

Cross-Coupling Reactions of Unactivated Alkyl Halides

by

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B. Sc., Honors, Chemistry, 1998

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Submitted to the Department of Chemistry
in Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY
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Massachusetts Institute of Technology

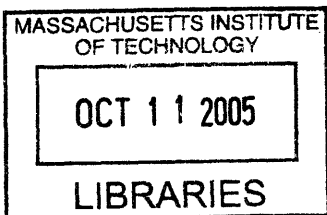
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ABSTRACT

My graduate research at MIT has been focused on the development of palladium- or nickel-catalyzed cross-coupling reactions using unactivated alkyl electrophiles (e.g., halides and sulfonates). Although aryl and alkenyl electrophiles have been commonly used in such processes, the utility of alkyl substrates has been underdeveloped, and merits further exploration.

We have developed the first palladium-based catalyst that is effective for Negishi couplings of primary alkyl electrophiles. A single protocol (2%Pd₂(dba)₃/8%P(Cyp)₃/NMI in THF/NMP at 80 °C) can be applied to a broad spectrum of electrophiles, including chlorides, bromides, iodides, and tosylates. Concerning the scope of the nucleophilic components, an array of alkyl-, alkenyl-, and arylzinc halides can be coupled. The process is tolerant of a variety of functional groups, including esters, amides, imides, nitriles, and heterocycles. Furthermore, geometrically-defined alkenylzinc species, generated from titanium-mediated hydrozincation of internal alkynes, can be directly used in the process.

Despite the progress in nickel- and palladium-catalyzed C(sp³)-C(sp³) bond formation, the methods had been limited to primary alkyl electrophiles. No doubt, the ability to use more challenging, secondary ones will further augment the usefulness of these metal-catalyzed processes. To this end, we have determined that Ni(cod)₂/*s*-Bu-Pybox can catalyze room-temperature Negishi couplings of an array of functionalized alkyl bromides and iodides. To the best of our knowledge, this is the first nickel- or palladium-catalyzed cross-coupling procedure for unactivated, β-hydrogen-containing secondary alkyl halides. In addition, preliminary studies using substrate-based probes suggest that the oxidative addition proceeds through a radical pathway. This may explain the unparalleled reactivity of the nickel catalyst.

As an extension of the nickel catalysis, we have established that the combination of Ni(cod)₂ and bathophenanthroline can effect Suzuki reactions of secondary halides and organoboronic acids. These organoboron reagents are particularly widely used in the cross-coupling chemistry, owing to their chemical stability, biological non-toxicity, and commercial availability. Again, mechanistic evidence has been collected to support the involvement of organic radicals during the oxidative addition step.

Thesis Supervisor: Gregory C. Fu

Title: Professor of Chemistry

Preface

Portions of this work have appeared in the following publications:

Zhou, J.; Fu, G. C. "Palladium-Catalyzed Negishi Cross-Coupling Reactions of Unactivated Alkyl Iodides, Bromides, Chlorides, and Tosylates" *J. Am. Chem. Soc.* **2003**, *125*, 12527-12530.

Zhou, J.; Fu, G. C. "Cross-Couplings of Unactivated Secondary Alkyl Halides: Room-Temperature Nickel-Catalyzed Negishi Reactions of Alkyl Bromides and Iodides" *J. Am. Chem. Soc.* **2003**, *125*, 14726-14727.

Zhou, J.; Fu, G. C. "Suzuki Cross-Couplings of Unactivated Secondary Alkyl Halides" *J. Am. Chem. Soc.* **2004**, *126*, 1340-1341.

Acknowledgment

I would like to thank my supervisor, Prof. Greg Fu, for taking me into his group and giving me all the freedom in my research activities, and also for the occasional guidance he has offered to (or “imposed on”) me so that I did not stray away from “the right direction”. His dedication to research, in-depth mastery of subjects, and meticulous synthesis of scientific manuscripts render him an ideal example of the teaching-by-example doctrine.

It has been a fulfilling experience to work among so many talented chemists. My first benchmate, Dr. Matthew Nertherton, unselfishly shared with me his know-how’s in both chemistry and lab management. I am truly grateful for that. The legendary Dr. Ken Tanaka finished 7 papers within 2 years, setting an almost unbreakable record in the Fu group. Dr. Matthias Eckhardt initiated and wrapped up a project during his 6 month stay, and, meanwhile, directed his own research group back in Germany on a daily basis! It was very pleasant to work beside Dr. Dave Powell in the palladium subgroup, whose amiability and open-mindedness made every conversation with him an enjoyable one. Dr. Christian Fischer is a machine. While I thought that my 222 reactions within 20 days once were some kind of a feat, it turned out that he keeps that pace almost every day. No wonder he is so productive. Dr. Ryan Wurz’s performance in the lab is also phenomenal, and I would like to express my special thanks to him for his painstakingly proofreading of my thesis.

Brian Hodous did a fantastic job in both succeeding his ketene additions and, at the same time, “keeping Greg happy”. Adam Littke, a marathoner, was piecing together his slim, award-winning thesis when I joined the lab. He allegedly “single-handedly revolutionized the cross-coupling chemistry”, which keeps us wondering which hand he has actually used. Ryo Shintani finished his Ph.D. degree within 4 years, and seems to have his career placed in a fast lane again at Kyoto University. Ivory Hills was always talking chemistry with someone in the lab, and seeking every opportunity that he could offer a hand. All the time, Ara Mermerian was either bragging his “silyl ketene acetals” or complaining all kinds of sufferings that he was going through. But that does not mean that he was not willing to help when needed. I really appreciate some of his timely helps.

I would also like to thank Jon Wilson for being such a pleasant baymate and being always there to chat about chemistry or anything else. It was an enriching experience to “slave-drive” Forrest Arp, whom reminded me of the training I once had before. During the course, I learnt much about the tutoring process. And I am very glad that he eventually survived. Others include Shih-Yuan Liu, Dr. Wayne Tang, Dr. Andrés Suárez, Dr. Erhard Bappert, Sunghee Son, Elaine Lee, and my volleyball teammates: Dr. Wade Downey, Dr. Fran Gonzalez, Dr. Thomas Maier, and Dr. Noriaki Kudo.

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Prof. Teck-Peng Loh was my mentor before I came to MIT. His passion in chemistry and chemical intuition are truly admirable. I am utterly grateful to him for having introduced me into the realm of chemistry, in which I find comfortable as home. Of many friends I made in his group, Qiying Hu later also moved to Cambridge to receive his postdoctoral training at Harvard. I had many Saturday night dinners at his place with him and his wife, Liting. Every time, Qiying would produce a piece of scrap paper and start to talk about his Diels-Alder reactions, hoping I could offer some suggestions. I guess I have much more from him than otherwise, and I hope our friendship will last with time.

I am forever indebted to my parents, who have always been supportive to my chemistry pursuit even in their difficult times. And I am also very lucky to have met my understanding and lovable girlfriend, Jeanne, at MIT.

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Abbreviations

BINAP	2,2'- bis(diphenylphosphino)-1,1'-binaphthyl
bipy	2,2'-bipyridine
cod	1,4-cyclooctadiene
Cy	cyclohexyl
Cyp	cyclopentyl
dba	dibenzylideneacetone
dppf	1,1'-bis(diphenylphosphino)ferrocene
DMA	<i>N,N</i> -dimethylacetamide
DMF	<i>N,N</i> -dimethylformamide
NMI	<i>N</i> -methylimidazole
DMPU	<i>N,N'</i> -dimethyl propylene urea
DMSO	dimethylsulfoxide
Eq	equation
equiv	equivalent(s)
GC	gas chromatography
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IAd	1,3-bis(1-adamantyl)imidazol-2-ylidene
Im	imidazole
IMes	1,3-bis(mesityl)imidazol-2-ylidene
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IR	infrared
NMP	<i>N</i> -methyl-2-pyrrolidinone
Py	pyridine
r.t.	room temperature
THF	tetrahydrofuran
TMETA	<i>N,N,N',N'</i> -tetramethylethylene-1,2-diamine

Chapter 1.

Palladium-Catalyzed Cross-Coupling Reactions of Primary Alkyl Electrophiles

1.1. Background

Palladium- and nickel-catalyzed cross-coupling reactions formally refer to the union of two organic groups from organometallic reagents and carbon electrophiles (usually halides and sulfonates). Originally, the chemistry was developed with harsh Grignard or organolithium reagents; today, protocols exist for mild organometallic compounds (typically $M^1 = B, Zn, Sn, \text{ or } Si$). This salient feature has important synthetic implications, thus allowing sensitive functional groups and elaborate structures to be present (Figure 1.1).¹

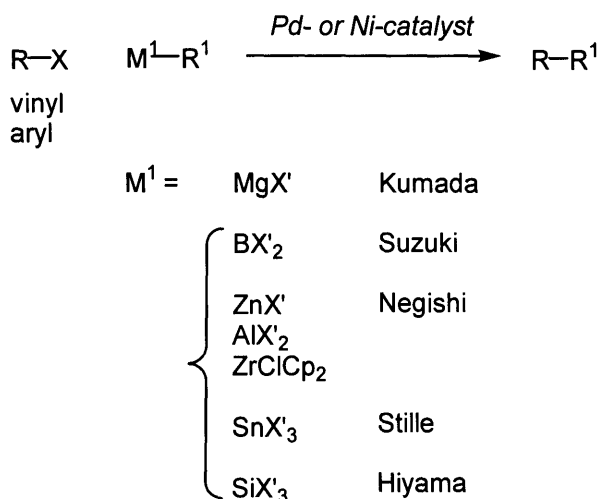


Figure 1.1. Overview of palladium- or nickel-catalyzed cross-coupling reactions.

A simplified catalytic cycle consists of three elementary steps (Figure 1.2): oxidative addition of C-X onto the metal center, transmetalation to produce diorganometal intermediates, and final reductive elimination to form cross-coupling products and to regenerate the active catalysts. Throughout the cycle, palladium/nickel is bound with its ligands, and its reactivity is profoundly influenced by the steric and electronic properties of these ligands. This paradigm serves as a useful guideline during our studies.

Although the prototype of the catalytic cycle was initially proposed for a nickel-catalyzed

¹ For leading references on functionalized organolithium and Grignard reagents, see: (a) Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414–4435. (b) Chinchilla, R.; Nájera, C.; Yus, M. *Tetrahedron* **2005**, *61*, 3139–3176 and references cited therein. However, these reagents usually exhibit low thermal stability.

Kumada reaction,² in general nickel catalysts display more variations due to the redox multiplicity of organonickel species.³ On the other hand, the Pd(0)/Pd(II) cycle is commonly accepted nowadays.⁴

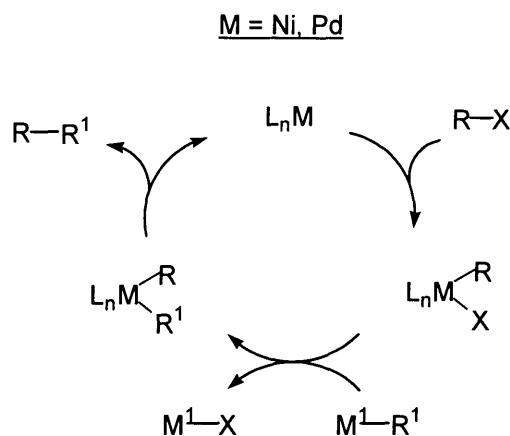


Figure 1.2. A prototypical palladium/nickel catalytic cycle.

Driven by their practical significance, these reactions have been developed into reliable, effective tools in chemical synthesis and still remain intensively studied today.⁵ This is certainly true for aryl, alkenyl, and activated alkyl (including allyl, benzylic, and oxoallyl) electrophiles. In contrast, for unactivated, β -hydrogen-containing alkyl halides/sulfonates, similar methods have been scarce until very recently. Activation of aliphatic electrophiles for cross-couplings had been considered a daunting task. With conventional ligands, the difficulty for palladium-based catalysis was commonly believed

² (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376. (b) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.-i.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958–1969.

³ Kochi, J. K. *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978; pp 393–398.

⁴ Although Pd(IV) intermediates have been proposed for some cross-coupling reactions, they are not considered to be common: Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83–90.

⁵ For reviews of metal-catalyzed cross-coupling reactions, see: (a) *Metal-Catalyzed Cross-coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. (b) *Cross-Coupling Reactions: A Practical Guide*; Miyaura, N., Ed.; Topics in Current Chemistry Series 219; Springer-Verlag: New York, 2002. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley Interscience: New York, 2002.

to be associated with relatively slow oxidative addition of $C_{\text{alkyl}}-X$ to palladium and facile β -hydride elimination of the resultant alkyl-metal intermediates.⁶

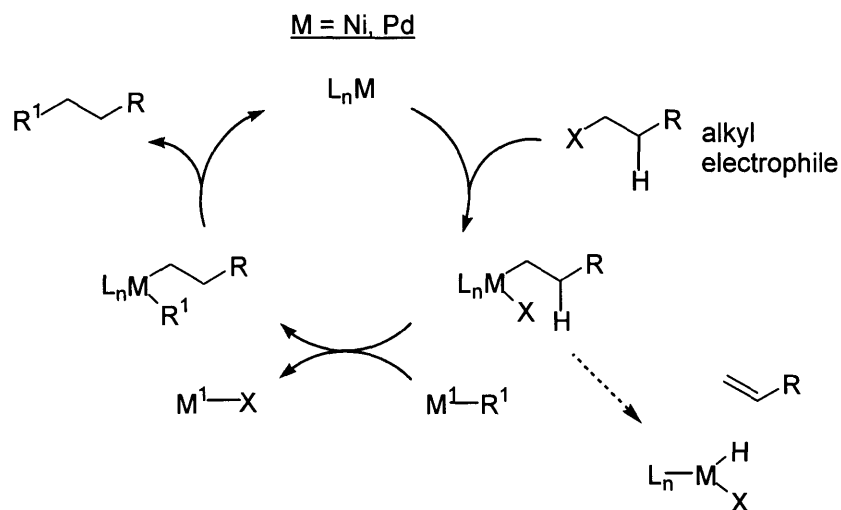


Figure 1.3. Pathways for palladium-catalyzed cross-coupling of alkyl electrophiles.

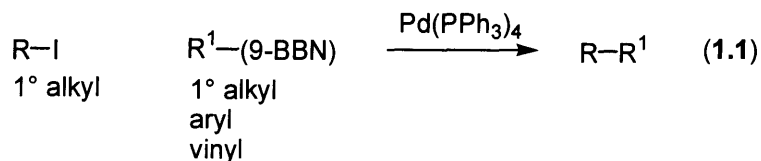
Nevertheless, the first examples of palladium-catalyzed cross-coupling reactions of unactivated alkyl halides were reported by Suzuki et al. in 1992. A common pre-catalyst, $Pd(PPh_3)_4$, was used, which promoted reactions with alkyl-, alkenyl-, and aryl-(9-BBN) reagents. However, its scope was limited to primary alkyl iodides (Eq 1.1). In addition, 6-iodo-1-hexene furnished both the desired product and a cyclized by-product. The rearrangement hints at least partial involvement of radicals during oxidative addition.⁷ Later, this catalytic system was employed in similar reactions with alkynylstannanes⁸ and alkynyl Grignard reagents.⁹

⁶ For an overview of the difficulty of achieving coupling reactions of alkyl electrophiles, see: (a) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384–387. (b) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3018–3020. (c) Luh, T.-Y.; Leung, M.-k.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187–3204.

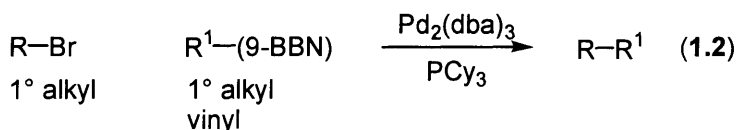
⁷ Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691–694.

⁸ Shimizu, R.; Fuchikami, T. *Tetrahedron Lett.* **2001**, *42*, 6891–6894.

⁹ L.-M. Yang, L.-F. Huang, T.-Y. Luh, *Org. Lett.* **2004**, *6*, 1461–1463.



When I started my graduate research in 2001 in the Fu group, a breakthrough had just been realized in palladium-catalyzed cross-couplings of alkyl halides, a project pioneered by Dr. Chaoyang Dai. The use of bulky, electron-rich tricyclohexylphosphine, instead of the commonly used triphenylphosphine, enabled alkyl bromides to react with alkyl- and vinyl-(9-BBN) reagents efficiently (Eq 1.2).¹⁰ Our current understanding of the structure-reactivity relationship of ligands will be presented later in this chapter.



Put in perspective, the above-mentioned Suzuki coupling laid the foundation for further development in this field. It is not difficult to imagine commonly used organozinc reagents to be the next candidate for these reactions. That marked my starting point in this chemistry.

Meanwhile, other Fu group members started to explore in other directions, such as extensions of the Suzuki reactions to alkyl chlorides¹¹ or tosylates,¹² replacement of alkyl-(9-BBN) reagents with arylboronic acids,¹³ and the use of organosilanes¹⁴ and alkenylstannanes¹⁵ instead of the organoboranes. Our adventures in these uncharted waters never lacked surprises. For example, the trialkylphosphine catalysts were outperformed by some alkyldiaminophosphines in Stille reactions using arylstannanes.¹⁶ In another case, in an attempt to develop analogous Sonogashira couplings, bulky carbene

¹⁰ Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100.

