Ruthenium-Catalyzed [3,3]-Sigmatropic Rearrangements of α-Branched Allyl Vinyl Ethers

by

Jessie Michael Penich

B.S. in Biochemistry, Saint Vincent College, 2008

Submitted to the Graduate Faculty of

Arts & Sciences in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2011

UNIVERSITY OF PITTSBURGH

Arts and Sciences

This thesis was presented

by

Jessie Michael Penich

It was defended on

May 6, 2011

and approved by

Professor Kay M. Brummond

Professor W. Seth Horne

Thesis Advisor: Professor Scott G. Nelson

Ruthenium-Catalyzed [3,3]-Sigmatropic Rearrangements of α-Branched Allyl Vinyl Ethers

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Previous research carried out in our group has demonstrated the ability of the cationic ruthenium complex $[CpRu(MeCN)_3]PF_6$ in tandem with a chiral picolinamide ligand and a Lewis acid co-catalyst to facilitate the catalytic, asymmetric [3,3]-sigmatropic rearrangement of α-unbranched aromatic allyl vinyl ethers at ambient temperature. This thesis describes my efforts to a.) extend the Ru-catalyzed Claisen methodology to α-branched substrates and b.) investigate the mechanism of this class of transformation. It was determined that $[CpRu(MeCN)_3]PF_6$ in conjunction with several novel *N*-phenol picolinomide ligands serve as highly-active catalysts for the rearrangement of α-branched aromatic allyl vinyl ethers. Although regio- and stereoselectivity are poor at this point, reactions proceed to complete conversion at ambient temperature in as little as 2 h in CH_2Cl_2 with no Lewis acid or any other additives required.

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ABBREVIATIONS

Ac	Acetyl
Ar	Aryl
bpy	2,2'-bipyridine
CH_2Cl_2	Methylene chloride
Cp	Cyclopentadienyl
Cp*	Pentamethyl cyclopentadienyl
DCC	*N,N'*-Dicyclohexylcarbodiimide
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
ee	Enantiomeric excess
equiv	Equivalent
NMR	Nuclear magnetic resonance
Ph	Phenyl
rt	Room temperature
THF	Tetrahydrofuran
Tol	Toluene
p-Ts	*p*-Toluenesulfonyl

PREFACE

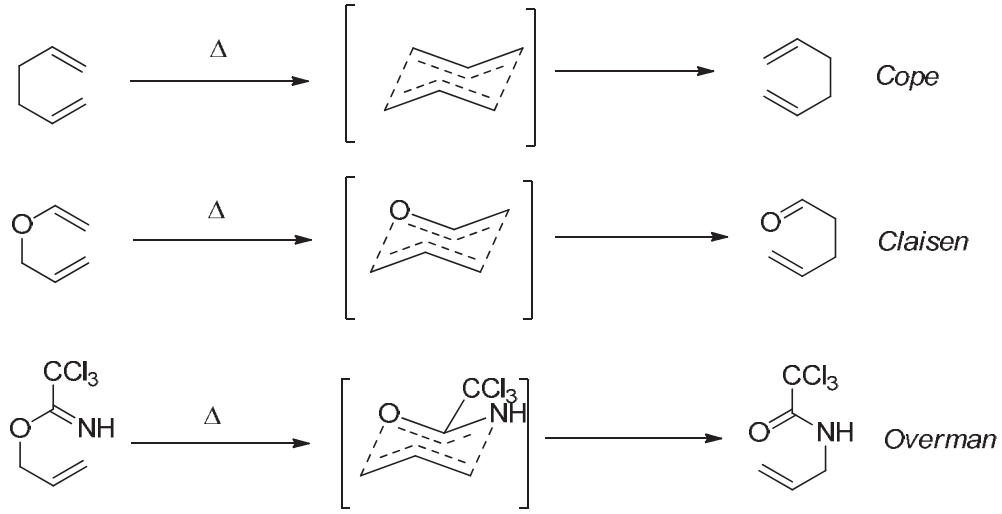
There are a number of people whom I would like to acknowledge for their support during my graduate career at the University of Pittsburgh. First and foremost, I would like to thank my family for all of their support and encouragement over the years. Secondly, I would like to express my gratitude to Profs. Kay Brummond and Seth Horne for serving on my thesis committee. I would like to extend a special measure of gratitude to my advisor, Prof. Scott Nelson, whose guidance, support, and patience fostered my development into a much better scientist than I was prior to my experience working in his laboratory. Finally, I would like to thank my colleagues in the Nelson group past and present for their hospitality, company, and advice during my tenure in the group.

1.0 INTRODUCTION

1.1 [3,3]-SIGMATROPIC REARRANGEMENTS

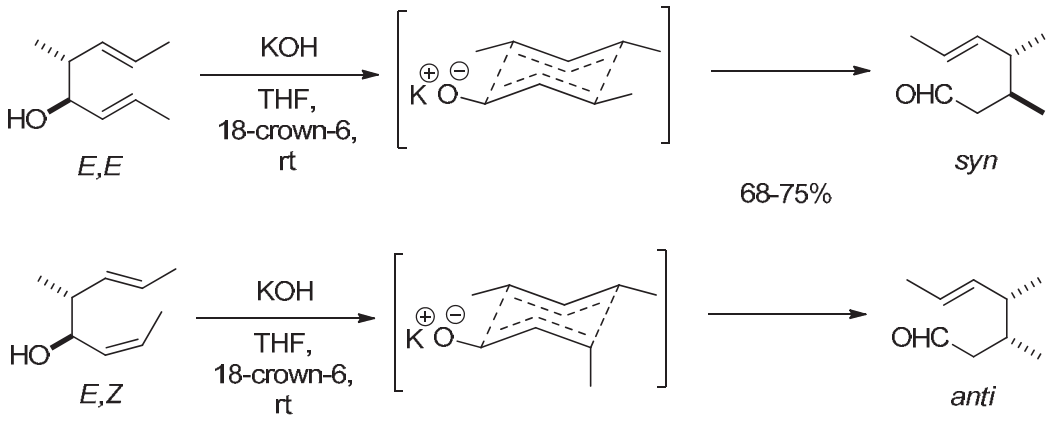
[3,3]-Sigmatropic rearrangements such as the Cope, Claisen, and Overman rearrangements have found vast utility in the synthesis of complex natural products, and several reviews have been published (Scheme 1).[1,2] While these concerted, pericyclic reactions offer a facile means of selective C-C and C-N bond formation, often with great stereospecificity, they can suffer from the drawback of requiring relatively harsh reaction conditions. For example, the thermal Claisen rearrangement of allyl vinyl ethers can require temperatures above 150 °C, which may be incompatible with many substrates.

Scheme 1. [3,3]-Sigmatropic rearrangement overview



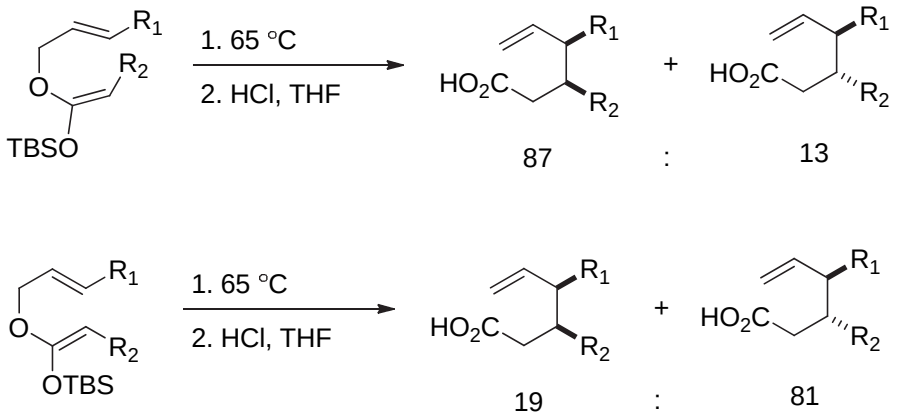
Several modifications have been developed to utilize the power of [3,3]-sigmatropic rearrangements under synthetically-useful conditions.[1-9] The anionic oxy-Cope rearrangement allows for the room-temperature rearrangement of 1,5-dienes (Scheme 2).[1,3] The driving force behind the reaction is the formation of a strong carbon-oxygen double bond.[1] Deprotonation of the alcohol raises the ground state energy of the starting materials to allow the rearrangement to proceed at much a lower temperature than is typically required (over 200 °C). With linear substrates such as those shown able, the reaction is stereospecific with *E,E*- and *E,Z*-substrates affording different stereoisomers (Scheme 2); the selectivity can be explained by invoking ordered, chair-like transition states.[3]

Scheme 2. Anionic oxy-Cope rearrangement



A popular method for running Claisen rearrangements under relatively mild conditions and with pre-defined stereocontrol is the Ireland ester enolate Claisen rearrangement of allylic silyl ketene acetals (Scheme 3).[1,2,4]

Scheme 3. Ireland-Claisen rearrangement



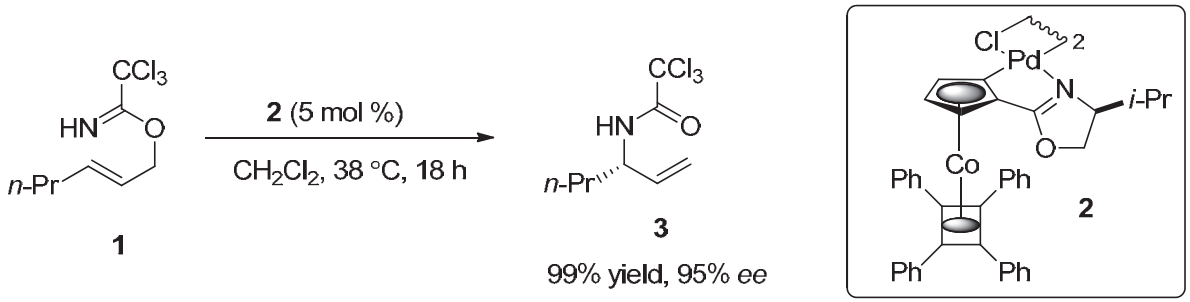
Silyl ketene acetals are typically accessed through the enolization of allylic esters. *E*- and *Z*-Silyl ketene acetals can be selectively formed by controlling the enolization conditions, allowing for convenient stereocontrol over the rearrangement.[4] Like the classic thermal rearrangement, the Ireland-Claisen rearrangement is believed to be a concerted process which proceeds through a chair-like transition state; *E*,*E*- and *Z*,*Z*-substrates favor the *anti* product while *E*,*Z*- and *Z*,*E*-substrates favor the *syn* product.

1.2 TRANSITION METAL-CATALYZED [3,3]-SIGMATROPIC REARRANGEMENTS

Transition metal-catalysis has demonstrated considerable promise for facilitating formal [3,3]-sigmatropic rearrangements under comparatively mild conditions.[2,5-9] Of particular noteworthiness is that the introduction of catalysts containing chiral ligands allows for the possibility of catalytic, asymmetric processes, such as the Pd-catalyzed enantioselective

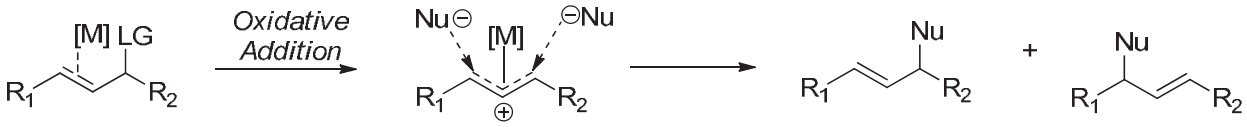
Overman rearrangement (Scheme 4).[5d,e] These reactions can afford direct access to enantioenriched products from achiral substrates, which the classic thermal reactions cannot achieve.

Scheme 4. Asymmetric Pd-catalyzed Overman rearrangement



One particular area of organotransition metal chemistry that has been investigated recently as a strategy for designing catalyzed rearrangements is the trapping of a metal π-allyl species with a nucleophile (Scheme 5).[1,6]

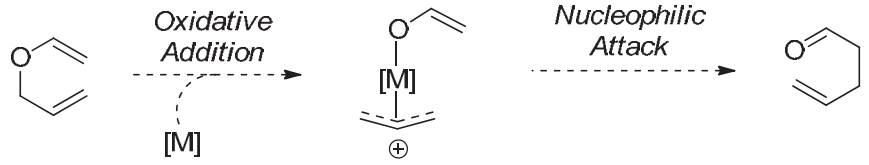
Scheme 5. Nucleophilic substitution via an η^3 metal-allyl complex



η^3 π-Allyl complexes are typically accessed through the oxidative addition of a transition metal complex to an allyl species containing a suitable leaving group.[6] These species are electrophilic on carbon and are prone to attack by nucleophiles at the terminal positions.[6] Two regioisomeric products are possible and selectivity can be achieved by varying the metal, ligands, nucleophile, and/or the substituents on the substrate; both steric and electronic factors are thought to have an

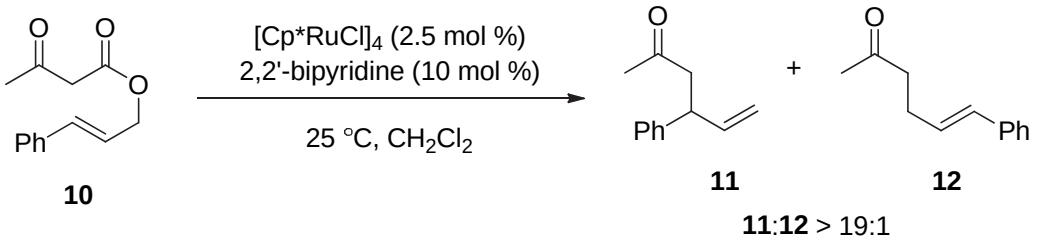
influence.[6] Conceivably, formal [3,3]-sigmatropic rearrangements could be achieved in this manner from the oxidative addition of the metal to the C-O bond of an allyl vinyl ether (or an analogous substrate), followed by attack of the resulting enolate on the metal-allyl complex (Scheme 6).

Scheme 6. Envisioned [3,3]-sigmatropic rearrangement via a metal-allyl intermediate



In 2004, Tunge and coworkers reported a decarboxylative Claisen (Carroll) rearrangement catalyzed by a 2,2'-bipyridine ruthenium complex at ambient temperature (Scheme 7).[7] These conditions are considerably milder than those required for the thermal variants, which typically proceed at 140-180 °C.[1,2]

Scheme 7. Ru-catalyzed Carroll rearrangement



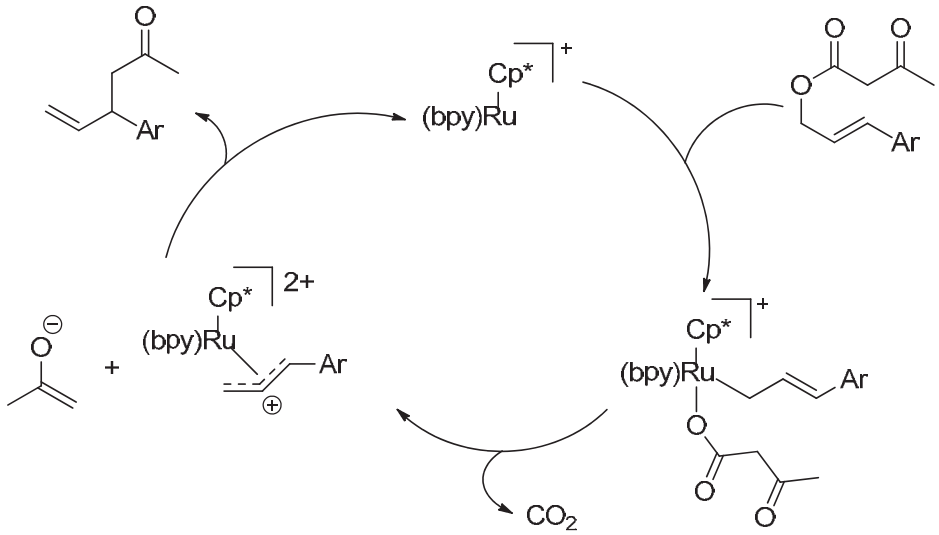
10 **11** **12**

11:**12** > 19:1

The reaction is general to several of aryl-substituted, α-unbranched allyl β-ketoesters.[7] The rate is accelerated with electron-donating aryl substituents (i.e., *p*-C_6H_4OMe) and hindered with the presence of electron-withdrawing aryls (i.e., *p*-C_6H_4Cl, *p*-$C_6H_4CF_3$).[7] The proposed mechanism

