C h a p t e r 2

Synthesis and Activity of New *Z*-Selective Cyclometalated Ruthenium Metathesis Catalysts

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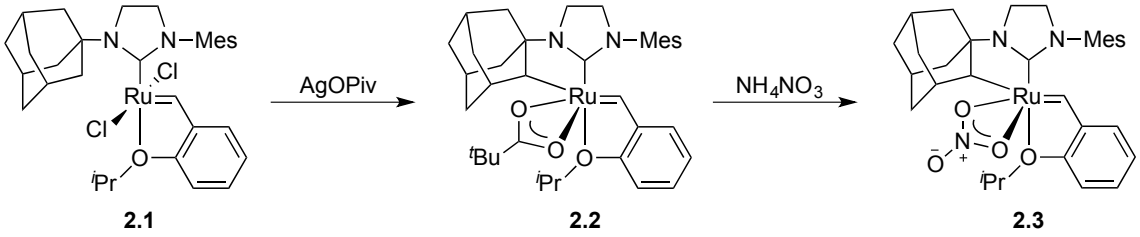
Abstract

A novel cyclometalated ruthenium-based metathesis catalyst bearing an *N*-2,6-diisopropylphenyl group was synthesized and subsequently shown to give near-perfect selectivity for the *Z*-olefin (>95% in most cases), as well as unparalleled TONs of up to 7400, in a variety of homodimerization and industrially relevant metathesis reactions. This derivative and other new catalytically active species were synthesized using an improved method employing sodium carboxylates to induce the salt metathesis and C–H activation of these cyclometalated complexes. All of these new ruthenium-based catalysts were highly *Z*-selective in the homodimerization of terminal olefins.

Introduction

As described in *Chapter 1*, a persistent challenge in olefin metathesis reactions is the control of stereoselectivity, as metathesis catalysts generally favor formation of the thermodynamically preferred *E*-olefin.[1] Recently, the synthesis and activity of the first examples of ruthenium-based *Z*-selective metathesis catalysts (**2.2**, **2.3**) containing a

cyclometalated *N*-heterocyclic carbene (NHC) ligand were reported.[2] The Ru-adamantyl bond is formed via an intramolecular C–H activation induced by the addition of silver pivalate (AgOPiv) (Scheme 2.1). Prior to the work outlined in this chapter, nitrato-catalyst **2.3** was the best *Z*-selective ruthenium-based metathesis catalyst, with turnover number (TONs) approaching 1000 and *Z*-selectivity on average around 90%. This catalyst has been shown to be effective for the synthesis of homo- and hetero-cross-products, highly *cis* polymers, and a variety of insect pheromones and macrocyclic musks.[2c,3]



Scheme 2.1. Synthetic route to previously reported C–H activated metathesis catalysts **2.2** and **2.3**. Mes = 2,4,6-trimethylphenyl.

Inspired by computational data, we hypothesized that increasing the steric bulk of the *N*-aryl group of **2.3** would further destabilize the *E*-selective transition state, thereby enhancing *Z*-selectivity.[4] However, as mentioned in *Chapter 1*, previous attempts to make significant alterations to the NHC substituents, both to the cyclometalated group and to the *N*-aryl group, generally resulted in decomposition upon exposure to AgOPiv.[5] In order to access stable cyclometalated species with various modifications to the NHC substituents, we sought to develop a milder approach to form this ruthenium–carbon bond. In this chapter, an improved method to induce the salt metathesis and C–H activation of ruthenium alkylidene complexes employing mild and economically viable sodium carboxylates is described, and the superior activity and selectivity of several new

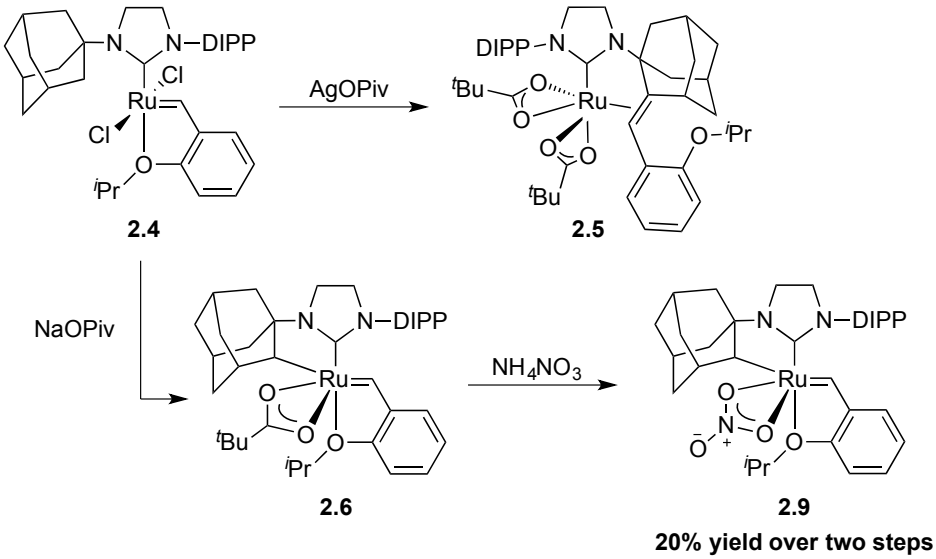
cyclometalated metathesis-active catalysts are explored. Through the use of this improved approach, we have uncovered the highly active catalyst **2.9**, which gives on average >95% *Z*-selectivity and TONs up to 7400 in the homodimerization of terminal olefin substrates. Significantly, this represents a near tenfold increase in activity relative to nitrato-catalyst **2.3**. Moreover, **2.9** meets or exceeds TONs reported for the most active *Z*-selective molybdenum- and tungsten-based systems in similar metathesis reactions.[6]

Results and Discussion

We initiated our studies by first employing sodium pivalate (NaOPiv) in place of AgOPiv during the C–H activation step. It was discovered that exposing the unactivated dichloride catalyst **2.1** to excess NaOPiv in a 1:1 mixture of THF and MeOH resulted in the clean formation of the desired cyclometalated catalyst **2.2** after heating at 40 °C for 6 h; this complex could then be converted to the nitrato-form (**2.3**) in 60% overall yield through the addition of excess ammonium nitrate. In comparison, the two-step synthesis of **2.3** using AgOPiv proceeds in 48% yield. It was additionally found that other sodium carboxylates could be used to effect the salt metathesis and C–H activation steps: Reaction of **2.1** with excess sodium acetate also resulted in complete conversion to **2.2**, although the C–H activation failed to reach full conversion with some of the catalysts described later in this chapter. Reducing the steric bulk of the carboxylate even further by employing sodium formate or sodium bicarbonate in the C–H activation of **2.1** resulted in no discernable conversion to the desired cyclometalated product.

In order to explore the utility and mildness of this new approach, we revisited a number of ruthenium complexes containing a variety of *N*-aryl and *N*-carbocyclic groups

that had decomposed when exposed to AgOPiv. As described in *Chapter 1*, attempts to replace the *N*-mesityl group of **2.3** with a bulkier *N*-2,6-diisopropylphenyl (DIPP) group, as in **2.4**, had resulted in substantial decomposition to **2.5** during the C–H activation step. Using NaOPiv, however, we were able to cleanly form the stable *N*-adamantyl-*N*-DIPP pivalate precursor (**2.6**) of catalyst **2.9** (Scheme 2.2).



Scheme 2.2. Decomposition and C–H activation pathways of precatalyst **2.4**. DIPP = 2,6-diisopropylphenyl.

We were also able to generate C–H activated *N*-3,5-dimethyladamantyl-*N*-mesityl (**2.7**) and *N*-adamantyl-*N*-2,6-methylisopropylphenyl (MIPP) (**2.8**) derivatives via this improved method. More extreme alterations to the chelating group, however, including exchanging the *N*-adamantane for an *N*-cyclohexyl or *N*-1-methylcyclohexyl group, resulted in the formation of cyclometalated catalysts that were inherently unstable. When these reactions were monitored by ^{1}H NMR spectroscopy, these complexes were seen to either decompose immediately to a ruthenium hydride species upon introduction of NaOPiv or form a metastable activated complex that was unisolable without noticeable decomposition.

Complexes observed to form a stable cyclometalated architecture were subsequently converted to the nitrato-form via ligand exchange with the pivalate group (Scheme 2.2), as past experience with catalyst **2.3** suggested that the nitrato-complexes would likely be more stable and show increased activity.[2c] However, while this was the case for complexes possessing a cyclometalated *N*-adamantyl group (complex **2.6** and the pivalate analogue of catalyst **2.8** were isolated and assayed to confirm this), catalyst **2.7** was more stable and easier to isolate in the pivalate-substituted form. Catalysts successfully synthesized using the NaOPiv method are depicted in Figure 2.1.

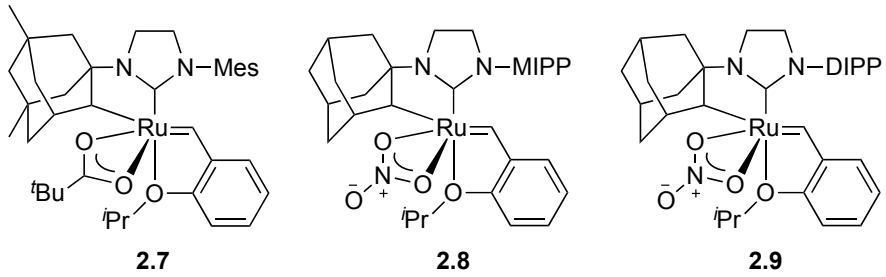
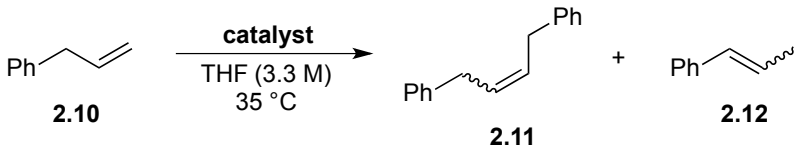


Figure 2.1. Catalysts **2.7–2.9**: Mes = 2,4,6-trimethylphenyl (**2.7**); MIPP = 2,6-methylisopropylphenyl (**2.8**); DIPP = 2,6-diisopropylphenyl (**2.9**).

In order to analyze the efficacy of these new complexes for metathesis, we first evaluated their performance in the homodimerization of allylbenzene (**2.10**, see Table 2.1). While a relatively facile substrate for homodimerization, allylbenzene is also prone to olefin isomerization to form **2.12**. Importantly, the extent of this side reaction depends heavily on the identity and stability of the catalyst, making **2.10** a good benchmark substrate.[7] Homodimerization reactions were generally run in THF at 35 °C with a high substrate concentration (3.3 M in **2.10**) and a catalyst loading varying between 0.1 and 2 mol %. Catalyst **2.8** was not soluble in THF, however; thus, all reactions using **2.8** were run in 1,2-dichloroethane (DCE). Experimentation with catalyst **2.9** demonstrated that using DCE in place of THF provided analogous results (see Table 2.2). For the

homocoupling of **2.10**, excellent conversions and near-perfect *Z*-selectivities (96-98%) were seen by ^{1}H NMR spectroscopy when using catalysts **2.7–2.9**, with **2.8** and **2.9** being the most selective for the homodimer **2.11** over the olefin isomerization product **2.12**.

Table 2.1. Homodimerization of Allylbenzene (2.10)



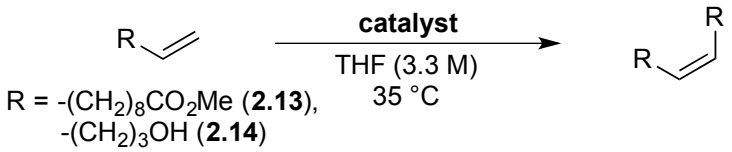
catalyst	loading, mol %	time, h	conv, %[a]	*Z*-**2.11**, %[a]	**2.11**/**2.12**[a]
2.7	2	1.5	94	96	16.6
2.8[b]	0.1	2	78	98	50
2.9	0.1	2	96	98	50

[a]Determined by ^{1}H NMR spectroscopy. [b]DCE was used in place of THF.

In order to differentiate between these very active catalysts, we turned to two more challenging homodimerization substrates, methyl 10-undecenoate (**2.13**) and the primary alcohol 4-pentenol (**2.14**), the latter of which has been indirectly implicated in the decomposition of previous generations of ruthenium metathesis catalysts.[8] Reactions were run utilizing the standard conditions described previously. Of the three catalysts, **2.9** gave the best results (see Table 2.2), providing the homodimerization products in high conversions (97% and 77% for **2.13** and **2.14**, respectively) with 98% *Z*-selectivity for both substrates. Catalyst **2.8** also demonstrated excellent selectivity (97% and 99% *Z* for **2.13** and **2.14**, respectively) but low conversions, particularly in the homodimerization of **2.14** (7%). The almost exclusive selectivity for the *Z*-olefin observed with **2.8** and **2.9** is likely a result of the steric bulk of the *N*-MIPP or *N*-DIPP group positioned over the alkylidene, which ensures that any approach of the terminal olefin in a manner that would produce an *E*-olefin is extremely disfavored.[4] Previously, the homodimer of **2.14** was

isolated in 67% yield with only 81% selectivity for the *Z*-olefin using catalyst **2.3**; thus, the development of **2.9** represents a significant improvement in the field of ruthenium-mediated *Z*-selective metathesis.

