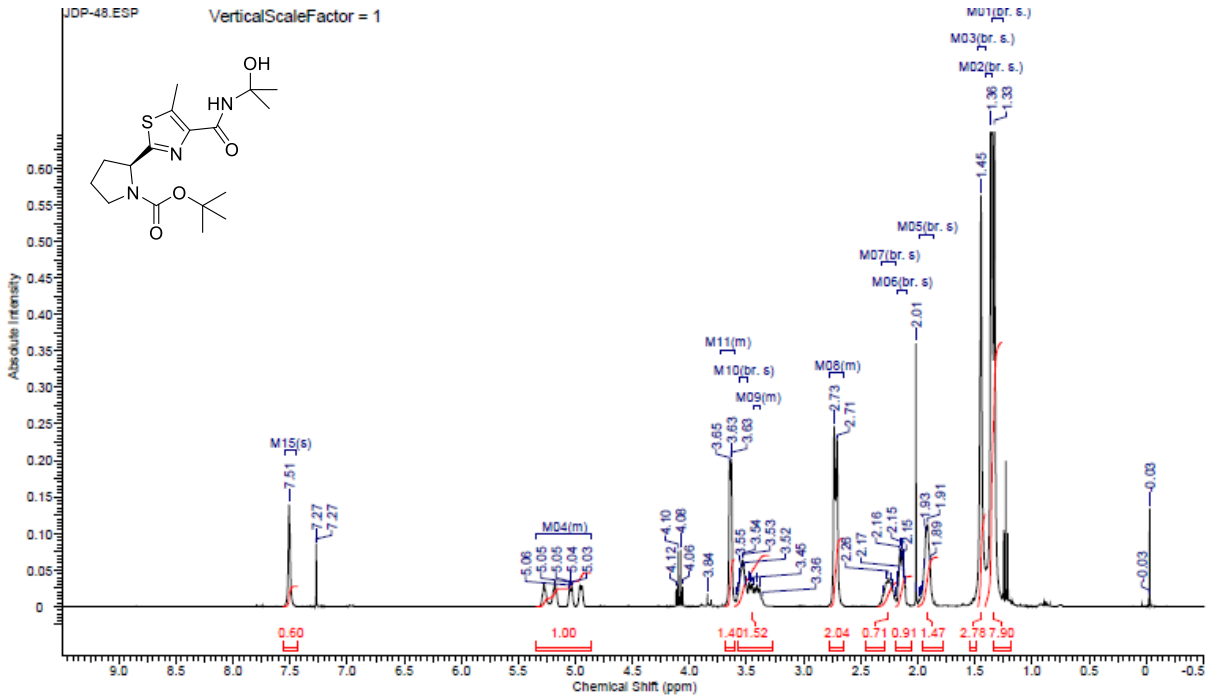
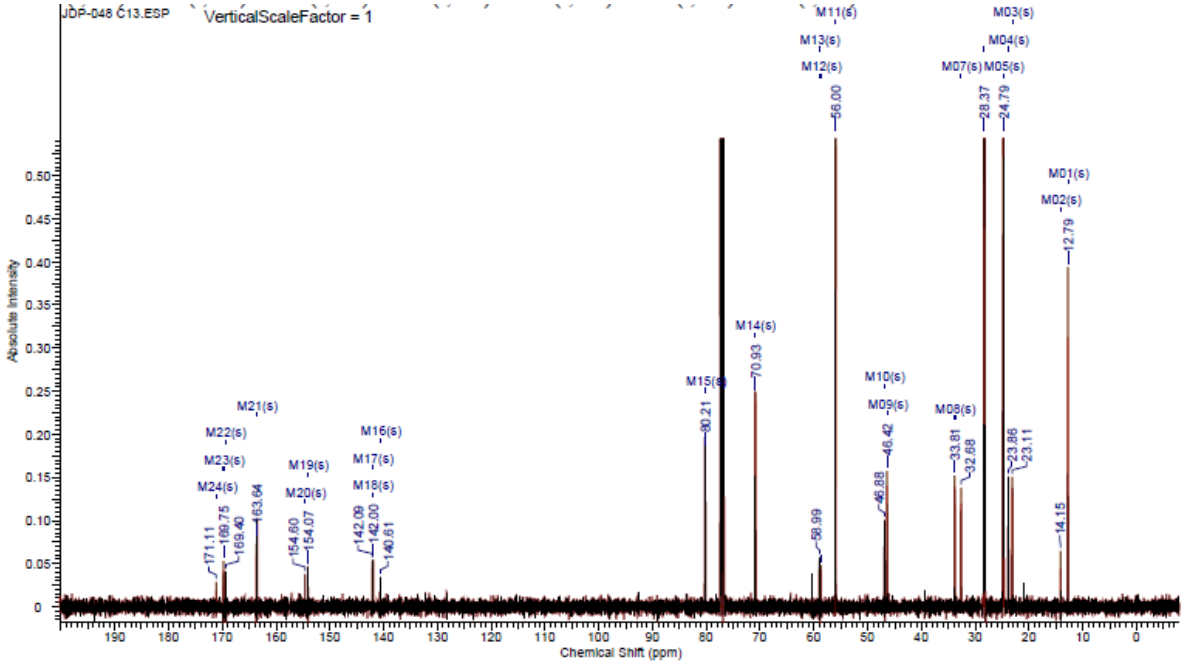
M07(s)
4.04
M06(d)
3.45
3.44
M05(m)
2.27
M04(dq)
2.29
2.05
2.03
2.01
2.00
1.98
1.96
M03(m)
1.33
1.36
M01(m)
M02(d)
0.97
0.95
0.82
0.81
0.80
0.77
1.73
0.92
2.95
1.04
6.02
2.97
3.00
Chemical Shift (ppm)
RS-35-CNMR.esp
VerticalScaleFactor = 1
M19(s)
166.95
M18(s)
155.83
M17(s)
M16(s)
140.27
M15(s)
130.45
M14(s)
79.09
M09(s)
M10(s)
64.74
67.71
M05(s)
M04(s)
M06(s)
M07(s)
M08(s)
28.24
35.00
32.77
M03(s)
M01(s)
M02(s)
19.32
19.04
24.68
Chemical Shift (ppm)