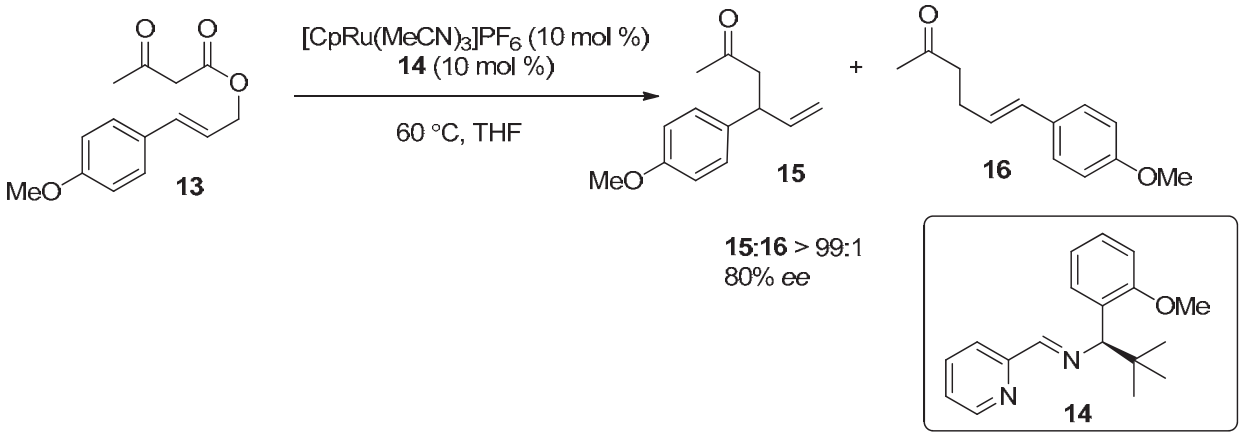
involves initial oxidative addition of Ru across the C-O bond to generate a Ru-allyl complex and acetoacetate (Scheme 8).[7] Decarboxylation of the acetoacetate results in the formation of an enolate, which attacks the allyl complex at the more highly-substituted terminus to afford the formal [3,3] product as the major regioisomer.[7] Competition experiments provide evidence for a freely-diffusing enolate as an intermolecular nucleophile as opposed to intramolecular attack by a ruthenium-bound enolate.[7]

Scheme 8. Proposed mechanism for Ru-catalyzed Carroll rearrangement



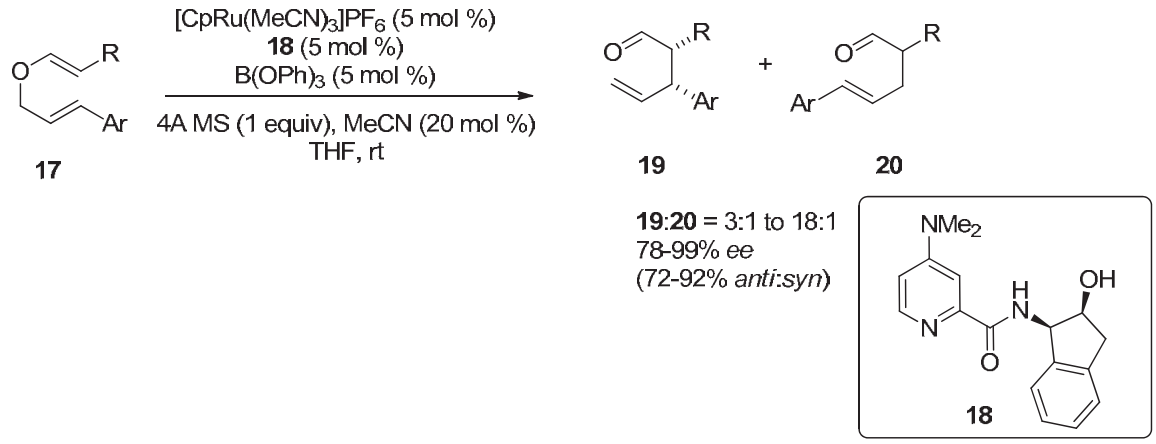
In 2007, Lacour and coworkers developed an enantioselective variant of the Ru-catalyzed Carroll rearrangement utilizing chiral pyridine-imine ligands such as **14** (Scheme 9).[8]

Scheme 9. Asymmetric Ru-catalyzed Carroll rearrangement



Until recently, direct oxidative addition of ruthenium across allyl vinyl C-O bonds as a route to catalyzed Claisen rearrangements had not been reported. In 2010, our group described the [3,3] rearrangement of α-unbranched, aromatic allyl vinyl ethers catalyzed by a cationic Ru(II) complex in conjunction with chiral picolinamide ligand **18** and a borate co-catalyst; the reactions proceed at ambient temperature and offer a high degree of control over regioselectivity as well as relative and absolute stereochemistry (Scheme 10).[9] When the product aldehydes contain stereogenic centers at the α and β positions, the *anti* relationship predominates (for *E*,*E*-ethers).[9] This is distinct from and complimentary to the thermal rearrangements of *E*,*E*-allyl vinyl ethers, which typically afford *syn* aldehydes.

Scheme 10. Catalytic, asymmetric Ru-catalyzed Claisen rearrangment of α-unbranched allyl vinyl ethers

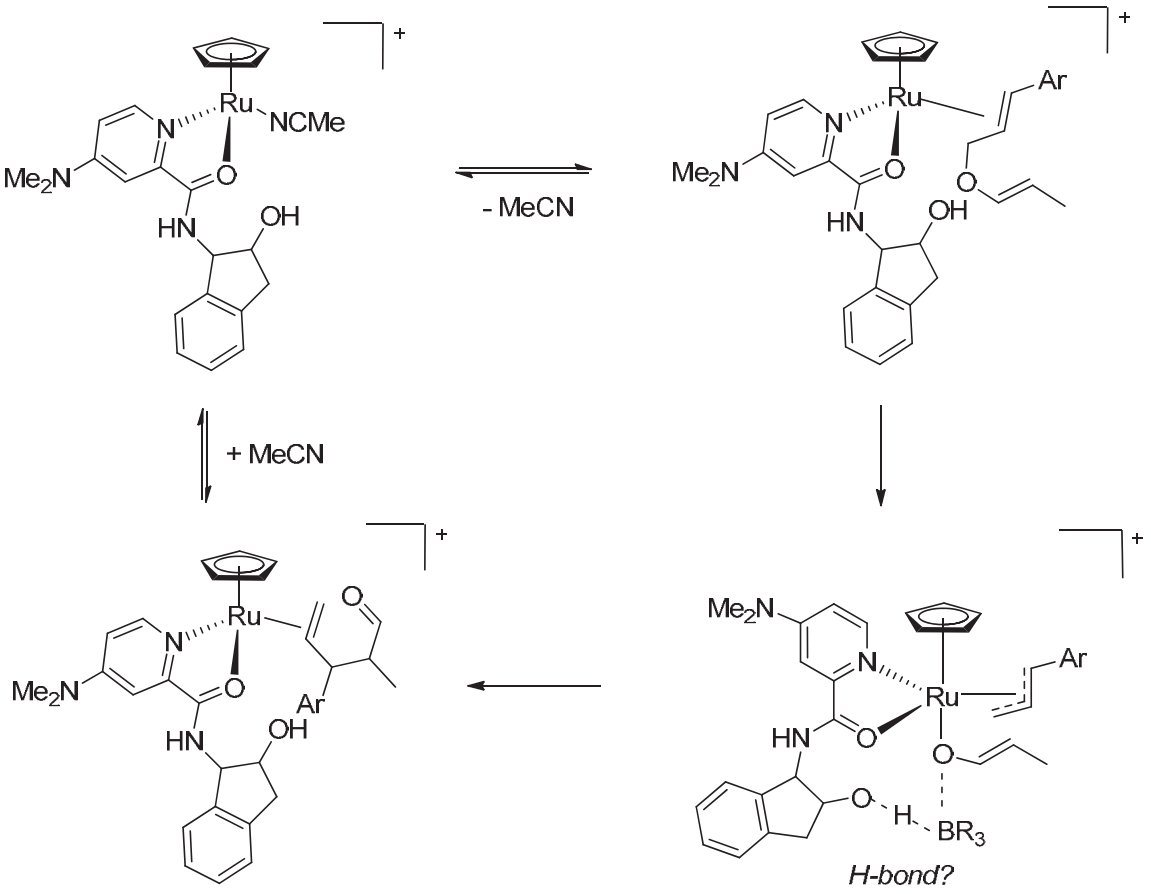


The reaction is general for a wide variety of ethers containing electron-donating and electron-withdrawing aryl substituents.[9] Optimal results were obtained when R = Me.[9] When R = Et, lower regio- and stereoselectivities were observed.[9] It is important for the allyl substituent to be aromatic to achieve good selectivity for the [3,3] rearrangement product.[9] When the aryl substituent was replaced with a cyclohexyl group, complete selectivity for the linear regioisomer was observed with poor stereoselectivity (26% *ee*); double catalyst loading (10 mol %) and a stronger Lewis acid ($B(O^pC_6H_4F)_3$) were required to drive the reaction to completion.[9] The reason for the preference of the linear isomer is not clear but might be related to steric factors. It is understandable that a higher catalyst loading and a more powerful Lewis acid are required for this substrate because the resulting Ru-allyl complex is not benzylic (as is the case with the aryl-substituted ethers). Due to the possibility of donation of electron density via resonance, benzylic carbocations are generally more stable than the analogous aliphatic carbocation so they are expected to be formed faster under a given set of conditions.

Although the reason is not known for certain at this time, the free hydroxyl group on the indanyl ring of the ligand is vital for the optimal function of the catalyst. Use of an analogous

ligand with a methoxy group in place of the hydroxyl resulted in incomplete conversion (45%) and only 21% *ee*.[9] One possible explanation for this observation is that the hydroxyl hydrogen engages in a hydrogen-bond type interaction with a borate-enolate complex, which helps to hold the reacting species in the correct orientation for the desired reaction to occur (Scheme 11). Scheme 11 outlines a plausible mechanism for the reaction that is analogous to the mechanism proposed by Tunge for the Ru-catalyzed Carroll rearrangement[7] (with the exception that the a Ru-enolate is proposed as the nucleophilic species rather than a freely-diffusing enolate).

Scheme 11. Proposed mechanism for Ru-catalyzed Claisen rearrangement of α-unbranched allyl vinyl ethers



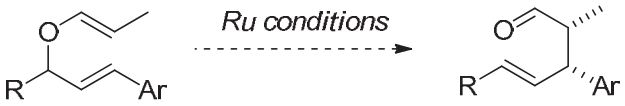
Following the dissociation of two acetonitrile ligands, the picolinamide ligand is believed to bind to the ruthenium through the pyridine nitrogen and amide oxygen. A third acetonitrile dissociates, allowing coordination of the substrate. The metal undergoes oxidative addition into the allylic C-O bond of the ether, yielding a Ru-allyl species and a ruthenium enolate. The enolate then attacks the less highly-substituted end of the allyl complex to afford the [3,3] rearrangement product. In order to reach full conversion, molecular sieves (1 equiv) and 20 mol % MeCN are required additives. While it is possible that the sieves are acting as a Lewis acid to aid in the activation of the ether C-O bond, it is more likely that their role in the reaction is to remove trace amounts of moisture. This is reasonable to claim because the cationic Ru complex should be very sensitive to water molecules, which could bind the metal as a ligand and poison the catalyst. The excess MeCN is believed to function as a competitive ligand to displace the aldehyde product from the metal so that another substrate molecule can bind and begin a new catalytic cycle; the observation that the reaction does not achieve full consumption of substrate in the absence of MeCN is a possible indication of product inhibition.

2.0 RESULTS AND DISCUSSION

2.1 RU-CATALYZED [3,3]-REARRANGEMENTS OF ALPHA-BRANCHED ALLYL VINYL ETHERS

The overall goal of this work was to extend the ruthenium-catalyzed Claisen methodology developed in our group to α-branched allyl vinyl ethers (Scheme 12).[9]

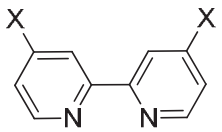
Scheme 12. Envisioned Ru-catalyzed Rearrangement of α-branched allyl vinyl ethers



In light of the high selectivity for the [3,3] (branched) product and *anti* stereoselectivity for α-unbranched substrates,[9] we hypothesized that exposing α-branched ethers (those of the type shown in Scheme 12) to similar conditions would result in an analogous reaction. The fact that the presence of an α-substituent on the substrate would change the steric properties of the system was an issue that was taken into consideration with regards to ligand design. Our ligands would need to possess the requisite stereoelectronic characteristics to catalyze [3,3]-sigmatropic rearrangements with the desired selectivity but not be so encumbering as to prevent the reacting species from achieving the required orientation for the desired reaction to occur. As a long-term

goal, we envisioned using an achiral ligand in conjunction with enantioenriched ethers (with regards to the α-substituent) to develop diastereoselective rearrangements. We believed that the development of this methodology would be a fruitful endeavor because it could provide a general, stereospecific method to forming carbon-carbon bonds under relatively mild conditions which could be useful in the context of synthesizing complex molecules. Even in the event that a synthetically-useful reaction could not be developed, undertaking this project could still provide valuable experimental insight into the mechanism and scope of Ru-catalyzed sigmatropic rearrangements.

Our preliminary experiments focused on the design of a catalyst system comprised of $[CpRu(MeCN)_3]PF_6$, a 2,2'-bipyridine-derived ligand, and $B(OPh)_3$. Ligands **21a-b** were chosen because we expected them to exhibit a similar bidentate bite angle as the picolinamide ligand **18**, allowing them to serve as achiral surrogates (Figure 1). Additionally, Tunge's work provides precedent for the oxidative addition of Ru^{II}(bpy) complexes into allylic C-O bonds to generate Ru-allyl complexes (albeit with ester C-O bonds instead of ether C-O bonds).[7] Conceivably, oxidative addition into a secondary C-O bond should be easier than addition into a primary C-O bond since the developing positive charge should be stabilized by the presence of an α-substituent via hyperconjugative interactions (Figure 2).



21a: X = H
21b: X = OMe

Figure 1. 2,2'-bipyridine ligands

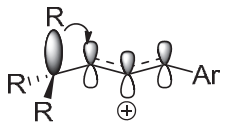


Figure 2. Hyperconjugative stabilization of an allyl-species by an α-substituient

Employing racemic ether **23** as the substrate, reactions were carried out with 5 mol % $[CpRu(MeCN)_3]PF_6$, 5 mol % ligand, and 5 mol % $B(OPh)_3$ in THF. **23** was selected because it was structurally similar to substrates of type **17**[9] and was easily accessible (two steps from cinnamaldehyde; see Experimental section for details). 2,2'-bipyridine ligand **21b** was envisioned as a more electron-rich alternative to **21a**, a property that we believed would aid in the oxidative addition of the catalyst complex into the ether C-O bond.

Disappointingly, none of the conditions screened elicited any appreciable reaction. From these results, we can conclude that catalyst systems comprised of a complex of 2,2'-biypridine ligand with $[CpRu(MeCN)_3]PF_6$ does not possess the required stereoelectronic properties to catalyze the rearrangement of α-branched ethers, and were not pursued further. The reason for the lack of reaction is not precisely known, but a plausible explanation is that steric interactions between the bipyridine ligand (which would be quite inflexible in a bidentate complex with the metal) and the ethyl substituent on the substrate could destabilize the catalyst-substrate complex, preventing oxidative addition of the ruthenium across the C-O bond (Figure 3).

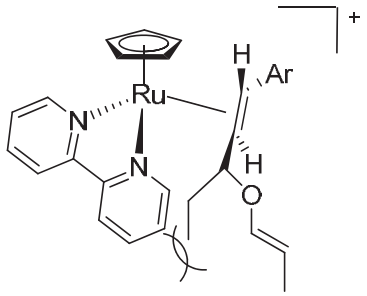
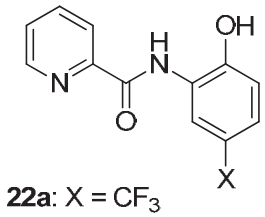


Figure 3. Steric considerations in Ru 2,2'-bipyridine complexes

With the 2,2'-bipyridine system showing little promise, we concentrated our efforts on the development of a novel series of *N*-phenol picolinamide ligands **22a-c** as more faithful analogs to **18** (Figure 4). It is envisioned that the ligands would coordinate to the ruthenium through the pyridine nitrogen and the amide oxygen in a similar manner to **18** (Figure 5). Steric interactions between the ligand and the α-substituent of the substrate should be diminished with the replacement of the second pyridine ring with an aminophenol moiety due to the freedom of the phenol ring to freely rotate around the amide-phenol bond.