Table 2.2. Homodimerization of 10-Methyl Undecenoate (2.13) and 4-Pentenol (2.14)

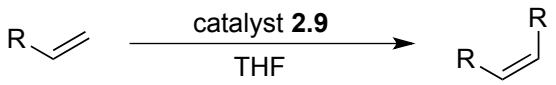


substrate	catalyst	loading, mol %	time, h	conv, %[a]	*Z*, %[a]
2.13	**2.7**	2	3	77	91
	2.8[b]	0.1	6	65	97
	2.9	0.1	6	97	98
2.14	**2.7**	2	1.5	83	80
	2.8[b]	0.1	2	7	99
	2.9	0.1	2	77	98
	2.9[b]	0.1	2	79	92

[a]Determined by ^{1}H NMR spectroscopy. [b]DCE was used in place of THF.

In order to further quantify the activity of the highly *Z*-selective catalyst **2.9**, we assayed its performance at room temperature (r.t.) and lower concentration (1 M in substrate). Under these conditions, similar conversions and *Z*-selectivities were observed compared to those recorded under standard conditions, although significantly longer reaction times were necessary. We additionally tested **2.9** at 0.01 mol % and were pleased to discover that it performed exceptionally well, reaching turnover numbers as high as 5800 and 7400 in the homodimerizations of **2.13** and **2.10**, respectively, while maintaining between 96 and >99% *Z*-selectivity in all cases. This is in comparison to previously reported TONs of up to 1000 for catalyst **2.3** in conjunction with ca. 90% *Z*-selectivity.[2c] Finally, isolated yields were obtained for all reactions employing catalyst **2.9**, including those run using the standard conditions, and are reported in Table 2.3.

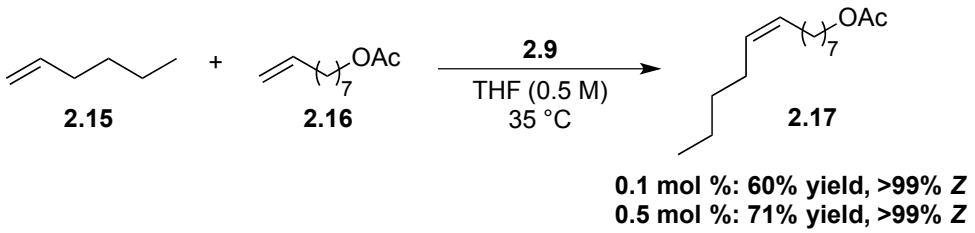
Table 2.3. Homodimerization of Terminal Olefin Substrates Using Catalyst 2.9



substrate	loading, mol %	conc., M	temp, °C	time, h	isolated yield, %	*Z*, %[a]	TON
2.10	0.1	3.3	35	2	84	96	840
	0.1	1	23	6.5	91	96	910
	0.01	7	35	2.5	74	98	7400
2.13	0.1	3.3	35	6.5	87	>99	870
	0.1	1	23	12	85	>99	850
	0.01	3.3	35	12	58	98	5800
2.14	0.1	3.3	35	2.5	81	98	810
	0.1	1	23	12	80	99	800
	0.01	3.3	35	4.5	15	98	1500

[a]Determined by ^{1}H NMR spectroscopy.

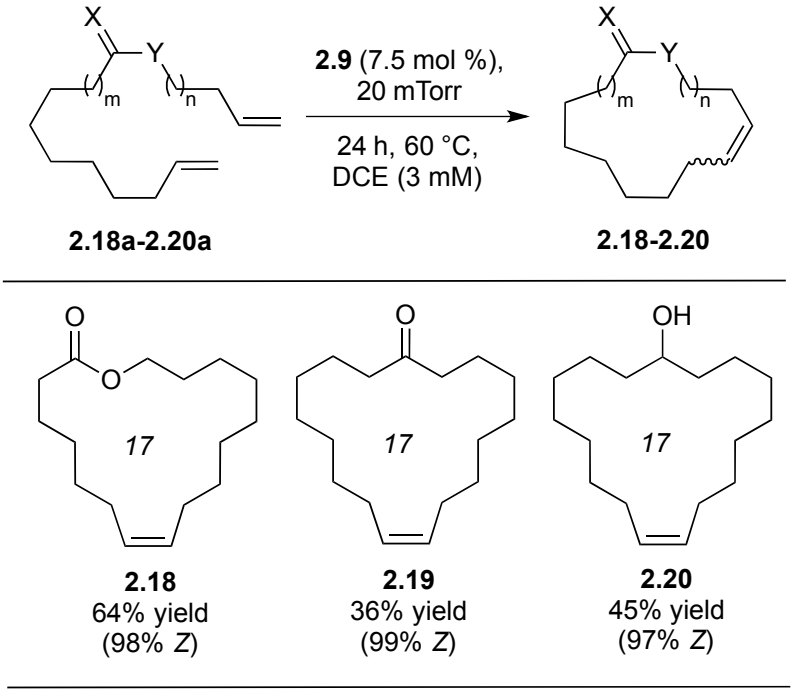
Having established the effectiveness of **2.9** in homodimerization reactions, we set about to further evaluate its activity and *Z*-selectivity by exploring more complex transformations. The reaction of 1-hexene (**2.15**) and 8-nonenyl acetate (**2.16**) to form the pheromone derivative **2.17** was previously described using catalyst **2.3**, proceeding in good yield (67%) with high *Z*-selectivity (91%) at a low catalyst loading (0.5 mol %).[2c] Catalyst **2.9** was able to catalyze this transformation with no observable formation of the *E*-isomer and in slightly higher yield (71%) at the same catalyst loading. Additionally, the catalyst loading could be lowered to 0.1 mol % and still provide a good yield of **2.17** (60%) while maintaining >99% *Z*-selectivity (Scheme 2.3). The expansion of this methodology to produce more complicated cross products with presumably total *Z*-selectivity should further enable its widespread use in the synthesis of *Z*-olefin-containing pheromones and other natural products.



Scheme 2.3. Synthesis of pheromone **2.17** using catalyst **2.9**.

We next evaluated catalyst **2.9** in macrocyclic ring-closing metathesis (mRCM).[9] Although *Z*-selective W- and Mo-based systems exhibit *Z*-selectivities as high as 97% for mRCM reactions,[10,11] catalyst **2.3** yields only ca. 85% *Z*-selectivity.[3c] Particularly problematic for **2.3** are substrates containing ketone or alcohol functionality, in which it is observed that the *Z*-isomer is readily degraded at high conversions. Thus, we were delighted to find that when dienes **2.18a–2.20a** were exposed to catalyst **2.9**, macrocycles **2.18–2.20** were all obtained in modest yields and with only trace amounts of the *E*-isomer evident by ^{1}H and ^{13}C NMR spectroscopy (Table 2.4). It is expected that this methodology will be applicable to the synthesis of a variety of natural products and pharmaceuticals, including a unique class of olfactory compounds known as macrocyclic musks. Many of these compounds contain a macrocyclic backbone either featuring a *Z*-olefin or bearing functionality stereospecifically installed using a *Z*-olefin.[9,12] In fact, **2.18** and **2.19** are both currently in demand by the perfume industry (marketed as ambrettolide and civetone, respectively).[12]

Table 2.4. *Z*-Selective Macrocyclizations Employing Catalyst 2.9[a]



[a]Isolated yields (*E*/*Z* ratios determined by ^{1}H- or ^{13}C-NMR spectroscopy).

Conclusions and Future Outlook

In summary, we have developed a new method to effect the salt metathesis and C–H activation of *Z*-selective ruthenium-based metathesis catalysts using sodium carboxylates. This approach has been used to synthesize several new stable cyclometalated species, all of which were found to be highly *Z*-selective in the homodimerizations of terminal olefin substrates. Notably, installation of an *N*-2,6-diisopropylphenyl group on the NHC led to significant improvements in activity and selectivity in the homocouplings of terminal olefins as well as industrially relevant metathesis reactions. Near-perfect selectivity for the *Z*-olefin (>95% in almost all cases) and unmatched TONs of up to 7400 were observed with catalyst **2.9**, all while retaining the ease of use associated with the ruthenium family of metathesis catalysts.

Since this paper was published in the *Journal of the American Chemical Society* in 2013, catalyst **2.9** has been studied extensively in a variety of transformations. Notably, this catalyst has been shown to effectively facilitate chemoselective cross-metathesis, reacting preferentially with terminal and internal *Z*-olefins in the presence of internal *E*-olefins.[13] Complex **2.9** is also effective for the cross-metathesis of allylic-substituted olefins, a challenging class of substrates for *Z*-selective metathesis due to their inherent bulk.[14] Finally, catalyst **2.9** exhibits high *cis,syndio*-selectivity in the ring-opening metathesis polymerization of norbornenes and norbornadienes, particularly when compared to previous cyclometalated systems such as **2.3** (see *Chapter 3*).[15] Additionally, in recent years, the NaOPiv method has been successfully extended to complexes containing cyclometalated *N*-2-adamantane and *N*-bornyl group.[16] Despite these achievements, however, there is still room for the continued development of *Z*-selective ruthenium metathesis catalysts. For example, the cyclometalated systems presented in this chapter are ineffective for the *Z*-selective cross-metathesis of two internal olefins or the formation of trisubstituted *Z*-olefins, transformations that have been reported for both *Z*-selective Mo- and W-based catalysts.[11,17] Overall, it is hoped that the insights gained in this study will contribute to new developments and discoveries in the ever-expanding field of ruthenium-mediated *Z*-selective olefin metathesis.

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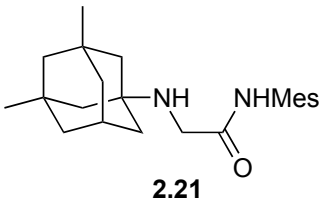
Supporting Information

General Information: All reactions were carried out in dry glassware under an argon atmosphere using standard Schlenk techniques or in a Vacuum Atmospheres Glovebox under a nitrogen atmosphere, unless otherwise specified. All solvents were purified by passage through solvent purification columns and further degassed by bubbling argon. C_6D_6 was purified by passage through a solvent purification column. $CDCl_3$ and CD_2Cl_2 were used as received. All substrates for olefin cross-metathesis (**2.10**, **2.13**, and **2.14**) were degassed with argon and filtered through a plug of neutral alumina prior to use. Dienes **2.18a–2.20a** were synthesized as disclosed previously.[3c] $RuCl_2(PCy_3)$(=CH-*o*-$O^iPrC_6H_4$) (**2.24**) was obtained from Materia, Inc. Precatalyst **2.4** was synthesized according to the literature procedure.[5] Other commercially available reagents and silica gel were used as received.

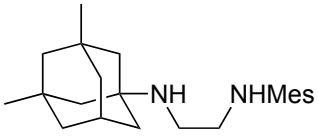
^{1}H NMR spectra were acquired at 400 or 500 MHz and ^{13}C NMR spectra at 101 or 126 MHz as $CDCl_3$ or C_6D_6 solutions unless otherwise noted. Chemical shifts are reported in ppm downfield from Me_4Si by using the residual solvent peak as an internal standard. Spectra were analyzed and processed using MestReNova Ver. 7.1.

High-resolution mass spectra (HRMS) were provided by the California Institute of Technology Mass Spectrometry Facility using a JEOL JMS-600H High Resolution Mass Spectrometer. All HRMS were by positive-ion EI or FAB.



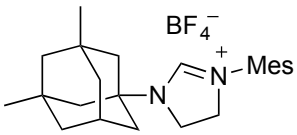
2.21

Preparation of 2.21: A three-neck 250 mL round-bottom flask equipped with a condenser was flame dried and charged with 2-chloro-*N*-mesitylacetamide (3.5 g, 17 mmol), memantine hydrochloride (3.0 g, 14 mmol, OChem Incorp.), and K_2CO_3 (4.8 g, 35 mmol). MeCN (110 mL) was added and the suspension was heated to 100 °C under an argon atmosphere for 24 h. After cooling to r.t., the mixture was filtered through celite, washing with CH_2Cl_2, and the filtrate was concentrated to a white powder. The crude mixture was dry loaded onto a silica gel column and purified via flash chromatography (SiO_2, eluent Et_2O) to give **2.21** (3.0 g, 60%) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (br s, 1H), 6.88 (s, 2H), 3.38 (s, 2H), 2.26 (s, 3H), 2.18 (s, 6H), 2.17 (m, 1H), 1.53 (br s, 1H), 1.49 (br d, J = 3.2 Hz, 2H), 1.31–1.27 (m, 8H), 1.14 (br q, J = 11.6 Hz, 2H), 0.86 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 136.4, 134.7, 131.4, 128.8, 52.8, 50.7, 49.0, 44.3, 42.8, 41.3, 32.4, 30.2, 30.1, 20.9, 18.5. HRMS (FAB+, (M+H)): Calculated—355.2749, Found—355.2766.