¹¹ Kirchhoff, J. H.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945–1947.

¹² Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910–3912.

¹³ Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662–13663.

¹⁴ Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616–5617.

¹⁵ Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718–3719.

¹⁶ Tang, H.; Menzel, K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5079–5082.

ligands were found to be uniquely effective.¹⁷ Even more surprisingly, cross-couplings with alkenylzirconocene chlorides, derived from alkynes and Schwartz's reagent, occurred smoothly in the absence of a phosphine ligand (Figure 1.4)!¹⁸

Around this time, other groups started to join this area of research. Beller and coworkers have applied our Pd/PCy₃ system in Kumada-type couplings between primary alkyl chlorides with arylmagnesium halides.¹⁹ Subsequently, they also successfully used a Pd/carbene catalyst for this transformation.²⁰ Very recently, Capretta's phosphadamantanes were demonstrated to achieve Suzuki couplings with alkyl chlorides, bromides, and tosylates. Their coupling partners included aryl- and alkylboronic acids as well as alkyl-(9-BBN) reagents (Figure 1.4).²¹

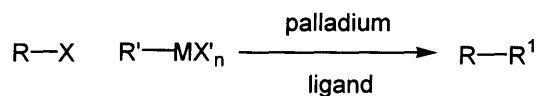
¹⁷ Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642–13643.

¹⁸ Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 82–83.

¹⁹ Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056–4059.

²⁰ Frisch, A. C.; Rataboul, F.; Zapf, A.; M. Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403–409.

²¹ Brenstrum, T.; Gerristma, D. A.; Adjabeng, G. M.; Frampton, C. S.; Britten, J.; Robertson, A. J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 7635–7639.



X	R'	MX' _n	ligand	reference
I	primary alkyl aryl vinyl	9-BBN	PPh ₃	7
I	alkynyl	SnBu ₃	PPh ₃	8
Br	alkynyl	MgX Li	PPh ₃	9

Br	primary alkyl vinyl	9-BBN	PCy ₃	10
Cl	primary alkyl	9-BBN	P(<i>t</i> -Bu) ₂ Me	11
OTs	primary alkyl	9-BBN	P(<i>t</i> -Bu) ₂ Me	12
Br	aryl	B(OH) ₂	P(<i>t</i> -Bu) ₂ Me	13
Br, I	aryl	Si(OMe) ₃	P(<i>t</i> -Bu) ₂ Me	14
Br	vinyl	SnBu ₃	P(<i>t</i> -Bu) ₂ Me	15
Br, I	aryl vinyl	SnBu ₃	PCy(pyrrolidinyl) ₂	16

Br, I	alkynyl	[Cu]	IAd	17
Cl, Br, I, OTs	vinyl	ZrClCp ₂	"ligand-free"	18
Cl	aryl	MgBr	PCy ₃ or IMes	19, 20
Cl, Br	aryl primary alkyl	B(OH) ₂	PA	21
Cl, Br, OTs	primary alkyl	9-BBN	PA	21

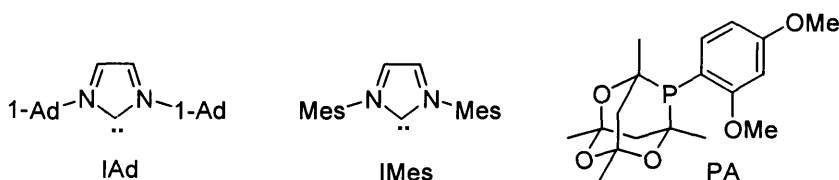
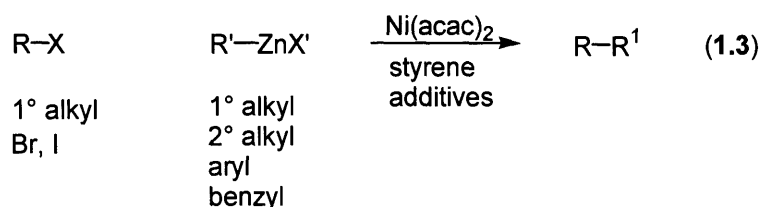


Figure 1.4. Overview of palladium-catalyzed cross-couplings of alkyl electrophiles.²²

²² For a recent review, see: Netherton, M. R.; Fu, G. C. *Top. Organomet. Chem.* **2005**, *14*, 85–108.

Concerning similar reactions with nickel catalysts, Knochel's group has discovered that in the presence of an electron-deficient additive (e.g., acetophenone, *m*- or *p*-trifluoromethylstyrene), Ni(acac)₂ promoted couplings of primary alkyl iodides with dialkyl-,²³ aryl-,²⁴ and benzyl²⁵-zinc reagents. These additives were proposed to facilitate reductive elimination from nickel.²⁶ This idea is substantiated by their earlier observation that alkyl halides carrying pendant olefin units smoothly underwent Negishi couplings without the need of these π -acceptor additives.²⁷ In the following years, the scope of this reaction was expanded to include secondary alkylzinc reagents, alkylzinc iodides, and primary alkyl bromides. For these less reactive zinc reagents, *n*-Bu₄NI was required. Knochel postulated that *n*-Bu₄NI activates the system by either forming more reactive "zincate" complexes or by changing the ionic strength of the medium (Eq 1.3).²⁸



1.2. Results and Discussion

Organozinc reagents are among the most popular partners for cross-couplings owing to several favorable features, including their high tolerance of functional groups, relatively high transmetalating ability, relatively low toxicity, and the availability of a number of methods for their preparation.^{1a,29,30} The diorganozinc reagents used in most of Knochel's

²³ Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2387–2390.

²⁴ Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186–11187.

²⁵ Piber, M.; Jensen, A. E.; Rottländer, M.; Knochel, P. *Org. Lett.* **1999**, *1*, 1323–1326.

²⁶ Giovannini, R.; Stüdemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544–3553.

²⁷ Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2723–2725.

²⁸ Jensen, A. E.; Knochel, P. *J. Org. Chem.* **2002**, *67*, 79–85.

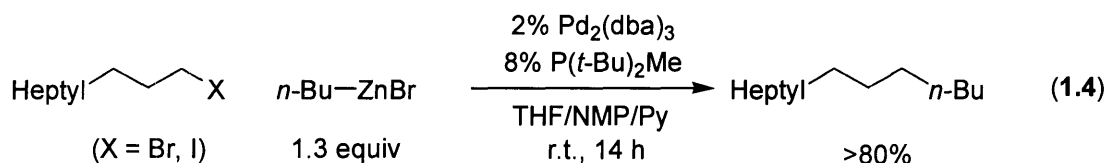
²⁹ For reviews and leading references on functionalized organozinc reagents, see: (a) *Organozinc Reagents, A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford: New York, 1999. (b) Knochel, P.; Almerna Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275–8319. (c) Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC Press: Boston, 1996. (d) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188.

³⁰ Ionic character of carbon-metal bonds has been quantified based on the Pauling's electronegativity scale: 43% for Li, 35% for Mg, and 18% for Zn: Chan, T. H. *Synthesis* **1979**, 761–786.

studies were prepared from either iodine/zinc exchange or boron/zinc transmetalation. These procedures, therefore, entailed additional synthetic efforts. His group has also used alkylzinc iodides, whose precursors, alkyl iodides, are rather unstable and usually decompose during prolonged storage. We envisioned that a more expeditious route would involve direct insertion of Rieke zinc[®] powder into C-Br bonds to make alkylzinc bromide solutions.³¹ Since many of these reagents have been made available through Aldrich, at the onset of the project we chose the simplest combination for our model reaction, i.e., *n*-decyl halides and *n*-butylzinc bromide.

1.2.1. Cross-Couplings with Primary Alkylzinc Halides

A focused screening with electron-rich phosphine-based catalysts quickly provided several leads; for instance, with Pd/P(*t*-Bu)₂Me the desired product was obtained in good yields at room temperature (Eq 1.4). Unfortunately, the protocol failed for most functionalized substrates.



Thus, we turned our attention to functionalized alkyl bromides, specifically, 3-benzyloxypropyl bromide (Eq 1.5). After re-evaluation of a variety of reaction parameters, we determined that 2% Pd₂(dba)₃/8% PCyp₃ with 1.2 equiv of NMI at 80 °C as the optimal conditions (70%; Table 1, entry 1).

³¹ For reviews and leading references, see: (a) Rieke, R. D.; Hanson, M. V. In *Organozinc Reagents, A Practical Approach*; Knochel, P., Jones, P., Eds.; Oxford: New York, 1999; pp. 23-36. (b) Rieke, R. D.; Hanson, M. V. *Tetrahedron* **1997**, *53*, 1925–1956.

Table 1.1. Influence of Ligands on the Efficiency of a Negishi Cross-Coupling

entry	ligand	yield (%) ^a	cone angle	pK _a
1	PCyp ₃	70	n.d.	n.d.
2	PCy ₃	65	170	9.7
3	P(<i>i</i> -Pr) ₃	59	160	9.3
4	P(<i>t</i> -Bu) ₂ Me	55	161	n.d.
5	P(<i>t</i> -Bu) ₃	3	182	11.4
6	PCyp ₂ (<i>t</i> -Bu)	14	167	n.d.
7	P(<i>n</i> -Bu) ₃	9	132	8.4
8	PCy ₂ Ph	56	162	n.d.
9	PCyPh ₂	19	153	5.1
10	PPh ₃	5	145	2.7
11	P(<i>p</i> -Me ₂ NPh) ₃	23	145	8.7
12	P(<i>p</i> -MeOPh) ₃	7	145	4.6
13	P(<i>o</i> -tol) ₃	1	194	3.1
14	P(2,4,6-trimethoxyphenyl) ₃	0	n.d.	n.d.
15	P(2-furyl) ₃	2	133	n.d.
16	Cy ₂ P(CH ₂) ₂ PCy ₂	0 ^b	142	n.d.
17	<i>rac</i> -BINAP	0 ^b	n.d.	n.d.
18	1,3-bis(mesityl)-4,5-dihydroimidazolium tetrafluoroborate	4	n.d.	n.d.
19	P(OPh) ₃	0	128	-2.0

^aYield according to GC, versus a calibrated internal standard.^bLigand loading: 4%.

Among the ligands that we investigated (Table 1.1), only trialkylphosphines of the appropriate size furnished active catalysts for this Negishi coupling. PCyp₃, which is commercially available, provided the highest yield (entry 1). Whereas PCy₃, P(*i*-Pr)₃, and P(*t*-Bu)₂Me³² were reasonably effective (entries 2-4), more or less bulky trialkylphosphines (entries 4-7) were substantially less productive under these conditions.

³² P(*t*-Bu)₂Me was first introduced during this work and later it found widespread use in several other Pd-catalyzed processes.

PCy₂Ph (entry 8), with a similar cone angle and less electron density on phosphorus, was slightly less active than PCyp₃. Other classes of ligands afforded much less of the desired product; those included PCyPh₂ (entry 9), triarylphosphines (entries 10-15), chelating phosphines (entry 16 and 17), an N-heterocyclic carbene (entry 18),³³ and a phosphite (entry 19). For the less effective ligands, the major identifiable side-products were the alkyl chloride and/or the alkane (from reduction of the alkyl bromide). The source of chloride is organozinc reagents in THF from Aldrich³⁴ and it was carried over from Rieke zinc[®] preparation from ZnCl₂.

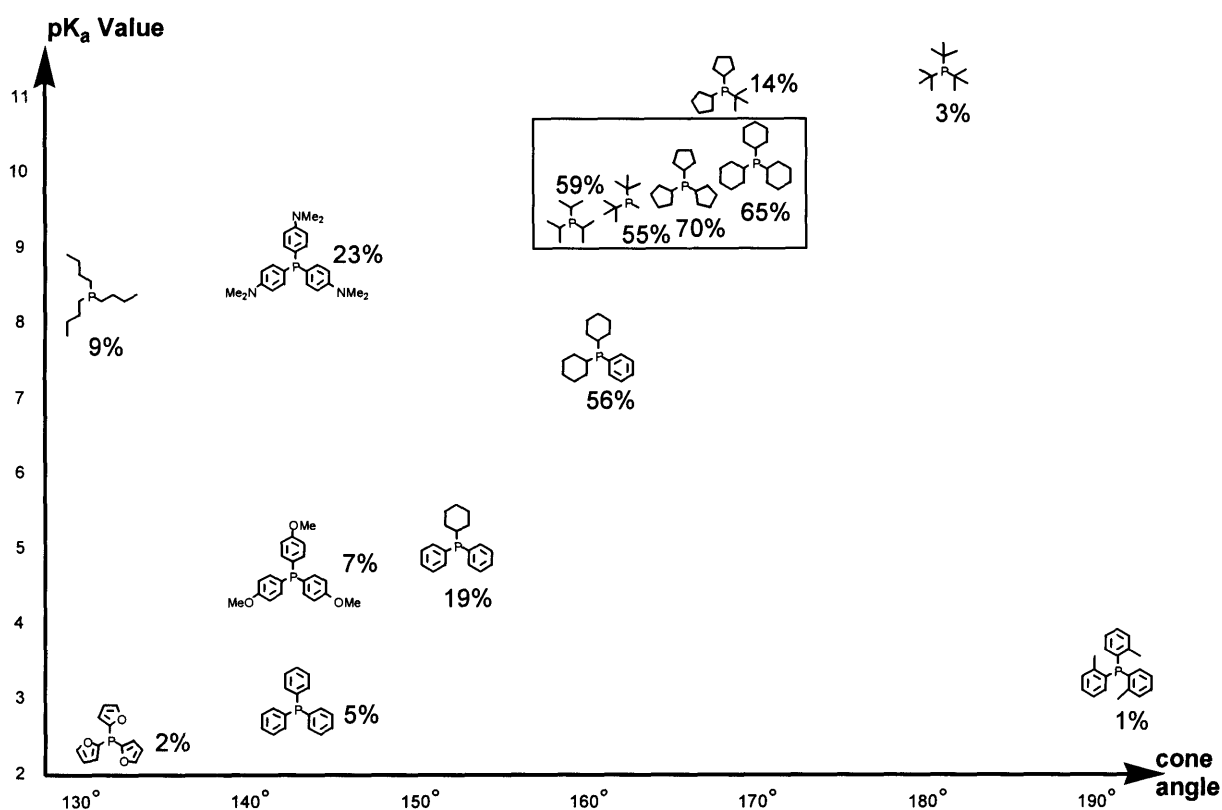


Figure 1.5. Dissection of steric and electronic impact of phosphines on catalytic activity.

³³ Very recently, a palladium/IPr catalyst has also emerged to effect Negishi couplings. Compared with our system, the scope of the new method is smaller and confined to primary alkyl bromides and primary alkylzinc bromides: Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805–3807.

³⁴ Aldrich certificates of analysis indicate they usually contain 2-3 wt% of chloride salt.

In order to better appreciate the effects of individual steric and electronic factors, the results are schematically projected onto a two-dimensional representation according to their Tolman cone angles and the pK_a values of their conjugate acids (Figure 1.5).^{35, 36} It immediately becomes clear that the best ligands fall into a small window (cone angle: 160°-170°). The reason behind this thought-provoking phenomenon will be discussed in the later part of this chapter.

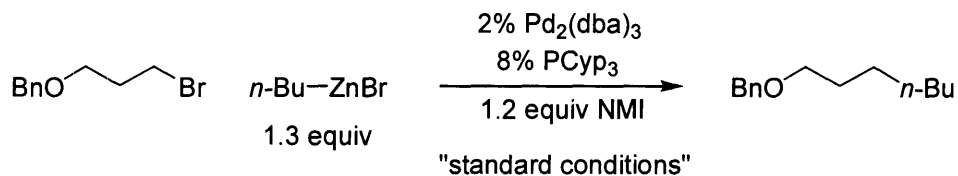
Knochel has noted that, with his catalyst system, alkylzinc iodides were significantly less reactive than diorganozinc reagents, therefore requiring Bu_4NI (3 equiv) to boost their reactivity.²⁸ We also faced a similar dilemma, and our remedies were nitrogen bases (NMI, pyridine, and DBU in Table 1.2, entries 1, 3, and 4, respectively). For example, the presence of NMI led to discernibly improved yield (54%→70% in entries 1 vs. 2), perhaps through activation of the organozinc halide toward transmetalation.³⁷ Such a role of NMI has been suggested previously in Et_2Zn addition to CO_2 .³⁸ It is further supported by our own observation that a stronger, bulky base, DIPEA, did not have a similar positive effect (entry 5). Due to its acidic hydrogen, imidazole terminated the cross-coupling (entry 6). The addition of a styrene derivative (*m*-trifluoromethylstyrene) or *n*- Bu_4NI (entries 7-9), which was critical for efficient coupling with Knochel's nickel-based catalyst, made no difference in our case.

³⁵ The cone angles and pK_a values are adopted from compilations: (a) Rahman, M. M.; Liu, H.-Y.; Eriks, K.; Prock, A.; Giering, W. P. *Organometallics* **1989**, *8*, 1-7. (b) Wilson, M. R.; Woska, D. C.; Prock, A.; Giering, W. P. *Organometallics* **1993**, *12*, 1742-1752.