22a: X = CF_3
22b: X = F
22c: X = OMe

Figure 4. Novel *N*-phenol picolinamide ligands

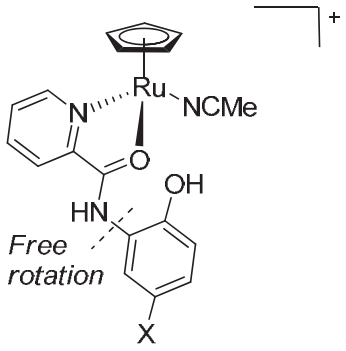


Figure 5. Proposed structure of Ru *N*-phenol picolinamide catalyst complex

Since previous work[9] has demonstrated the importance of a free hydroxyl group on the *N*-moiety for catalytic activity, we incorporated a free phenol group into the design of our new ligands. To modulate this interaction, ligands with electron-withdrawing (CF_3, F) and electron-donating (OMe) groups *para* to the phenol group were synthesized. If the phenol group were serving as a hydrogen bond donor (as shown in Scheme 11) we predicted that the presence of a *para* electron-withdrawing group would enhance the interaction. On the other hand, if the lone electron pairs of the phenol group were acting as a Lewis base then the presence of a *para* electron-donating group should enhance the interaction. Additionally, the increased acidity of the phenol group in comparison to the hydroxyl group would be expected to make it a better hydrogen bond donor and a weaker Lewis base than the hydroxyl group of **18**. It is estimated that the pKa of the phenol group is approximately 10.21 when X = OMe, 9.95 when X = F, and less than 9.95 when X = CF_3; the pKa of phenol is approx. 9.98.[10]

Employing **23** as the substrate, a series of reactions were carried out using the new catalysts (Table 1, entries 1-3). To our delight, excellent to full conversion (85-100%) was observed within 24 hours at ambient temperature in THF. A slight but clear trend of increasing conversion with increasing electron-deficient character of the ligand was observed. Since it

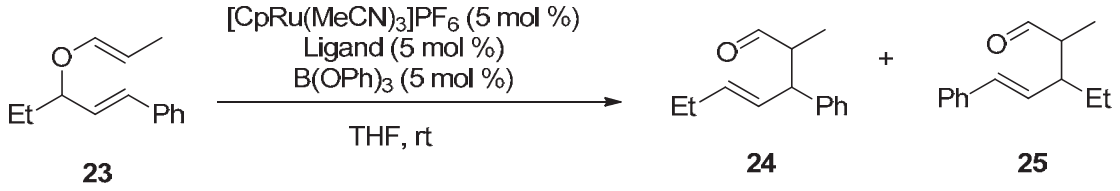
would be reasonable to predict that complexes containing ligands with better electron-donating properties would undergo oxidative addition more readily, this trend initially seemed counterintuitive. However, more electron-rich complexes would also be expected to have an increased susceptibility to oxidative degradation (by trace oxygen), which might explain the observation that the ligand containing the electron-donating *p*-methoxy substituent (**22c**) afforded the lowest conversion while the comparatively electron-deficient **22a** facilitated the highest conversion.

Regio- and stereoselectivity were problematic at this point. There was no clear preference for either the [3,3] or [1,3] rearrangement product and a slight preference for the *syn* [3,3] product over the *anti* [3,3] product. Like the rearrangements of α-unbranched substrates,[9] 5 mol % $B(OPh)_3$ is a required Lewis acid co-catalyst and the reaction suffered from poor conversion (12%) in its absence (Table 1, entry 4). The lack of regio- and stereoselectivity suggests that the energy difference between the transition states giving rise to each product is low enough to be insignificant at ambient temperature.

Exposure of an isolated aldehyde (lacking the α-substituent) to the catalyst did not result in any appreciable reaction, suggesting that the regioselectivity issues are not the result of thermodynamic equilibrium; this is not surprising considering that the requisite oxidative addition into an allylic C-C bond would be relatively difficult. In contrast to the rearrangements of the α-unbranched ethers, molecular sieves and additional acetonitrile are not required for complete consumption of the substrate. The observation that molecular sieves are not required would suggest that this system is less sensitive to trace amounts of moisture while the observation that acetonitrile is not required for complete conversion suggests that the reactions do not suffer from product inhibition. The second observation may be indicative of a less

tightly-constrained environment at the catalyst center, which could explain the diminished regio- and stereoselectivty in our system compared to the α-unbranched reaction.

Table 1. Ru-catalyzed rearrangement of an α-branched allyl vinyl ether using novel *N*-phenol picolinamide ligands[a]

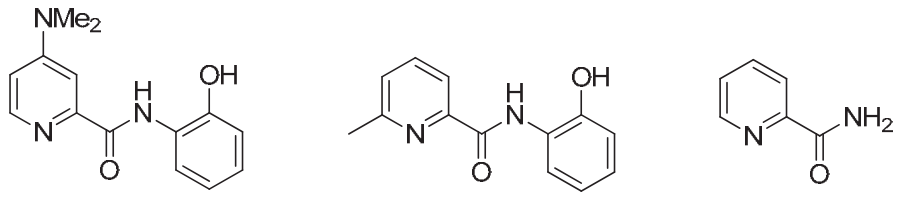


23 **24** **25**

entry	Ligand	Time (h)	Conversion (%)[b]	**24**:**25**	*anti*:*syn*
1	**22a**	23	100	1:1.07	1:1.88
2	**22b**	23	96	1:1.12	1:1.95
3	**22c**	23	85	1.04:1	1:1.76
4[c]	**22b**	23	12	N/A	N/A

[a]Reactions were carried out with a substrate concentration of .5 M. [b]Conversion based on disappearance of substrate resonances in the crude ^{1}H NMR spectrum. [c]No $B(OPh)_3$.

Now that we had an active set of catalysts for the rearrangement of α-branched allyl vinyl ethers we set out to address the issues of poor regio- and stereoselectivity. We proposed several modifications to our ligand design in an effort to render the reaction more synthetically useful (Figure 4).



26 **27** **28**

Figure 6. Alternative ligands for rearrangement of α-unbranched ethers

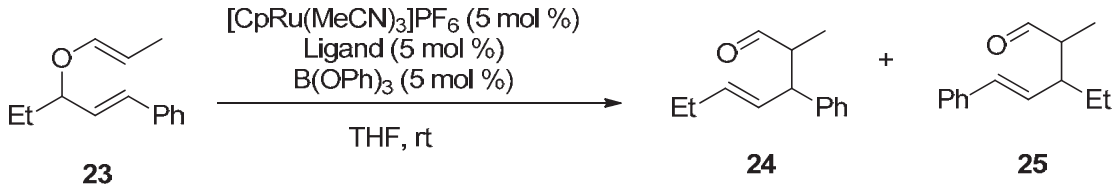
Ligand **26** was designed on the premise that the electron-donating dimethylamino substituent would enhance the activity of the catalyst, as was observed for the rearrangements of α-unbranched ethers.[9] We believed that oxidative addition into the C-O bond would be facilitated by a more electron-rich catalyst. These conditions proved unsuccessful, as only trace amounts of rearrangement product were observed (Table 2, entry 1). The reason is unclear at this point, but must be related to the presence of the 4-dimethylamino substituent. As discussed earlier, the electron-rich nature of this ligand might increase the susceptibility of the catalyst complex to degradation by trace oxygen.

We synthesized ligand **27** to investigate the effect that a 6-methyl substituent on the pyridine ring would have on the rearrangement. It was envisioned that increasing steric bulk at the pyridine ring might force the reacting species to orient in such a way in that attack of the enolate at one terminus of the allyl complex would be more clearly favored over the other, thus increasing selectivity for either the [3,3] or [1,3] product. Complete conversion was observed, along with a slight increase in the [3,3] *syn*:*anti* ratio (Table 2, entry 2). However, there was no significant effect on the ratio of [3,3] to [1,3] products. These results suggest that substituents on the pyridine ring of the ligand are too remote from the key bond-forming events to have any appreciable effect on the reaction.

The use of picolinamide **28** as the ligand resulted in no appreciable reaction, affirming the importance of the *N*-aromatic substituent on the ligand (Table 2, entry 3). One possible explanation for the failure of this catalyst is that the free -NH_2 group could serve to poison the system through coordinating with the metal center of another molecule of the catalyst via its lone pair; the resulting aggregate species may be too sterically-encumbered to bind the substrate in a

productive manner. Alternatively, the *N*-aromatic moiety may play an important role in holding the substrate in the proper orientation for the reaction to proceed.

Table 2. Ru-catalyzed rearrangement of an α-branched allyl vinyl ether with alternative ligands[a]



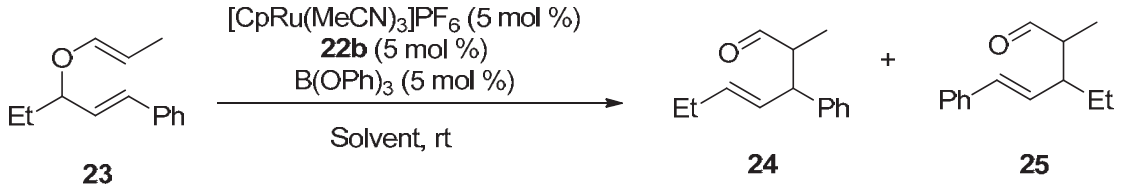
entry	Ligand	Time (h)	Conversion (%)[b]	**24**:**25**	*anti*:*syn*
1	**26**	23	Trace	N/A	N/A
2	**27**	23	100	1.28:1	1:2.92
3	**28**	23	Trace	N/A	N/A

[a]Reactions were carried out with a substrate concentration of .5 M. [b]Conversion based on disappearance of substrate resonances in the crude ^{1}H NMR spectrum.

At this point we focused our efforts on investigating the effects of various solvents on our Ru-catalyzed rearrangements. CH_2Cl_2, acetone, *N*,*N*-dimethylformamide, and toluene were among the solvents screened (Table 3). We expected the system to behave differently in non-coordinating solvents such as CH_2Cl_2 and toluene than it would in coordinating solvents such as THF, acetone, and DMF. It was predicted that the reaction would be most facile in solvents such as THF, acetone, and DMF because solvent molecules can better stabilize the developing positive charge on the forming Ru-allyl species via coordination. Additionally, the highly polar character of these solvents should facilitate better overall solubility for the cationic ruthenium catalyst. It was predicted that the reaction would be slower in non-coordinating solvents such as CH_2Cl_2 and toluene because of a lower ability to stabilize developing charges. However, we

envisioned that an increase in regioselectivity might be observed in these solvents due to increased concentration of the positive character at the benzylic position of the Ru-allyl species as a result of decreased solvent stabilization. No meaningful improvements in selectivity were observed, but the reaction proceeded much more cleanly in CH_2Cl_2 (in terms of the appearance of the crude ^1H NMR spectrum). Gratifyingly, the catalyst also appeared to be much more active in CH_2Cl_2 as no Lewis acid co-catalyst was required; full consumption of the substrate was detected by ^1H NMR spectroscopy in as little as 2 hours. The origin for this increased activity is unclear at this point, although it has been observed that the ligand-metal complex is completely soluble in CH_2Cl_2 whereas a small amount of particulate matter is typically present in THF. In toluene, a significant amount of particulate matter is present, suggesting that poor solubility is likely a prime factor for the poor conversion that is observed (38%). In summary, CH_2Cl_2 is the optimal solvent for the rearrangement of α-branched allyl vinyl ethers as evidenced by the greatly increased activity of the catalyst.

Table 3. Ru-catalyzed rearrangement of an α-branched allyl vinyl ether in various solvents[a]



23 **24** **25**

entry	Solvent	Time (h)	Conversion (%)[b]	**24**:**25**	*anti*:*syn*
1	CH_2Cl_2	23	100	1.67:1	1:1.72
2[c]	CH_2Cl_2	65	100	1.68:1	1:1.64
3[c]	CH_2Cl_2	2	100	1.53:1	1:1.87
4[c,d]	CH_2Cl_2	65	100	1.19:1	1:1.53
5[c,e]	CH_2Cl_2	15	93	1.82:1	1:2.17
6[f,g]	Acetone	17	>15	N/A	N/A
7	DMF	25	50	1:1.51	N/A
8	Tol	24	38	1:3.95	N/A

[a]Reactions were carried out with a substrate concentration of .5 M. [b]Conversion based on disappearance of substrate resonances in the crude ^{1}H NMR spectrum. [c]No $B(OPh)_3$.[d].25 M substrate concentration. [e]No ligand. [f]**22c** used as ligand. [g]Significant unidentifiable compound(s) present in crude ^{1}H NMR spectrum.

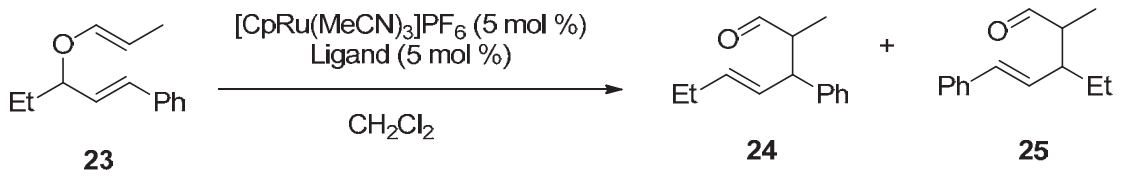
It should be noted that in the absence of ruthenium, the reaction does not proceed, verifying the essential role of catalytic ruthenium and ruling out the possibility of simple Brønstead-acid catalysis by the phenol proton of the ligand. With 5 mol % ruthenium alone in CH_2Cl_2 (no ligand or Lewis acid), the reaction proceeded with slightly better regio- and stereoselectivity (Table 3, entry 5). However, the reaction is much slower, affording 93%

conversion after 15 hours (compared to full conversion after 2 hours when **22b** is present). From this result it can be concluded that while the *N*-phenol picolinamide ligand is not essential for catalysis to occur, its presence vastly improves the rate of the reaction. The observation that the ruthenium by itself does not catalyze the reaction of α-unbranched ethers demonstrates the higher inherent reactivity of branched substrates in these reactions. The reason for the vast rate increase in the presence of the ligand could be attributed to the fact that it is a better electron donor than acetonitrile. This affords a more electron-rich complex, which should oxidatively add into the allylic C-O bond of the ether more readily. Finally, decreasing the substrate concentration by half appears to have a slight negative effect on the selectivity (Table 3, entry 4). This observation implies that the C-C bond-forming step of the reaction does not appear to be concentration-dependent, supporting a mechanism which involves intramolecular attack of a Ru-bound enolate on the Ru-allyl fragment (although not necessarily ruling out the intermediacy of a freely-diffusing enolate as is proposed in similar reactions).[7]

Considering the high activity of our catalyst system in CH_2Cl_2 at ambient temperature we investigated lowering the temperature as a means of improving regio- and stereoselectivity. Unfortunately, no significant improvements in selectivity were observed and conversion became problematic under 0 °C (Table 4). At -78 °C, no appreciable reaction was observed even after one week (Table 4, entry 4). Still, it is noteworthy that the reaction proceeds to over 90% conversion at 0 °C in the absence of Lewis acid, a testament to the high inherent activity of our catalyst system. These results suggest that while a relationship between reaction rate and temperature clearly exists, manipulating it as a way to improve selectivity does not appear to be productive. The observation that poor regioselectivity is still observed in cases where the

reaction proceeds very slowly (Table 4, entry 3) suggests that the difference in the energy barrier to reach the transition states giving rise to the two regioisomeric products is relatively low.

Table 4. Ru-catalyzed rearrangement of an α-branched allyl vinyl ether at various temperatures[a]



23 **24** **25**

entry	Ligand	Temperature (°C)	Time (h)	Conversion (%)[b]	**24**:**25**	*anti*:*syn*
1	**22b**	0	7	91	1.52:1	1:1.97
2	**22c**	-15	7	Trace	N/A	N/A
3[c]	**22c**	-15	7	21	1.44:1	1:2.14
4	**22b**	-78	7 days	Trace	N/A	N/A

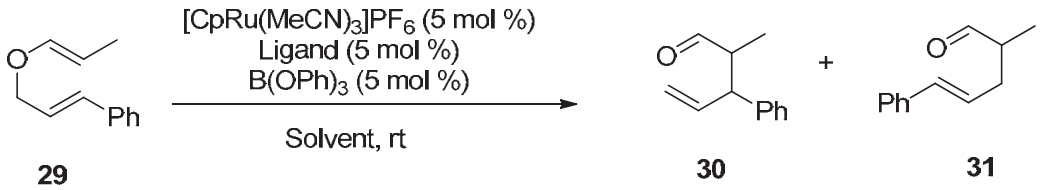
[a]Reactions were carried out with a substrate concentration of .5 M. [b]Conversion based on disappearance of substrate resonances in the crude ^{1}H NMR spectrum. [c]5 mol% $B(OPh)_3$ present.