2.22

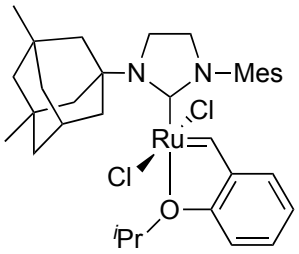
Preparation of 2.22: A two-neck 100 mL RB flask equipped with a condenser was dried and charged with $LiAlH_4$ (1.3 g, 34 mmol) and THF (50 mL). A separate 25 mL RB flask was dried and charged with **2.21** (3.0 g, 8.4 mmol) and THF (20 mL). The solution of **2.21** was then added dropwise to the $LiAlH_4$ suspension. After the addition was complete, the suspension was heated to 80 °C for 24 h, after which it was cooled to r.t. and carefully quenched via the sequential, dropwise addition of H_2O (1.3 mL), 15% NaOH solution (1.3 mL), and H_2O (4.0 mL). The quenched reaction was stirred for 5 h under air and then filtered through celite, washing with Et_2O. The filtrate was concentrated to give **2.22** (2.8 g, 98%), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2H), 3.04 (t, *J* = 4.4 Hz, 2H), 2.85 (t, *J* = 4.8 Hz, 2H), 2.34 (s, 6H), 2.28 (s, 3H), 2.20 (br s, 1H), 1.55 (s, 2H), 1.38–1.32 (m, 8H), 1.19–1.17 (m, 2H), 0.92 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 130.6, 129.4, 129.2, 52.1, 51.0, 49.5, 49.2, 43.1, 41.4, 40.9, 32.4, 30.4, 30.3, 20.6, 18.6. HRMS (FAB+, (M+H)): Calculated—341.2957, Found—341.2964.



2.23

Preparation of 2.23: A 100 mL round-bottom flask was dried and charged with **2.22** (1.0 g, 2.9 mmol), NH_4BF_4 (0.34 g, 3.2 mmol), and $CH(OMe)_3$ (6.0 mL, 28 mmol). The solution was heated to 100 °C for 4 h, cooled to r.t., and concentrated. The resulting

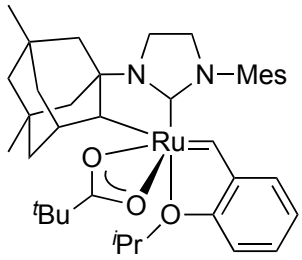
orange-red residue was washed with cold ^{n}BuOH:toluene (1:1) to give a white precipitate that was collected by filtration. Drying the precipitate under vacuum gave **2.23** (0.49 g, 44%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 6.89 (s, 2H), 4.31–4.13 (m, 4H), 2.27 (m, 1H), 2.26 (s, 3H), 2.22 (s, 6H), 1.65 (br s, 2H), 1.61 (br q, *J* = 11.6 Hz, 4H), 1.36 (br q, *J* = 14.4 Hz, 4H), 1.21 (br s, 2H), 0.91 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 139.9, 135.2, 130.7, 129.6, 59.3, 50.4, 49.6, 46.3, 44.9, 41.6, 39.0, 32.6, 29.7, 29.4, 20.8, 17.4. HRMS (FAB+, (M-BF_4)): Calculated—351.2800, Found—351.2755.



2.25

Preparation of 2.25: In a glovebox, a solution of **2.23** (0.49 g, 1.1 mmol) in hexanes (30 mL) was treated with $KCOMe_2Et$ (0.14 g, 0.91 mmol), and the mixture was allowed to stir at 35 °C for 1.5 h. To the reaction mixture was then added **2.24** (0.64 g, 1.1 mmol), upon which the mixture was removed from the glovebox and allowed to stir at 65 °C for 3.5 h. The precipitated solids were filtered and washed well with warm hexanes and pentane to give **2.25** (0.54 g, 89%) as a green powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 16.90 (s, 1H), 7.55 (ddd, *J* = 8.8, 7.3, 1.9 Hz, 1H), 7.06 (s, 2H), 6.95–6.88 (m, 2H), 6.86 (dd, *J* = 7.5, 1.8 Hz, 1H), 5.09 (hept, *J* = 6.3 Hz, 1H), 4.12 (s, 2H), 4.06–3.98 (m, 2H), 3.90–3.82 (m, 2H), 2.70 (p, *J* = 3.1 Hz, 1H), 2.46 (s, 3H), 2.25 (s, 6H), 2.04 (dd, *J* = 11.9, 1.8 Hz, 2H), 1.81 (d, *J* = 12.2 Hz, 2H), 1.74 (dt, *J* = 12.6, 2.8 Hz, 2H), 1.63 (d, *J* = 6.1 Hz, 6H), 1.47 (dt, *J* = 12.6, 2.4 Hz, 2H), 1.31–1.17 (m, 2H), 0.97 (s, 6H). ^{13}C NMR (126

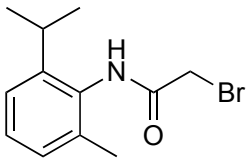
MHz, $CDCl_3$) δ 312.4, 207.8, 152.4, 145.9, 139.6, 138.5, 138.1, 130.8, 129.8, 123.9, 122.8, 113.5, 74.4, 58.9, 51.2, 50.7, 47.3, 44.7, 42.4, 42.2, 33.0, 31.3, 30.4, 22.6, 21.3, 18.5. HRMS (FAB+, (M)): Calculated—670.2031, Found—670.2028.



2.7

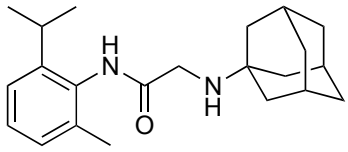
Preparation of 2.7: In a glovebox, a 20 mL scintillation vial was charged with **2.25** (0.10 g, 0.16 mmol), NaOPiv (0.19 g, 1.5 mmol), THF (2.0 mL), and MeOH (2.0 mL). The vial was capped, removed from the glovebox, and heated to 40 °C for 4.5 h, during which a color change from green to brown to dark purple was observed. The vial was then returned to the box, where the solvent was removed under high vacuum and the residue dissolved in CH_2Cl_2 (15 mL), filtered through celite, and concentrated to a deep purple residue. The residue was recrystallized from Et_2O at -35 °C. The resulting crystals were washed with cold Et_2O (3 x 5 mL) to give **2.7** (20 mg, 18%) as a bright purple solid. ^{1}H NMR (400 MHz, C_6D_6) δ 14.83 (s, 1H), 7.46 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 6.83 (br s, 1H), 6.76 (br s, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 4.79 (sept, *J* = 6.8 Hz, 1H), 3.91 (s, 1H), 3.47–3.40 (m, 2H), 3.27–3.14 (m, 2H), 2.57 (br s, 1H), 2.43 (s, 3H), 2.29 (s, 3H), 2.21 (s, 3H), 1.73 (br d, *J* = 11.2 Hz, 1H), 1.60 (br d, *J* = 10.8 Hz, 1H), 1.53–1.51 (m, 4H), 1.43–1.39 (m, 2H), 1.26 (s, 9H), 1.18 (q, *J* = 6.4 Hz, 4H), 1.03 (d, *J* = 9.6 Hz, 1H), 0.89 (br s, 4H), 0.77 (br d, *J* = 12.8 Hz, 1H), 0.67 (br d, *J* = 10.4 Hz, 1H), 0.62 (s, 3H), 0.31 (br d, *J* = 9.6 Hz, 1H). ^{13}C NMR (101 MHz, C_6D_6) δ 259.0, 214.9, 154.2, 143.8, 138.0, 137.0, 136.8, 136.5, 129.9, 129.7, 125.6,

123.1, 122.8, 113.9, 74.5, 66.5, 64.1, 52.1, 51.7, 48.8, 46.6, 42.6, 41.3, 39.8, 39.1, 38.6, 33.4, 32.1, 30.8, 30.7, 28.9, 27.8, 21.6, 21.2, 21.0, 19.1, 19.0. HRMS (FAB+, [(M+H)-H_2]): Calculated—700.3178, Found—700.3181.



2.26

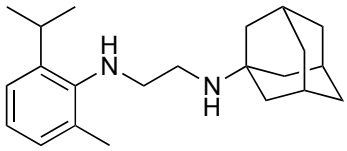
Preparation of 2.26: Bromoacetyl chloride (2.8 mL, 34 mmol) was added dropwise to a 0 °C solution of 2-isopropyl-6-methylaniline (5.0 g, 34 mmol) and K_2CO_3 (9.4 g, 68 mmol) in MeCN (70 mL). The solution was warmed to r.t., stirred overnight, filtered over celite, and concentrated. Recrystallization from CH_2Cl_2/hexanes provided **2.26** (5.5 g, 60%) as a colorless solid. ^{1}H NMR δ 7.77 (br s, 1H), 7.24 (m, 1H), 7.18 (m, 1H), 7.11 (m, 1H), 4.08 (s, 2H), 3.06 (m, 1H), 2.24 (s, 3H), 1.21 (d, J = 6.9 Hz, 6H). ^{13}C NMR δ 164.3, 145.7, 135.9, 131.6, 128.4, 128.3, 123.7, 29.2, 28.7, 23.5, 18.5. HRMS (FAB+, (M+H)): Calculated—270.0493, Found—270.0480.



2.27

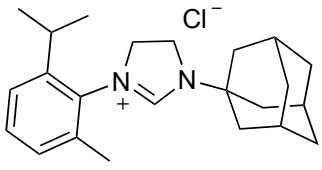
Preparation of 2.27: Compound **2.26** (2.4 g, 8.9 mmol) and 1-adamantylamine (92.0 g, 13 mmol) were dissolved in MeCN (30 mL), K_2CO_3 (1.9 g, 14 mmol) was added, and the solution was refluxed for 24 h. After cooling to r.t., the mixture was filtered over celite and concentrated. The residue was then dissolved in CH_2Cl_2 and filtered over a pad of silica gel (eluent 10% MeOH in CH_2Cl_2). Removal of the solvent *in vacuo* provided **2.27** (3.0 g, 94%) as a peach solid. ^{1}H NMR δ 9.15 (br s, 1H), 7.18 (m, 1H), 7.16 (m, 1H),

7.09 (m, 1H), 3.44 (s, 2H), 3.04 (m, 1H), 2.23 (s, 3H), 2.11 (m, 3H), 1.58–1.72 (m, 14H), 1.20 (d, J = 6.9 Hz, 6H). ^{13}C NMR δ 171.9, 145.2, 135.6, 132.8, 128.1, 127.5, 123.3, 51.1, 44.0, 42.9, 36.5, 29.5, 28.7, 23.4, 18.8. HRMS (FAB+, (M+H)): Calculated—341.2593, Found—341.2603.



2.28

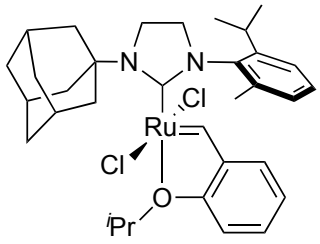
Preparation of 2.28: $LiAlH_4$ (1.0 g, 26 mmol) was added portion-wise to a 0 °C solution of compound **2.27** (3.0 g, 8.8 mmol) in THF (45 mL), and the resulting solution was brought to r.t. and refluxed for 72 h. The mixture was then cooled to 0 °C and carefully quenched via the sequential, dropwise addition of H_2O (1.0 mL), 10% *aq.* NaOH (1.0 mL), and H_2O (1.0 mL). The solution was then dried with $MgSO_4$, filtered, and concentrated. Flash chromatography of the residue (SiO_2, eluent 66% Et_2O in pentanes) provided **2.28** (1.8 g, 62%) as a yellow oil. ^{1}H NMR δ 7.08 (m, 1H), 6.98 (m, 1H), 6.91 (m, 1H), 3.30 (m, 1H), 3.06 (m, 2H), 2.86 (m, 2H), 2.32 (s, 3H), 2.08 (m, 3H), 1.59–1.73 (m, 15H), 1.23 (d, J = 6.9 Hz, 6H). ^{13}C NMR δ 145.1, 140.8, 130.6, 128.4, 123.6, 122.4, 51.1, 50.1, 42.9, 42.5, 40.7, 36.6, 29.5, 27.5, 24.0, 19.1. HRMS (FAB+, (M+H)): Calculated—327.2800, Found—327.2800.



2.29

Preparation of 2.29: A solution of compound **2.28** (1.3 g, 4.0 mmol) in Et_2O (7.0 mL) was treated with HCl (4.0 mL, 2.0 M in Et_2O) and stirred for 15 min at r.t. The resulting

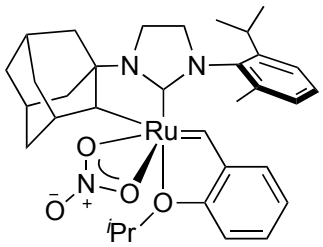
solid was filtered, washed with Et_2O, and dried, then suspended in $CH(OEt)_3$ and refluxed for 2 h. After cooling to r.t. and concentrating, the solid residue was washed rigorously with Et_2O to provide **2.29** (0.75 g, 50%) as a tan powder. ^{1}H NMR δ 8.79 (br s, 1H), 7.32 (m, 1H), 7.22 (m, 1H), 7.13 (m, 1H), 4.55 (m, 1H), 4.43 (m, 2H), 4.25 (m, 1H), 2.93 (m, 1H), 2.41 (s, 3H), 2.27 (m, 3H), 2.18–2.08 (m, 6H), 1.74 (m, 6H), 1.28 (d, J = 6.8 Hz, 6H). ^{13}C NMR δ 156.0, 146.5, 135.9, 132.0, 130.6, 129.2, 124.8, 58.2, 52.1, 45.5, 41.1, 35.4, 29.2, 28.7, 24.8, 24.2, 18.7. HRMS (FAB+, (M-Cl)): Calculated—337.2644, Found—337.2652.