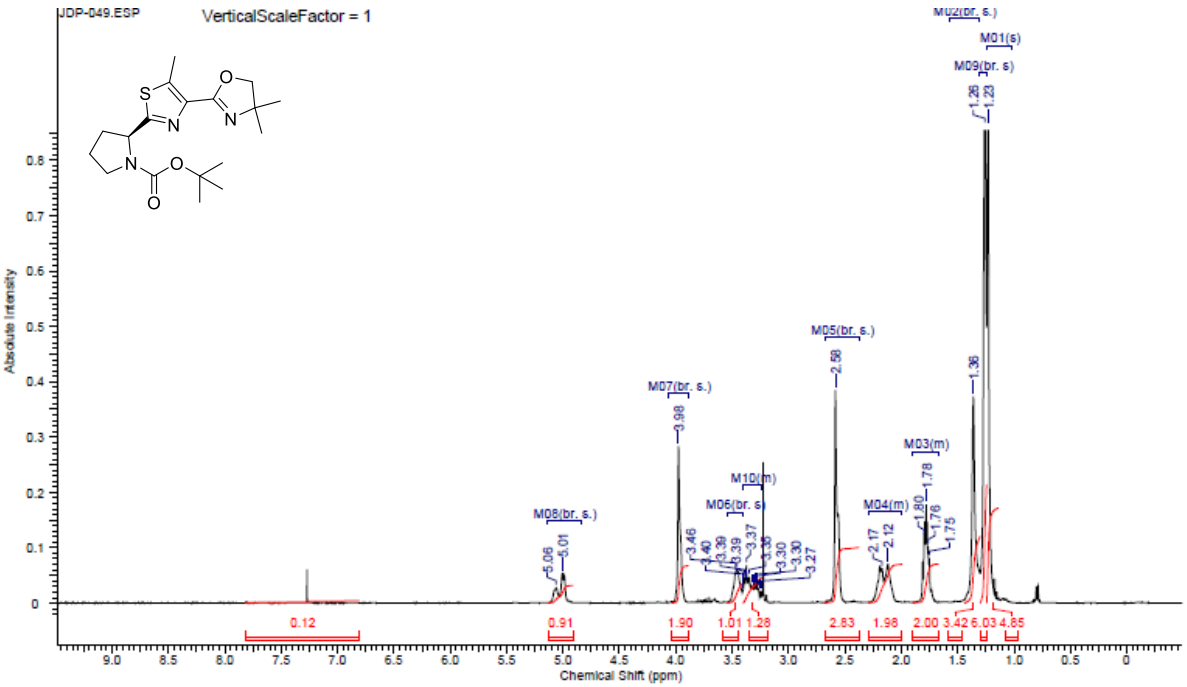

JDP-8.ESP
VerticalScaleFactor = 1
OH
O
N
H
O
O
O
N
O
O
M08(s)
3.77
M02(s)
1.47
M01(d)
1.20
1.18
7.27
7.26
7.27
M09(m)
M10(dd)
4.60
4.59
4.57
4.57
4.32
4.31
4.29
M07(m)
3.48
3.38
M05(br. s.)
2.76
M03(m)
2.40
2.29
2.19
M04(m)
1.94
0.81
0.79
2.63
1.90
0.48
1.95
1.73
9.00
3.41
Absolute Intensity
Chemical Shift (ppm)