³⁶ The cone angle and pK_a value of $PCyp_3$ are not available, but they have been suggested to be slightly less than those of PCy_3 : Cole, M. L.; Hibbs, D. E.; Jones, C.; Smithies, N. A. *J. Chem. Soc., Dalton Trans.* **2000**, 545-550.

³⁷ We have noticed an upfield shift of ^{31}P NMR signal upon addition of *n*- $BuZnBr$ to $PCyp_3$ (from 6.5 to 0 ppm). Addition of NMI then brought the peak back to 4.5 ppm.

³⁸ Inoue, S.; Yokoo, Y. *J. Organomet. Chem.* **1972**, *39*, 11-16.

Table 1.2. Effect of the Additives on the Efficiency of the Model Reaction

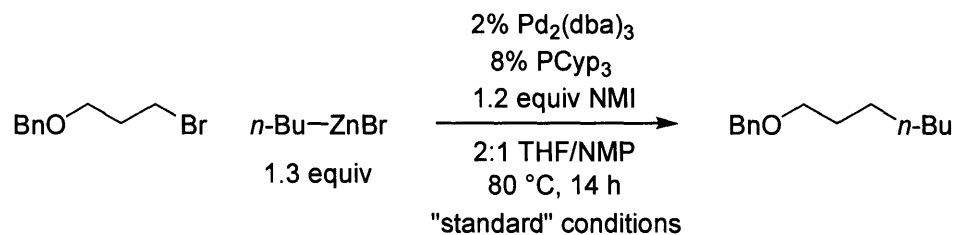
entry	change from the standard conditions	yield (%) ^a
1	none	70
2	without NMI	54
3	NMI → Pyridine	68
4	NMI → DBU	68
5	NMI → DIPEA	55
6	NMI → Imidazole	0
7	NMI → <i>m</i> -CF ₃ -styrene (1.0 equiv)	55
8	additional <i>m</i> -CF ₃ -styrene (1.0 equiv)	70
9	additional <i>n</i> -Bu ₄ NI (3.0 equiv)	70

^aYield according to GC, versus a calibrated internal standard.

The impact of other parameters on the course of the reaction is illustrated in Table 1.3. In the absence of Pd₂(dba)₃ or PCyp₃, none of the desired product was generated (entries 2 and 3, respectively). From an extensive survey of solvents, a 2:1 mixture of THF and NMP emerged as the best; for example, the cross-coupling was significantly less efficient in THF alone (entry 4). The use of NMP as a cosolvent may increase the solvent polarity, thus accelerating the oxidative addition.³⁹ The Negishi reaction did proceed at lower temperature, albeit in lower yield (entry 5). A decrease in the phosphine: Pd ratio from 2:1 to 1:1 (entry 1 vs. entry 6) also resulted in a decreased yield of the desired compound. Finally, a reduced catalyst loading (2% Pd) can be employed, with just a small loss in cross-coupling efficiency (entry 7).

³⁹ For more detailed studies of solvent effect on oxidative addition of similar PdL₂ complexes, see: Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749–5752.

Table 1.3. Effect of Various Reaction Parameters on the Efficiency of a Negishi Cross-Coupling

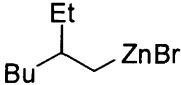
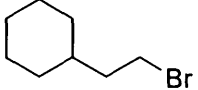
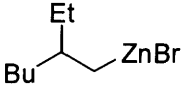
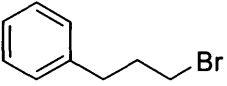
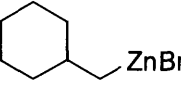
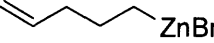
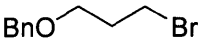
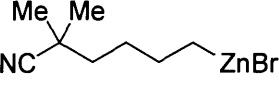
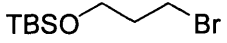
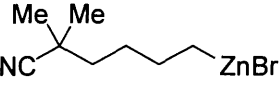
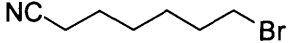
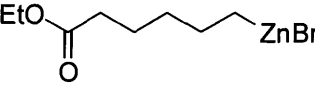


entry	change from the standard conditions	yield (%) ^a
1	none	70
2	without Pd	0
3	without PCyp ₃	0
4	without NMP	48
5	at 30 °C	43
6	with 4% PCyp ₃	55
7	with 1% Pd ₂ (dba) ₃ , 4% PCyp ₃	65

^aYield according to GC, versus a calibrated internal standard.

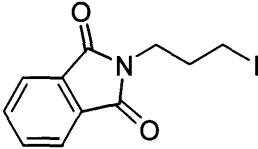
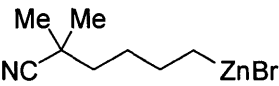
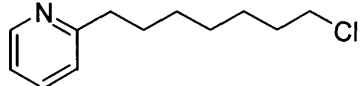
Our optimized conditions (Pd₂(dba)₃/PCyp₃) were suitable for Negishi cross-couplings of a range of primary alkyl bromides with alkylzinc reagents (Table 1.4). The catalyst system can tolerate functional groups such as olefins, ethers, nitriles, and esters (entries 5-8).

Table 1.4. Negishi Cross-Couplings of Alkyl Bromides with Alkylzinc Reagents

		$\begin{array}{c} 2\% \text{ Pd}_2(\text{dba})_3 \\ 8\% \text{ PCyp}_3 \\ 1.2 \text{ equiv NMI} \\ \hline 2:1 \text{ THF/NMP} \\ 80^\circ \text{C, 14 h} \end{array}$			
	R-Br	R ¹ -ZnBr 1.3 equiv	→	R-R ¹	
entry	R-Br	R ¹ -ZnBr			yield (%) ^a
1	<i>n</i> -Dec-Br	<i>n</i> -Bu-ZnBr			90
2	<i>n</i> -Dec-Br				89
3					76
4					83
5	<i>n</i> -Dec-Br				52
6					68
7					67
8					65

^a Isolated yield (average of two runs).

Table 1.5. Negishi Cross-Couplings of Alkyl Iodides, Tosylates, and Chlorides with Alkylzinc Reagents

		$\begin{array}{c} 2\% \text{ Pd}_2(\text{dba})_3 \\ 8\% \text{ PCyp}_3 \\ 1.2 \text{ equiv NMI} \\ \hline 2:1 \text{ THF/NMP} \\ 80 \text{ }^\circ\text{C, 14 h} \end{array}$		
		R-X	$\text{R}^1\text{-ZnBr}$ 1.3 equiv	R-R^1
entry		R-X	$\text{R}^1\text{-ZnBr}$	yield (%) ^a
1		<i>n</i> -Dec-I	<i>n</i> -Bu-ZnBr	87
2			<i>n</i> -Bu-ZnBr	48
3		<i>n</i> -Dodec-OTs	<i>n</i> -Bu-ZnBr	86
4		NC-CH ₂ (CH ₂) ₆ -OTs		64
5		<i>n</i> -Dec-Cl	<i>n</i> -Bu-ZnBr	97
6			<i>n</i> -Bu-ZnBr	77
7		Br-CH ₂ (CH ₂) ₄ -Cl	<i>n</i> -Bu-ZnBr	70 ^b

^aIsolated yield (average of two runs). ^bAlkyl halide:organozinc = 1:2.6. Product: double Negishi cross-coupling.

After we finished investigating Negishi reactions of alkyl bromides, we wondered whether the conditions could be applicable to other classes of carbon electrophiles (Table 1.5). To our satisfaction, cross-coupling products were isolated from an array of primary alkyl iodides (entries 1 and 2), tosylates (entries 3 and 4), and even chlorides (entries 5-7). As observed for alkyl bromides, a variety of functional groups were tolerated. Because organozinc reagents from Aldrich can contain 2-3 wt% chloride salt, some trans-halogenation ($\text{RBr} \rightarrow \text{RCl}$) occurred under the cross-coupling conditions. As a consequence, selective mono-functionalization of 1-bromo-6-chlorohexane (entry 7) cannot be achieved.

Any discussion of a reaction scope would not be complete without a proper definition of its limitations. Our system certainly has its boundaries, especially with more elaborate substrates (Figure 1.6). First, certain functional groups (e.g., nitriles, amides, and esters), when placed 2-4 carbons away from leaving groups, usually inhibit the catalysis; the closer, the worse. We attribute this to internal coordination of these groups to palladium, thus impeding transmetalation. Second, substrates **1.1-1.4** were prone to undergo β -elimination after oxidative addition, and afforded little coupling products. Third, substrates **1.5** carrying terminal acetylene units gave complicated mixtures. We attribute this to the incompatibility of the acetylenic hydrogens with the reaction conditions,⁴⁰ since **1.5** worked well with arylsilanes in Hiyama couplings.¹⁴ Fourth, with respect to steric concerns on the alkyl electrophiles, one branch at the β position can be tolerated, but not two (e.g., neopentyl bromide). Fifth, allyl and benzyl bromides did not yield any product.

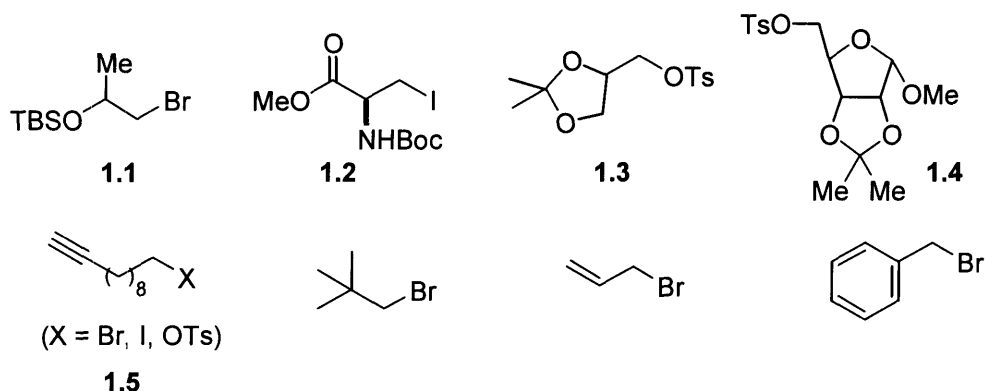


Figure 1.6. Additional alkyl halides and tosylates tested in Pd-catalyzed alkylations.

In addition to the electrophiles, we have surveyed other alkylzinc halides, and have made some interesting observations (Figure 1.7): (a) nitrile and ester groups in **1.6** and **1.7** shut down the desired coupling pathway. Even a seemingly “innocuous” vinyl group **1.8** reduced the reactivity (only ~50% yield with unfunctionalized, linear alkyl bromides). We suspect that these groups may occupy an open coordination site and interfere with

⁴⁰ Knochel has prepared an alkylzinc iodide bearing an acetylenic hydrogen: Knoess, H. P.; Furlong, M. T.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1991**, *56*, 5974–5978.

reductive elimination; (b) in terms of steric concerns, β -substitutions were well tolerated, e.g., even neopentylzinc bromide **1.9** afforded >70% of product with unhindered alkyl bromides; (c) benzyl- and allylzinc bromides failed to provide >5% of products with *n*-nonyl bromide, probably due to their relatively low propensity toward transmetalation; (d) *n*-decylzinc iodide²⁸ turned out to be less productive in our studies, furnishing <40% chemical yields with simple bromides; (e) under the standard conditions, Et₂Zn reacted with varying success: 68% yield of the product with *n*-decyl bromide, 37% with the iodide, and <5% with the chloride and tosylate.

As this project was drawing to its conclusion, Beller's group reported a Pd(OAc)₂/PCy₃ combination for reactions of alkyl chlorides with aryl Grignard reagents.¹⁹ Naturally we became interested in testing the Kumada-type reaction. Surprisingly, our Pd₂(dba)₃/PCyp₃ system can not at all simulate their chemistry, and it also completely failed to effect the reaction between *n*-decyl chloride and *n*-BuMgBr.

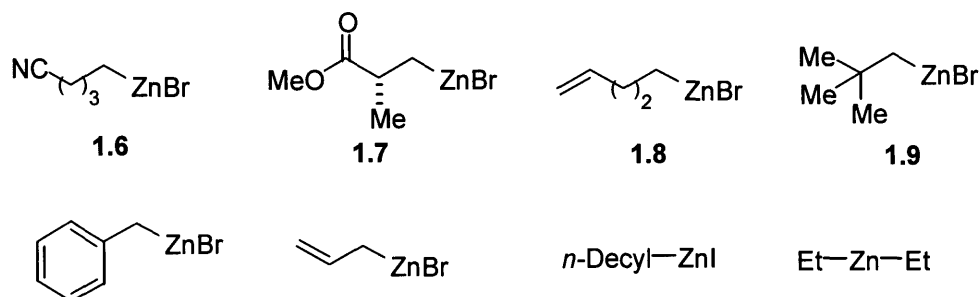


Figure 1.7. Additional primary alkylzinc reagents tested in the palladium-catalyzed Negishi reactions.

1.2.2. Cross-Couplings with Secondary Alkylzinc Halides

Secondary alkylzinc reagents deserve some special comments. They did participate in the cross-coupling process, but after a secondary-to-primary alkyl rearrangement as depicted in Figure 1.8. As a result, straight-chain products were isolated from reactions with simple primary bromides, e.g., about 60% yield with isopropyl or *sec*-heptyl zinc bromide. Presumably the process occurs through a sequence of β -hydride elimination and migratory re-insertion into olefins.⁴¹ Such a problem has been encountered before in palladium/monophosphine-catalyzed Negishi cross-couplings of aryl halides with branched alkylzinc reagents.⁴²

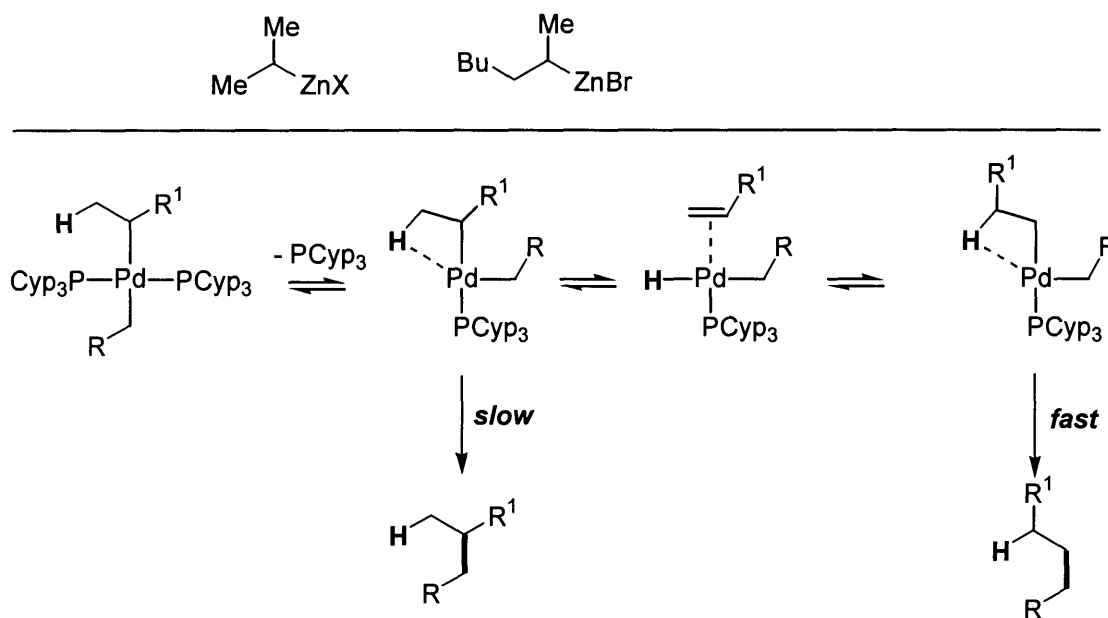


Figure 1.8. A possible route for primary to secondary alkyl isomerization.

We then dedicated some efforts to resolve this problem, with only limited success (Eq 1.6). Out of about fifty phosphines, only 1,1'-ferrocene-based bisphosphines⁴³ and Josiphos ligands could fully block this undesired pathway. Unfortunately, only about

⁴¹ Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9268–9269.

⁴² Hayashi, T.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1979**, *21*, 1871–1874.

⁴³ Prepared by treatment of 1,1'-dilithioferrocene·TMEDA with R_2PCl , according to reported procedures: (a) Bishop, J. J.; Davidson, A.; Katcher, M. L.; Lichtenberg, D. W.; Merrill, R. E.; Smart, J. C. *J. Organomet. Chem.* **1971**, *27*, 241–249. (b) Cullen, W. R.; Kim, T.-J. *Organometallics* **1983**, *2*, 714–719.