2.30

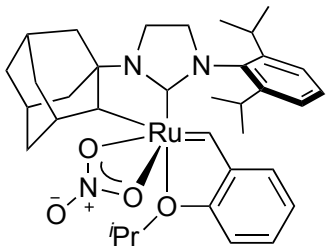
Preparation of 2.30: In a glovebox, $KCOMe_2Et$ (75 mg, 0.57 mmol) was added to a suspension of compound **2.29** (0.19 g, 0.52 mmol) in hexanes (6.0 mL). The solution was stirred at 35 °C for 30 minutes before adding **2.24** (0.31 g, 0.52 mmol), at which point the solution was removed from the glovebox. The solution was stirred for 2 h at 65 °C and then cooled to r.t. The resulting precipitate was filtered and washed thoroughly with warm hexanes to provide **2.30** (0.22 g, 65%) as a green solid. ^{1}H NMR δ 16.9 (s, 1H), 7.54 (m, 1H), 7.49 (m, 1H), 7.22 (m, 1H), 6.92 (m, 1H), 6.87 (m, 1H), 6.85 (m, 1H), 5.07 (m, 1H), 3.98–4.11 (m, 2H), 3.84–3.92 (m, 2H), 3.15 (m, 1H), 2.96 (m, 5H), 2.42 (m, 2H), 2.32 (s, 3H), 1.94 (m, 3H), 1.83 (m, 3H), 1.69 (d, J = 6.2 Hz, 3H), 1.60 (d, J = 6.2 Hz, 3H), 1.18 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H). ^{13}C NMR δ 310.5, 208.2, 152.5, 148.7, 145.2, 140.6, 137.9, 130.6, 129.1, 128.9, 124.8, 123.8, 122.5, 113.2, 74.2,

57.2, 52.7, 44.5, 42.2, 36.1, 30.0, 27.6, 25.5, 23.8, 22.7, 22.3, 18.9. HRMS (FAB+, (M)): Calculated—656.1875, Found—656.1894.



2.8

Preparation of 2.8: In a glovebox, a solution of NaOPiv (0.30 g, 1.5 mmol) in MeOH (2.0 mL) was added to a solution of **2.30** (0.15 g, 0.15 mmol) in THF (2.0 mL). The mixture was removed from the glovebox, heated at 50 °C for 21 h, and then brought back into the glovebox and concentrated. The resulting residue was taken up in CH_2Cl_2, filtered over a pad of celite, and concentrated. The solid was then dissolved in THF (8.0 mL), and NH_4NO_3 (0.12 g, 1.5 mmol) was added. After stirring for 3 h, the mixture was concentrated, taken up in CH_2Cl_2, filtered over a pad of celite, and concentrated again. Rigorous washing of the resulting solid with Et_2O provided **2.8** (0.70 g, 72%) as a purple solid. ^{1}H NMR δ 15.0 (s, 1H), 7.48 (m, 1H), 7.42 (m, 1H), 7.13 (m, 1H), 7.08 (m, 1H), 6.99 (m, 1H), 6.97 (m, 1H), 5.10 (m, 1H), 3.95 (m, 1H), 3.78–3.99 (m, 4H), 3.72 (m, 1H), 3.15 (m, 1H), 2.23 (m, 1H), 2.18 (s, 3H), 2.18 (*overlapped*, 1H), 2.06 (m, 1H), 1.99 (m, 1H), 1.92 (m, 1H), 1.72 (m, 1H), 1.65 (m, 1H), 1.59 (m, 1H), 1.55 (m, 2H), 1.48 (d, J = 6.2 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H), 1.17 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 6.8 Hz, 3H), 0.98 (m, 2H), 0.24 (m, 1H). ^{13}C NMR δ 266.4, 213.1, 154.7, 147.6, 143.1, 138.0, 137.3, 128.7, 128.3, 127.1, 124.0, 123.4, 123.4, 112.9, 74.4, 67.6, 52.6, 43.2, 42.3, 40.3, 37.9, 37.7, 37.6, 33.3, 31.0, 29.8, 28.3, 26.3, 23.6, 21.4, 20.6, 17.5. HRMS (FAB+, [(M+H)-H_2]): Calculated—646.2219, Found—646.2239.



2.9

Preparation of 2.9: In a glovebox, a 250 mL Schlenk flask was charged with **2.4** (0.50 g, 0.73 mmol), NaOPiv (0.92 g, 7.4 mmol), THF (32 mL), and MeOH (16 mL). The flask was sealed, removed from the glovebox, and heated to 40 °C for 4 d, during which the solution was observed to change color from green to brown to dark purple. The solvent was removed under high vacuum and the Schlenk flask transferred back into the glovebox. The residue was then dissolved in CH_2Cl_2 (80 mL), filtered through celite, and concentrated to a deep purple residue consisting of a mixture of the C–H activated product and pivalic acid. To this mixture was added NH_4NO_3 (0.72 g, 9.0 mmol) and THF (35 mL). The reaction was allowed to stir for 3 h and then concentrated. The resulting residue was dissolved in C_6H_6 (70 mL), filtered through celite, and concentrated. Trituration with Et_2O (3 x 15 mL) provided **2.9** (100 mg, 20%) as a bright purple powder. ^{1}H NMR (500 MHz, C_6D_6) δ 15.21 (s, 1H), 7.45 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.19 (qd, *J* = 5.8, 5.2, 2.5 Hz, 3H), 7.00 (dd, *J* = 6.8, 2.5 Hz, 1H), 6.85 (t, *J* = 7.4 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 4.54 (hept, *J* = 6.3 Hz, 1H), 4.10 (s, 1H), 3.83–3.71 (m, 2H), 3.59 (ddd, *J* = 11.7, 10.1, 8.1 Hz, 1H), 3.36 (ddd, *J* = 11.0, 9.7, 8.1 Hz, 1H), 3.26–3.15 (m, 2H), 2.25 (t, *J* = 3.0 Hz, 1H), 2.06 (p, *J* = 3.3 Hz, 1H), 1.94 (tt, *J* = 11.9, 2.4 Hz, 2H), 1.77 (*overlapped*, 2H), 1.75 (d, *J* = 6.7 Hz, 3H), 1.63 (p, *J* = 3.4 Hz, 1H), 1.55–1.44 (m, 2H), 1.43 (*overlapped*, 1H), 1.42 (d, *J* = 6.4 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.14 (*overlapped*, 1H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.10 (*overlapped*, 1H),

0.97 (d, J = 6.1 Hz, 3H), 0.58 (dt, J = 12.2, 2.6 Hz, 1H). ^{13}C NMR (126 MHz, C_6D_6) δ 267.5, 211.9, 154.8, 147.5, 147.4, 143.4, 135.6, 129.2, 126.9, 124.8, 124.2, 123.4, 123.4, 113.2, 74.4, 66.4, 63.2, 54.1, 43.0, 41.6, 40.3, 38.0, 37.8, 37.7, 33.3, 30.9, 29.8, 29.0, 28.7, 27.9, 26.8, 23.6, 23.1, 21.1, 20.3. HRMS (FAB+, [(M+H)-H_2]): Calculated—674.2566, Found—674.2532.

General Procedure for Homodimerization Reactions: In a glovebox, a 4 mL vial was charged with catalyst (0.014 mmol) and THF (1.0 mL) to make a stock solution (0.014 M). A portion of the catalyst stock solution (70 μL, ca. 1.0 μmol, 0.1 mol %) was then added to a 4 mL vial containing substrate (1.0 mmol) and THF (100 μL, *ca.* 3.3 M). The reaction was placed into an aluminum block on an IKA temperature-controlled hotplate preheated to 35 °C and stirred while open to the glovebox atmosphere. After the completion of the reaction (as determined by ^{1}H NMR spectroscopy), the vial was removed from the glovebox and quenched with oxygen. The product was then isolated either via flash chromatography on silica gel or by removal of the starting material *in vacuo* according to literature procedures. The percentage of *Z*-olefin product was determined by ^{1}H NMR spectroscopy. All spectra were consistent with previous literature reports.[2b]

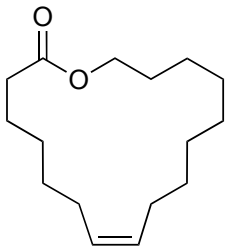
General Procedure for the Synthesis of 2.17 Using Catalyst 2.9: In a glovebox, a 20 mL vial was charged with **2.15** (3.1 mL, 25 mmol), **2.16** (520 μL, 2.5 mmol), and THF (1.4 mL). **2.9** (8.5 mg, 0.013 mmol, 0.5 mol %) was added, and the reaction was stirred at 35 °C in an open vial. After 2 h, the vial was removed from the glovebox, quenched with

excess ethyl vinyl ether (1.5 mL) and stirred for 1 h. The solvent was then removed *in vacuo*. The crude mixture was purified by flash chromatography (SiO_2, eluent hexanes to 4% ethyl acetate in hexanes) two times to provide the pure *Z*-isomer of **2.17** (430 mg, 71%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34 (m, 2H), 4.05 (t, J = 6.8 Hz, 2H), 2.00–2.04 (m, 7H), 1.60–1.63 (m, 2H), 1.29–1.36 (m, 12H), 0.88–0.91 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 130.1, 129.9, 64.8, 32.1, 29.8, 29.3, 28.7, 27.3, 27.1, 26.0, 22.5, 21.2, 14.1. HRMS (EI+, (M+H)): Calculated—241.2168, Found—241.2174.

Synthesis of 2.17 at 1 mol % Catalyst Loading: Following the general procedure, **2.9** (1.7 mg, 2.5 μmol, 0.1 mol %) was added to a solution of **2.15** (3.1 mL, 25 mmol) and **2.16** (520 μL, 2.5 mmol) in THF (1.4 mL) to produce the pure *Z*-isomer of **2.17** (360 mg, 60%) as a colorless oil.

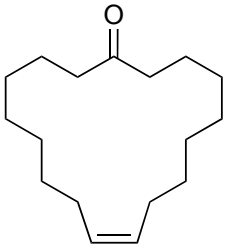
General Procedure for Macrocyclizations Using Catalyst 2.9: In a glovebox, a 500 mL Strauss flask was charged with a solution of diene (0.45 mmol) in DCE (90 mL), and a solution of **2.9** (0.034 mmol, 7.5 mol %) dissolved in DCE (1.0 mL) was added. The flask was sealed, brought out of the glovebox, and subjected to a single freeze-pump-thaw cycle. Keeping the flask under a static vacuum of *ca.* 20 mTorr, the reaction was heated at 60 °C. After 24 h, the mixture was cooled, quenched with excess ethyl vinyl ether, and concentrated. Flash chromatography of the residue (SiO_2, eluent 2% Et_2O in pentanes for compounds **2.18** and **2.19** and 10% Et_2O in pentanes for compound **2.20**) provided the product. The percentage of *Z*-olefin product was determined by ^{1}H or

quantitative ^{13}C NMR spectroscopy.[18] Quantitative ^{13}C measurements were acquired at 126 MHz (decoupled, without NOE, 13 second delay time).



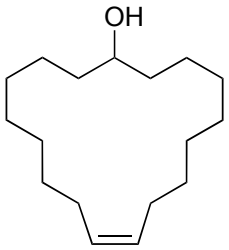
2.18

Preparation of 2.18: According to the general procedure for macrocyclizations, diene **2.18a** (62 mg, 0.22 mmol) was reacted with **2.9** (12 mg, 0.018 mmol) to provide **2.18** (35 mg, 64% yield, 98% *Z*) as a colorless oil. ^1H NMR δ 5.32 (m, 2H), 4.13 (t, J = 5.4 Hz, 2H), 2.33 (t, J = 6.5 Hz, 2H), 2.04 (m, 4H), 1.63 (m, 4H), 1.21–1.43 (m, 14H). ^{13}C NMR δ 174.0, 130.2, 130.0, 63.7, 34.6, 29.4, 28.8, 28.7, 28.5 (2C), 28.4, 27.7, 27.0, 26.8, 25.3 (2C). HRMS (EI+, (M)): Calculated—252.2089, Found—252.2084.



2.19

Preparation of 2.19: According to the general procedure for macrocyclizations, diene **2.19a** (60 mg, 0.22 mmol) was reacted with **2.9** (12 mg, 0.018 mmol) to provide **2.19** (20 mg, 36% yield, 99% *Z*) as a colorless solid. ^1H NMR δ 5.34 (m, 2H), 2.40 (t, J = 6.7 Hz, 4H), 2.01 (m, 4H), 1.62 (m, 4H), 1.21–1.39 (m, 16H). ^{13}C NMR δ 212.6, 130.2 (2C), 42.5 (2C), 29.0 (2C), 28.6 (2C), 28.2 (2C), 28.1 (2C), 26.7 (2C), 23.9 (2C). HRMS (EI+, (M)): Calculated—250.2297, Found—250.2289.



2.20

Preparation of 2.20: According to the general procedure for macrocyclizations, diene **2.20a** (62 mg, 0.22 mmol) was reacted with **2.9** (12 mg, 0.018 mmol) to provide **2.20** (23 mg, 42% yield, 97% *Z*) as a colorless solid. ^{1}H NMR δ 5.34 (m, 2H), 3.72 (m, 1H), 2.04 (m, 4H), 1.50 (m, 4H), 1.22–1.40 (m, 21H). ^{13}C NMR δ 130.2 (2C), 70.4, 35.7 (2C), 29.0 (2C), 28.2 (2C), 28.0 (2C), 27.9 (2C), 26.8 (2C), 23.5 (2C). HRMS (EI+, (M)): Calculated—252.2453, Found—252.2463.