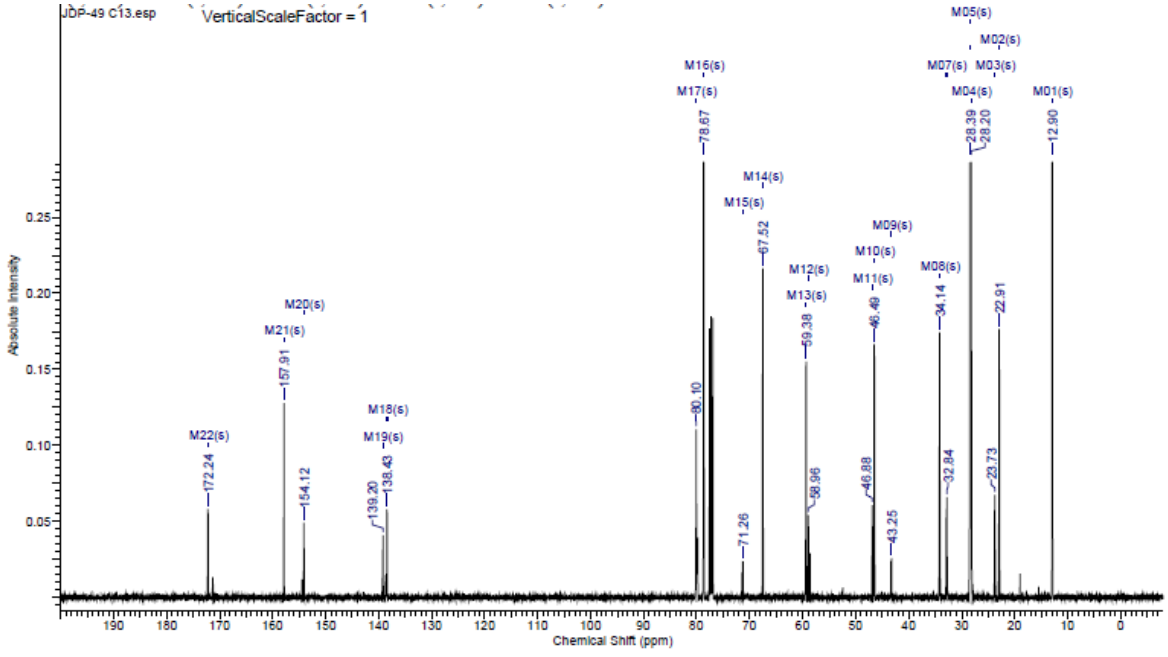

JDP-ORC-014-2.ESP
VerticalScaleFactor = 1
S
N
O
O
N
O
O
M02(s)
M01(s)
1.34
M09(s)
3.93
M06(s)
2.74
1.49
M04(br. s.)
M05(m)
1.46
1.92
1.84
M03(m)
3.62
3.60
3.57
3.51
3.49
2.29
2.29
M10(m)
5.16
5.12
5.10
1.29
0.65
2.50
2.00
2.44
2.15
0.04
2.42
0.02
3.92
4.83
Absolute Intensity
Chemical Shift (ppm)