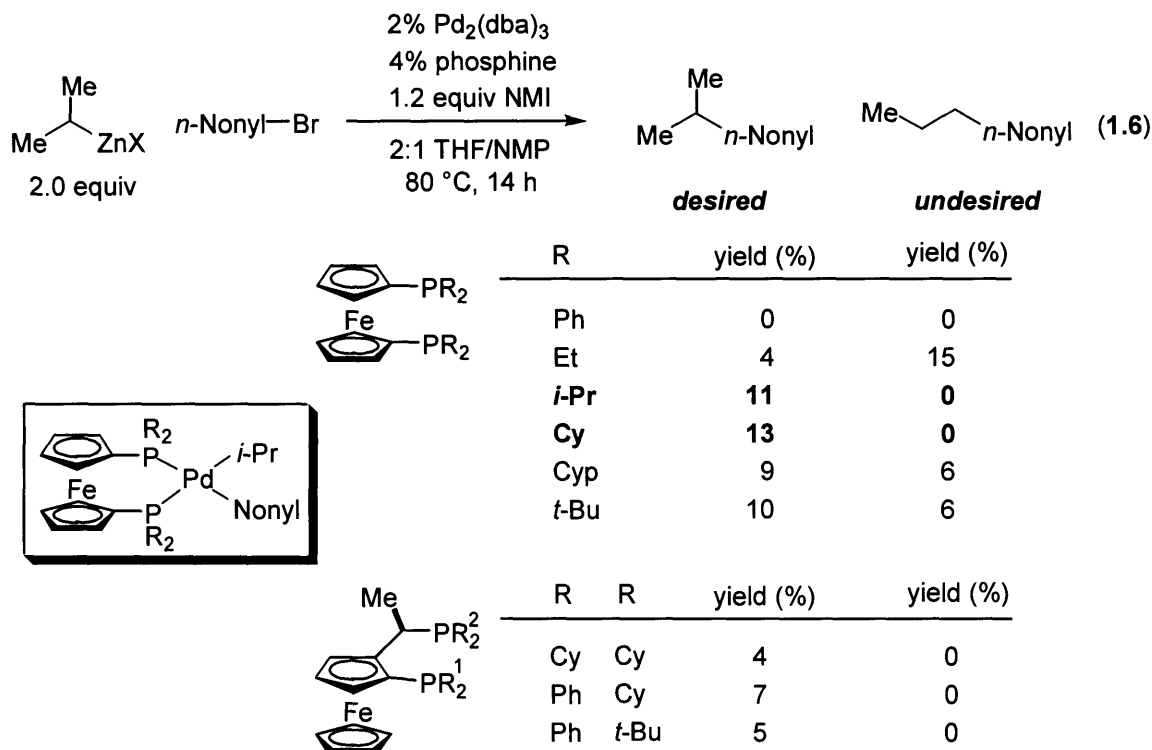


Figure 1.9. Cross-couplings with secondary alkylzinc reagents.

10% of the desired product was formed with electron-rich dppf analogs, whereas dppf itself was inert (Figure 1.9). In spite of the full conversion, the rest of the starting material went on to elimination and reduction. The chelating nature of these ligands probably helps to minimize the isomerization process by occupying the fourth coordination site. Their large bite angles (e.g., 99° for dppf and 96° for (*R*)-(*S*)-Ph₂PF-PCy₂⁴⁴) may also facilitate reductive elimination by forcing the two organic groups closer to each other,⁴⁵ meanwhile, still capable of enforcing a square planar geometry. Compared to a tetrahedral complex, the square planar one contains a smaller natural bond angle formed by R-Pd-R¹, and hence, is better poised to undergo the reductive elimination process. The use of chelating bisphosphines with large bite angles has been

⁴⁴ Togni, A.; Breutel, C.; Soares, M. C.; Zanetti, N.; Gerfin, T.; Gramlich, V.; Spindler, F.; Rihs, G. *Inorg. Chim. Acta* **1994**, *222*, 213–224. The bite angle for the (*R*)-(*R*)-isomer is determined to be 94°: Gambs, C.; Consiglio, G.; Togni, A. *Helv. Chem. Acta* **2001**, *84*, 3105–3126.

⁴⁵ (a) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158–163. (b) Brown, J. M.; Guiry, P. J. *Inorg. Chim. Acta* **1994**, *220*, 249–259. (c) Kamer, P. C.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Acc. Chem. Res.* **2001**, *34*, 895–904.

employed by Hayashi⁴⁵ and Kamer⁴⁶ previously in coupling reactions with bromobenzene. One potential pitfall, which may be occurring in this case, is that reductive elimination is usually slower from a tetra-coordinated intermediate than from a tri-coordinated complex. This widespread idea has recently received some support from kinetic studies in related palladium-catalyzed C-N bond formations.⁴⁷

1.2.3. Cross-Couplings with Alkenyl- and Arylzinc Halides

The cross-coupling partners are not limited to only alkylzinc reagents. Thus, Pd₂(dba)₃/PCyp₃ coupled alkyl bromides (Table 5, entries 1-5), iodides (entries 6-8), tosylates (entry 9), and chlorides (entry 10) with alkenylzincs (geminally and cis-substituted). In addition, some arylzinc reagents were suitable substrates (entries 11 and 12). The examples in Table 1.6 demonstrate that the catalyst again tolerated a variety of functional groups (e.g., esters, acetals, ethers, amides, and imides).

Like many other trialkylphosphines, PCyp₃ undergoes oxidation upon exposure to air.⁴⁸ We have determined that the corresponding air-stable phosphonium salt, [HPCyp₃]BF₄, can serve as a substitute for PCyp₃ in our Negishi cross-couplings.⁴⁹ Under the reaction conditions, the excess zinc reagent (1.6 equiv) deprotonates the phosphonium salt and liberates free PCyp₃ to bind to palladium. As illustrated in Table 1.6, the phosphonium salt and the phosphine typically furnished comparable yields.

⁴⁶ Kranenburg, M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **1998**, 155–157.

⁴⁷ Yamashita, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 5344–5345.

⁴⁸ We observed 8% oxidation of PCyp₃ in 2:1 THF/NMP after overnight in a capped, but not sealed, NMR tube.

⁴⁹ This useful strategy was initially conceived by Dr. Matthew Netherton in our group: Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295–4298.

Table 1.6. Negishi Cross-Couplings of Alkyl Electrophiles with Alkenyl- and Arylzinc Reagents

		$\begin{array}{c} 2\% \text{ Pd}_2(\text{dba})_3 \\ 8\% \text{ PCyp}_3 \text{ or } [\text{HCyp}_3]\text{BF}_4 \\ 1.2 \text{ equiv NMI} \\ \longrightarrow \\ 2:1 \text{ THF/NMP} \\ 80^\circ\text{C}, 12 \text{ h} \end{array}$		
		R-X	$\text{R}^1\text{-ZnX}^1$	R-R^1
		1.6 equiv		
entry	R-X	R ¹ -ZnX ¹	isolated yield (%)	
			PCyp ₃	[HCyp ₃]BF ₄
1	<i>n</i> -Dec-Br		93	93
2			68	71
3	THPO-Br		76	77
4	BnO-Br		83	75
5			81	72
6	<i>n</i> -Dec-I		98	93
7	<i>n</i> -Dec-I		93	93
8			74	76
9			58	53
10			73	78
11			74	69
12	<i>n</i> -Dec-I	Ph-ZnX^1	65	62

We have tested some additional alkenylzinc species other than those used in Table 1.6, (Figure 1.10). 1-Methyl-1-propenylzinc halide **1.9** (mixture of trans/cis isomers) gave desired products in a 3:1 E/Z ratio. The unsubstituted vinylzinc reagent **1.10** gave >70% of products with *n*-decyl bromides and iodides, but was problematic with functionalized substrates (often <10% chemical yield). This result is rationalized by its relatively low transmetalating ability, which may also explain failures with 2,3-dihydro-2-pyranyl- (**1.11**),⁵⁰ 2-cyclohexenyl- (**1.12**),⁵¹ and 1-propynylzinc reagents. Steric hindrance also had adverse effects on the reaction, e.g., *o*-tolylzinc halide did not furnish any coupling product.

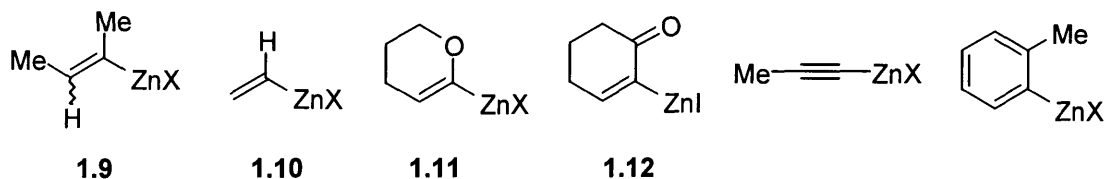
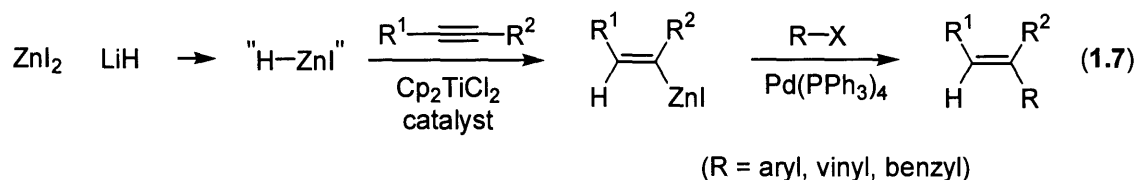


Figure 1.10. Additional alkenylzinc reagents tested in palladium-catalyzed Negishi reactions.

⁵⁰ Prepared by treatment of dihydropyran with *t*-BuLi in pentane/THF at -78 °C followed by transmetalation to ZnCl₂: Jarowicki, K.; Kocienski, P. J.; Qun, L. *Org. Synth.* **2002**, *79*, 11–14.

⁵¹ Prepared from 2-iodo-2-cyclohexenone and zinc powder activated with TMSCl/1,2-dibromoethane: Prasad, A. S. B.; Knochel, P. *Tetrahedron* **1997**, *53*, 16711–16720.

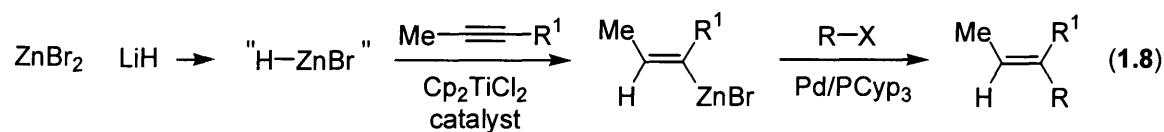
Most of the alkenylzinc halides used thus far were prepared by organolithium/Grignard→ZnCl₂ transmetalation. In order to circumvent the use of these harsh reagents, we envisaged that hydrozincation of alkynes would be a valuable alternative. Indeed, such a method already exists. In 1995, Sato and coworkers reported a titanium-catalyzed syn hydrometalation of internal alkynes with ZnI₂ and LiH. In their proposed catalytic cycle, Cp₂TiH is the key intermediate; it carries out the hydrometalation and then transfers the resulting alkenyl group to zinc salts. In addition, these in situ generated reagents have been shown to cross-couple with aryl/vinyl/benzyl halides under conventional Pd(PPh₃)₄ catalysis (Eq 1.7).⁵²

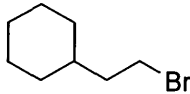
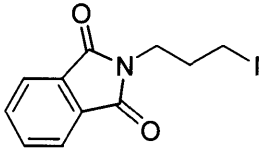
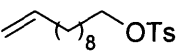


We tried to implement Sato's hydrozincation method into our newly established palladium-catalysis (Eq 1.8), but our first few trials led to no avail. A close scrutiny of the conditions suggested switching the nitrogen atmosphere to argon, since reduction of nitrogen by low-valent titanium complexes was well documented.⁵³ By further switching from zinc iodides to bromides, we succeeded in using these alkenylzinc solutions for our cross-couplings with aliphatic electrophiles in a one-pot manner (Table 1.7). As in Sato's publication, exclusive syn hydrometalation occurred to provide stereochemically defined trisubstituted olefins as end products. In the case of 1-phenylpropyne, zinc preferentially resided in proximity to the phenyl group and led to coupling products with excellent regioselectivity (95:5). It is remarkable that all these reactions took place in the presence of lithium and titanium salts, which further demonstrates the robust nature of our Pd/PCyp₃ catalyst.

⁵² Gao, Y.; Harada, K.; Hata, T.; Urabe, H.; Sato, F. *J. Org. Chem.* **1995**, *60*, 290–291.

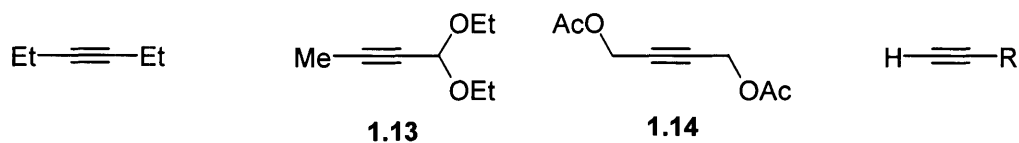
⁵³ (a) Vol'pin, M. E.; Shur, V. B. *Nature* **1966**, *209*, 1236. (b) van Tamelen, E. E.; Seeley, D.; Schneller, S.; Rudler, H.; Cretney, W. *J. Am. Chem. Soc.* **1970**, *92*, 5251–5253. (c) Hori, M.; Mori, M.; *J. Org. Chem.* **1995**, *60*, 1480–1481. (d) Mori, M.; Hori, K.; Akashi, M.; Hori, M.; Sato, Y.; Nishida, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 636–637. (e) Hori, K.; Mori, M. *J. Am. Chem. Soc.* **1998**, *120*, 7651–7652.

Table 1.7. One-Pot Hydrozincation/Negishi Cross-Coupling of Alkyl Electrophiles

entry	Me—C≡C—R ¹	R—X	yield (%)	
			PCyp ₃	[HPCyp ₃] ₂ BF ₄
1	Me—C≡C—Me	Ph—(CH ₂) ₃ —Br	63	48
2	Me—C≡C—Me	PhO—(CH ₂) ₃ —Br	53	51
3 ^a	Me—C≡C—Ph		61	63
4	Me—C≡C—Me		69	72
5 ^a	Me—C≡C—Ph		59	62

^a The product is an ~95:5 mixture of regioisomers.

During our study, we also examined several other acetylenes (Figure 1.11). 3-Hexyne gave <30% of products, and we could not isolate any of the desired compounds from the other two functionalized alkynes **1.13** and **1.14**, which was not unexpected. Terminal alkynes bearing acidic hydrogens are not suitable substrates for this method, either.

**Figure 1.11.** Additional alkynes explored in hydrozincation-cross-couplings.

1.2.4. Cross-Couplings with Aryl Electrophiles

Finally, encouraged by our recent success with unactivated alkyl electrophiles, we subjected some aryl electrophiles to the Pd/PCyp₃ catalyst (Table 1.8). Under the standard conditions, good conversions were obtained with phenyl bromide, iodide, and triflate; unfortunately, more challenging chloride and tosylate substrates were not efficiently consumed.⁵⁴

Table 1.8. Negishi Cross-Couplings of Phenyl Electrophiles with Organozinc Reagents

Ph-X	R ¹ -ZnBr 1.6 equiv	2% Pd ₂ (dba) ₃ 8% PCyp ₃ 1.2 equiv NMI 2:1 THF/NMP 80 °C, 14 h	→	Ph-R ¹
X		with <i>n</i> -BuZnBr (%)		with PhZnBr (%)
Cl		3		5
Br	→	84		80
I		77		84
OTs		2		n.d.
OTf		n.d.		73

^aYield according to GC, versus a calibrated internal standard.

1.3. Mechanistic Aspects

For these palladium-catalyzed reactions of alkyl electrophiles, we were intrigued that they only work in the presence of trialkylphosphines with cone angles of 160°-170°. Through the work of Dr. Matthew Netherton¹² and Ivory Hills³⁹ in our group, we have gained some insight into these reactions, especially about oxidative addition. First, the steric demand of these ligands favors the formation of PdL₂ complexes over PdL or PdL₃

⁵⁴ We have not fine-tuned the conditions yet to ascertain whether aryl chlorides and tosylates will eventually yield to the Pd/PCyp₃ catalysis.

species.^{55,56} In fact, the PdL₂ complexes (L = PCy₃ or P(*t*-Bu)₂Me) have been isolated and shown to oxidatively add into C-X bonds of primary alkyl electrophiles.^{12,39} And the addition was impeded by added free phosphines, suggesting that PdL₂ species are directly responsible for the oxidative addition. Second, these electron-rich phosphines can increase electron density on the palladium center and, thus, enhance the metal reactivity. By deuterium labeling of an alkyl electrophile, the oxidative addition was shown to proceed *mainly* with configurational inversion on the carbon center. This is consistent with an S_N2-type pathway.⁵⁷ Third, the steric bulk of the ligands may also help to minimize β-hydride elimination from PdL₂RBr by shielding palladium from agnostic interactions with β hydrogens. Indeed, one of such oxidative addition products is isolable, and has been crystallographically characterized. Fourth, the size of the phosphines may encourage the dissociation of one ligand to form the putative T-shaped intermediates for the reductive elimination.^{58,59,60} Putting all the information together, we propose a catalytic cycle depicted in Figure 1.12.