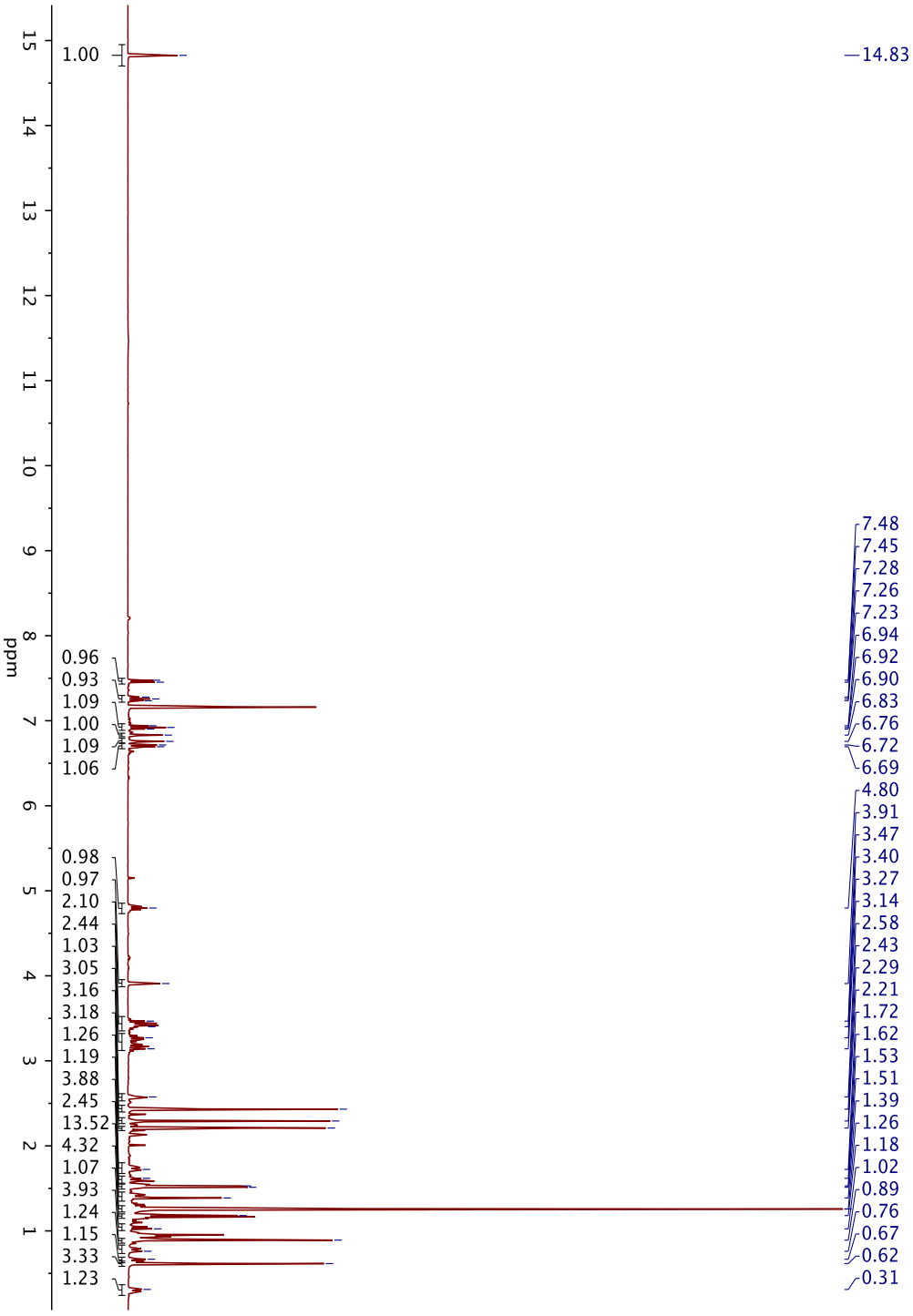


Figure 2.2. ^{1}H NMR (400 MHz, C_6D_6) spectrum of **2.7**.

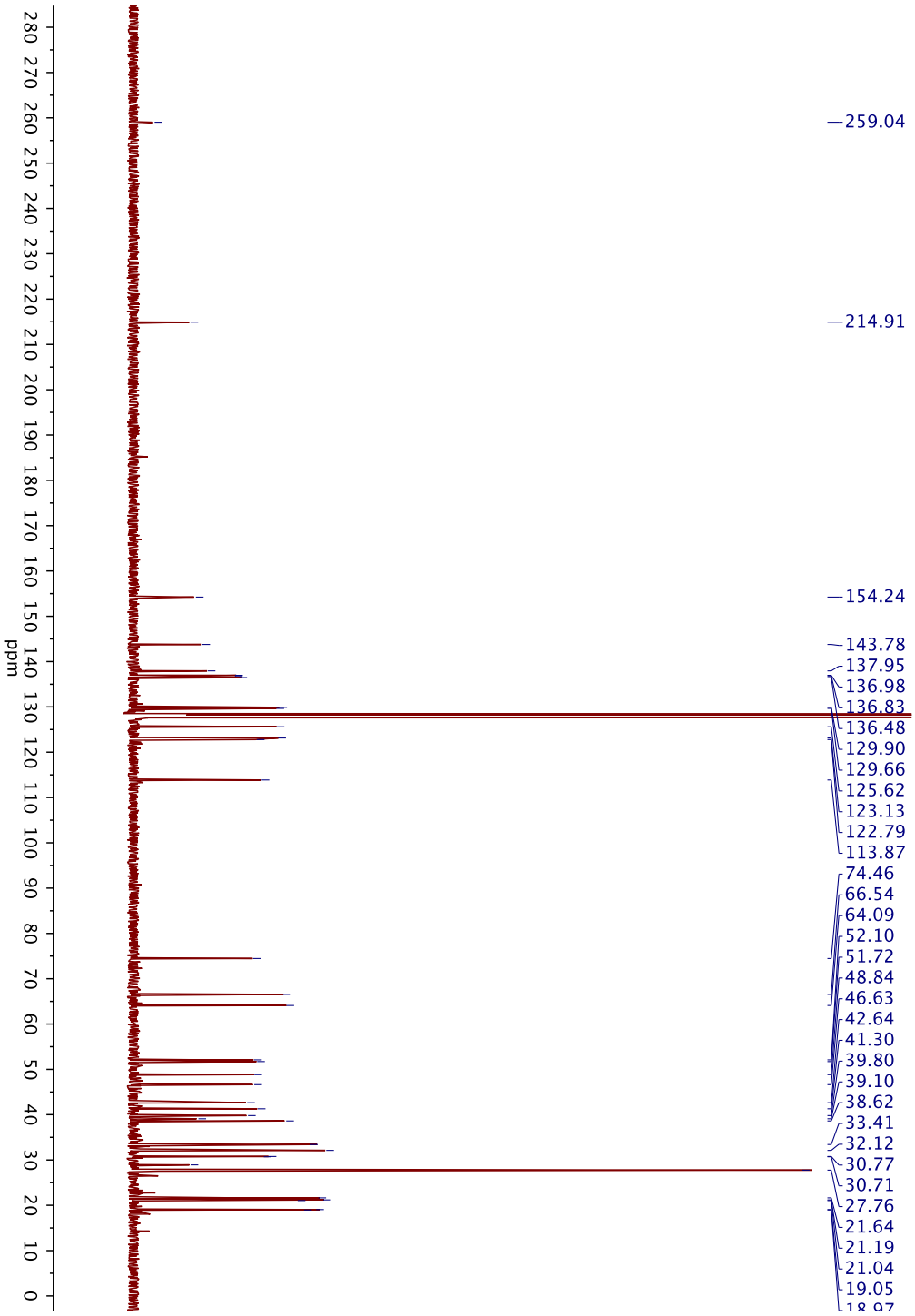


Figure 2.3. ^{13}C NMR (101 MHz, C_6D_6) spectrum of **2.7**.

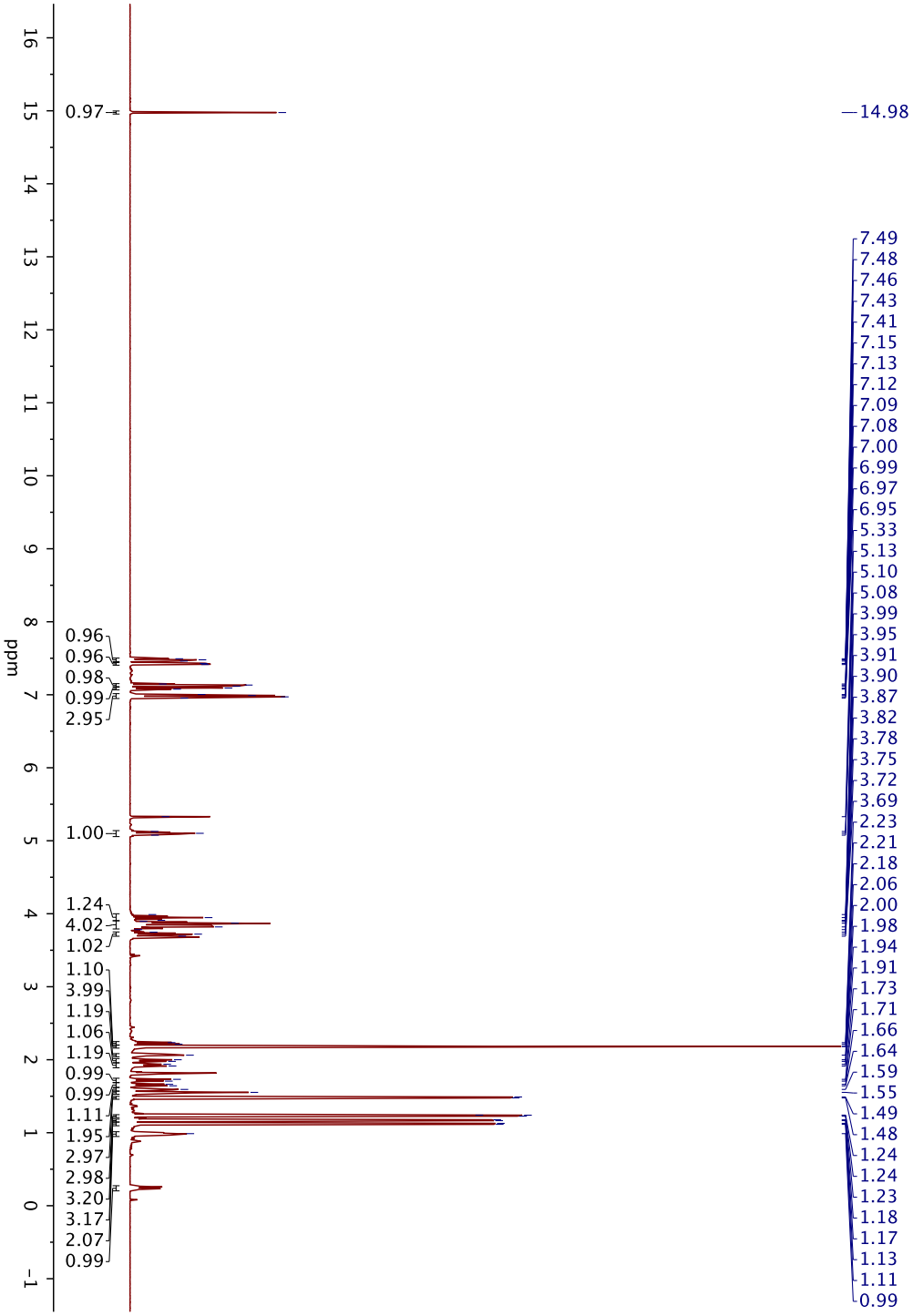


Figure 2.4. ^{1}H NMR (500 MHz, CD_2Cl_2) spectrum of **2.8**.

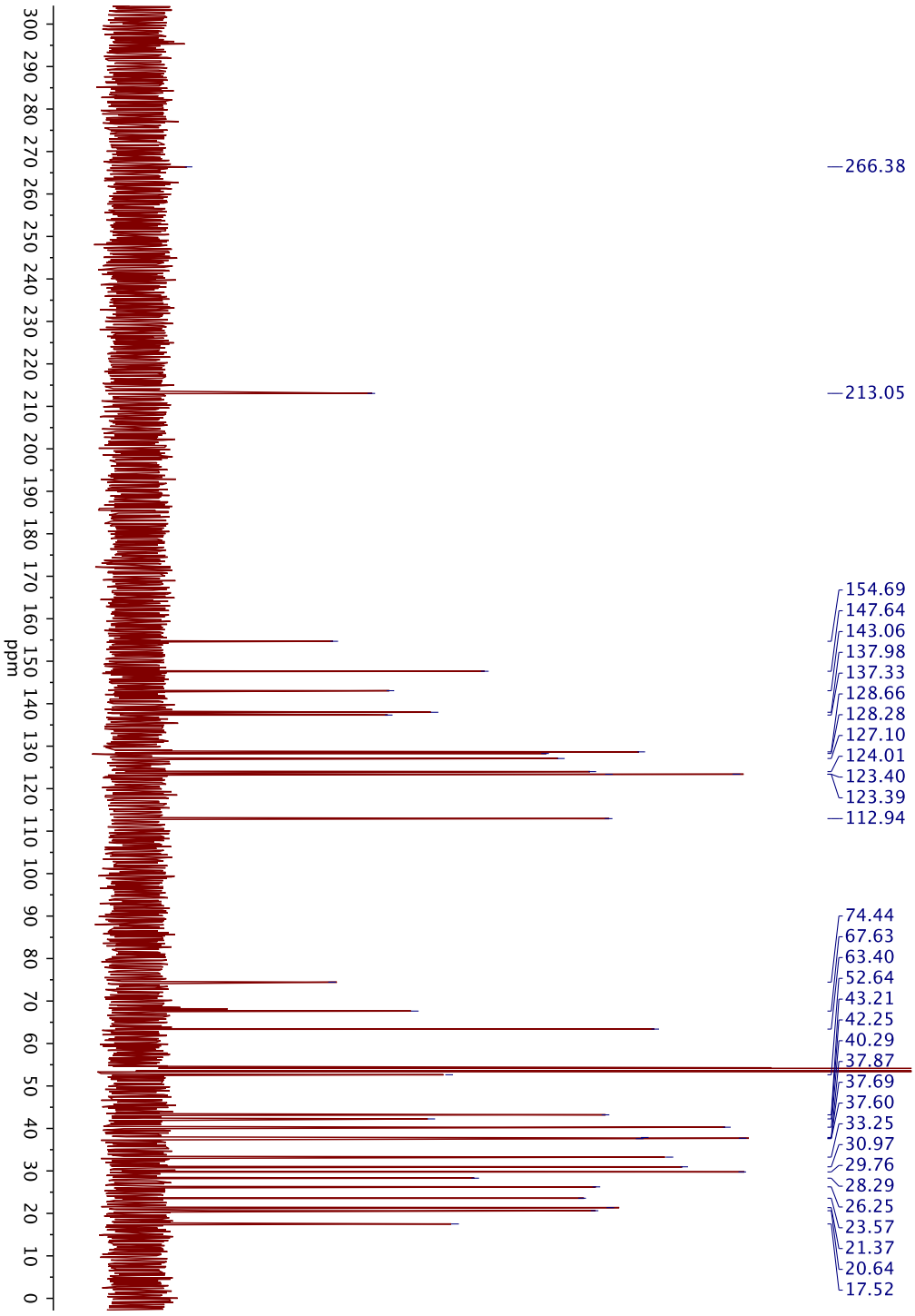


Figure 2.5. ^{13}C NMR (126 MHz, CD_2Cl_2) spectrum of **2.8**.