2.2 RU-CATALYZED [3,3]-REARRANGEMENTS OF ALPHA-UNBRANCHED ALLYL VINYL ETHERS

With attempts to develop our catalyst system into a synthetically-useful transformation largely unsuccessful to this point, we proceeded to investigate the mechanism of the transformation in more detail. In order to more directly compare our system with the established

conditions for the rearrangement of α-unbranched allyl vinyl ethers,[9] we carried out a series of experiments in which an α-unbranched substrate was exposed to our conditions (Table 5). Although our system utilizes achiral *N*-phenol picolinamide ligands in place of the chiral aminoindanol-derived picolinamide **18**, we expected to observe similar trends in regio- and stereoselctivity if analogous mechanisms are operative.

Table 5. Ru-catalyzed rearrangement of an α-unbranched allyl vinyl ether using novel *N*-phenol picolinamide ligands[a]



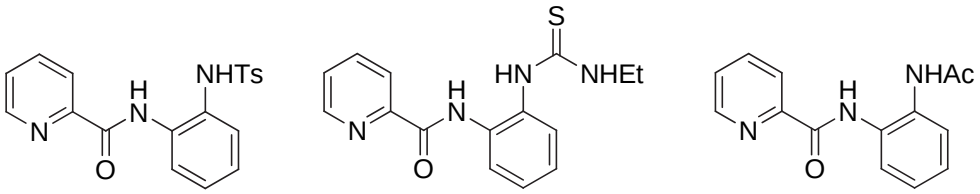
entry	Ligand	Solvent	Time (h)	Conversion (%)[b]	**30**:**31**	*anti*:*syn*
1	**22b**	THF	15	85	1:1.18	1.36:1
2[c]	**22b**	THF	15	Trace	N/A	N/A
3	**22b**	CH_2Cl_2	16	100	1:1.57	1:1.03
4[c]	**22b**	CH_2Cl_2	16	78	1:3.7	1.07:1
5	**22c**	CH_2Cl_2	18	100	1:2	1.27:1

[a]Reactions were carried out with a substrate concentration of .5 M. [b]Conversion based on disappearance of substrate resonances in the crude ^{1}H NMR spectrum. [c]No $B(OPh)_3$.

The data presented in Table 5 suggests that the reaction of **29** under the conditions indicated clearly differs from the established reaction. Whereas the established reaction[9] has a large selectivity for the *anti*-[3,3] rearrangement product, it is greatly diminished under our conditions. Stereoselectivity is virtually nonexistent and the small degree of regioselectivity

appears to favor the [1,3] product in all discernable cases. As with our rearrangements of α-branched substrates, the catalyst appears to be more active in CH_2Cl_2 than it is in THF. However, 5 mol % $B(OPh)_3$ is required to achieve full conversion in CH_2Cl_2, unlike the rearrangement of α-branched ethers in this solvent. As previously discussed, the generally lower reactivity of the α-unbranched ethers could be attributed to the formation of a higher-energy primary Ru-allyl complex, which may require the coordination of the Lewis acid to activate the C-O bond. Finally, it should be noted that our conditions are generally more active than those for the established reaction, requiring no additives (i.e. MeCN or molecular sieves) to achieve full consumption of the starting materials. As is the case with the rearrangements of α-unbranched substrates, the poor regioselectivity suggests that the energy difference between the transition states giving rise to each product is relatively small and the lack of necessity for MeCN suggests a "loose" environment at the catalyst center that does not suffer significantly from product inhibition.

With evidence that our catalyst system featuring picolinomides **22a-c** differs from the established system, we investigated the importance of the free -OH group on the phenol ring. As previously discussed, the hydroxyl group is important for achieving full conversion and good stereoselectivity in reactions of α-unbranched substrates employing **18**. To determine the necessity of the corresponding phenol group our system, we designed a novel family of picolinamides **32a-c** derived from monoprotected 1,2-phenylenediamines (Figure 5).

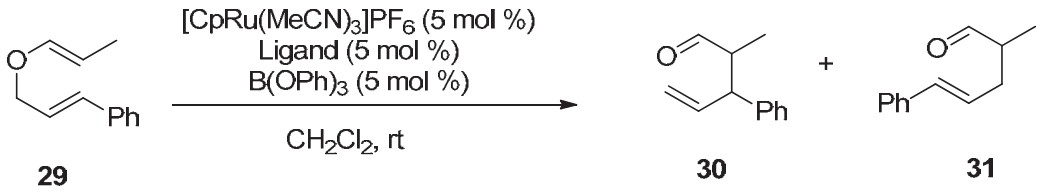


32a **32b** **32c**

Figure 7. 1,2-Phenylenediamine-derived picolinamide ligands

Ligands **32a-c** were studied in the rearrangement of α-unbranched ether **29** (Table 6). From the data obtained, several claims can be made. First, the phenol group that is present on ligands **22a-c** is not necessary for complete consumption of the starting material. However, the necessity of a hydrogen-bond donor cannot be dismissed since **32a-c** contain a hydrogen atom and lone electron pair on the nitrogen *ortho* to the picolinamide moiety. Full conversion was achieved with ligands **32a** and **32c** (Table 6, entries 1 and 3). **32b** performed incompetently in the reaction for reasons that are not completely clear at this point; one explanation is that the sulfur atom coordinates to the ruthenium, poisoning the catalyst. Secondly, the identity of the *N*-protecting group has some degree of influence on the regioselectivity of the reaction. Both **32a** and **32c** favor the [1,3] product more than **22b** does under the same conditions (CH_2Cl_2, $B(OPh)_3$). This is most apparent with **32c**, which favors the [1,3] product by a factor of 3.57:1. The reason for the increased selectivity for the [1,3] product with these ligands (in comparison to the phenol ligands) is unclear, but it may be steric in origin since it would be more favorable electronically for developing positive charge to be concentrated at the benzylic position, where nucleophilic attack affords the [3,3] product.

Table 6. Ru-catalyzed rearrangement of an α-unbranched allyl vinyl ether using novel 1,2-phenylenediamine-derived picolinamide ligands[a]

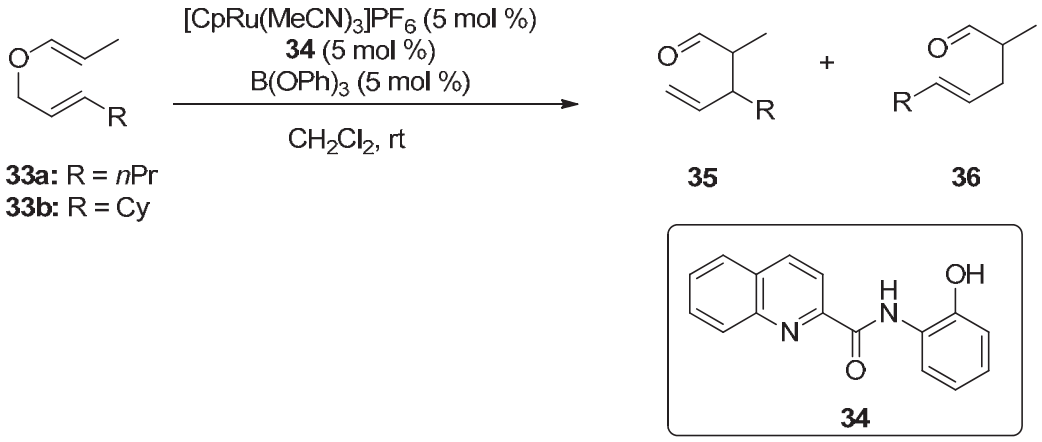


entry	Ligand	Time (h)	Conversion (%)[b]	**30**:**31**	*anti*:*syn*
1	**32a**	22	100	1:2.13	1:1.136
2	**32b**	21	Trace	N/A	N/A
3	**32c**	21	100	1:3.57	1:1.33

[a]Reactions were carried out with a substrate concentration of .5 M. [b]Conversion based on disappearance of substrate resonances in the crude ^{1}H NMR spectrum.

Until this point, our studies focused on the rearrangements of allyl vinyl ethers possessing an aromatic substituent at the allylic position. In our next series of experiments, we investigated the rearrangement of substrates containing an alkyl substituent at the allylic position (Scheme 19). Unfortunately, preliminary results were not very encouraging. The crude ^{1}H NMR spectra were not very clean and many of the peaks were unidentifiable. To further complicate matters, the synthesis of the substrates was complicated by overisomerization of the precursor diallyl ether; the substrates were contaminated with significant amounts of divinyl ether even when the isomerization was terminated after several minutes. Note that the quinaldic acid-derived ligand **34** behaves similarly to **22b** in the reaction of aromatic ether **29**; full conversion is observed but with less-defined regio- and stereoselectivity.

Scheme 13. Rearrangement of α-unbranched ethers containing allylic alkyl substituents

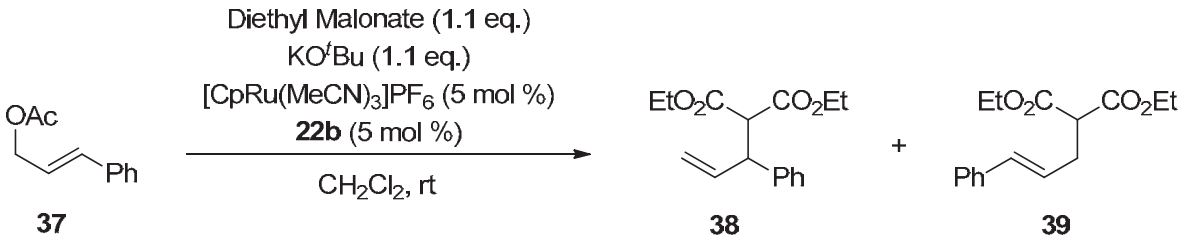


2.3 RU-CATALYZED SUBSTITUTION OF ALLYLIC ACETATES BY AN EXTERNAL NUCLEOPHILE

Another area that we investigated was the use of an external nucleophile to trap the Ru-allyl complex believed to be generated under our *N*-phenol picolinamide conditions. As our sigmatropic rearrangements have attempted to exploit, Ru-allyl complexes are known to undergo attack by nucleophiles at the more highly-substituted terminus.[7-9] However, this does not appear to be the case in our system for both α-branched and α-unbranched Claisen substrates, which afford poor regioselectivity. Using cinnamyl acetate **37** as the substrate and diethyl malonate as the nucleophile, we attempted the allylic substitution under our novel conditions (Table 7). After 21 hours, all of the acetate appeared to have been consumed via ^{1}H NMR and the branched product **38** was the predominant regioisomer (Table 7, entry 1). When the reaction was carried out in the absence of ligand, **38** was still the predominant regioisomer, but the selectivity was

much lower and consumption of the acetate was not complete (Table 7, entry 2). In the absence of ruthenium and ligand, no substitution product was observed, verifying the involvement of catalytic ruthenium in the reaction (Table 7, entry 3).

Table 7. Ru-catalyzed substitution of cinnamyl acetate with diethyl malonate carbanion[a]



37 **38** **39**

entry	Time (h)	Conversion (%)[b]	**38**:**39**
1	21	100	4.14:1
2[c]	21	70	1.14:1
3[d]	21	N/A	N/A

[a]Reactions were carried out with a substrate concentration of .5 M. [b]Conversion based on disappearance of substrate resonances in the crude ^{1}H NMR spectrum. [c]No ligand. [d]No ligand or Ru.

From these data, it can be claimed that presence of *N*-phenol picolinamide ligand **22b** improves the conversion and selectivity for the branched product in the Ru-catalyzed allylic substitution of cinnamyl acetate. Clearly, this system behaves differently than our Claisen system, the reason for which is unclear at this point. One explanation could be that the anion of diethylmalonate is a relatively mild nucleophile while the enolates generated from oxidative addition into allyl vinyl ether C-O bonds would be expected to be significantly more reactive. Therefore, it may be the case that the diethylmalonate anion is low enough in energy that it

selectively attacks one end of the allyl complex while the enolates generated in the Claisen reactions are too high in energy to achieve the same level of discrimination. However, this explanation still does not adequately account for the high [3,3] selectivities for the Claisen rearrangement of α-unbranched substrates using the aminoindanol-derived ligand **18**, illustrating the importance of the indanyl moiety in that system.

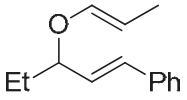
3.0 CONCLUSION

In conclusion, we have developed a system for the ambient-temperature rearrangement of α-branched aromatic allyl vinyl ethers utilizing Trost's ruthenium complex and novel *N*-phenol picolinamide ligands. Preliminary results demonstrate that the system is highly-active but suffers from poor regio- and stereoselectivity; altering the ligand, solvent, concentration, and/or temperature did not afford any significant improvements in selectivity. Our system is clearly different from that which was developed previously in our group for the *anti*-selective [3,3] rearrangement of α-unbranched ethers as is evidenced by the poor selectivity of that reaction under our new conditions. For reasons that are still completely unclear, this behavior is contrary to what would normally be expected from reactions involving nucleophilic attack on Ru-allyl species, which tend to give attack at the more highly-substituted terminus. The expected selectivity for the branched regioisomer is observed when our system is used to catalyze nucleophilic allylic substitution reactions, in clear contrast to our rearrangement reactions.

4.0 EXPERIMENTAL

General Information. Unless otherwise specified, all reactions were carried out in flame-dried glassware under an atmosphere of N_2 utilizing standard inert atmosphere techniques for manipulating reagents and solvents. Anhydrous tetrahydrofuran, diethyl ether, methylene chloride, toluene, and *N*,*N*-dimethylformamide were obtained by passage through successive alumina- and Q5-packed columns on a solvent purification system; methylene chloride employed in the Ru-catalyzed rearrangements was further degassed by purging with a stream of dry N_2 for approx. 30-60 min. $[Ir(COE)Cl]_2$, PCy_3, $NaBPh_4$, $B(OPh)_3$, $[CpRu(CH_3CN)_3]PF_6$, compounds **22a-c**, **23, 26-29, 32a-c**, **33a-b**, **34**, and **37** were stored and weighed out in an N_2-filled glovebox. All other reagents and solvents were used as received from commercial suppliers unless indicated otherwise. Compounds **23**, **29**, and **33a-b** and their di(allyl) ether precursors were prepared in accordance with published procedures.[11,12] ^{1}H NMR spectra were acquired on a Bruker Avance 300 spectrometer at ambient temperature and the indicated magnetic field strengths. Chemical shifts are reported in parts per million (ppm) relative to residual $C\underline{\mathbf{H}}Cl_3$ (7.27 ppm) or DMSO (2.48 ppm) and coupling constants (*J*) are reported in Hz. IR spectra (ν_{max}) were obtained on an FT-IR spectrometer as thin films on NaCl plates. Analytical thin-layer chromatography (TLC) was performed on 0.25 mm silica gel 60-F plates; visualization was achieved with ultraviolet light (UV), *p*-anisaldehyde stain, phosphomolybdic acid (PMA) stain,

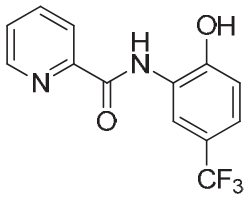
and/or potassium permanganate ($KMnO_4$). Flash chromatography was performed on silica gel (230-240 mesh).



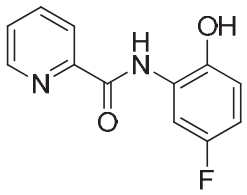
((E)-3-((E)-Prop-1-en-1-yloxy)pent-1-en-1-yl)benzene (23): The literature procedure[11] was followed employing (E)-(3-(allyloxy)pent-1-en-1-yl)benzene (250 mg, 1.2 mmol), $[Ir(cC_8H_{14})_2Cl]_2$ (5.6 mg, 6.2 μmol), PCy_3 (10.0 mg, 0.037 mmol), and $NaBPh_4$ (4.2 mg, 0.012 mmol). After 3 h the reaction was opened to the atmosphere and stirred for approx. 10 min and was then concentrated in vacuo. The crude residue was purified by flash chromatography on SiO_2 (99:1 hexanes/Et_2O) to afford 170 mg (68%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.26 (m, 5H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.04-6.12 (m, 2H), 4.90 (dt, *J* = 6.6, 5.7 Hz, 1H), 4.10 (dd, *J* = 7.5, 1.5 Hz, 1H), 1.60-1.76 (m, 2H), 1.54 (d, *J* = 6.0 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H); IR ν_{max}^{neat} cm^{-1}: 3030, 2970, 2940, 1680, 1670, 1495, 1450, 1170, 970, 920, 750, 690; HRMS (EI) *m/z* calcd for $C_{14}H_{18}O$ (M^+): 202.1358; found: 202.1353.