⁵⁵ Ivory Hills has isolated Pd[P(*t*-Bu)₂Me]₃ in solid state, but when re-dissolved in solution, it completely transformed into Pd[P(*t*-Bu)₂Me]₂ and the free phosphine. Addition of more P(*t*-Bu)₂Me to this solution did not change the chemical shifts. A similar phenomenon has been recorded previously with Pd[P(*i*-Pr)₃]₃: Kuran, W.; Musco, A. *Inorg. Chim. Acta.* **1975**, *12*, 187–193.

⁵⁶ ³¹P NMR studies have showed that at room temperature palladium complexes of P(*i*-Pr)₃ or PCy₃ exist as PdL₂ in solution; at lower temperature, additional PdL₃ species appear: Mann, B. E.; Musco, A. *J. Chem. Soc., Dalton Trans.* **1975**, 1673–1677.

⁵⁷ Osborn has gained experimental evidence suggesting that a *dominant* pathway for alkyl halide addition to Pd(PEt₃)₃ involves radicals; he also suggested PdL₂ instead of PdL₃ was the species undergoing the addition: (a) Kramer, A. V.; Labinger, J. A.; Bradley, J. S.; Osborn, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 7145–7147. (b) Kramer, A. V.; Osborn, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 7832–7833.

⁵⁸ Yamamoto has invoked three-coordinate R₂PdL intermediates for reductive elimination from bis(phosphine)dialkylpalladium(II) complexes, based on inhibition by added phosphines: Ozawa, F.; Ito, T.; Nakamura, Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1867–1880.

⁵⁹ The T-shaped organopalladium intermediates in cross-couplings have been inferred from multiple kinetic and spectroscopic studies, but only recently have monomeric, three-coordinate arylpalladium halides been confirmed by X-ray crystallography: (a) Stambuli, J. P.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9346–9347. (b) Stambuli, J. P.; Incarvito, C. D.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 1184–1194.

⁶⁰ Stille has shown that in the presence of MeI, reductive elimination can go through a different route. Both *trans*-dimethyl(TRANSPHOS)palladium and *cis*-bis(phosphine)dimethylpalladium reacted with MeI to form triorganopalladium(IV) intermediates, which then underwent reductive elimination: (a) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933–4941. (b) Moravskiy, A.; Stille, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 4182–4186.

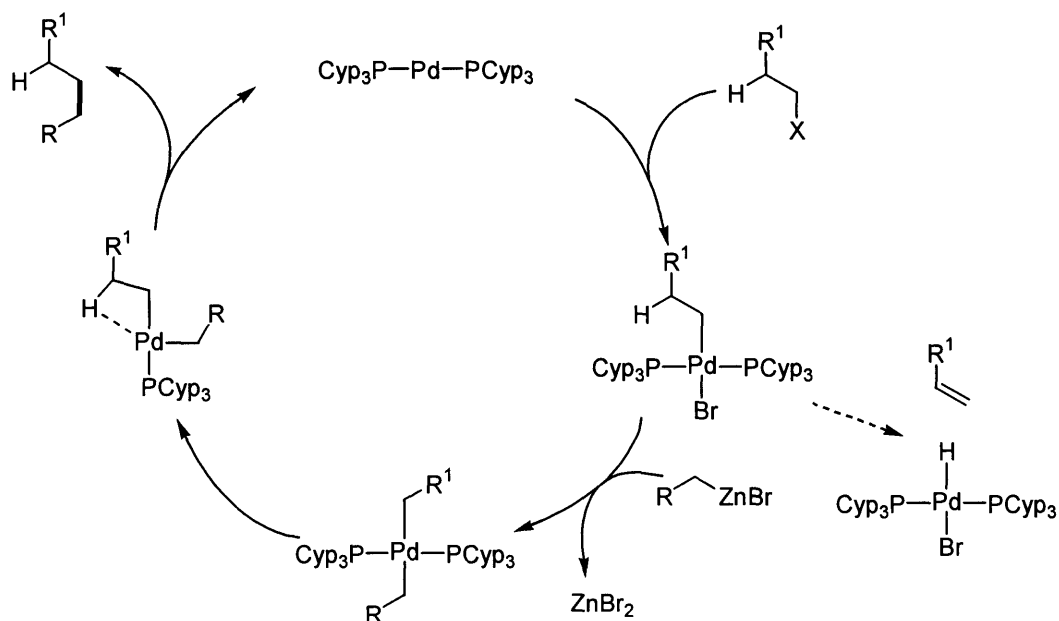


Figure 1.12. Hypothetical catalytic cycle of palladium-catalyzed Negishi coupling.

To gain some understanding of our $\text{Pd}_2(\text{dba})_3/\text{PCyp}_3$ system, we have conducted some preliminary ^{31}P NMR studies on the reaction between *n*-decyl bromide and *n*-butylzinc bromide under conditions closely resembling the standard conditions.⁶¹ By comparing chemical shifts with authentic or related compounds,⁶² individual species can be identified (Figure 1.13). Mixing of $\text{Pd}_2(\text{dba})_3$ and PCyp_3 quickly produced two broad peaks in ~1:1 ratio, each corresponding to PdL_2 and the free phosphine.⁶³ Then, *n*-decyl bromide was added into this solution, and we immediately observed PdL_2HBr and the free ligand (within 5 min), which were soon followed by the appearance of PdL_2RBr . To our astonishment, the claimed “true” catalyst, PdL_2 , did not show up until 20 min later.⁶⁴ After 90 min, the mixture was composed of PdL_2HBr (50%), PdL_2 (20%), PdL_2RBr (5%),

⁶¹ ^{31}P NMR was recorded on a 400 MHz Bruker instrument with 85% phosphoric acid as an external standard. The stoichiometry of the reaction was identical to the original conditions: 2% $\text{Pd}_2(\text{dba})_3$, 8% PCyp_3 , 1.2 equiv of NMI, 1.0 equiv of *n*-decyl bromide, and 1.3 equiv of *n*-butylzinc bromide. The reaction was performed in 2:1 THF/NMP at 60 °C (instead of 80 °C). After 14 h, 76% of the product was formed in an NMR tube (86% yield in a reaction vial at 80 °C).

⁶² $\text{Pd}(\text{PCyp}_3)_2$ was prepared by Dr. Matthew Netherton from PCyp_3 and $(\pi\text{-allyl})\text{PdCp}$, according to: (a) Yoshida, T.; Otsuka, S. *Inorg. Synth.* **1990**, *28*, 113–119. (b) Otsuka, S.; Yoshida, T.; Matsumoto, M.; Nakatsu, K. *J. Am. Chem. Soc.* **1976**, *98*, 5850–5858. Chemical shifts of several reference compounds were kindly provided by Luke Firmansjah in our group.

⁶³ We always noticed precipitation of some palladium black in these NMR experiments.

⁶⁴ The involvement of $\text{PdL}_2(\text{dba})$ is discounted in the reaction based on the ^{31}P chemical shift (31 ppm) of an analogous complex, $\text{PdCy}_2(\text{dba})$: Paul, F.; Patt, J.; Hartwig, J. F. *Organometallics* **1995**, *14*, 3030–3039.

and the free ligand (25%). So, in the absence of a coupling partner, we have detected the catalyst, its oxidative addition product, and β -hydride elimination byproduct. By further incorporation of the organozinc reagent and NMI in the beginning, the resting state of the catalyst was elucidated to be PdL_2 , along with an additional peak at 3 ppm. Based on our previous observation that *n*-BuZnBr and NMI can shift the PCyp_3 signal, we tentatively assign this unknown peak to a zinc(II) complex of both PCyp_3 and NMI.

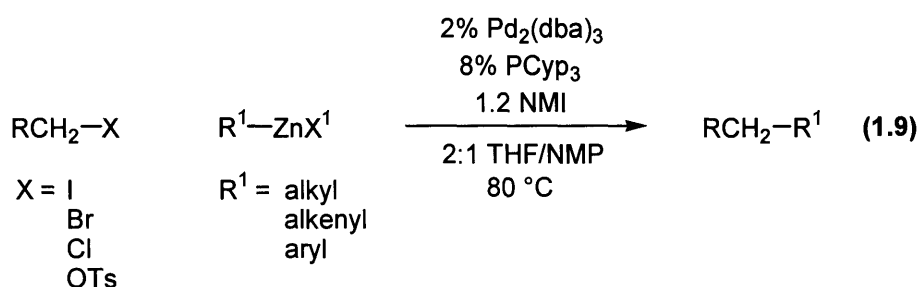
$\begin{array}{c} \text{Br} \\ \\ \text{Cyp}_3\text{P}-\text{Pd}-\text{PCyp}_3 \\ \\ \text{H} \end{array}$	$\text{Cyp}_3\text{P}-\text{Pd}-\text{PCyp}_3$	$\begin{array}{c} \text{Br} \\ \\ \text{Cyp}_3\text{P}-\text{Pd}-\text{PCyp}_3 \\ \\ n\text{-Decyl} \end{array}$	PCyp_3
45 ppm	40 ppm	22 ppm	6.5 ppm
<hr/>			
Reference Compounds			
$\begin{array}{c} \text{Br} \\ \\ \text{Cy}_3\text{P}-\text{Pd}-\text{PCy}_3 \\ \\ \text{H} \end{array}$	$\text{Cy}_3\text{P}-\text{Pd}-\text{PCy}_3$	$\begin{array}{c} \text{Br} \\ \\ \text{Cy}_3\text{P}-\text{Pd}-\text{PCy}_3 \\ \\ n\text{-Bu} \end{array}$	PCy_3
42 ppm	40 ppm	22 ppm	11 ppm
$\begin{array}{c} \text{Br} \\ \\ \text{Me}(t\text{-Bu})_2\text{P}-\text{Pd}-\text{P}(t\text{-Bu})_2\text{Me} \\ \\ \text{H} \end{array}$	$\text{Me}(t\text{-Bu})_2\text{P}-\text{Pd}-\text{P}(t\text{-Bu})_2\text{Me}$	$\begin{array}{c} \text{Br} \\ \\ \text{Me}(t\text{-Bu})_2\text{P}-\text{Pd}-\text{P}(t\text{-Bu})_2\text{Me} \\ \\ n\text{-Decyl} \end{array}$	$\text{P}(t\text{-Bu})_2\text{Me}$
53 ppm	41 ppm	28 ppm	12 ppm

Figure 1.13. ^{31}P chemical shifts of species relevant to catalysis.

1.4. Conclusion

In summary, we have developed a catalyst system that is effective for Negishi reactions of a broad spectrum of unhindered primary alkyl electrophiles (Eq 1.9). In terms of versatility, this Pd/PCyp_3 -based catalyst is unique among all of the methods that had been described previously for coupling alkyl electrophiles—the same catalyst is effective for many classes of alkyl electrophiles, including chlorides, bromides, iodides,

and tosylates. Furthermore, a range of organozinc (alkyl, alkenyl, and aryl) reagents may be employed, and the functional-group compatibility of the catalyst is good. We have also defined the limitations of this method, which include inhibition by proximal functional groups, elimination of β leaving groups, and sluggish reactions with sterically demanding electrophiles.^{65,66} Perhaps the most disappointing constraint of this reaction is its failure with secondary alkyl halides/tosylates, which will be the targets of my research later.



⁶⁵ Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527–12530. This paper is ranked the fourth most requested document under the category of chemistry and related science in 2004 via CAS online services: CAS Science Spotlight. <http://www.cas.org/spotlight/request.html> (accessed July 2005).

⁶⁶ We thank Johnson Matthey for gifts of palladium compounds.

1.5. Experimental

I. General

The following reagents were purchased: *N*-methylpyrrolidinone (NMP; anhydrous in a Sure-Seal bottle; Fluka), Pd₂(dba)₃ (Johnson Matthey), *N*-methylimidazole (NMI; stored over 4 Å molecular sieves; Avocado), PCyp₃ (Strem), PCy₃ (Strem), P(*i*-Pr)₃ (Strem), P(*t*-Bu)₂Me (Strem), P(*t*-Bu)₃ (Alfa-Aesar), P(*n*-Bu)₃ (Sigma), PCy₂Ph (TCI), PCyPh₂ (Strem), PPh₃ (Alfa-Aesar), P(*p*-Me₂NPh)₃ (Organometallics), P(*p*-MeOPh)₃ (Alfa-Aesar), P(*o*-Tol)₃ (Strem), P(2,4,6-trimethoxyphenyl)₃ (Strem), P(2-furyl)₃ (Strem), Cy₂P(CH₂)₂PCy₂ (dcpe; Strem), *rac*-BINAP (Aldrich), 1,3-bis(mesityl)-4,5-dihydroimidazolium tetrafluoroborate (Strem), P(OPh)₃ (Aldrich), *n*-BuZnBr (0.5 M in THF in a Sure-Seal bottle; Aldrich), 2-ethylhexylzinc bromide (0.5 M in THF in a Sure-Seal bottle; Aldrich), cyclohexylmethylzinc bromide (0.5 M in THF in a Sure-Seal bottle; Aldrich), 4-pentenylzinc bromide (0.5 M in THF in a Sure-Seal bottle; Aldrich), 5-cyano-5-methylhexylzinc bromide (0.5 M in THF in a Sure-Seal bottle; Aldrich), 6-ethoxy-6-oxohexylzinc bromide (0.5 M in THF in a Sure-Seal bottle; Aldrich), 1-phenylvinylzinc bromide (0.5 M in THF in a Sure-Seal bottle; Aldrich), PhZnBr (0.5 M in THF in a Sure-Seal bottle; Aldrich), 1-methylvinylmagnesium bromide (0.5 M in THF in a Sure-Seal bottle; Aldrich), 2-methyl-1-propenylmagnesium bromide (0.5 M in THF in a Sure-Seal bottle; Aldrich), *p*-methoxyphenylmagnesium bromide (0.5 M in THF in a Sure-Seal bottle; Aldrich), lithium hydride (powder; stored in a glove box; Aldrich), titanocene dichloride (stored in a glove box; Strem), zinc chloride (anhydrous; Strem), zinc bromide (anhydrous; Strem; dried at 150 °C overnight under vacuum and stored in a glove box), 2-butyne (Avocado), 1-phenyl-1-propyne (Aldrich), 1-bromo-3-benzyloxypropane (Aldrich), *n*-decyl bromide (Alfa-Aesar), 2-cyclohexylethyl bromide (Aldrich), 1-bromo-3-phenylpropane (Aldrich), 1-bromo-3-(*t*-butyldimethylsiloxy)propane (Aldrich), 7-bromoheptanenitrile (Aldrich), *n*-decyl iodide (Avocado), *n*-dodecyl *p*-toluenesulfonate (Acros), *n*-decyl chloride (Aldrich), 1-bromo-6-chlorohexane (Avocado), 2-(3-bromopropoxy)-tetrahydro-2*H*-pyran (Aldrich), 4-chlorobutyraldehyde diethyl acetal (Alfa-Aesar), ethyl 6-bromohexanoate (Avocado), 2-(3-bromopropyl)-1*H*-isoindole-

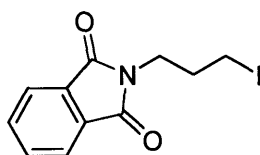
1,3(2*H*)-dione (Avocado), 6-bromohexanoyl chloride (Avocado), 2-picoline (stored over KOH pellets; Aldrich), diethylamine (Avocado), 3-cyclohexenylmethanol (Aldrich), 11-undecenyl alcohol (Alfa-Aesar), tetrafluoroboric acid (48 wt% in water; Aldrich).

THF was dried by passage through a neutral alumina column. 6-Bromohexyl pivalate was prepared according to a literature procedure.⁶⁷ The liquid alkyl halides/tosylates were purged with argon before use.

All reactions were conducted in oven-dried glassware under an inert atmosphere with magnetic stirring.

II. Preparation of Substrates and [HPCyp₃]BF₄

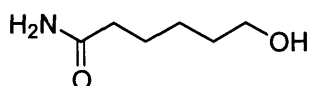
These procedures have not been optimized.



2-(3-Iodopropyl)-1*H*-isoindole-1,3(2*H*)-dione [5457-29-4]⁶⁸ (Table 1.5, entry 2). A solution of 2-(3-bromopropyl)-1*H*-isoindole-1,3(2*H*)-dione (3.00 g, 11.2 mmol) and NaI (8.40 g, 55.8 mmol) in acetone (anhydrous; 25 mL) was refluxed for 14 h. The solvent was then removed, and the resulting residue was extracted (CH₂Cl₂/10% Na₂S₂O₃ solution). The CH₂Cl₂ layer was dried over anhydrous MgSO₄, and the solvent was removed to give 3.52 g (100%) of the product as a yellow solid. The product was stored in the dark at 0 °C.

¹H NMR (CDCl₃, 400 MHz): δ 7.87-7.84 (m, 2H), 7.76-7.72 (m, 2H), 3.78 (t, *J* = 6.8 Hz, 2H), 3.18 (t, *J* = 7.2 Hz, 2H), 2.26 (tt, *J* = 7.2, 6.8 Hz, 2H).

¹³C NMR (CDCl₃, 100 MHz): δ 168.7, 134.5, 132.4, 123.8, 39.0, 33.0, 1.7.



⁶⁷ Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662–13663.

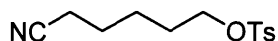
⁶⁸ Yeh, M. C. P.; Chen, H. G.; Knochel, P. *Org. Synth.* **1992**, *70*, 195–203.