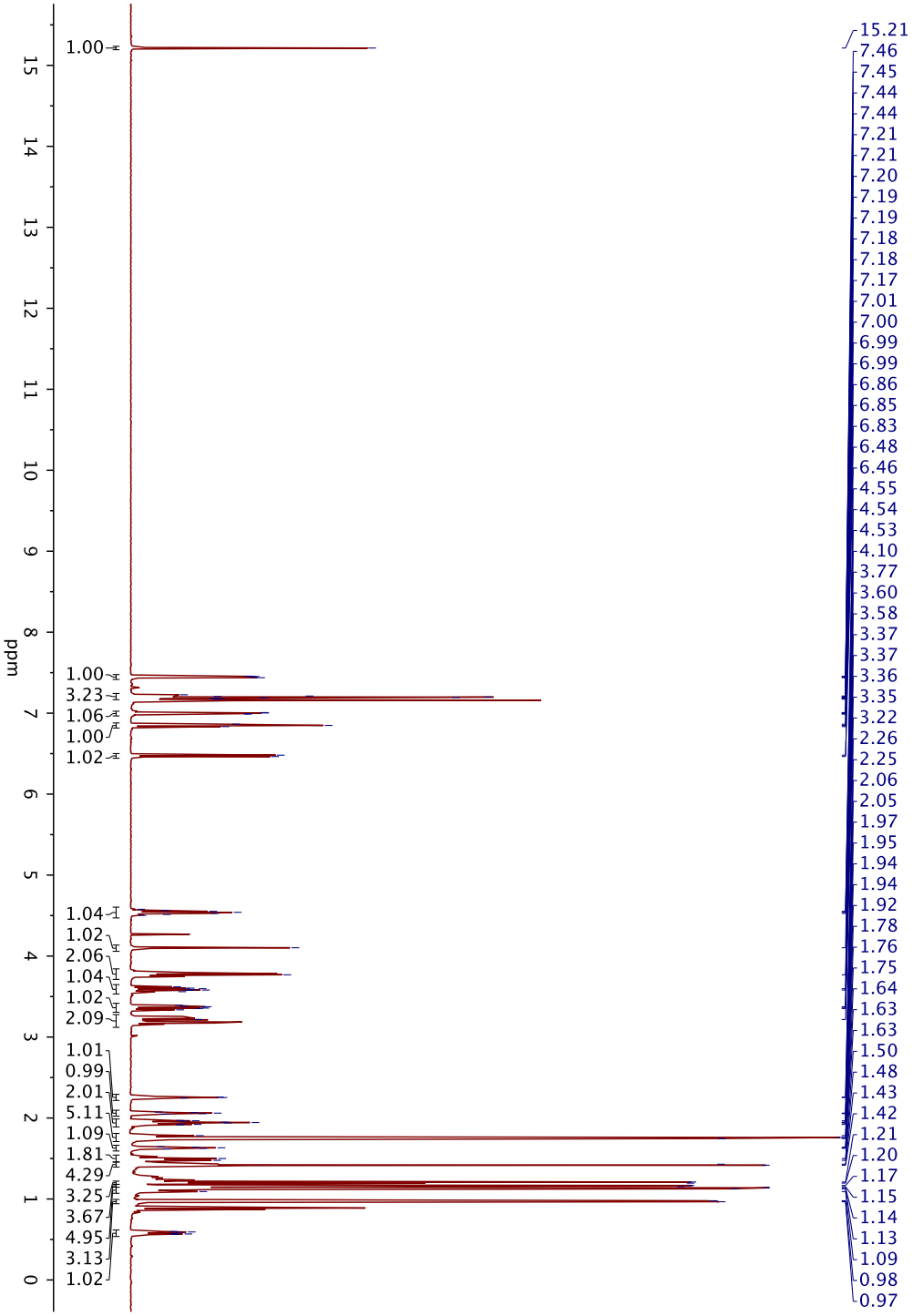


Figure 2.6. ^{1}H NMR (500 MHz, C_6D_6) spectrum of **2.9**.

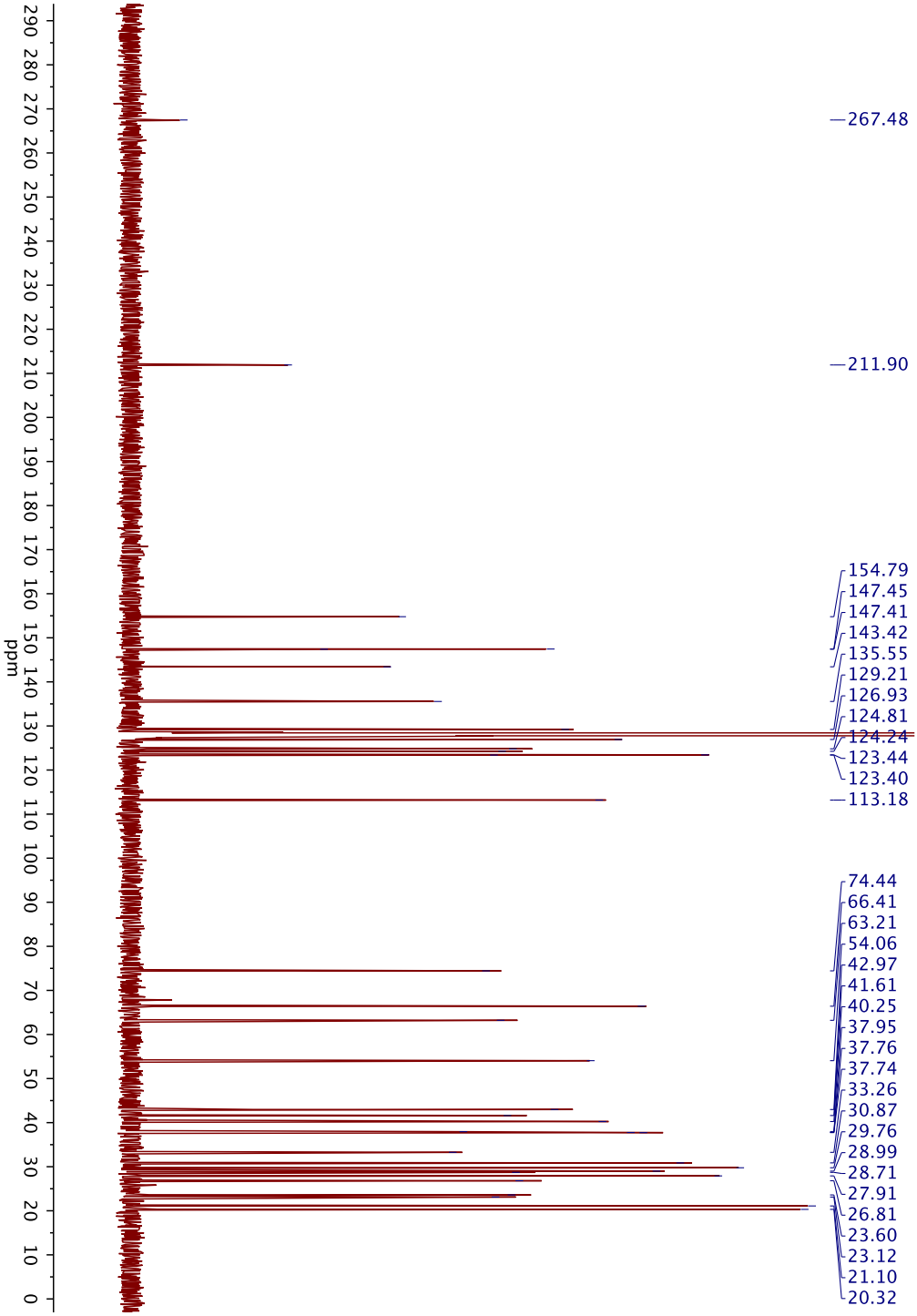


Figure 2.7. ^{13}C (126 MHz, C_6D_6) spectrum of **2.9**.

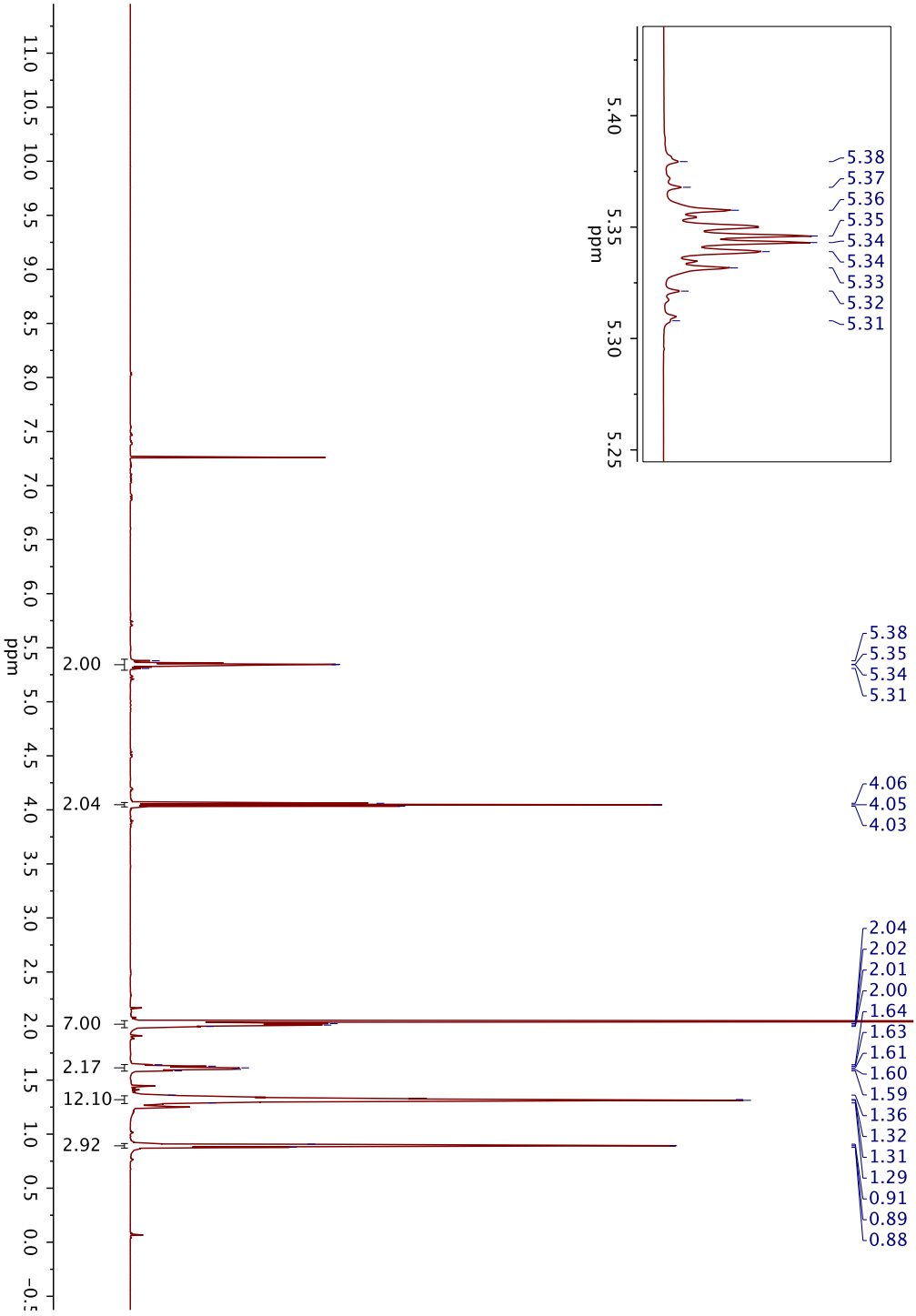


Figure 2.8. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **2.17**.