General Procedure A. Synthesis of Ligands 22a-c: To a flame-dried 20 mL scintillation vial equipped with a rubber septum was added picolinic acid (1 equiv) and thionyl chloride (6.8 equiv). The dark-green, heterogeneous solution was heated at 50 °C under an N_2 atmosphere for 1 h. The resulting homogenous purple solution was allowed to cool to ambient temperature and concentrated in vacuo to afford the acid chloride as a solid, dark-purple residue. To this vial was then added the aminophenol (1 equiv),[13] 2 mL of dry toluene, and triethylamine (1.1 equiv). The vial was sealed and heated to 80 °C under an N_2 atmosphere for 40 h; reaction progress was monitored by TLC. After cooling to ambient temperature, the reaction mixture was concentrated

in vacuo and the solid residue was dissolved in methylene chloride or chloroform and washed with 10 mL of 10% HCl (aq) followed by 20 mL of 5% $NaHCO_3$ (aq). The organics were dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo to afford the crude product as a solid. The crude residue was purified by flash chromatography on SiO_2.

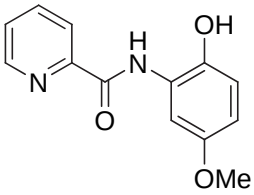


***N*-(2-Hydroxy-5-(trifluoromethyl)phenyl)picolinamide (22a):** General Procedure A was followed employing picolinic acid (100 mg, 0.81 mmol), thionyl chloride (0.4 mL, 5.5 mmol), 2-amino-4-(trifluoromethyl)phenol (144 mg, 0.81 mmol) and triethylamine (0.12 mL, 0.89 mmol). The crude product was dissolved in methylene chloride prior to the acid-base washings and was purified by flash chromatography on SiO_2 (3:2 hexanes/EtOAc) to afford 19 mg (8.3%) of the title compound as a faint-pink solid. ^{1}H NMR (300 MHz, DMSO d-6): δ 11.32 (br s, 1H), 10.54 (br s, 1H), 8.73-8.75 (m, 2H), 8.18 (d, *J* = 7.5 Hz, 1H), 8.09 (t, *J* = 6.0 Hz, 1H), 7.70 (t, *J* = 5.1 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H); IR ν_{max}^{neat} cm^{-1}: 3110, 1670, 1600, 1520, 1450, 1380, 1340, 1110, 810, 740, 690; HRMS (ESI^+) *m/z* calcd for $C_{13}H_{10}F_3N_2O_2$ $[(M + H)^+]$: 283.0694; found: 283.0685.

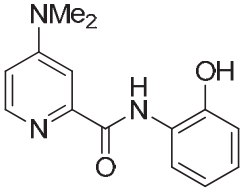


***N*-(5-Fluoro-2-hydroxyphenyl)picolinamide (22b):** General Procedure A was followed employing picolinic acid (100 mg, 0.81 mmol), thionyl chloride (0.4 mL, 5.5 mmol), 2-amino-4-fluorophenol (103 mg, 0.81 mmol) and triethylamine (0.12 mL, 0.89 mmol). The crude product was dissolved in chloroform prior to the acid-base washings and was purified by flash chromatography on SiO_2 (3:2 hexanes/EtOAc) to afford 74 mg (39%) of the title compound as a red-orange solid. ^{1}H NMR (300 MHz, DMSO d-6): δ 10.50 (br s, 1H), 10.30 (br s, 1H), 8.73 (d, *J* = 0.9 Hz, 1H), 8.13-8.28

(m, 2H), 8.08 (t, *J* = 7.8 Hz, 1H), 7.69 (t, *J* = 4.2 Hz, 1H), 6.90 (t, 1H), 6.81 (t, *J* = 8.4 Hz, 1H); IR ν_{max}^{neat} cm^{-1}: 3442, 1670, 1448, 1370, 1264, 870, 796, 730, 673; HRMS (ESI^+) *m/z* calcd for $C_{12}H_9FKN_2O_2$ [$(M + K)^+$]: 271.0285; found: 271.0298.

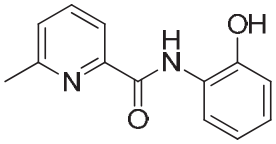


***N*-(2-Hydroxy-5-methoxyphenyl)picolinamide (22c):** General Procedure A was followed employing picolinic acid (100 mg, 0.81 mmol), thionyl chloride (0.4 mL, 5.5 mmol), 2-amino-4-methoxyphenol (113 mg, 0.81 mmol) and triethylamine (0.12 mL, 0.89 mmol). The crude product was dissolved in chloroform prior to the acid-base washings and was purified by flash chromatography on SiO_2 (13:7 hexanes/EtOAc) to afford 93 mg (47%) of the title compound as a dark-purple solid. ^1H NMR (300 MHz, $CDCl_3$): δ 10.19 (br s, 1H), 8.65 (d, *J* = 4.2 Hz, 1H), 8.60 (s, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.93 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 4.8 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 6.72-6.77 (m, 2H), 3.77 (s, 3H); IR ν_{max}^{neat} cm^{-1}: 3310, 3110, 1670, 1595, 1530, 1450, 1420, 1370, 1270, 1210, 1030, 730, 690; HRMS (ESI^+) *m/z* calcd for $C_{13}H_{12}KN_2O_3$ [$(M + K)^+$]: 283.0485; found: 283.0496.



4-(Dimethylamino)-*N*-(2-hydroxyphenyl)picolinamide (26): To a flame-dried 20 mL scintillation vial equipped with a rubber septum and Teflon stirrer was added 4-(dimethylamino)picolinic acid (100 mg, 0.60 mmol) and thionyl chloride (0.31 mL, 4.2 mmol). The milky, white solution was heated at 50 °C for 2 h under an N_2 atmosphere; reaction progress was monitored by TLC. The resulting yellow solution was allowed to cool to ambient temperature and concentrated in vacuo to afford a solid, yellow residue. To this vial was then added 2-aminophenol (66 mg, 0.60 mmol), 2 mL of dry

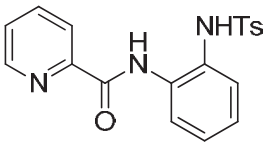
toluene, and triethylamine (0.092 mL, 0.66 mmol). The vial was sealed and the gold, heterogeneous solution was heated to 100 °C under an N_2 atmosphere for 20 h. After cooling to ambient temperature, the reaction mixture was concentrated in vacuo and the brown, solid residue dissolved in chloroform and washed with 20 mL of sat. $NaHCO_3$ (aq). The organics were dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo to afford the crude product as a brown solid. The crude product was purified by flash chromatography on SiO_2 (3:2 hexanes/EtOAc) to afford 14 mg (9%) of the title compound as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.35 (br s, 1H), 8.21 (d, 1H), 7.52 (d, 1H), 7.11-7.16 (m, 2H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.90 (t, *J* = 7.2 Hz, 1H), 6.74 (s, 1H), 6.59 (d, 1H), 3.07 (s, 6H).



***N*-(2-Hydroxyphenyl)-6-methylpicolinamide (27):** To a flame-dried 20 mL scintillation vial equipped with a rubber septum and Teflon stirrer was added 6-methylpicolinic acid (100 mg, 0.73 mmol) and thionyl chloride (0.53 mL, 7.3 mmol). The heterogeneous solution was heated with stirring at 60 °C for 3 h under an N_2 atmosphere. The resulting homogenous, pink solution was allowed to cool to ambient temperature and concentrated in vacuo to afford the acid chloride as a solid, dark-purple residue. To this vial was then added 2-aminophenol (80 mg, 0.73 mmol), 2 mL of dry toluene, and triethylamine (0.11 mL, 0.80 mmol). The vial was sealed and the purple, heterogeneous solution was heated to 80 °C for 22 h; reaction progress was monitored by TLC. After cooling to ambient temperature, the reaction mixture was concentrated in vacuo and the tan, solid residue dissolved in chloroform and washed with 10 mL of 10% HCl (aq) followed by 20 mL of 5% $NaHCO_3$ (aq). The organics were dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo to afford the crude product as a tan solid. The crude product was purified by flash chromatography on

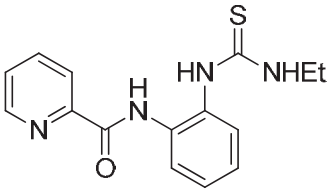
SiO_2 (3:1 hexanes/EtOAc) to afford 37 mg (22%) of the title compound as a yellow solid. ^{1}H NMR (300 MHz, DMSO d-6): δ 10.47 (br s, 1H), 10.21 (br s, 1H), 8.35 (d, *J* = 8.1 Hz, 1H), 7.90-7.97 (m, 2H), 7.52 (d, *J* = 6.6 Hz, 1H), 6.91-6.93 (m, 2H), 6.82 (t, 1H), 2.57 (s, 3H); IR ν_{max}^{neat} cm^{-1}: 2990, 1655, 1596, 1591, 1552, 1456, 1366, 750, 741; HRMS (ESI$^+$) *m/z* calcd for $C_{13}H_{12}KN_2O_2$ [(M + K)$^+$]: 267.0536; found: 267.0543.

General Procedure B. Synthesis of Ligands 32a-c: To a flame-dried 10 mL round-bottom flask equipped with a rubber septum and Teflon stirrer was added picolinic acid (1.2 equiv), monoprotected 1,2-phenylenediamine (1 equiv), and 0.5 mL of dry methylene chloride. The mixture was stirred at ambient temperature under an N_2 atmosphere for several minutes then cooled to 0 °C in an ice/water bath. DCC (1.5 equiv) was added dropwise over 15-30 min as a solution in methylene chloride (0.5 mL). The reaction was stirred at 0 °C and the cold bath was allowed to warm to ambient temperature over a period of 22-23 h. The reaction was then filtered through a pad of Celite eluting with methylene chloride and the filtrate was concentrated in vacuo to afford the crude product. The crude product was purified by flash chromatography on SiO_2 and, if necessary, precipitated from the indicated solvent system.

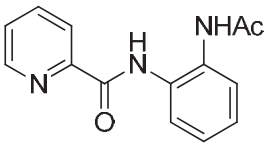


***N*-(2-(4-Methylphenylsulfonamido)phenyl)picolinamide (32a):** General Procedure B was followed employing picolinic acid (56 mg, 0.46 mmol), *N*-(2-aminophenyl)-4-methylbenzenesulfonamide (100 mg, 0.38 mmol),[14] and DCC (118 mg, 0.57 mmol). The crude product was purified by flash chromatography on SiO_2 (1:1 hexanes/EtOAc) followed by precipitation from EtOH/hexanes. After washing with pentane, approx. 30 mg (21%) of the title compound was afforded as a white solid. ^{1}H NMR (300 MHz,

DMSO d-6): δ 10.55 (br s, 1H), 9.75 (br s, 1H), 8.73 (d, *J* = 4.8 Hz, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 8.06-8.09 (m, 2H), 7.68 (t, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 2H), 7.01 (t, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 2.24 (s, 3H); IR ν_{max}^{neat} cm^{-1}: 3280, 3070, 2810, 2740, 1670, 1590, 1540, 1460, 1410, 1340, 1170, 750, 690; HRMS (ESI^+) *m/z* calcd for $C_{19}H_{17}KN_3O_3S$ [$(M + K)^+$]: 406.0628; found: 406.0633.

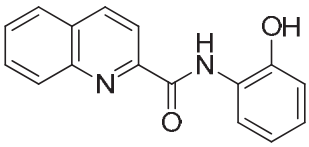


***N*-(2-(3-Ethylthioureido)phenyl)picolinamide (32b):** General Procedure B was followed employing picolinic acid (75 mg, 0.61 mmol), 1-(2-aminophenyl)-3-ethylthiourea (100 mg, 0.51 mmol),[15] and DCC (157 mg, 0.76 mmol). The crude product was purified by flash chromatography on SiO_2 (9:11 hexanes/EtOAc) followed by precipitation from EtOAc/hexanes. After washing with pentane, approx. 42 mg (27%) of the title compound was afforded as a yellow solid. ^{1}H NMR (300 MHz, DMSO d-6): δ 10.43 (br s, 1H), 9.14 (br s, 1H), 8.66 (d, *J* = 4.2 Hz, 1H), 8.15-8.19 (m, 2H), 8.07 (t, *J* = 7.8 Hz, 1H), 7.80 (br s, 1H), 7.67 (t, *J* = 4.8 Hz, 1H), 7.33 (t, 1H), 7.26 (d, 1H), 7.16 (d, 1H), 3.44-3.46 (m, 2H), 1.00-1.07 (m, 3H); IR ν_{max}^{neat} cm^{-1}: 3410, 1640, 1530, 1480, 1460, 1440, 1230, 750, 690, 620; HRMS (ESI^+) *m/z* calcd for $C_{15}H_{16}KN_4OS$ [$(M + K)^+$]: 339.0682; found: 339.0695.



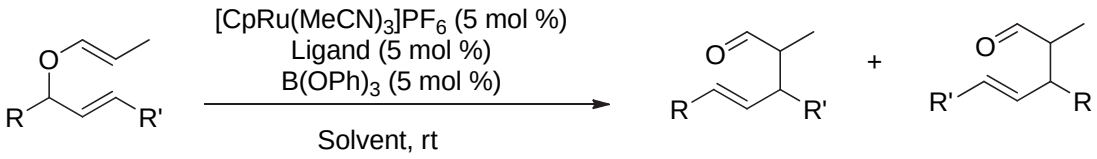
***N*-(2-Acetamidophenyl)picolinamide (32c):** General Procedure B was followed employing picolinic acid (90 mg, 0.73 mmol), *N*-(2-aminophenyl)acetamide (100 mg, 0.61 mmol),[16] and DCC (189 mg, 0.91 mmol). The crude product was purified by flash chromatography on SiO_2 (1:1 hexanes/EtOAc) to afford 135 mg (87%) of the title compound as a tan solid. ^{1}H NMR (300 MHz, DMSO d-6): δ 10.35 (br s, 1H),

9.90 (br s, 1H), 8.71 (d, J = 4.8 Hz, 1H), 8.15 (d, 1H), 8.06 (t, 1H), 7.99 (d, 1H), 7.69 (t, 1H), 7.30 (t, 2H), 7.18 (t, 1H), 2.10 (s, 3H); IR ν_{max}^{neat} cm^{-1}: 3470, 1670, 1600, 1520, 1298, 752, 590; HRMS (ESI^+) *m/z* calcd for $C_{14}H_{13}KN_3O_2$ [$(M + K)^+$]: 294.0645; found: 294.0662.



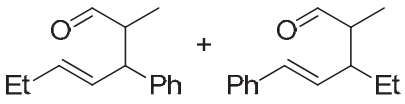
***N*-(2-hydroxyphenyl)quinoline-2-carboxamide (34)[17]:** To a flame-dried 20 mL scintillation vial equipped with a rubber septum and Teflon stirrer was added quinaldic acid (100 mg, 0.58 mmol) and thionyl chloride (0.29 mL, 4.0 mmol). The heterogeneous pink solution was heated at 65 °C for 4 h under an N_2 atmosphere. At this time an additional amount of thionyl chloride (0.29 mL, 4.0 mmol) was added to the reaction, which was subsequently heated for another 2.5 h. The resulting homogenous, orange solution was allowed to cool to ambient temperature and concentrated in vacuo to afford the acid chloride as a solid residue. To this vial was then added 1 mL of dry THF and triethylamine (0.12 mL, 0.87 mmol). The heterogeneous reaction was stirred under an N_2 atmosphere and cooled to approx. 0 °C using an ice/water bath. A solution of 2-aminophenol (63 mg, 0.58 mmol) in 1 mL THF was added dropwise over several minutes and the reaction was stirred at 0 °C for approximately 30 min. The reaction was allowed to gradually warm to ambient temperature and was stirred until complete as monitored by TLC. The solid residue was dissolved in approx. 10 mL of chloroform and washed with 20 mL of deionized H_2O The organics were dried over anhydrous Na_2SO_4, decanted, and concentrated in vacuo to afford the crude product as an orange solid. The crude product was purified by recrystallization from hot EtOH to afford 80 mg (52%) of the title compound as an orange solid. ^1H NMR (300 MHz, DMSO d-6): δ 10.65 (br s, 1H), 10.31 (br s, 1H), 8.66 (d, J = 8.1 Hz, 1H), 8.39 (d, J = 7.5 Hz, 1H), 8.29 (d, J = 8.7 Hz, 1H), 8.14

(t, *J* = 9.0 Hz, 2H), 7.90 (t, *J* = 6.9 Hz, 1H), 7.75 (t, *J* = 6.9 Hz, 1H), 6.94-6.98 (m, 2H), 6.83-6.89 (m, 1H).