6-Hydroxyhexanoamide [4547-52-8].⁶⁹ A suspension of ϵ -caprolactone (10.0 g, 87.7 mmol) in a conc. aq NH_3 solution (100 mL) was vigorously stirred at r.t. for 12 h. Then, the water was removed at 80 °C on a rotary evaporator, and the resulting solid was dissolved in CH_2Cl_2 (20 mL) and precipitated with Et_2O (20 mL). After vigorously stirring the mixture for 5 min and then letting it stand for 4 h, the white solids were collected by filtration and washed sequentially with EtOH and Et_2O . Concentration of the filtrate furnished additional crystals. Total yield: 8.30 g, 72%.

^1H NMR (CD_3CN , 400 MHz): δ 6.28 (br s, 1H), 5.85 (br s, 1H), 3.50 (t, $J = 6.6$ Hz, 2H), 2.87 (br s, 1H), 2.16 (t, $J = 7.4$ Hz, 2H), 1.61-1.47 (m, 4H), 1.39-1.33 (m, 2H).

^{13}C NMR (CD_3CN , 100 MHz): δ 176.0, 61.8, 35.6, 32.7, 25.7, 25.6.

HRMS (ESI): Calcd for $\text{C}_6\text{H}_{14}\text{NO}_2$ ($\text{M}+\text{H}$)⁺: 132.1019. Found: 132.1020.



6-(*p*-Toluenesulfonyloxy)hexanenitrile (Table 1.5, entry 4). THF (20 mL) and Et_3N (2.90 mL, 20.8 mmol) were added to a flask containing 6-hydroxyhexanoamide (2.48 g, 18.9 mmol) and *p*-toluenesulfonyl chloride (4.31 g, 22.6 mmol). The suspension was stirred at 50 °C for 14 h. Then, the solvent was evaporated, and the resulting residue was purified by flash chromatography (pentane/EtOAc 10:1), which afforded 0.70 g (14%) of the product.

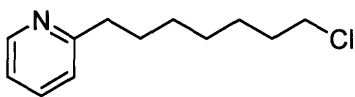
^1H NMR (CDCl_3 , 400 MHz): δ 7.78 (d, $J = 8.3$ Hz, 2H), 7.37 (d, $J = 8.0$ Hz, 2H), 4.03 (t, $J = 6.2$ Hz, 2H), 2.46 (s, 3H), 2.34 (t, $J = 7.1$ Hz, 2H), 1.73-1.59 (m, 4H), 1.52-1.46 (m, 2H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 145.4, 133.2, 130.4, 128.3, 119.8, 70.3, 28.5, 25.2, 25.1, 22.1, 17.4.

IR (thin film): 2943, 2871, 2245, 1598, 1357, 1176 cm^{-1} .

HRMS (ESI): Calcd for $\text{C}_{13}\text{H}_{17}\text{NNaO}_3\text{S}$ ($\text{M}+\text{Na}$)⁺: 290.0827. Found: 290.0815.

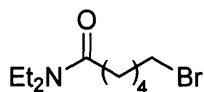
⁶⁹Zürn, L. *Justus Liebigs Ann. Chem.* **1960**, *631*, 56–60.



2-(7-Chloroheptyl)pyridine [237763-54-1]⁷⁰ (Table 1.5, entry 6). *n*-BuLi (2.65 M in hexane; 5.7 mL, 15 mmol) was added dropwise to a solution of 2-picoline (1.46 mL, 15 mmol) in THF (8 mL) at -78 °C. The resulting red solution was warmed to r.t. over 20 min, and then it was transferred to a Schlenk tube that contained a solution of 1-bromo-6-chlorohexane (2.24 mL, 3.00 g, 15 mmol) in THF (8 mL) at -78 °C. The mixture was then warmed to r.t. and stirred for 12 h. The reaction was quenched with MeOH (2 mL), and the solvents were removed under partial vacuum. The resulting oil was distilled (0.2 Torr, 93-95 °C) to give 2.01 g (64%) of the product as a yellow oil.

¹H NMR (CDCl₃, 400 MHz): δ 8.53 (d, $J = 4.1$ Hz, 1H), 7.59 (td, $J = 1.8, 7.7$ Hz, 1H), 7.14 (d, $J = 7.8$ Hz, 1H), 7.10 (dd, $J = 4.9, 5.9$ Hz, 1H), 3.53 (t, $J = 6.8$ Hz, 2H), 2.79 (t, $J = 7.7$ Hz, 2H), 1.80-1.71 (m, 4H), 1.47-1.37 (m, 6H).

¹³C NMR (CDCl₃, 100 MHz): δ 162.7, 149.6, 136.7, 123.1, 121.3, 45.6, 38.8, 33.0, 30.2, 29.6, 29.1, 27.2.



***N,N*-Diethyl 6-bromohexanamide [150514-56-0]** (Table 1.6, entry 5). 6-Bromohexanoyl chloride (3.93 mL, 25.0 mmol) was added dropwise over 10 min to a 0 °C solution of DMAP (54 mg, 0.25 mmol), Et₃N (5.20 mL, 37.5 mmol), and Et₂NH (2.61 mL, 25 mmol) in CH₂Cl₂ (50 mL). The resulting mixture was stirred at 0 °C for 1.0 h, and then the yellow suspension was passed through a pad of silica gel (washing with Et₂O). The filtrate was concentrated, and the residue was distilled under partial vacuum (150 mTorr, 95 °C) to give 6.06 g (99%) of the desired product as a colorless oil.

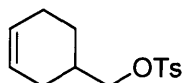
¹H NMR (CDCl₃, 400 MHz): δ 3.44-3.28 (m, 6H), 2.31 (t, $J = 7.3$ Hz, 2H), 1.89 (dd, J

⁷⁰Jansen, A.; Pitter, S. *Monatsh. Chem.* **1999**, *130*, 783–794.

= 7.1, 6.9 Hz, 2H), 1.68 (dd, $J = 7.6, 6.7$ Hz, 2H), 1.49 (dd, $J = 7.9, 7.3$ Hz, 2H), 1.17 (t, $J = 7.1$ Hz, 3H), 1.11 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 172.2, 42.3, 40.5, 34.2, 33.2, 33.0, 28.4, 24.9, 14.8, 13.5.

HRMS (ESI): Calcd for $\text{C}_{10}\text{H}_{20}\text{NNaOBr}$ ($\text{M}+\text{Na}$) $^+$: 272.0620. Found: 272.0628.



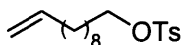
3-Cyclohexene-1-methanol *p*-toluenesulfonate [92864-78-3] (Table 1.6, entry 9).

3-Cyclohexenylmethanol (2.08 mL, 2.00 g, 17.8 mmol) and Et_3N (2.60 mL, 18.7 mmol) were added to a solution of *p*-toluenesulfonyl chloride (3.38 g, 17.8 mmol) in THF (20 mL). The initially clear solution became cloudy within a few minutes. After 12 h of stirring at r.t., a white suspension had formed. Pentane (20 mL) was added, and then the suspension was passed through Celite, which was washed with pentane. The filtrate was concentrated, and the residue was purified by flash chromatography (pentane/ Et_2O 100:3), which furnished 2.15 g (45%) of the desired product as a colorless oil.

^1H NMR (CDCl_3 , 400 MHz): δ 7.80 (d, $J = 8.4$ Hz, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 5.67-5.57 (m, 2H), 3.91 (d, $J = 6.6$ Hz, 2H), 2.46 (s, 3H), 2.11-1.94 (m, 4H), 1.76-1.66 (m, 2H), 1.32-1.22 (m, 1H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 145.1, 133.4, 130.3, 128.3, 127.4, 125.4, 74.8, 33.5, 28.0, 25.1, 24.4, 22.1.

HRMS (ESI): Calcd for $\text{C}_{14}\text{H}_{18}\text{NaO}_3\text{S}$ ($\text{M}+\text{Na}$) $^+$: 289.0869. Found: 289.0864.



10-Undecen-1-ol *p*-toluenesulfonate [51148-67-5] (Table 1.5, entry 5).

11-Undecenyl alcohol (5.89 mL, 5.00 g, 29.4 mmol) and Et_3N (4.09 mL, 29.4 mmol) were added to a solution of *p*-toluenesulfonyl chloride (5.60 g, 29.4 mmol) in THF (20 mL).

The mixture was stirred at 70 °C (white solids appeared within the first 10 min). After 8 h, the resulting suspension was mixed with pentane (20 mL) and passed through a pad of silica gel (Et₂O washings). The filtrate was concentrated, and the residue was purified by flash chromatography (pentane/Et₂O 100:2) to give 5.27 g (58%) of the desired product as a colorless oil.

¹H NMR (CDCl₃, 400 MHz): δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 5.86-5.77 (m, 1H), 5.03-4.93 (m, 2H), 4.04 (t, *J* = 6.5 Hz, 2H), 2.47 (s, 3H), 2.07-2.02 (m, 2H), 1.68-1.61 (m, 2H), 1.39-1.24 (m, 12H).

¹³C NMR (CDCl₃, 100 MHz): δ 145.0, 139.6, 133.6, 130.2, 128.3, 114.6, 71.1, 34.2, 29.7 (two overlapping resonances), 29.4, 29.3 (two overlapping resonances), 29.2, 25.7, 22.0.

[HPCyp₃]BF₄. Under an argon atmosphere in a scintillation vial, HBF₄ (48 wt% in water; 1.64 mL, 12.6 mmol) was added dropwise to a solution of PCyp₃ (1.06 g, 4.45 mmol) in CH₂Cl₂ (10 mL). The reaction mixture was stirred vigorously at r.t. for 10 min, and then water (5 mL) was added and the organic layer was removed by pipet. The aqueous layer was shaken with CH₂Cl₂ (10 mL), and the organic layer was again removed by pipet. The combined organic extracts were dried over anhydrous MgSO₄, filtered, and concentrated to give a white solid, which was re-dissolved in hot acetone (10 mL) and then precipitated with hexane (20 mL) to give a fine white powder (1.44 g, 99%).

¹H NMR (CDCl₃, 400 MHz): δ 6.17 (dd, *J* = 474.3, 5.2 Hz, 1H), 2.70-2.62 (m, 3H), 2.26-2.19 (m, 6H), 1.86-1.75 (m, 18H).

¹³C NMR (CDCl₃, 100 MHz): δ 29.5, 28.7 (d, *J* = 45.9 Hz), 26.3 (d, *J* = 11.3 Hz).

³¹P NMR (CDCl₃, 100 MHz): δ 32.0.

IR (KBr pellet): 3421, 2984, 2923, 2361, 2336, 2017, 1236 cm⁻¹.

HRMS (EI): Calcd for C₁₅H₂₈P (M)⁺: 239.1923. Found: 239.1930.

mp: 252 °C (decomposition).

III. Negishi Cross-Coupling Reactions

Representative Procedure for the Optimization Studies (Tables 1.1-1.3). In a glove box, Pd₂(dba)₃ (4.6 mg, 0.0050 mmol), PCyp₃ (5.0 μL, 4.8 mg, 0.020 mmol), THF (0.15 mL), and dry NMP (0.4 mL) were added sequentially to a vial. The resulting mixture was stirred at r.t. for 3 min, resulting in a yellow-green solution. *n*-BuZnBr (0.5 M in THF; 0.65 mL, 0.32 mmol), NMI (25 μL, 0.30 mmol), *n*-hexadecane (GC internal standard; 29 μL, 0.10 mmol), and 1-bromo-3-benzyloxypropane (46 μL, 58 mg, 0.25 mmol) were added, and then the vial was closed with a Teflon-coated screw cap, sealed with electrical tape, taken out of the glove box, and stirred in an 80 °C oil bath. After 14 h, an aliquot was passed through silica gel and analyzed by gas chromatography.

Benzyl *n*-heptyl ether [16519-20-3]. ¹H NMR (CDCl₃, 400 MHz): δ 7.38-7.28 (m, 5H), 4.54 (s, 2H), 3.50 (t, *J* = 6.6 Hz, 2H), 1.67-1.62 (m, 2H), 1.41-1.29 (m, 8H), 0.92 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (CDCl₃, 100 MHz): δ 139.1, 128.8, 128.1, 127.9, 73.3, 71.0, 32.3, 30.2, 29.6, 26.6, 23.1, 14.5.

Procedure for Tables 1.4 and 1.5 (no glove box). Pd₂(dba)₃ (9.2 mg, 0.010 mmol) was added to a Schlenk tube equipped with a stir bar. The air was removed by evacuating/refilling with argon (three times), and then PCyp₃ (10 μL, 9.6 mg, 0.040 mmol), THF (0.3 mL), and dry NMP (0.8 mL) were added. After stirring for 3 min at r.t., the yellow-green solution was treated with the alkylzinc bromide solution (0.5 M in THF; 1.3 mL, 0.65 mmol), NMI (50 μL, 0.60 mmol), and the alkyl halide/tosylate (0.50 mmol). The reaction mixture was stirred in an oil bath for 14 h at 80 °C, and then it was diluted with pentane (2 mL) and passed through a short pad of silica gel (to remove inorganic salts and NMP). The filtrate was then concentrated, and the residue was purified by flash chromatography.

***n*-Tetradecane [629-59-4] (Table 1.4, entry 1).** *n*-BuZnBr (0.5 M in THF; 1.3 mL, 0.65 mmol) and *n*-decyl bromide (111 mg, 0.50 mmol) were used. Solvent for chromatography: pentane. Colorless oil (89 mg, 90%).

¹H NMR (CDCl₃, 400 MHz): δ 1.33-1.29 (m, 24H), 0.91 (t, *J* = 7.0 Hz, 6H).

¹³C NMR (CDCl₃, 100 MHz): δ 32.4, 30.2 (two overlapping resonances), 30.1, 29.8,

23.1, 14.5.

The NMR spectra and the GC retention time were identical to those of an authentic sample (Aldrich).

5-Ethylhexadecane [125182-41-4] (Table 1.4, entry 2). 2-Ethylhexylzinc bromide (0.5 M in THF; 1.3 mL, 0.65 mmol) and *n*-decyl bromide (111 mg, 0.50 mmol) were used. Solvent for chromatography: pentane. Colorless oil (113 mg, 89%).

^1H NMR (CDCl_3 , 400 MHz): δ 1.28-1.24 (m, 29H), 0.93-0.83 (m, 9H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 39.2, 33.6, 33.3, 32.4, 30.6, 30.2, 30.15 (two overlapping resonances), 30.10, 29.8, 29.4, 27.2, 26.3, 23.6, 23.1, 14.61, 14.55, 11.3.

(4-Ethylcyclohexyl)cyclohexane (Table 1.4, entry 3). 2-Ethylhexylzinc bromide (0.5 M in THF; 1.3 mL, 0.65 mmol) and 2-cyclohexylethyl bromide (98 mg, 0.50 mmol) were used. Solvent for chromatography: pentane. Colorless oil (85 mg, 76%).

^1H NMR (CDCl_3 , 400 MHz): δ 1.73-1.69 (m, 4H), 1.31-1.15 (m, 22H), 0.93-0.83 (m, 6H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 39.3, 38.5, 38.2, 33.9 (two overlapping resonances), 33.3, 29.4, 27.2, 26.9, 26.3, 24.3, 23.6, 14.6, 11.3.

IR (thin film): 2923, 2853, 1449 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{16}\text{H}_{32}$ (M) $^+$: 224.2504. Found: 224.2503.

(4-Cyclohexylbutyl)benzene [6199-25-3] (Table 1.4, entry 4).

Cyclohexylmethylzinc bromide (0.5 M in THF; 1.3 mL, 0.65 mmol) and 1-bromo-3-phenylpropane (102 mg, 0.50 mmol) were used. Solvent for chromatography: pentane. Colorless oil (90 mg, 83%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.34-7.28 (m, 2H), 7.23-7.19 (m, 3H), 2.64 (t, $J = 7.7$ Hz, 2H), 1.74-1.57 (m, 7H), 1.41-1.14 (m, 8H), 0.93-0.90 (m, 2H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 143.4, 128.8, 128.6, 126.0, 38.1, 37.8, 36.5, 33.9, 32.3, 27.2, 27.0, 26.9.

HRMS (EI): Calcd for $\text{C}_{16}\text{H}_{24}$ (M) $^+$: 216.1873. Found: 216.1881.

1-Pentadecene [13360-61-7] (Table 1.4, entry 5). 4-Pentenylzinc bromide (0.5 M in THF; 1.3 mL, 0.65 mmol) and *n*-decyl bromide (111 mg, 0.50 mmol) were used. Solvent for chromatography: pentane. Colorless oil (55 mg, 52%).

^1H NMR (CDCl_3 , 400 MHz): δ 5.89-5.79 (m, 1H), 5.05-4.94 (m, 2H), 2.07 (dd, $J = 6.8, 6.7$ Hz, 2H), 1.42-1.29 (m, 22H), 0.91 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 139.7, 114.5, 34.3, 32.4, 32.3, 30.12, 30.10, 30.06, 30.0, 29.9, 29.8, 29.6, 29.4, 23.1, 14.5.