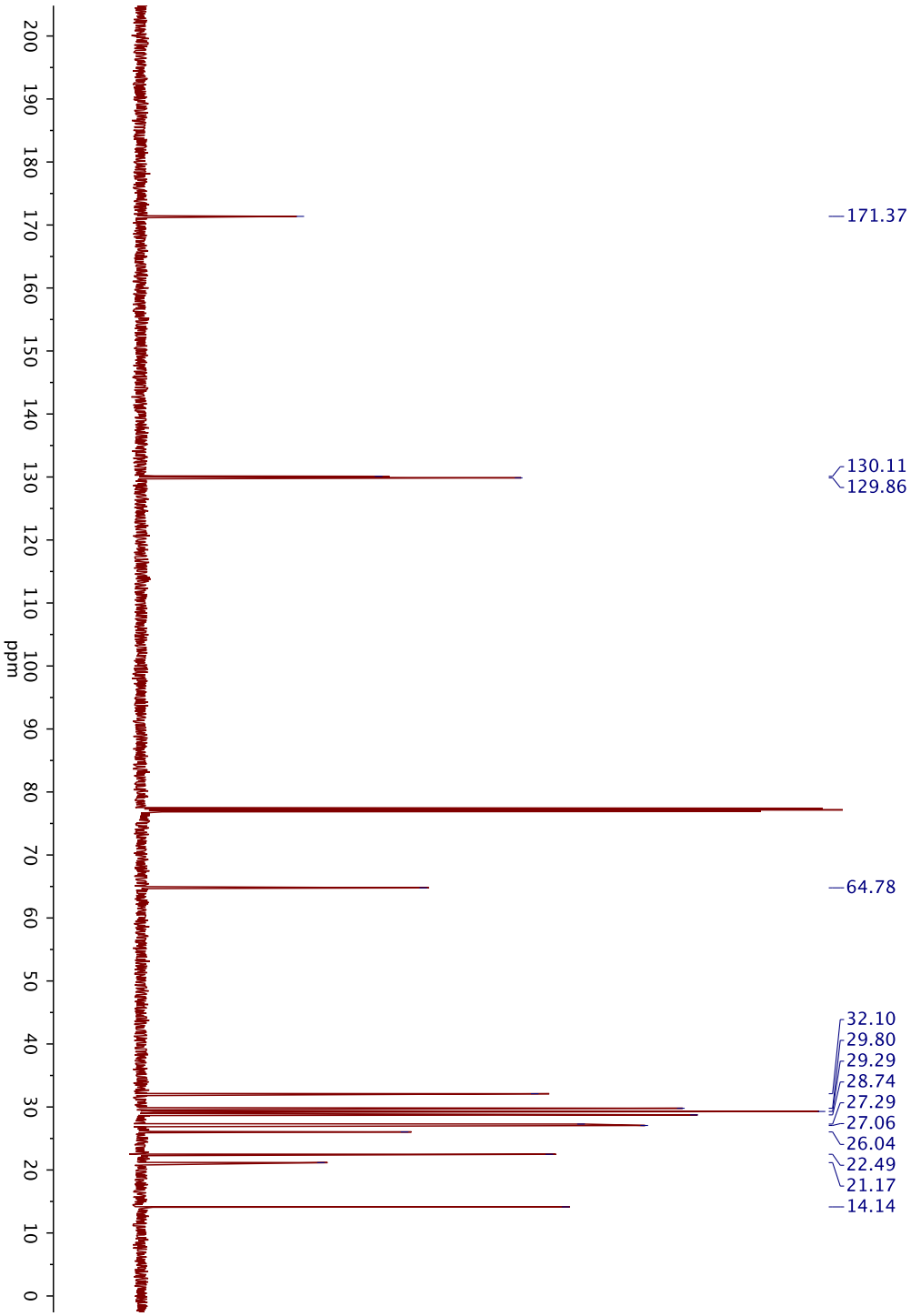


Figure 2.9. ^{13}C (126 MHz, $CDCl_3$) spectrum of **2.17**.

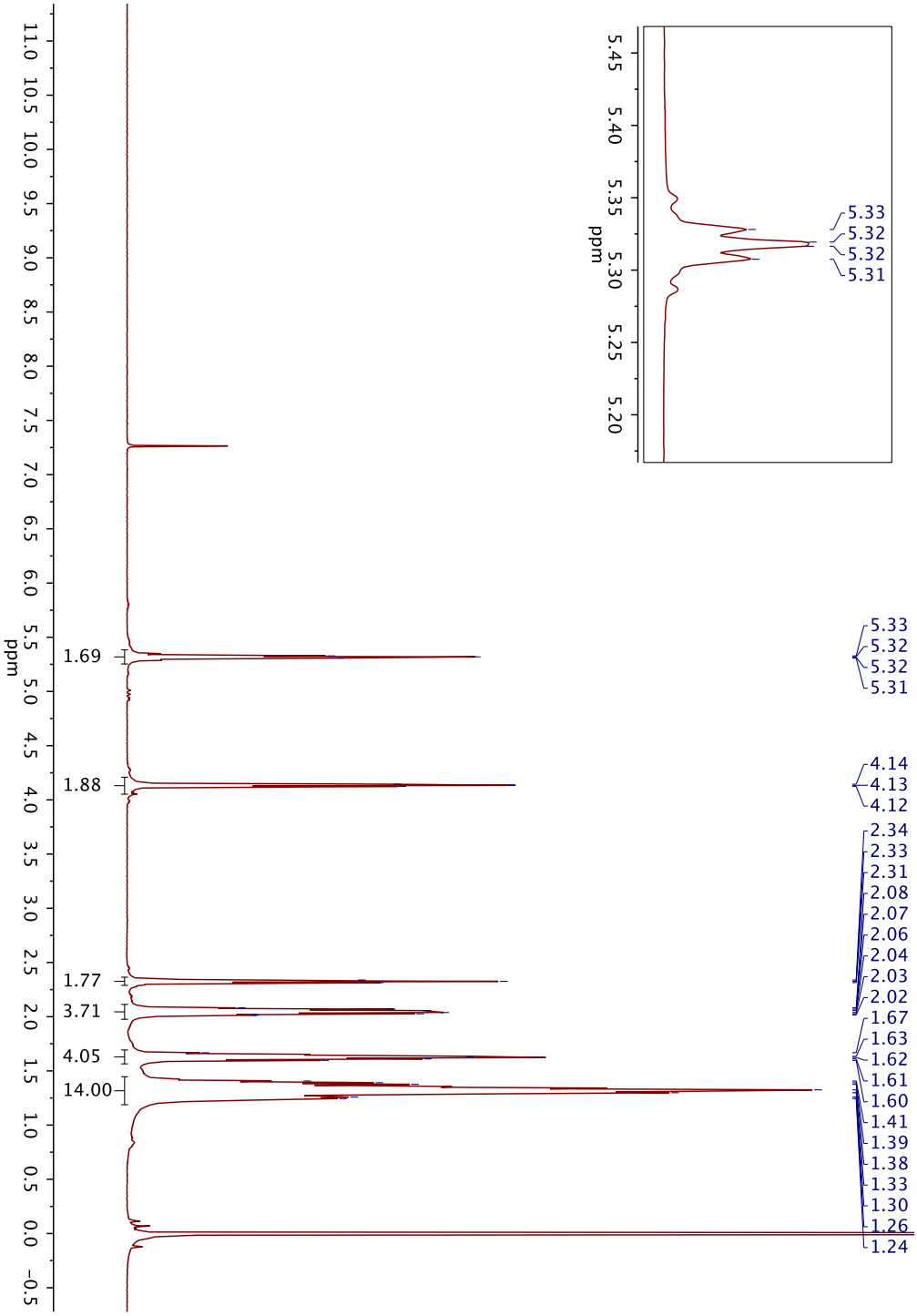


Figure 2.10. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **2.18**.

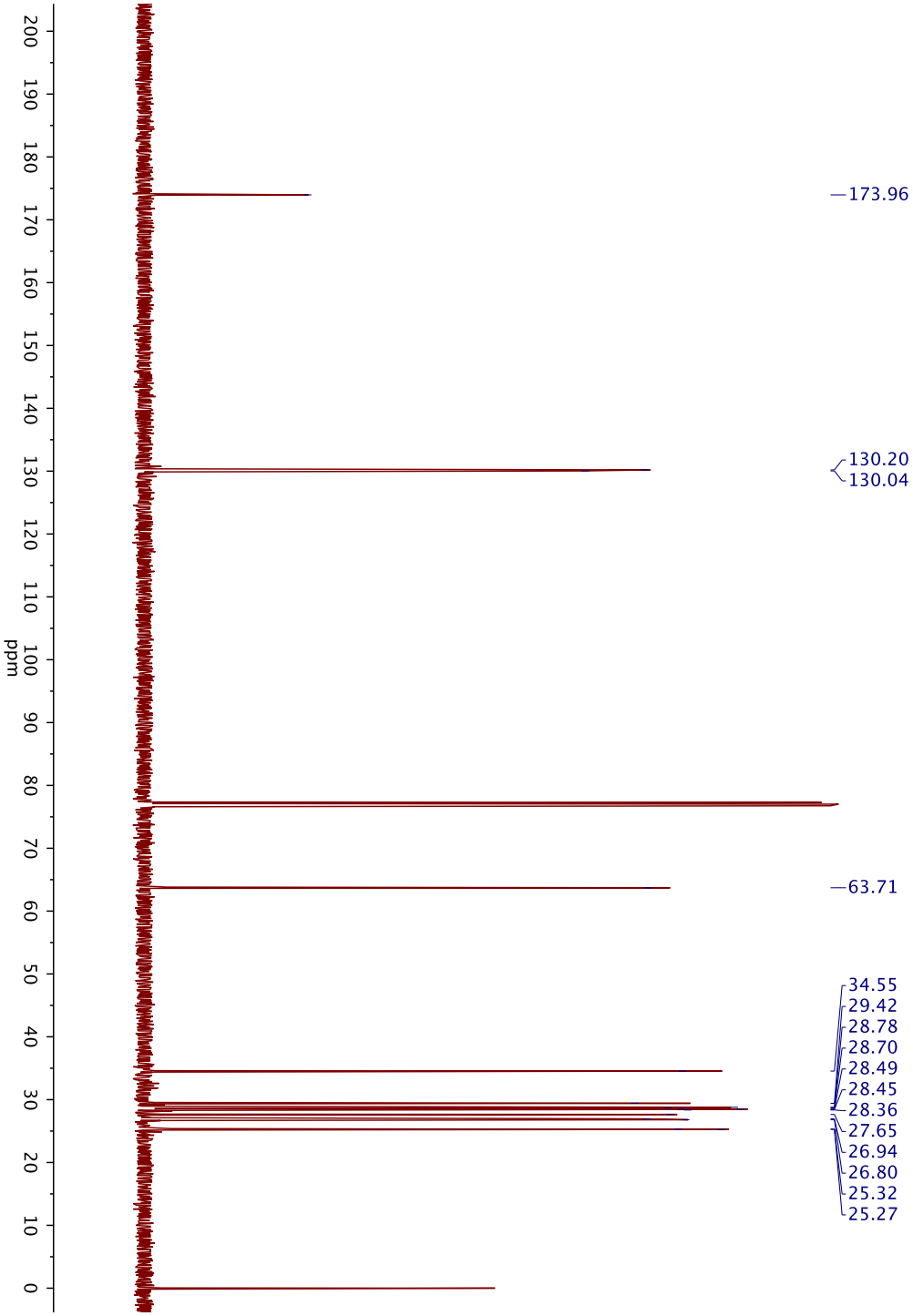


Figure 2.11. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of **2.18**.

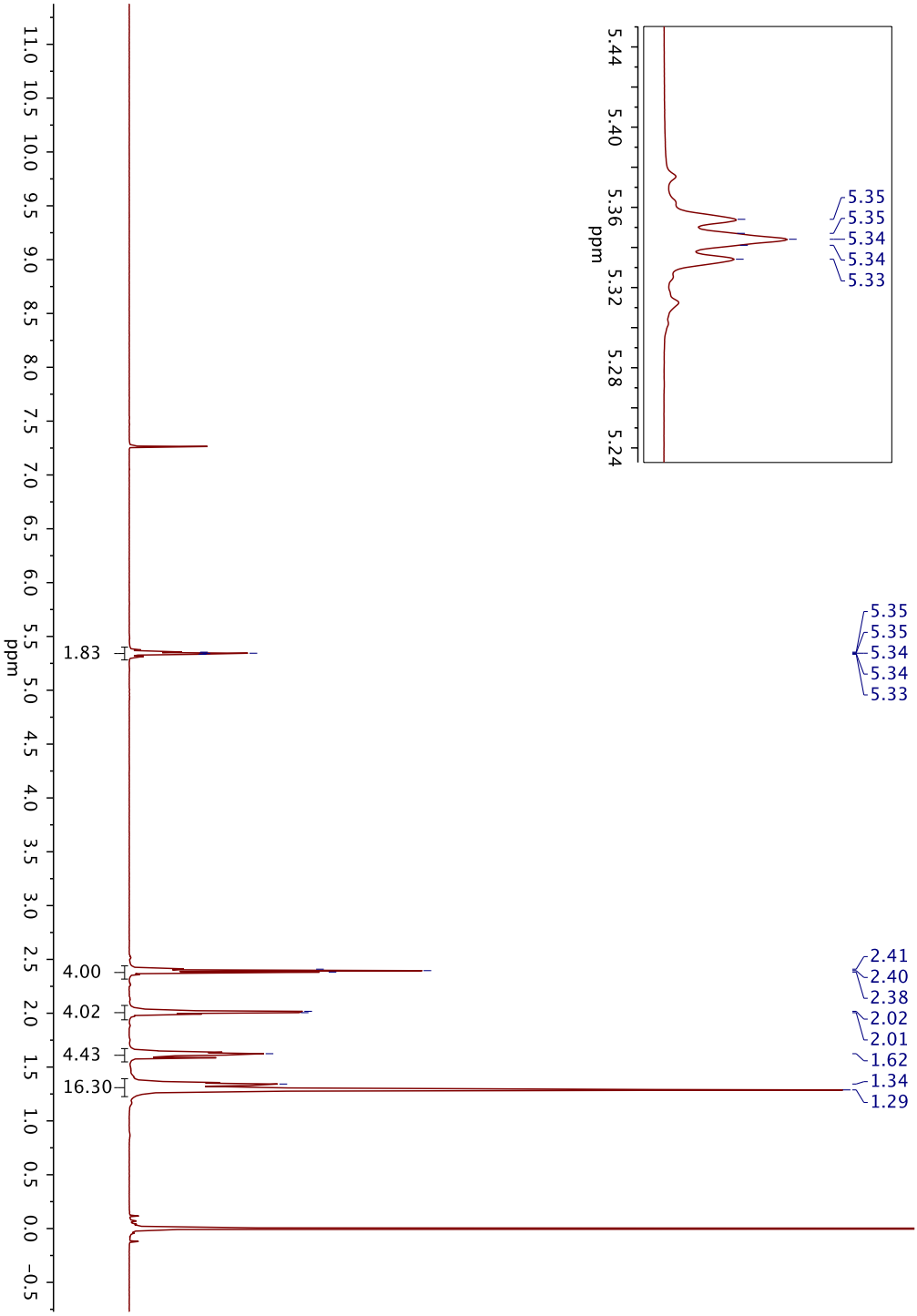


Figure 2.12. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **2.19**.