General Procedure C. Ru-catalyzed Rearrangements of Allyl Vinyl Ethers: In a N_2-filled glovebox, $[CpRu(CH_3CN)_3]PF_6$ (5 mol %) and ligand (5 mol %) were weighed out and placed into a 2 dram vial. Solvent (THF, toluene, or DMF) was added via syringe and the resulting solution (bright-orange to deep-red in color) was set aside for 30 min with periodic agitation. Typical preparations utilized the appropriate amount of solvent to provide a substrate concentration of 0.5 M. In another 2 dram vial, equipped with a Teflon stirrer, substrate (1 equiv) was measured out and combined with $B(OPh)_3$ (5 mol %, if used). The solution containing Ru and ligand was transferred to the vial containing the substrate. The vial was sealed with a rubber septum and removed from the glovebox. Parafilm® was wrapped around the septum and the solution was stirred at ambient temperature for the duration of the reaction. At the specified time, the reaction was opened to the atmosphere, stirred for 5 min, and diluted with pentane (approx. 2x the reaction volume) to afford a heterogenous solution. After an additional 5 min of stirring, the solution was filtered through a pipet packed with Celite containing a small layer (1 cm) of Florisil. After flushing the column several times with pentane, the filtrate was concentrated in vacuo to afford the crude product as an oil, which was characterized by ^1H NMR spectroscopy.

General Procedure D. Ru-catalyzed Rearrangements of Allyl Vinyl Ethers: In a N_2-filled glovebox, $[CpRu(CH_3CN)_3]PF_6$ (5 mol %) and ligand (5 mol %) were weighed out and placed into a 2 dram vial. The vial was sealed with a rubber septum and removed from the glovebox; Parafilm® was wrapped around the septum. Solvent (CH_2Cl_2 or acetone) was added via syringe and the resulting solution (dark-red in color) was set aside for 30 min with periodic agitation. Typical preparations utilized the appropriate amount of solvent to provide a substrate concentration of 0.5 M. In another 2 dram vial, equipped with a Teflon stirrer, substrate (1 equiv) was measured out and combined with $B(OPh)_3$ (5 mol %, if used). The vial was sealed with a rubber septum and removed from the glovebox. The solution containing Ru and ligand was transferred to the vial containing the substrate via syringe. Parafilm® was wrapped around the septum and the solution was stirred at ambient temperature for the duration of the reaction. At the specified time, the reaction was opened to the atmosphere, stirred for 5 min, and diluted with pentane (approx. 2x the reaction volume) to afford a heterogeneous solution. After an additional 5 min of stirring, the solution was filtered through a pipet packed with Celite containing a small layer (1 cm) of Florisil. After flushing the column several times with pentane, the filtrate was concentrated in vacuo to afford the crude product as an oil, which was characterized by ^1H NMR spectroscopy.

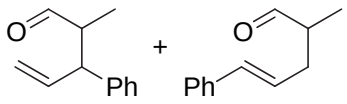


24 **25**

(E)-2-methyl-3-phenylhept-4-enal (24)[12] and **(E)-3-ethyl-2-methyl-5-phenylpent-4-enal (25):** General Procedure C or D was followed employing 0.05 g or 0.1 g of **23**. The crude ^1H NMR spectrum indicated the presence of four compounds; **24** and **25** were each present as mixtures of two diastereomers; regio- and stereoisomers were inseparable by standard flash

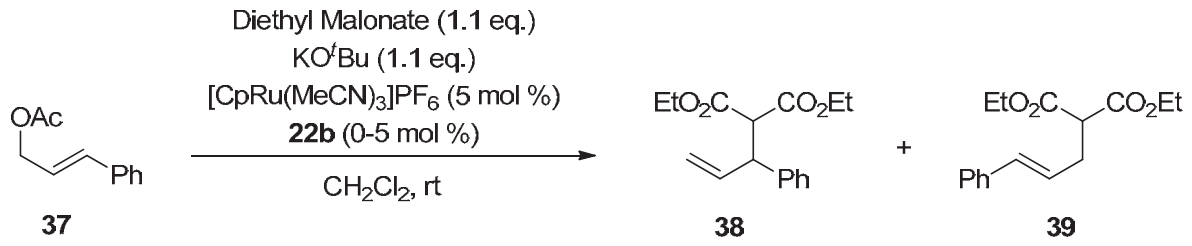
chromatographic techniques. Product distributions were determined as follows. Aldehydes **24** were identified by comparison to the literature spectrum of the compound exhibiting the *syn* stereochemical relationship between the α and β substituents.[18] The triplet at δ = 3.48 ppm was used as a reference point for identifying the *syn* isomer of **24** while the triplet at δ = 3.59 ppm was assigned to be the corresponding resonance for the *anti* isomer; the *anti:syn* ratio for **24** was typically determined from the ratio of the integrations of these two resonances in the crude ^{1}H NMR spectrum. The ratio of **24:25** was typically determined from the ratio of the sum of the triplets at δ = 3.48, 3.59 (total **24** present) to the sum of the doublets of doublets at δ = 5.90, 6.05 (total **25** present). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73*** (d, 1H), 9.68*/*** (m, 2H), 9.55** (d, 1H), 7.18-7.37*/**/*** (m, 20H), 6.40-6.45*** (m, 2H), 6.05*** (dd, 1H), 5.90*** (dd, 1H), 5.50-5.70*/** (m, 4H), 3.59** (t, 1H), 3.49* (t, 1H), 2.70-2.90*/** (m, 2H), 2.35-2.60*** (m, 2H), 2.00-2.05*/** (m, 4H), 1.40-1.70*** (m, 4H), 1.01-1.15**/*** (m, 6H), 0.90-0.99 */**/***(m, 18H).

* *syn*-**24**, ** *anti*-**24**, *** **25**

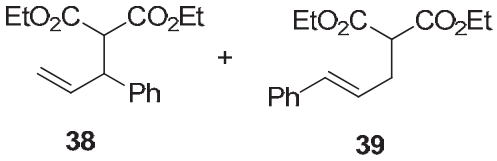


30 **31**

2-methyl-3-phenylpent-4-enal (30)[11] and **(E)-2-methyl-5-phenylpent-4-enal (31)[11]:** General Procedure C or D was followed employing 0.05 or 0.1 g of **29**. The crude ^{1}H NMR spectrum indicated the presence of three compounds; **30** was present as a mixture of two diastereomers. Products were identified and their ratios were determined by comparison to literature values.[11]



General Procedure E. Ru-catalyzed Alkylation of Cinnamyl Acetate: In an N_2-filled glovebox, [CpRu(CH_3CN)$_3$]PF_6 (5 mol %) and **22b** (5 mol %, if used) were weighed out and placed into a 2 dram vial. The vial was sealed with a rubber septum and removed from the glovebox; Parafilm® was wrapped around the septum. CH_2Cl_2 was added via syringe and the resulting dark-red solution was set aside for 30 min with periodic agitation. Typical preparations utilized the appropriate amount of solvent to provide a substrate concentration of 0.5 M. In another 2 dram vial equipped with a Teflon stirrer, substrate (1 equiv) was measured out and combined with KO^{t}Bu (1.1 equiv). The vial was sealed with a rubber septum and removed from the glovebox. The solution containing Ru and ligand was transferred to the vial containing the substrate via syringe and diethyl malonate (1.1 equiv) was added to the resulting solution via syringe. Parafilm® was wrapped around the septum and the viscous solution was stirred at ambient temperature for the duration of the reaction. At the specified time, the reaction was opened to the atmosphere, stirred for 5 min, and diluted with pentane (approx. 2x the reaction volume) to afford a heterogeneous solution. After an additional 5 min of stirring, the solution was filtered through a pipet packed with Celite containing a small layer (1 cm) of Florisil. After flushing the column several times with diethyl ether, the filtrate was concentrated in vacuo to afford the crude product as an oil, which was characterized by ^{1}H NMR spectroscopy.



38 39

Diethyl 2-(1-phenylallyl)malonate (38)[19] and **diethyl 2-cinnamylmalonate (39)[19]:** General Procedure E was followed employing 0.05 g of **37**. The crude ^{1}H NMR spectrum indicated the presence of **37**, **38**, **39** and diethyl malonate; products were identified and their ratios were determined by comparison to literature values.[19]