9-Benzyloxy-2,2-dimethylnonanenitrile (Table 1.4, entry 6). 5-Cyano-5-methylhexylzinc bromide (0.5 M in THF; 1.3 mL, 0.65 mmol) and 1-bromo-3-benzyloxypropane (116 mg, 0.50 mmol) were used. Solvent for chromatography: pentane/EtOAc 100:3 \rightarrow 100:4. Yellow oil (80 mg, 68%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.38 (m, 5H), 4.53 (s, 2H), 3.49 (t, $J = 6.6$ Hz, 2H), 1.66-1.63 (m, 2H), 1.51 (br s, 4H), 1.42-1.35 (m, 12H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 139.1, 128.8, 128.1, 127.9, 125.7, 70.8, 41.5, 32.8, 30.1, 30.0, 29.7, 27.1 (two overlapping resonances), 26.5, 25.6.

IR (thin film): 2935, 2859, 2233, 1719, 1275 cm^{-1} .

HRMS (ESI): Calcd for $\text{C}_{18}\text{H}_{27}\text{NNaO}$ ($\text{M}+\text{Na}$) $^+$: 296.1990. Found: 296.1971.

9-*t*-Butyldimethylsiloxy-2,2-dimethylnonanenitrile (Table 1.4, entry 7). 5-Cyano-5-methylhexylzinc bromide (0.5 M in THF; 1.3 mL, 0.65 mmol) and 1-bromo-3-(*t*-butyldimethylsiloxy)propane (106 mg, 0.50 mmol) were used. Solvent for chromatography: pentane/ CH_2Cl_2 100:30 \rightarrow 100:50 \rightarrow 100:100. Colorless oil (100 mg, 67%).

^1H NMR (CDCl_3 , 400 MHz): δ 3.62 (t, $J = 6.6$ Hz, 2H), 1.53-1.51 (br, 6H), 1.35 (br, 12H), 0.92 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 125.7, 63.6, 41.5, 33.2, 32.8, 30.0, 29.6, 27.1, 26.4, 26.1, 25.6, 18.8, -4.8 .

IR (thin film): 2935, 2858, 2235, 1472, 1101 cm^{-1} .

HRMS (ESI): Calcd for $\text{C}_{17}\text{H}_{35}\text{NNaOSi}$ ($\text{M}+\text{Na}$) $^+$: 320.2380. Found: 320.2370.

Ethyl 12-cyanododecanoate [133310-02-8] (Table 1.4, entry 8). 6-Ethoxy-6-oxohexylzinc bromide (0.5 M in THF; 1.3 mL, 0.65 mmol) and 7-bromoheptanenitrile (96 mg, 0.50 mmol) were used. Solvent for chromatography: pentane/EtOAc 100:5 \rightarrow 100:7.5. Yellow oil (82 mg, 65%).

^1H NMR (CDCl_3 , 400 MHz): δ 4.13 (q, $J = 7.1$ Hz, 2H), 2.36-2.27 (m, 4H), 1.68-1.60

(m, 4H), 1.46-1.43 (m, 2H), 1.29-1.24 (m, 15H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 174.3, 120.3, 60.6, 34.8, 29.8, 29.7 (two overlapping resonances), 29.6, 29.5, 29.2, 29.1, 25.8, 25.4, 17.5, 14.7.

***n*-Tetradecane [629-59-4] (Table 1.5, entry 1).** *n*-BuZnBr solution (0.5 M in THF; 1.3 mL, 0.65 mmol) and *n*-decyl iodide (134 mg, 0.50 mmol) were used. Solvent for chromatography: pentane. Colorless oil (86 mg, 87%).

The NMR (^1H and ^{13}C) spectra and the GC retention time were identical to those of an authentic sample (Aldrich).

2-Heptyl-1*H*-isoindole-1,3(2*H*)-dione [71510-40-2] (Table 1.5, entry 2). *n*-BuZnBr solution (0.5 M in THF; 1.3 mL, 0.65 mmol) and a solution of 2-(3-iodopropyl)-1*H*-isoindole-1,3(2*H*)-dione (158 mg, 0.50 mmol) in NMP (0.8 mL) were used. Solvent for chromatography: pentane/EtOAc 100:3 \rightarrow 100:4. Yellow oil (59 mg, 48%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.86-7.82 (m, 2H), 7.74-7.70 (m, 2H), 3.68 (t, $J = 7.3$ Hz, 2H), 1.69-1.64 (m, 2H), 1.35-1.26 (m, 8H), 0.87 (t, $J = 6.8$ Hz, 3H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 168.9, 134.2, 132.6, 123.5, 38.5, 32.1, 29.3, 29.0, 27.2, 23.0, 14.5.

***n*-Hexadecane [544-76-3] (Table 1.5, entry 3).** *n*-BuZnBr solution (0.5 M in THF; 1.3 mL, 0.65 mmol) and *n*-dodecyl *p*-toluenesulfonate (157 mg, 0.50 mmol) were used. 80 °C, 40 h. Solvent for chromatography: pentane. Colorless oil (93 mg, 86%).

The NMR (^1H and ^{13}C) spectra and the GC retention time were identical to those of an authentic sample (Aldrich).

11-Cyano-2,2-dimethylundecanenitrile (Table 1.5, entry 4). 5-Cyano-5-methylhexylzinc bromide (0.5 M in THF; 1.3 mL, 0.65 mmol) and 6-*p*-toluenesulfonyloxyhexanenitrile (134 mg, 0.50 mmol) were used. 80 °C, 40 h. Solvent for chromatography: pentane/Et₂O 3:1. Colorless oil (70 mg, 64%).

^1H NMR (CDCl_3 , 400 MHz): δ 2.34 (t, $J = 7.1$ Hz, 2H), 1.67-1.62 (m, 2H), 1.49-1.42 (m, 6H), 1.33-1.31 (m, 14H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 125.7, 120.3, 41.4, 32.8, 29.9, 29.63, 29.56, 29.1, 29.0, 27.1, 25.7, 25.6, 17.5.

IR (thin film): 2933, 2234, 1470 cm^{-1} .

HRMS (ESI): Calcd for C₁₄H₂₄N₂Na (M+Na)⁺: 243.1831. Found: 243.1837.

***n*-Tetradecane [629-59-4] (Table 1.5, entry 5).** *n*-BuZnBr solution (0.5 M in THF; 1.3 mL, 0.65 mmol) and *n*-decyl chloride (90 mg, 0.50 mmol) were used. 80 °C, 40 h. Solvent for chromatography: pentane. Colorless oil (96 mg, 97%).

The NMR (¹H and ¹³C) spectra and the GC retention time were identical to those of an authentic sample (Aldrich).

2-Undecylpyridine [80401-50-9] (Table 1.5, entry 6). *n*-BuZnBr solution (0.5 M in THF; 1.3 mL, 0.65 mmol) and 2-(7-chloroheptyl)pyridine (106 mg, 0.50 mmol) were used. 80 °C, 40 h. Solvent for chromatography: pentane/EtOAc 100:3 → 100:4. Yellow oil (90 mg, 77%).

¹H NMR (CDCl₃, 400 MHz): δ 8.53 (d, *J* = 4.8 Hz, 1H), 7.59 (td, *J* = 7.6, 1.8 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.10 (dd, *J* = 7.4, 4.9 Hz, 1H), 2.79 (t, *J* = 7.7 Hz, 2H), 1.73 (tt, *J* = 7.7, 7.0 Hz, 2H), 1.36-1.26 (m, 16H), 0.89 (t, *J* = 6.6 Hz, 3H).

¹³C NMR (CDCl₃, 100 MHz): δ 163.0, 149.6, 136.6, 123.1, 121.2, 38.9, 32.3, 30.4, 30.1, 30.04, 29.98, 29.9, 29.84, 29.76, 23.1, 14.6.

***n*-Tetradecane [629-59-4] (Table 1.5, entry 7).** *n*-BuZnBr solution (0.5 M in THF; 1.3 mL, 0.65 mmol) and 1-bromo-6-chlorohexane (51 mg, 0.25 mmol) were used. 80 °C, 40 h. Solvent for chromatography: pentane. Colorless oil (dialkylated product; 35 mg, 70%).

Procedure A for Table 1.6 (with PCyp₃ and a commercially available organozinc reagent). In a glove box, Pd₂(dba)₃ (9.2 mg, 0.010 mmol), PCyp₃ (10 μL, 9.6 mg, 0.040 mmol), and dry NMP (0.8 mL) were added to a vial. The reaction mixture was stirred for 3 min at r.t., and then the resulting yellow-green solution was treated with the organozinc bromide (0.5 M in THF; 1.60 mL, 0.80 mmol), NMI (50 μL, 0.60 mmol), and the alkyl halide/tosylate (0.50 mmol). The vial was closed with a Teflon-coated screw cap, sealed with electrical tape, and taken out of the glove box. The reaction mixture was stirred in an 80 °C oil bath for 12 h, and then pentane (2 mL) was added. The reaction mixture was passed through a short pad of silica gel (to remove inorganic salts and NMP), the filtrate was concentrated, and the residue was purified by flash chromatography.

Procedure B for Table 1.6 (with [HPCyp₃]BF₄ and a commercially available

organozinc reagent; no glove box). In air, Pd₂(dba)₃ (9.2 mg, 0.010 mmol) and [HPCyp₃]BF₄ (13 mg, 0.040 mmol) were added to a Schlenk tube. The air was removed by evacuating/refilling with argon (three times), and then dry NMP (0.8 mL) was added. The reaction mixture was stirred for 3 min at r.t., and then the resulting yellow-green solution was treated with the organozinc bromide (0.5 M in THF; 1.60 mL, 0.80 mmol), NMI (50 μL, 0.60 mmol), and the alkyl halide/tosylate (0.50 mmol). The reaction mixture was stirred in an 80 °C oil bath for 12 h, and then pentane (2 mL) was added. The reaction mixture was passed through a short pad of silica gel (to remove inorganic salts and NMP), the filtrate was concentrated, and the residue was purified by flash chromatography.

1-Methyleneundecylbenzene [115146-99-1] (Table 1.6, entry 1). 1-Phenylvinylzinc bromide (0.5 M in THF; 1.6 mL, 0.80 mmol) and *n*-decyl bromide (111 mg, 0.50 mmol) were used. Solvent for chromatography: pentane. Colorless solid (Procedure A: 114 mg, 93%; Procedure B: 114 mg, 93%).

¹H NMR (CDCl₃, 400 MHz): δ 7.47-7.44 (m, 2H), 7.39-7.35 (m, 2H), 7.33-7.28 (m, 1H), 5.31 (d, *J* = 1.5 Hz, 1H), 5.10 (d, *J* = 1.4 Hz, 1H), 2.55 (t, *J* = 7.6 Hz, 2H), 1.52-1.46 (m, 2H), 1.39-1.30 (m, 14H), 0.93 (t, *J* = 6.7 Hz, 3H).

¹³C NMR (CDCl₃, 100 MHz): δ 149.2, 141.9, 128.6, 127.7, 126.5, 112.4, 35.8, 32.4, 30.1 (two overlapping resonances), 29.9, 29.8 (two overlapping resonances), 28.7, 23.2, 14.6.

IR (thin film): 2926, 2854, 1628, 1466 cm⁻¹.

HRMS (EI): Calcd for C₁₈H₂₈ (M)⁺: 244.2186. Found: 244.2185.

1-Methyleneundecylbenzene [115146-99-1] (Table 1.6, entry 7). 1-Phenylvinylzinc bromide (0.5 M in THF; 1.6 mL, 0.80 mmol) and *n*-decyl iodide (134 mg, 0.50 mmol) were used. Solvent for chromatography: pentane. Colorless solid (Procedure A: 114 mg, 93%; Procedure B: 113 mg, 93%).

2-(4-Phenyl-4-pentenyl)-1*H*-isoindole-1,3(2*H*)-dione (Table 1.6, entry 8). 1-Phenylvinylzinc bromide (0.5 M in THF; 1.6 mL, 0.80 mmol) and 2-(3-iodopropyl)-1*H*-isoindole-1,3(2*H*)-dione (158 mg, 0.50 mmol) were used in Procedure A; in Procedure B, the iodide was introduced as a solution in NMP (0.8 mL). Solvent for chromatography:

pentane/EtOAc 100:7. White solid (Procedure A: 107 mg, 74%; Procedure B: 111 mg, 76%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.84-7.82 (m, 2H), 7.74-7.71 (m, 2H), 7.41-7.39 (m, 2H), 7.35-7.31 (m, 2H), 7.30-7.26 (m, 1H), 5.31 (s, 1H), 5.13 (d, $J = 1.2$ Hz, 1H), 3.76 (t, $J = 7.2$ Hz, 2H), 2.59 (t, $J = 7.7$ Hz, 2H), 1.89 (dd, $J = 7.7, 7.2$ Hz, 2H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 168.8, 147.6, 141.4, 134.3, 132.5, 128.8, 127.9, 126.5, 123.6, 113.2, 38.1, 33.0, 27.5.

IR (KBr pellet): 3083, 3024, 2943, 1699, 1401, 1030 cm^{-1} .

HRMS (ESI): Calcd for $\text{C}_{19}\text{H}_{17}\text{NNaO}_2$ ($\text{M}+\text{Na}$) $^+$: 314.1151. Found: 314.1155.

4-(2-Phenyl-2-propenyl)cyclohexene (Table 1.6, entry 9). 1-Phenylvinylzinc bromide (0.5 M in THF; 1.6 mL, 0.80 mmol) and 3-cyclohexene-1-methanol *p*-toluenesulfonate (133 mg, 0.50 mmol) were used. Solvent for chromatography: pentane. Colorless oil (Procedure A: 56 mg, 58%; Procedure B: 52 mg, 53%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.45-7.42 (m, 2H), 7.37-7.33 (m, 2H), 7.31-7.29 (m, 1H), 5.67-5.61 (m, 2H), 5.31 (d, $J = 1.8$ Hz, 1H), 5.07 (d, $J = 1.5$ Hz, 1H), 2.55-2.45 (m, 2H), 2.10-1.93 (m, 3H), 1.81-1.65 (m, 3H), 1.31-1.21 (m, 1H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 147.4, 141.7, 128.7, 127.7, 127.4, 126.8, 126.7, 114.1, 43.1, 32.00, 31.99, 29.0, 25.4.

IR (thin film): 3022, 2917, 2837, 1626, 1436 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{15}\text{H}_{18}$ (M) $^+$: 198.1403. Found: 198.1406.

6,6-Diethoxy-2-phenyl-1-hexene (Table 1.6, entry 10). 1-Phenylvinylzinc bromide (0.5 M in THF; 1.6 mL, 0.80 mmol) and 4-chlorobutylaldehyde diethyl acetal (91 mg, 0.50 mmol) were used. Solvent for chromatography: pentane/EtOAc 100:2. Yellow oil (Procedure A: 91 mg, 73%; Procedure B: 97 mg, 78%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.43-7.42 (m, 2H), 7.37-7.33 (m, 2H), 7.31-7.28 (m, 1H), 5.30 (s, 1H), 5.09 (s, 1H), 4.50 (t, $J = 5.6$ Hz, 1H), 3.64-3.58 (m, 2H), 3.52-3.44 (m, 2H), 2.56 (t, $J = 7.3$ Hz, 2H), 1.70-1.65 (m, 2H), 1.59-1.52 (m, 2H), 1.20 (t, $J = 7.1$ Hz, 6H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 148.6, 141.6, 128.7, 127.7, 126.6, 112.9, 103.1, 61.2, 35.4, 33.4, 23.7, 15.7.

IR (thin film): 2975, 2930, 2876, 1444, 1374, 1129, 1063 cm^{-1} .

HRMS (ESI): Calcd for $\text{C}_{16}\text{H}_{24}\text{NaO}_2$ ($\text{M}+\text{Na}$)⁺: 271.1669. Found: 271.1674.

Decylbenzene [104-72-3] (Table 1.6, entry 12). PhZnBr (0.5 M in THF; 1.6 mL, 0.80 mmol) and *n*-decyl iodide (134 mg, 0.50 mmol) were used. Solvent for chromatography: pentane. Colorless oil (Procedure A: 70 mg, 65%; Procedure B: 68 mg, 62%).

¹H NMR (CDCl_3 , 400 MHz): δ 7.36-7.32 (m, 2H), 7.26-7.22 (m, 3H), 2.67 (t, $J = 7.7$ Hz, 2H), 1.68 (q, $J = 7.7$ Hz, 2H), 1.38-1.30 (m, 14H), 0.96 (t, $J = 7.1$ Hz, 3H).

¹³C NMR (CDCl_3 , 100 MHz): δ 143.4, 128.8, 128.7, 126.0, 36.5, 32.4, 32.0, 30.11, 30.09, 30.01, 29.8 (two overlapping resonances), 23.2, 14.6.

Both spectra were identical to those of an authentic sample (Aldrich).