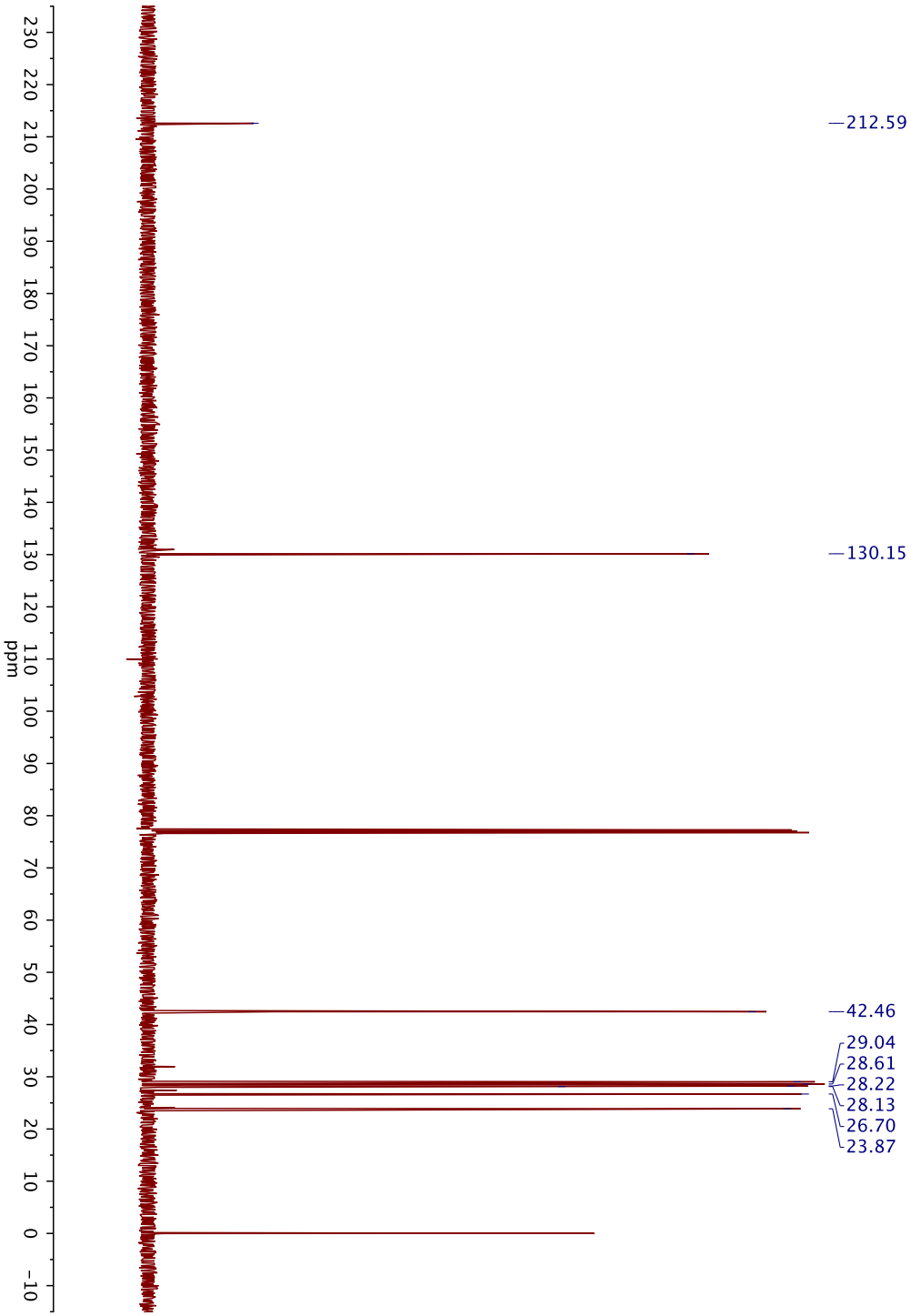


Figure 2.13. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of **2.19**.

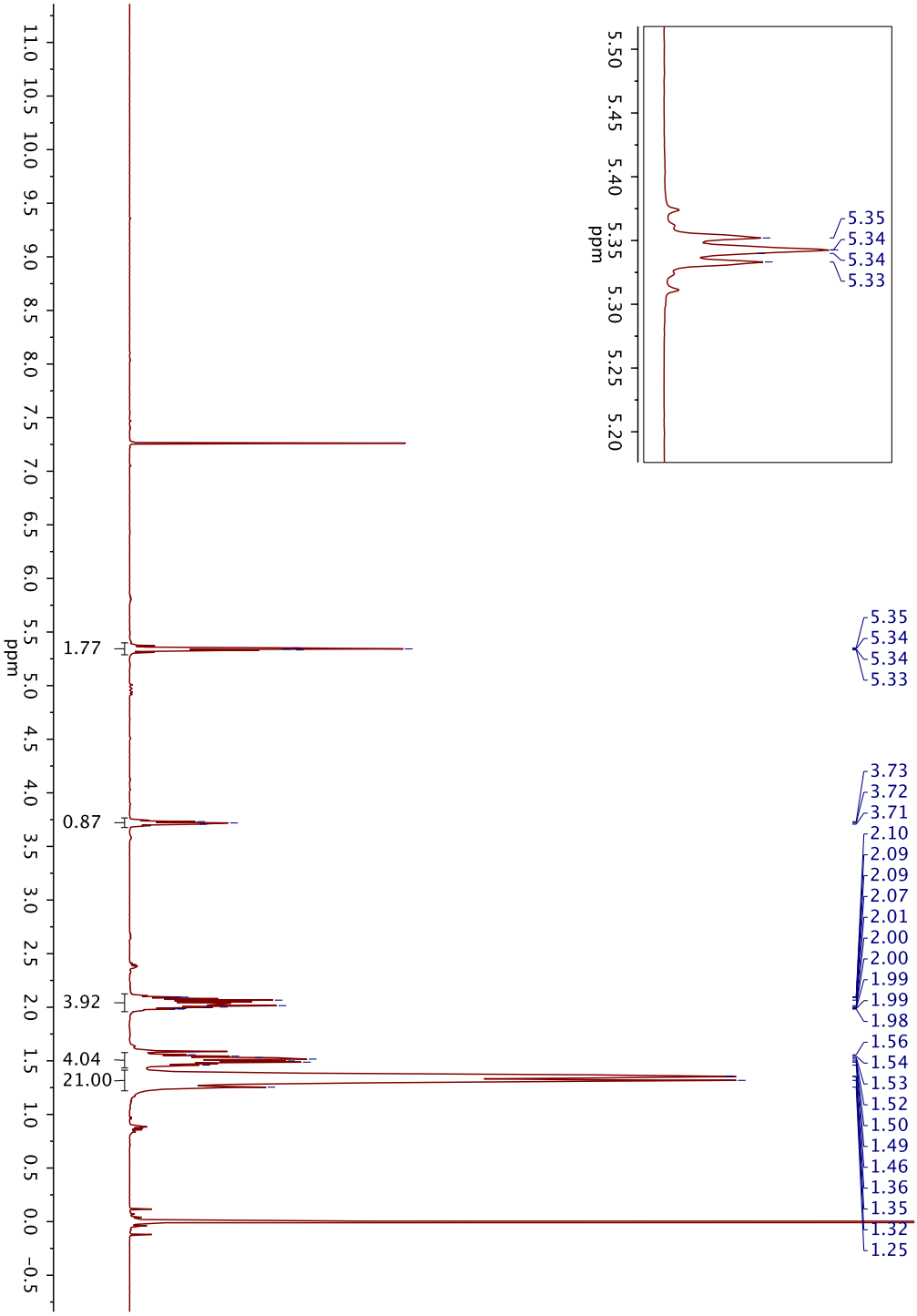


Figure 2.14. ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **2.20**.

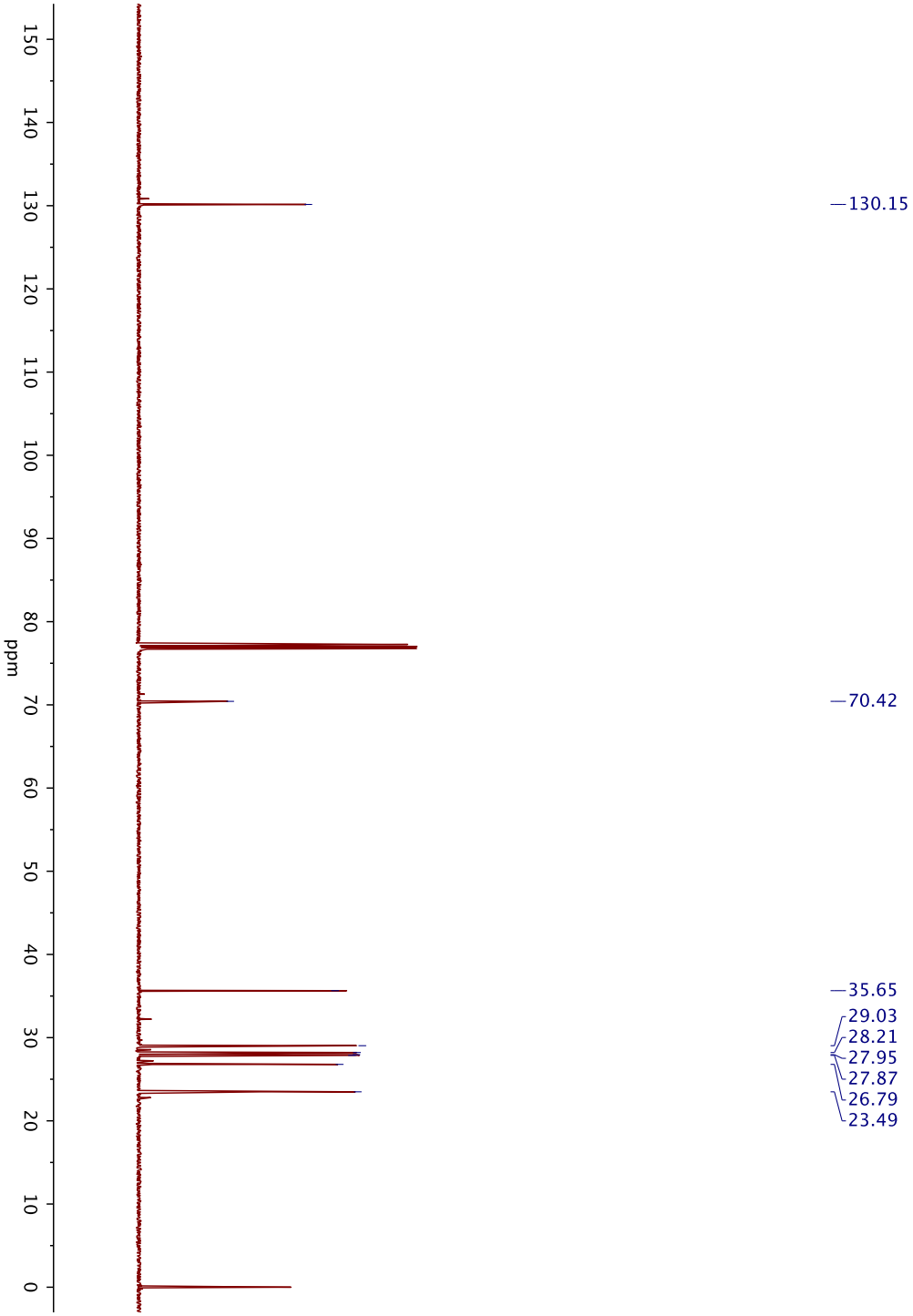


Figure 2.15. ^{13}C NMR (126 MHz, $CDCl_3$) spectrum of **2.20**.