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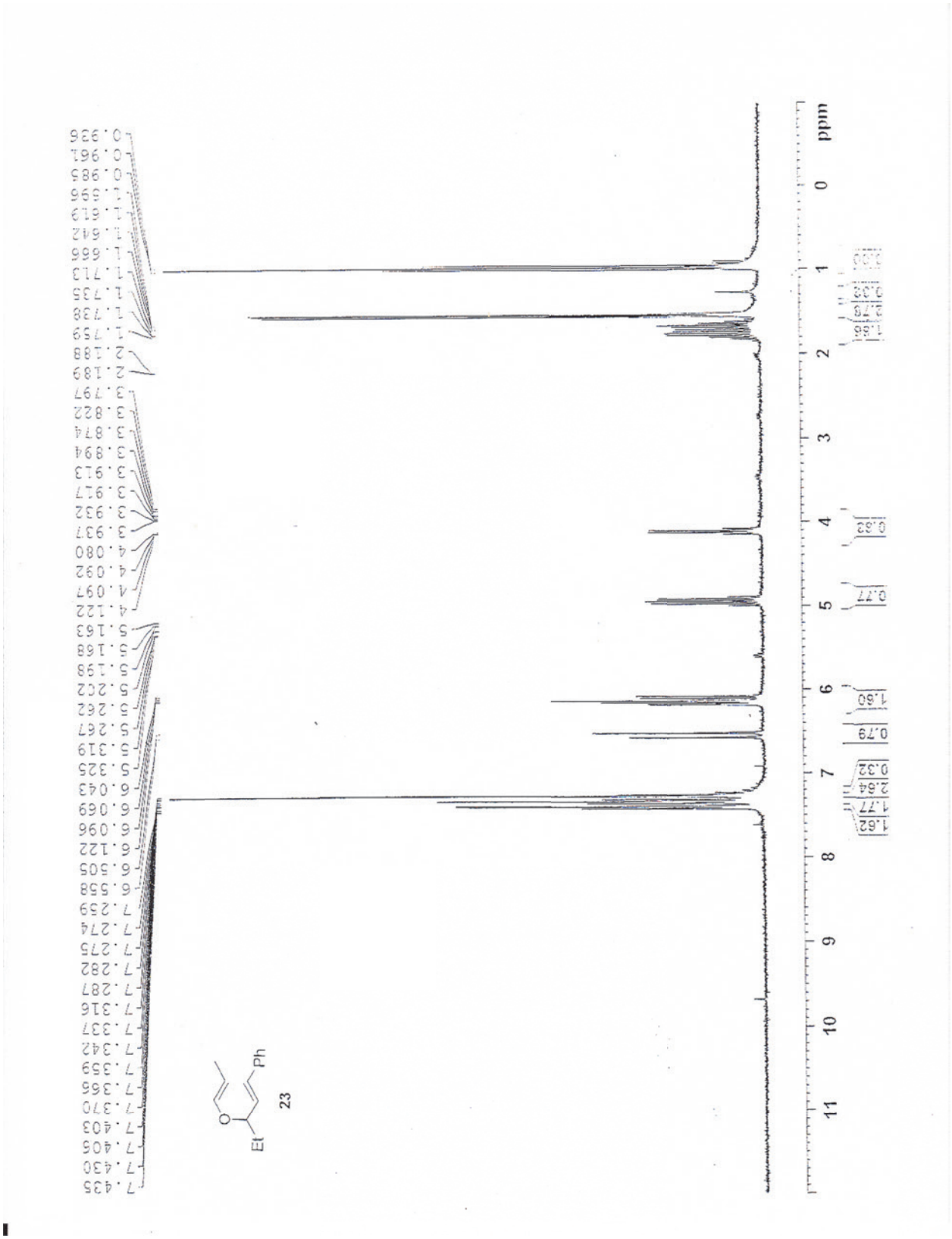
6.0 SPECTRA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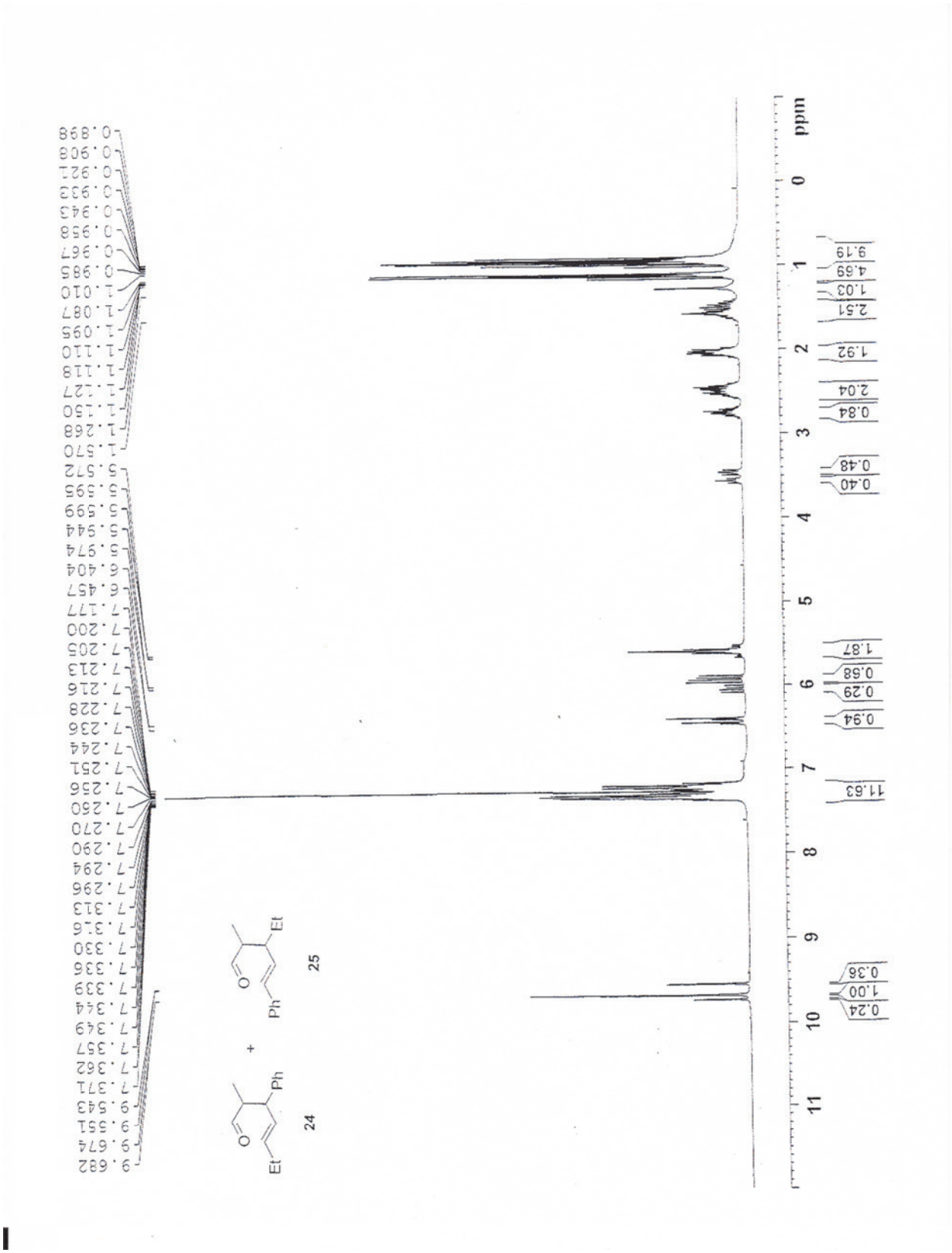
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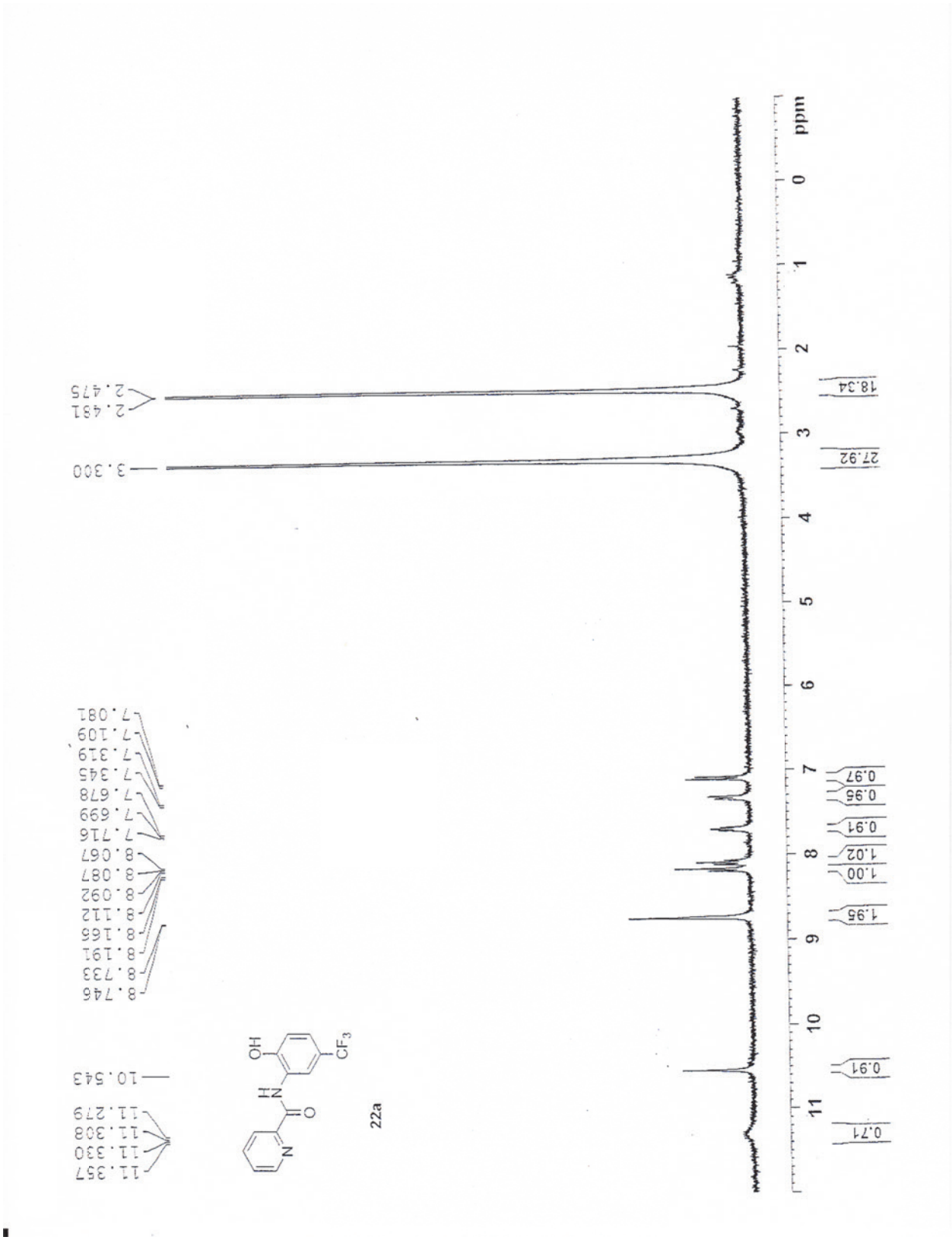
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8.067
7.716
7.699
7.678
7.345
7.319
7.109
7.081
3.300
2.481
2.475
22a
ppm
0.71
0.91
11
10
9
1.95
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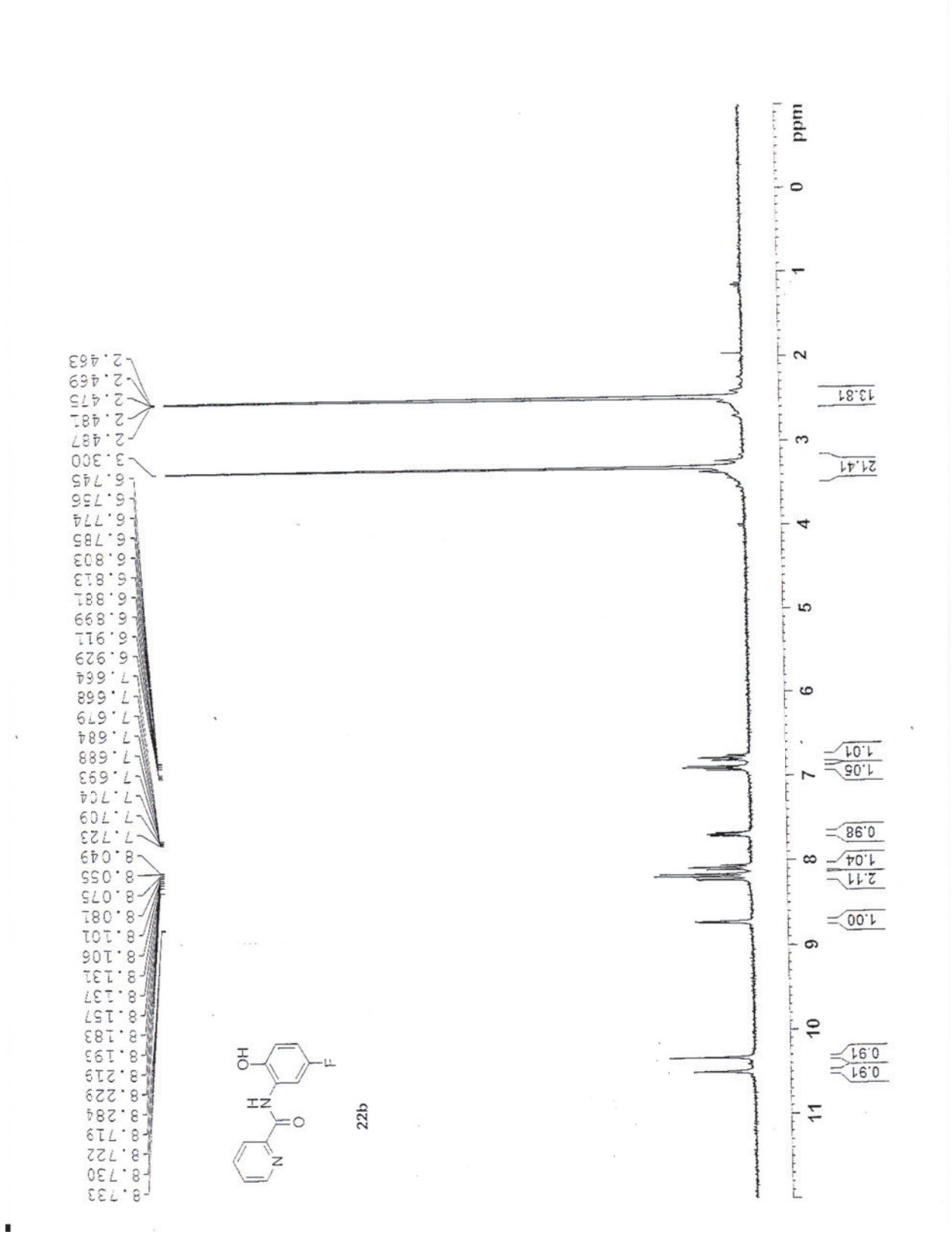
4
3
2
1
0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8.049
7.723
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7.704
7.693
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7.684
7.679
7.668
7.664
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6.899
6.881
6.813
6.803
6.785
6.774
6.756
6.745
3.300
2.487
2.481
2.475
2.469
2.463
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F
N
H
O
N
22b
ppm
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4