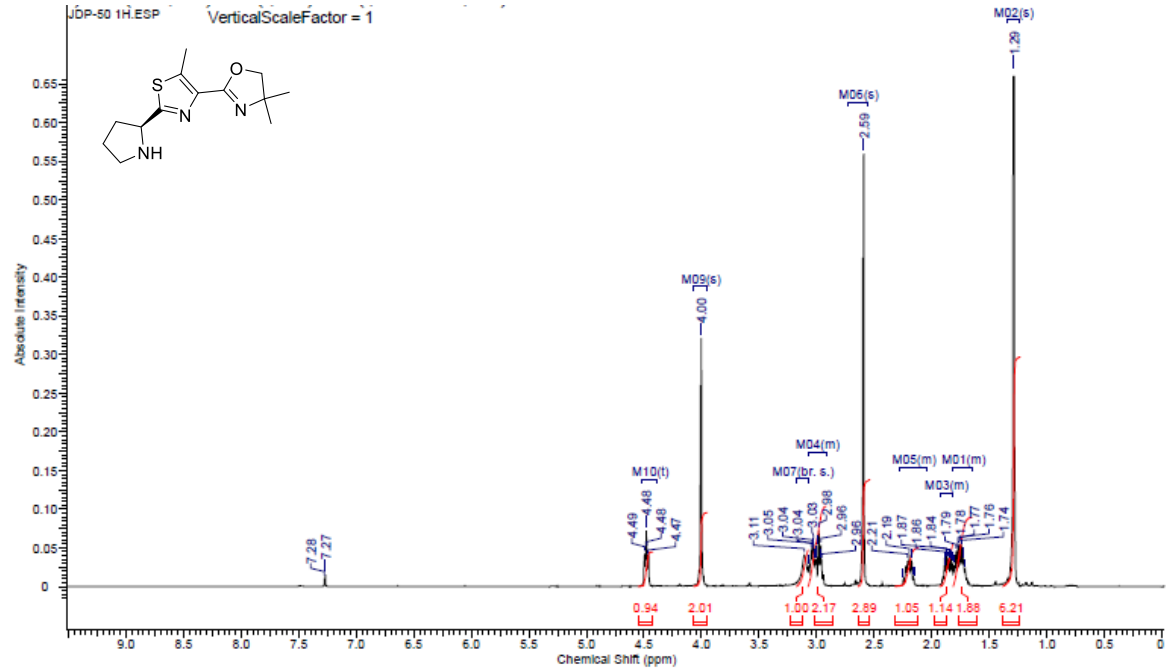

JDP-17.ESP
VerticalScaleFactor = 1
OH
S
N
N
O
O
O
M01(br. s.)
M08(br. s.)
M02(br. s.)
M03(br. s.)
M04(br. s.)
M05(br. s.)
M06(br. s.)
1.37
1.49
2.78
1.96
1.29
1.27
2.29
3.57
5.09
0.03
0.81
1.82
2.41
1.80
2.00
3.08
5.32
Absolute Intensity
Chemical Shift (ppm)
JDP-17-C13.ESP
VerticalScaleFactor = 1
M06(s)
M07(s)
M08(s)
M05(s)
M09(s)
28.27
28.38
M21(s)
M22(s)
M23(s)
M24(s)
M20(s)
M19(s)
M18(s)
M17(s)
M16(s)
M15(s)
M14(s)
M12(s)
M13(s)
M11(s)
M10(s)
M04(s)
M02(s)
M03(s)
M01(s)
171.63
171.26
170.59
164.44
163.94
154.19
145.48
141.66
131.71
128.50
80.59
59.27
58.71
46.99
46.60
33.95
32.56
23.96
23.16
21.04
14.17
13.19
TMS
Absolute Intensity
Chemical Shift (ppm)

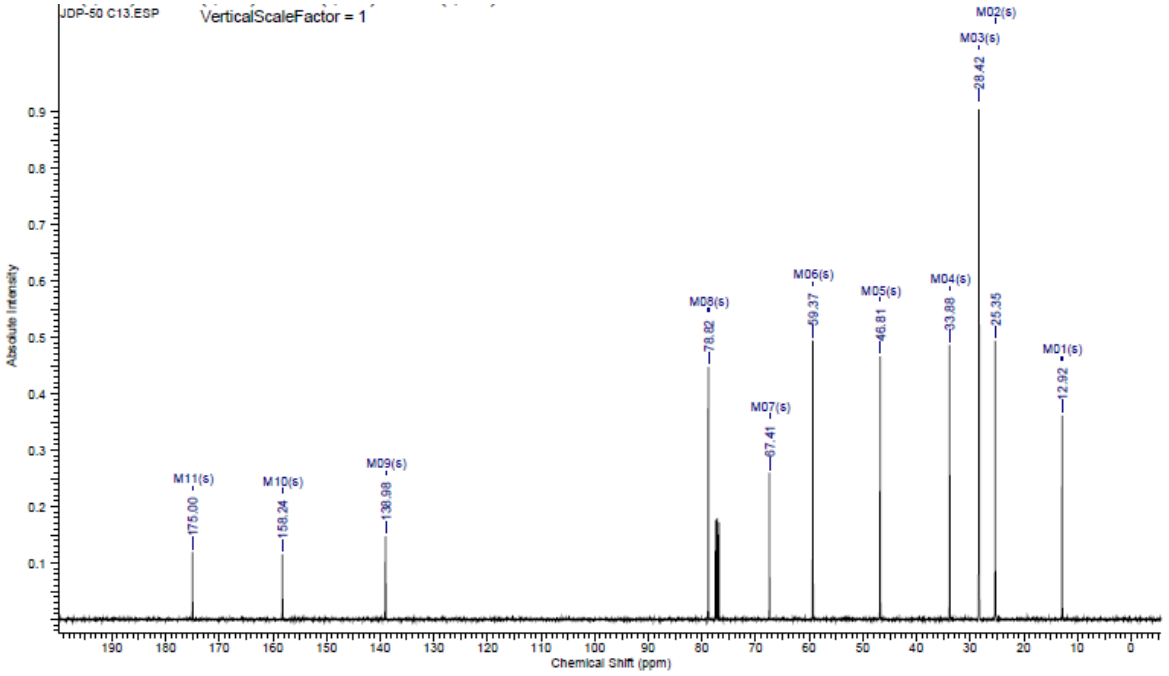

JDP-48.ESP
VerticalScaleFactor = 1
OH
HN
S
N
N
O
O
O
M01(br. s.)
M03(br. s.)
M02(br. s.)
M05(br. s.)
M07(br. s)
M06(br. s)
M11(m)
M10(br. s)
M09(m)
M08(m)
M04(m)
M15(s)
Absolute Intensity
Chemical Shift (ppm)


JDP-048 C13.ESP
VerticalScaleFactor = 1
M11(s)
M13(s)
M12(s)
M03(s)
M04(s)
M07(s)
M05(s)
M01(s)
M02(s)
M14(s)
M15(s)
M10(s)
M09(s)
M08(s)
M21(s)
M22(s)
M23(s)
M24(s)
M19(s)
M20(s)
M16(s)
M17(s)
M18(s)
Absolute Intensity
Chemical Shift (ppm)


JDP-049.ESP
VerticalScaleFactor = 1
M02(br. s.)
M01(s)
M09(br. s)
M05(br. s.)
M07(br. s.)
M03(m)
M10(m)
M06(br. s)
M04(m)
M08(br. s.)
Absolute Intensity
Chemical Shift (ppm)


JDP-49 C13.esp
VerticalScaleFactor = 1
M05(s)
M02(s)
M07(s)
M03(s)
M04(s)
M01(s)
M16(s)
M17(s)
M14(s)
M15(s)
M09(s)
M10(s)
M12(s)
M11(s)
M08(s)
M13(s)
M20(s)
M21(s)
M18(s)
M19(s)
M22(s)
Absolute Intensity
Chemical Shift (ppm)


JDP-50 1H.ESP
VerticalScaleFactor = 1
Absolute Intensity
Chemical Shift (ppm)
M02(s)
1.29
M06(s)
2.59
M09(s)
4.00
M04(m)
M10(t)
M07(br. s.)
M05(m)
M01(m)
M03(m)
7.28
7.27
4.49
4.48
4.48
4.47
3.11
3.05
3.04
3.04
3.03
2.98
2.96
2.96
2.21
2.19
1.87
1.86
1.84
1.79
1.78
1.77
1.76
1.74
0.94
2.01
1.00
2.17
2.89
1.05
1.14
1.88
6.21


JDP-50 C13.ESP
VerticalScaleFactor = 1
Absolute Intensity
Chemical Shift (ppm)
M02(s)
M03(s)
28.42
M08(s)
78.82
M06(s)
59.37
M05(s)
46.81
M04(s)
33.88
25.35
M01(s)
12.92
M07(s)
67.41
M11(s)
175.00
M10(s)
158.24
M09(s)
138.98