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7
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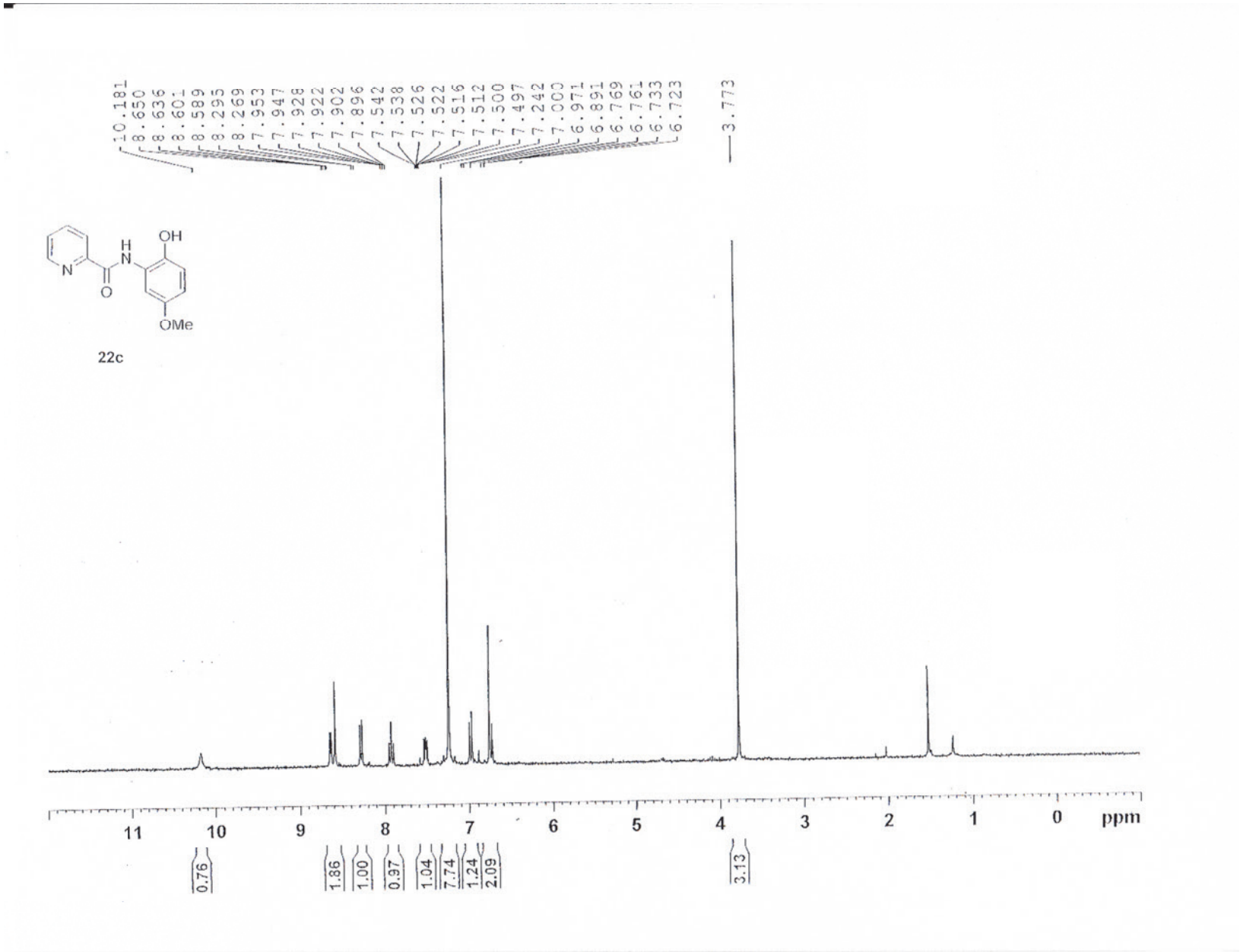
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10
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8
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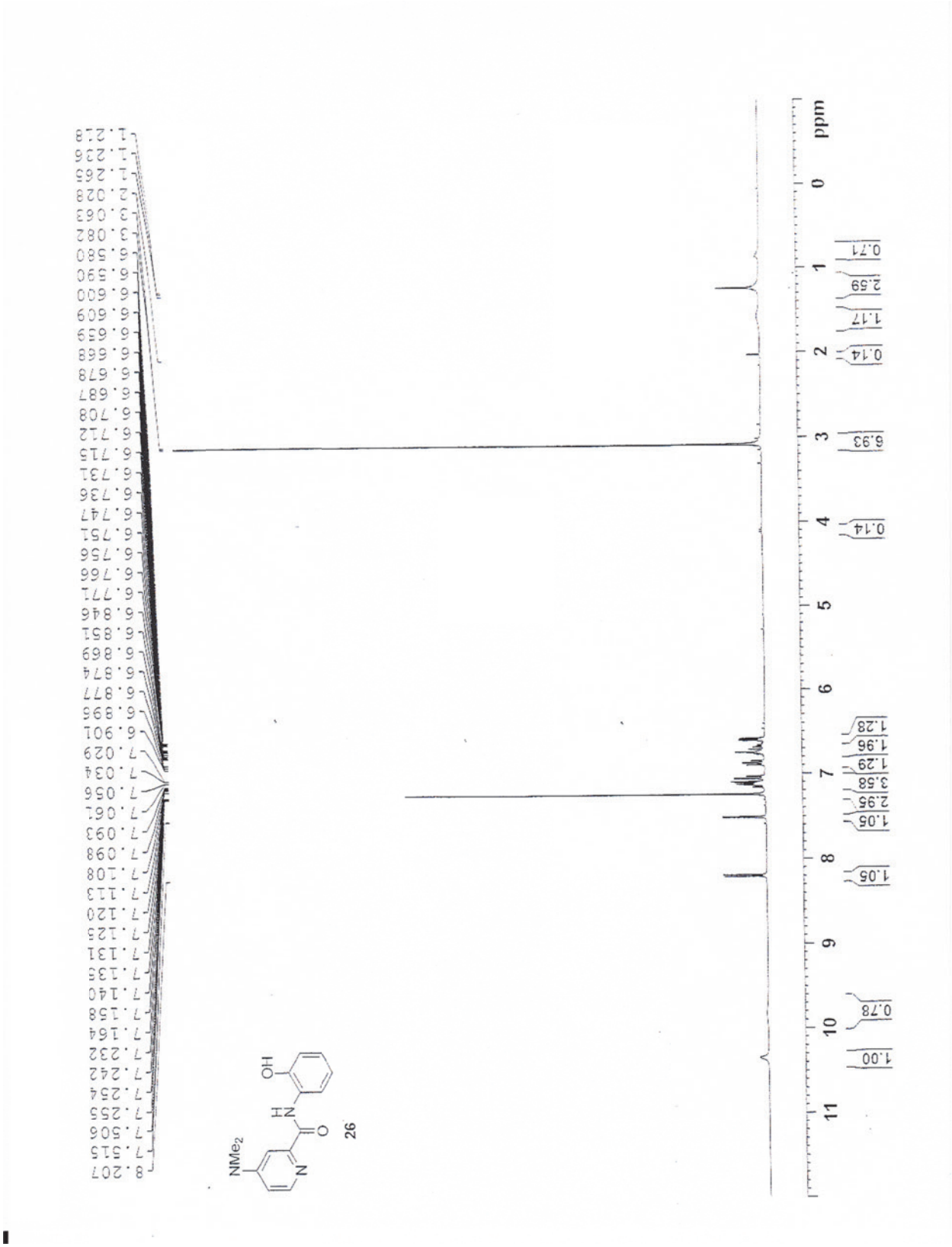
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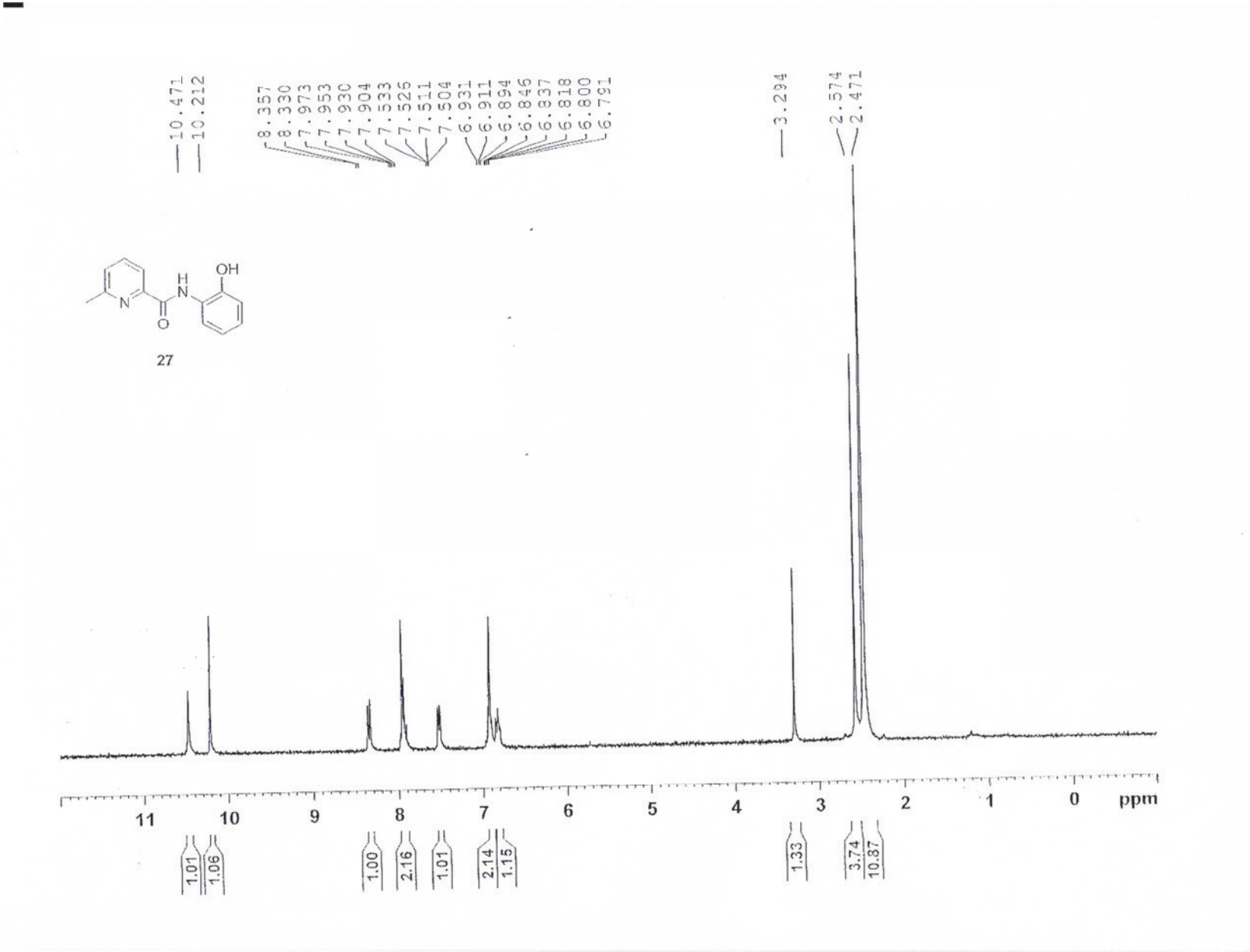
N
26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8
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3
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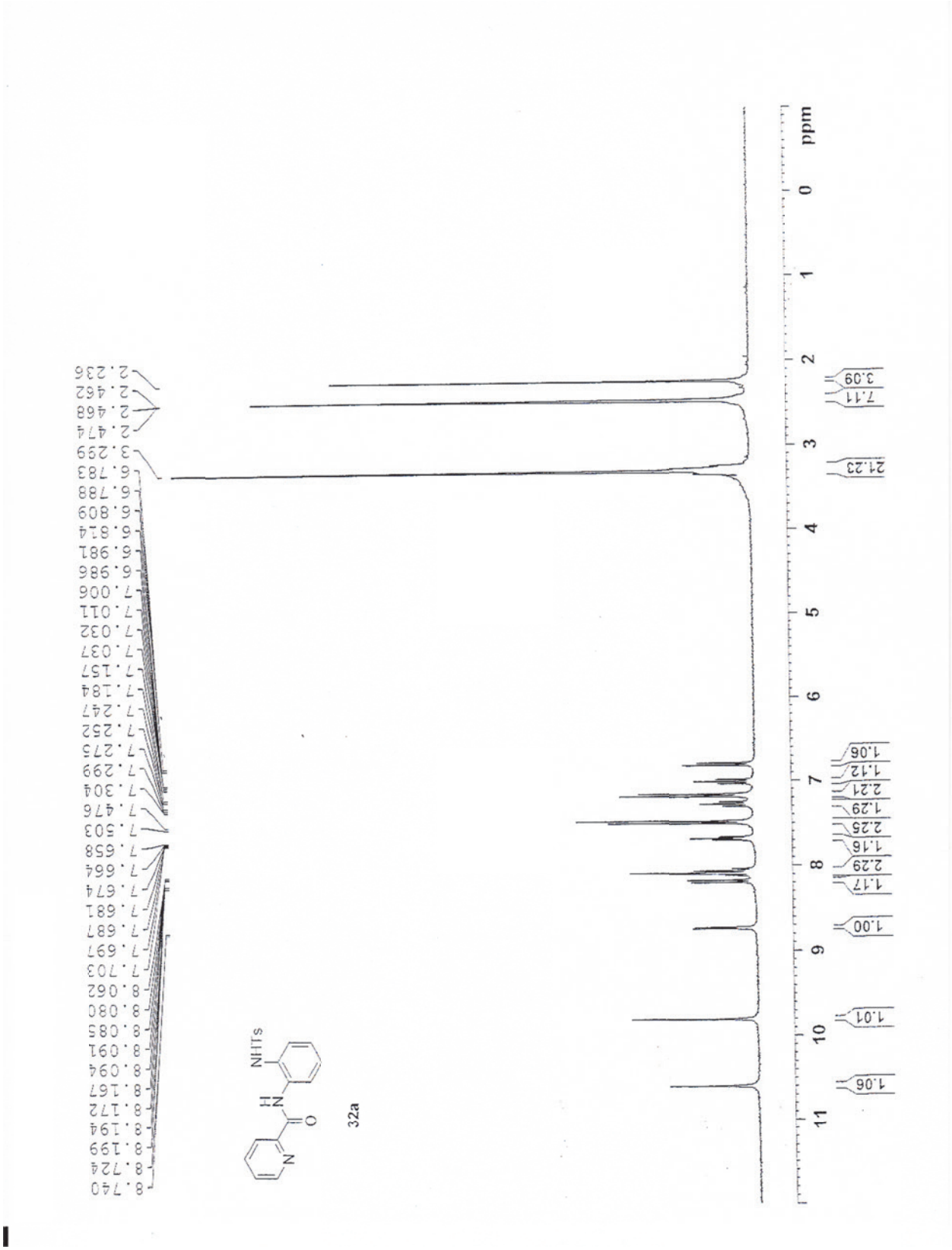
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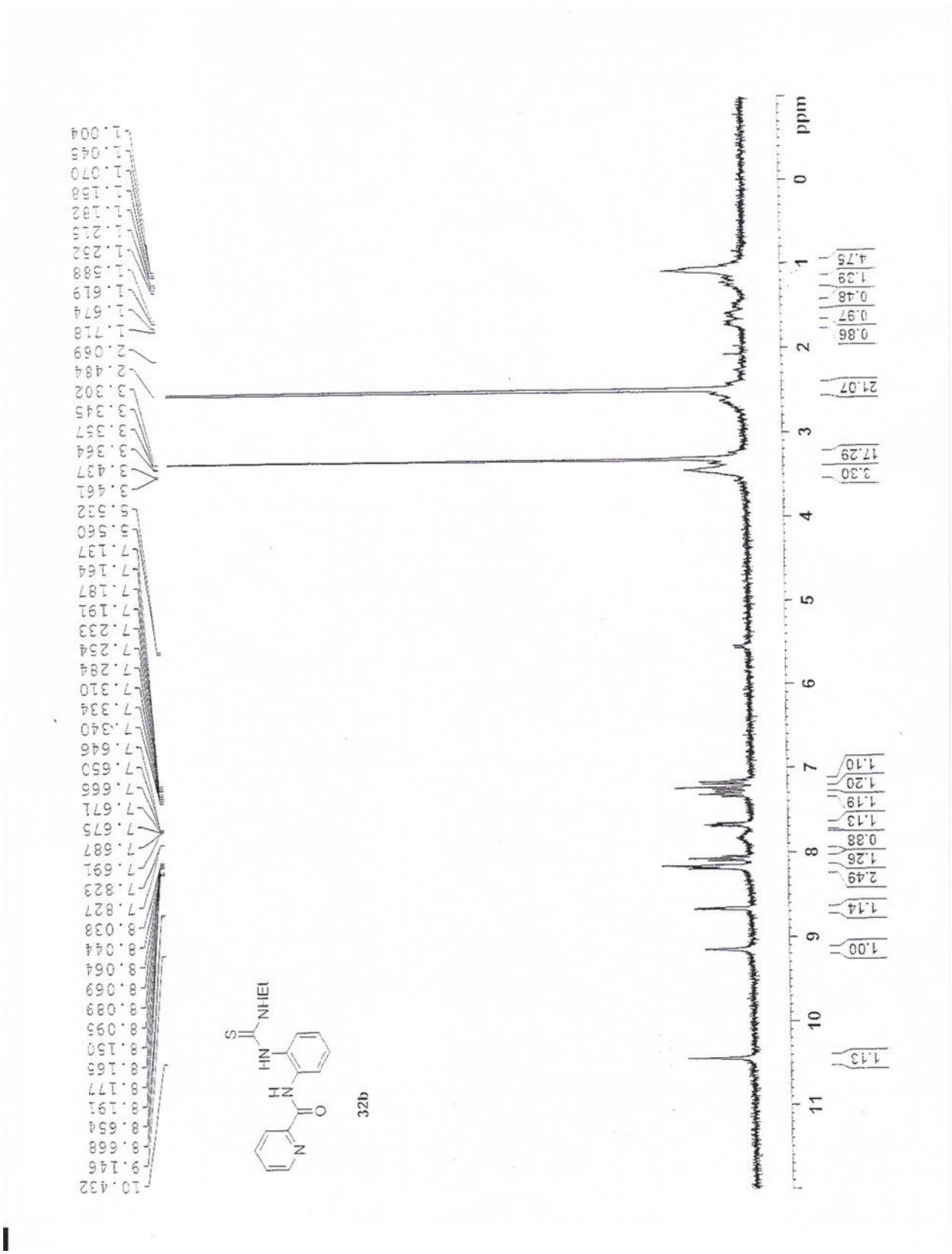
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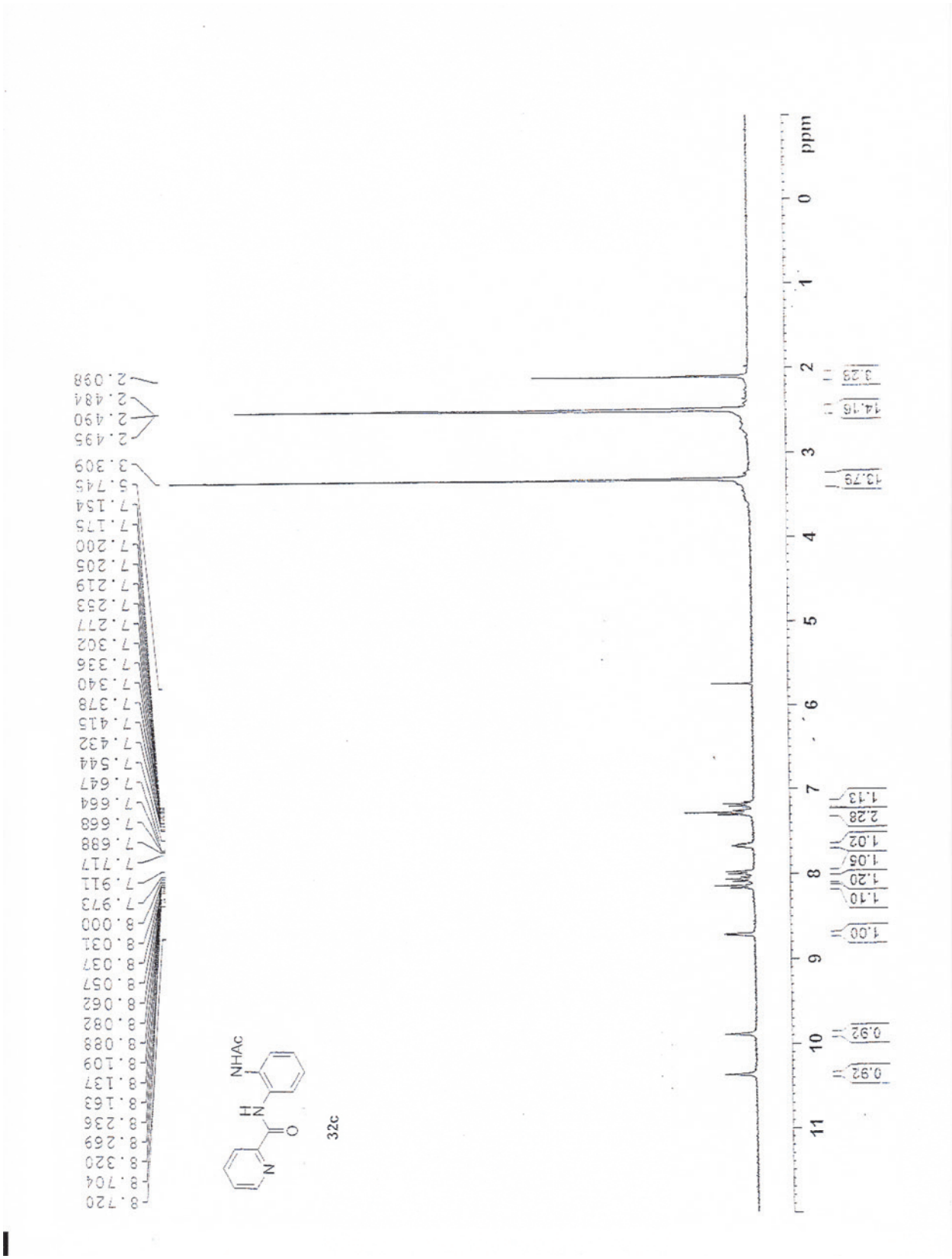
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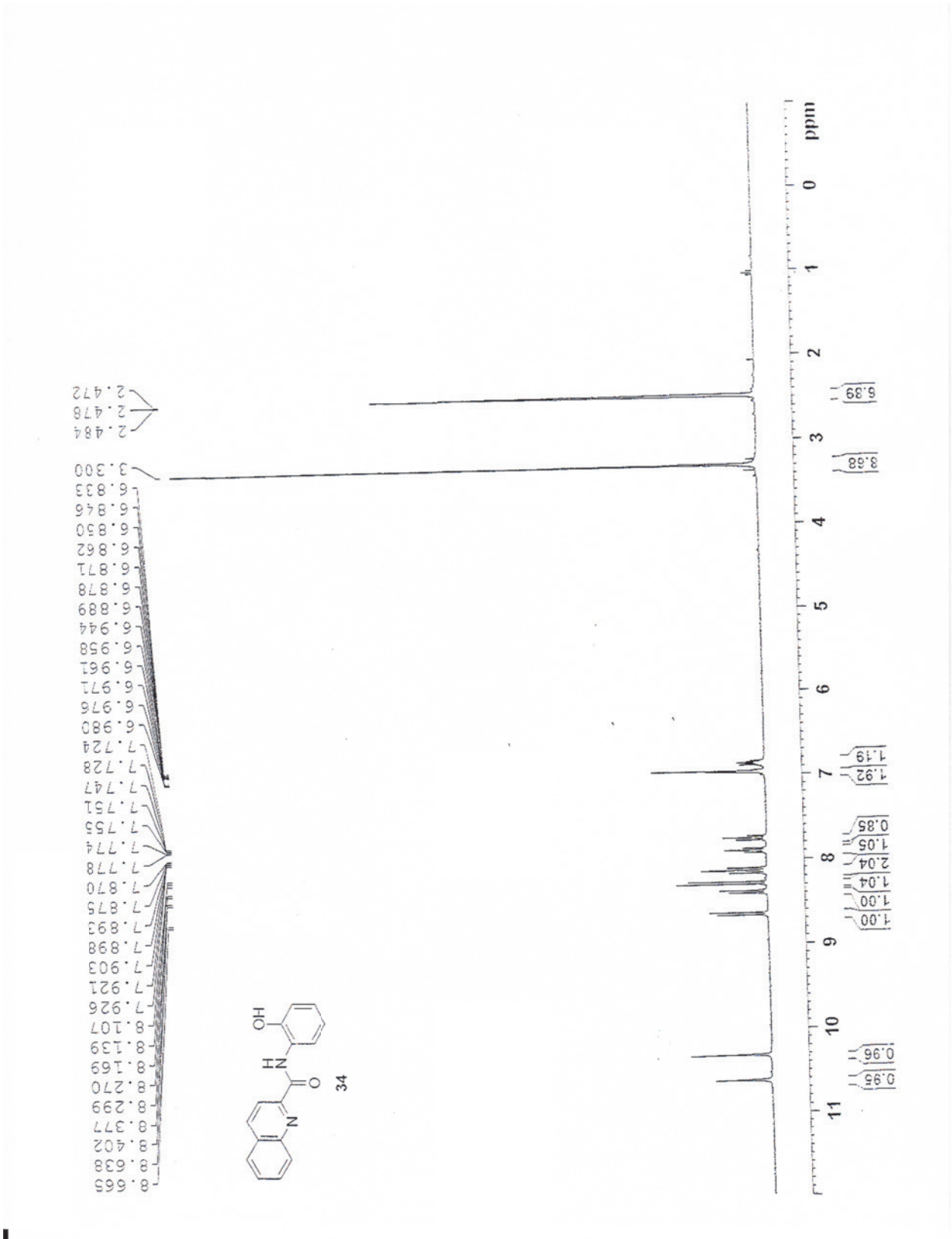
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