Procedure C for Table 1.6 (with PCyp₃ and a Grignard reagent/ ZnCl_2). In a glove box, anhydrous ZnCl_2 granules (109 mg, 0.80 mmol) and 1.6 mL of a solution of the Grignard reagent (0.5 M in THF; 0.80 mmol) were vigorously stirred for 20 min. To the resulting suspension was added sequentially dry NMP (0.8 mL), PCyp₃ (10 μL , 9.6 mg, 0.040 mmol), NMI (50 μL , 0.60 mmol), the alkyl halide/tosylate (0.50 mmol), and then Pd₂(dba)₃ (9.2 mg, 0.010 mmol). The vial was closed with a Teflon-coated screw cap, sealed with electrical tape, and taken out of the glove box. The reaction mixture was stirred in an 80 °C oil bath for 12 h, and then pentane (2 mL) was added. The reaction mixture was passed through a short pad of silica gel (to remove inorganic salts and NMP), the filtrate was concentrated, and the residue was purified by flash chromatography.

Procedure D for Table 1.6 (with [HPCyp₃]BF₄ and a Grignard reagent/ ZnCl_2 ; no glove box). In air, Pd₂(dba)₃ (9.2 mg, 0.010 mmol) and [HPCyp₃]BF₄ (13 mg, 0.040 mmol) were added to a Schlenk tube. The air was removed by evacuating/refilling with argon (three times), and then a ZnCl_2 solution (0.5 M in THF; 1.6 mL, 0.80 mmol) was added. A solution of the Grignard reagent (0.5 M in THF; 0.80 mmol) was introduced dropwise over 30 seconds, and the resulting mixture was stirred for 1 min. To this brown suspension was added the alkyl halide/tosylate (0.50 mmol), NMI (50 μL , 0.60 mmol), and then dry NMP (1.6 mL) (*The addition sequence is important*). The reaction mixture was stirred in an 80 °C oil bath for 12 h, and then pentane (2 mL) was added. The

reaction mixture was passed through a short pad of silica gel (to remove inorganic salts and NMP), the filtrate was concentrated, and the residue was purified by flash chromatography.

7-Methyl-7-octenyl pivalate (Table 1.6, entry 2). 1-Methylvinylmagnesium bromide (0.5 M in THF; 1.6 mL, 0.80 mmol) and 6-bromohexyl pivalate (133 mg, 0.50 mmol) were used. Solvent for chromatography: pentane/Et₂O 100:1. After concentration under reduced pressure, the yellow residue was treated with dry MeOH (2 mL). The resulting mixture was allowed to stand overnight, and then the small amount of phosphine-containing yellow solid was removed by filtration through a short plug of Celite in a Pasteur pipet (MeOH washings). The filtrate was concentrated to give a yellow oil that was pure according to ¹H and ¹³C NMR spectroscopy (Procedure C: 77 mg, 68%; Procedure D: 80 mg, 71%).

¹H NMR (CDCl₃, 400 MHz): δ 4.70 (s, 1H), 4.67 (s, 1H), 4.06 (t, *J* = 6.6 Hz, 2H), 2.01 (t, *J* = 7.3 Hz, 2H), 1.72 (s, 3H), 1.67-1.60 (m, 2H), 1.47-1.32 (m, 6H), 1.21 (s, 9H).

¹³C NMR (CDCl₃, 100 MHz): δ 179.0, 146.4, 110.1, 64.8, 39.1, 38.1, 29.2, 29.0, 27.8, 27.6, 26.2, 22.7.

IR (thin film): 2970, 2934, 2859, 1731, 1285, 1156 cm⁻¹.

HRMS (ESI): Calcd for C₁₄H₂₆NaO₂ (M+Na)⁺: 249.1825. Found: 249.1831.

2-(4-Methyl-4-pentenyl-oxo)-tetrahydro-2H-pyran (Table 1.6, entry 3). 1-Methylvinylmagnesium bromide (0.5 M in THF; 1.6 mL, 0.80 mmol) and 2-(3-bromopropoxy)tetrahydro-2H-pyran (112 mg, 0.50 mmol) were used. Solvent for chromatography: pentane/Et₂O 100:2. Colorless oil (Procedure C: 70 mg, 76%; Procedure D: 71 mg, 77%).

¹H NMR (CDCl₃, 400 MHz): δ 4.72 (s, 1H), 4.70 (s, 1H), 4.59 (t, *J* = 4.2 Hz, 1H), 3.91-3.85 (m, 1H), 3.78-3.72 (m, 1H), 3.54-3.48 (m, 1H), 3.43-3.37 (m, 1H), 2.14-2.04 (m, 2H), 1.88-1.80 (m, 1H), 1.79-1.69 (m, 6H), 1.62-1.51 (m, 4H).

¹³C NMR (CDCl₃, 100 MHz): δ 145.8, 110.3, 99.3, 67.6, 62.7, 34.7, 31.1, 28.1, 25.9, 22.8, 20.1.

IR (thin film): 2942, 2871, 1651, 1442, 1034 cm⁻¹.

HRMS (ESI): Calcd for C₁₁H₂₀NaO₂ (M+Na)⁺: 207.1356. Found: 207.1356.

Benzyl 5-methyl-4-hexenyl ether [131721-93-2] (Table 1.6, entry 4). 2-Methyl-1-propenylmagnesium bromide (0.5 M in THF; 1.6 mL, 0.80 mmol) and benzyl 3-bromopropyl ether (116 mg, 0.50 mmol) were used. The reaction mixture was passed through a short silica-gel column with pentane/Et₂O 100:2. The yellow fractions were combined and concentrated under partial vacuum to give a yellow oil, which was treated with dry MeOH (2 mL). The resulting mixture was allowed to stand overnight, and then the small amount of phosphine-containing yellow solid was removed by filtration through a short plug of Celite in a Pasteur pipet (MeOH washings). The filtrate was concentrated, and the residue was purified by flash chromatography (pentane/Et₂O 100:1). Yellow oil (Procedure C: 84 mg, 83%; Procedure D: 76 mg, 75%).

¹H NMR (CDCl₃, 400 MHz): δ 7.38-7.28 (m, 5H), 5.14 (t, *J* = 7.2 Hz, 1H), 4.53 (s, 2H), 3.50 (d, *J* = 6.6 Hz, 2H), 2.10 (m, 2H), 1.72-1.59 (m, 8H).

¹³C NMR (CDCl₃, 100 MHz): δ 139.1, 132.3, 128.8, 128.0, 127.9, 124.4, 73.3, 70.4, 30.3, 26.1, 25.0, 18.1.

IR (thin film): 2965, 2927, 2855, 1453, 1102 cm⁻¹.

HRMS (ESI): Calcd for C₁₄H₂₀NaO (M+Na)⁺: 227.1406. Found: 227.1407.

***N,N*-Diethyl 8-methyl-8-nonenamide (Table 1.6, entry 5).** 2-Methyl-1-propenylmagnesium bromide (0.5 M in THF; 1.6 mL, 0.80 mmol) and *N,N*-diethyl 6-bromohexanamide (123 mg, 0.50 mmol) were used. Solvent for chromatography: pentane/EtOAc 6:1. Colorless oil (Procedure C: 91 mg, 81%; Procedure D: 81 mg, 72%). ¹H NMR (CDCl₃, 400 MHz): δ 5.11 (t, *J* = 7.1 Hz, 1H), 3.37 (q, *J* = 7.1 Hz, 2H), 3.30 (q, *J* = 7.1 Hz, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.97 (d, *J* = 6.6 Hz, 2H), 1.68-1.61 (m, 5H), 1.59 (s, 3H), 1.34 (t, *J* = 3.5 Hz, 4H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.11 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (CDCl₃, 100 MHz): δ 172.7, 131.7, 125.1, 42.3, 40.4, 33.6, 30.1, 29.6, 28.3, 26.1, 25.9, 18.1, 14.8, 13.5.

IR (thin film): 2932, 1644, 1430 cm⁻¹.

HRMS (ESI): Calcd for C₁₄H₂₇NNaO (M+Na)⁺: 248.1985. Found: 248.1986.

2-Methyl-1-dodecene [16435-49-7] (Table 1.6, entry 6). 1-Methylvinylmagnesium bromide (0.5 M in THF; 1.6 mL, 0.8 mmol) and *n*-decyl iodide (134 mg, 0.50 mmol) were used. Solvent for chromatography: pentane. Colorless oil (Procedure C: 82 mg,

98%; Procedure D: 78 mg, 93%).

^1H NMR (CDCl_3 , 400 MHz): δ 4.71 (s, 1H), 4.69 (s, 1H), 2.03 (t, $J = 7.4$ Hz, 2H), 1.74 (s, 3H), 1.48-1.40 (m, 2H), 1.30 (br s, 14H), 0.91 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 146.8, 109.9, 38.3, 32.3, 30.05 (two overlapping resonances), 29.98, 29.8 (two overlapping resonances), 28.1, 23.1, 22.8, 14.5.

Ethyl 6-(4-methoxyphenyl)hexanoate [59339-35-4] (Table 1.6, entry 11). *p*-Methoxyphenylmagnesium bromide (0.5 M in THF; 1.6 mL, 0.80 mmol) and ethyl 6-bromohexanoate (112 mg, 0.50 mmol) were used. Solvent for chromatography: pentane/EtOAc 100:3. Colorless oil (Procedure C: 92 mg, 74%; Procedure D: 86 mg, 69%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.13-7.10 (m, 2H), 6.87-6.83 (m, 2H), 4.14 (q, $J = 7.2$ Hz, 2H), 3.81 (s, 3H), 2.58 (t, $J = 7.6$ Hz, 2H), 2.31 (t, $J = 7.6$ Hz, 2H), 1.71-1.69 (m, 4H), 1.41-1.36 (m, 2H), 1.27 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 174.2, 158.1, 135.0, 129.7, 114.1, 60.6, 55.7, 35.2, 34.7, 31.8, 29.1, 25.3, 14.7.

IR (thin film): 2934, 2857, 1733, 1513, 1246 cm^{-1} .

HRMS (ESI): Calcd for $\text{C}_{15}\text{H}_{22}\text{NaO}_3$ ($\text{M}+\text{Na}$) $^+$: 273.1461. Found: 273.1464.

Procedure E (Table 1.7). Anhydrous ZnBr_2 (180 mg, 0.80 mmol) and LiH (15 mg, 18 mmol) were added to a Schlenk tube in a glove box. The flask was removed from the glove box and placed under an argon atmosphere. THF (1 mL) was added, and the resulting gray suspension was vigorously stirred at r.t. for 3 h. The flask was then chilled to -78 $^\circ\text{C}$, and the alkyne (freshly purged with argon, 0.80 mmol) and Cp_2TiCl_2 (20 mg, 0.080 mmol) were added. The reaction mixture was allowed to warm to r.t. over 1 h, during which time the stirred suspension turned from orange to yellow to brown/black. The reaction mixture was vigorously stirred for 2 additional hours, and then the flask was taken into a glove box, and the dark suspension was passed through an Acrodisc (CR PTFE 0.45 μm membrane) with the aid of THF (0.6 mL). The resulting dark filtrate was treated with dry NMP (0.8 mL), PCyp_3 (9.6 mg, 0.040 mmol) or $[\text{HPCyp}_3]\text{BF}_4$ (13 mg, 0.040 mmol), NMI (50 μL , 0.60 mmol), the alkyl halide/tosylate (0.50 mmol), and then $\text{Pd}_2(\text{dba})_3$ (9.2 mg, 0.010 mmol). The vessel was sealed, removed from the glove box,

and heated in an 80 °C oil bath with stirring for 12 h. Pentane (2 mL) was then added, and the dark reaction mixture was passed through a short pad of silica gel (to remove inorganic salts and NMP), the filtrate was concentrated, and the residue was purified by flash chromatography.

(*E*)-4-Methyl-4-hexenylbenzene (Table 1.7, entry 1). 2-Butyne (43 mg, 0.80 mmol) and 1-bromo-3-phenylpropane (102 mg, 0.50 mmol) were used. Solvent for chromatography: pentane. Colorless oil (PCyp₃: 55 mg, 63%; [HPCyp₃]BF₄: 42 mg, 48%).

¹H NMR (CDCl₃, 400 MHz): δ 7.35-7.32 (m, 2H), 7.25-7.21 (m, 3H), 5.31-5.26 (qd, *J* = 6.6, 1.2 Hz, 1H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.09 (t, *J* = 7.8 Hz, 2H), 1.82-1.74 (m, 2H), 1.66-1.63 (m, 6H).

¹³C NMR (CDCl₃, 100 MHz): δ 143.2, 136.0, 128.9, 128.7, 126.0, 119.0, 39.7, 36.0, 30.2, 16.0, 13.8.

IR (thin film): 2934, 2859, 1496, 1453 cm⁻¹.

HRMS (EI): Calcd for C₁₃H₁₈ (M)⁺: 174.1403. Found: 174.1399.

(*E*)-4-Methyl-4-hexenyl phenyl ether (Table 1.7, entry 2). 2-Butyne (43 mg, 0.80 mmol) and 3-bromopropyl phenyl ether (113 mg, 0.50 mmol) were used. The crude mixture was passed through a short silica-gel column (pentane/Et₂O 100:2). The yellow fractions were combined and concentrated under partial vacuum to give a yellow oil, which was treated with dry MeOH (2 mL). The resulting mixture was allowed to stand overnight, and then the small amount of phosphine-containing yellow solid was removed by filtration through a short plug of Celite in a Pasteur pipet (MeOH washings). The filtrate was concentrated, and the residue was purified by flash chromatography (pentane/Et₂O 200:1). Yellow oil (PCyp₃: 50 mg, 53%; [HPCyp₃]BF₄: 49 mg, 51%).

¹H NMR (CDCl₃, 400 MHz): δ 7.33-7.29 (m, 2H), 6.98-6.92 (m, 3H), 5.28 (qd, *J* = 6.7, 1.3 Hz, 1H), 3.96 (t, *J* = 6.6 Hz, 2H), 2.18 (t, *J* = 6.6 Hz, 2H), 1.95-1.88 (m, 2H), 1.66 (s, 3H), 1.61 (dd, *J* = 6.7, 1.0 Hz, 3H).

¹³C NMR (CDCl₃, 100 MHz): δ 159.5, 135.2, 129.8, 120.9, 119.4, 114.9, 67.8, 36.3, 27.9, 16.0, 13.8.

IR (thin film): 2921, 1601, 1498, 1246 cm⁻¹.

HRMS (EI): Calcd for C₁₃H₁₈O (M)⁺: 190.1352. Found: 190.1355.

(Z)-5-Cyclohexyl-3-phenyl-2-pentene (Table 1.7, entry 3). 1-Phenyl-1-propyne (93 mg, 0.80 mmol) and 1-bromo-2-cyclohexylethane (98 mg, 0.50 mmol) were used. Solvent for chromatography: pentane. Colorless oil (PCyp₃: 70 mg, 61%, regioselectivity 94:6; [HPCyp₃]BF₄: 72 mg, 63%, regioselectivity 94:6).

¹H NMR (CDCl₃, 400 MHz): δ 7.39-7.35 (m, 2H), 7.29-7.25 (m, 1H), 7.20-7.18 (m, 2H), 5.57 (q, *J* = 6.8 Hz, 1H), 2.38 (t, *J* = 7.0 Hz, 2H), 1.72-1.65 (m, 5H), 1.59 (d, *J* = 6.8 Hz, 3H), 1.25-1.19 (m, 6H), 0.91-0.83 (m, 2H).

¹³C NMR (CDCl₃, 100 MHz): δ 142.7, 141.7, 128.9, 128.4, 126.6, 121.0, 37.8, 37.0, 36.5, 33.7, 27.2, 26.8, 15.1.

IR (thin film): 2922, 2851, 1494, 1448 cm⁻¹.

HRMS (EI): Calcd for C₁₇H₂₄ (M)⁺: 228.1873. Found: 228.1882.

2-[(E)-4-Methyl-4-hexenyl]-1H-isoindole-1,3(2H)-dione (Table 1.7, entry 4). 2-Butyne (43 mg, 0.80 mmol) and 2-(3-iodopropyl)-1H-isoindole-1,3(2H)-dione (158 mg, 0.50 mmol) were used. Solvent for chromatography: pentane/EtOAc 100:4. Yellow solid (PCyp₃: 84 mg, 69%; [HPCyp₃]BF₄: 87 mg, 72%).

¹H NMR (CDCl₃, 400 MHz): δ 7.90-7.85 (m, 2H), 7.77-7.72 (m, 2H), 5.27 (qd, *J* = 6.7, 1.2 Hz, 1H), 3.69 (t, *J* = 7.4 Hz, 2H), 2.09 (t, *J* = 7.6 Hz, 2H), 1.82 (dd, *J* = 7.6, 7.4 Hz, 2H), 1.64 (s, 3H), 1.58 (dd, *J* = 6.7, 0.9 Hz, 3H).

¹³C NMR (CDCl₃, 100 MHz): δ 168.9, 134.8, 134.3, 132.6, 123.6, 119.6, 38.3, 37.3, 27.0, 15.9, 13.8.

IR (KBr pellet): 2940, 2880, 1702, 1356, 1040 cm⁻¹.

HRMS (ESI): Calcd for C₁₅H₁₇NNaO₂ (M+Na)⁺: 266.1151. Found: 266.1156.

(Z)-12-Phenyl-1,12-tetradecadiene (Table 1.7, entry 5). 1-Phenyl-1-propyne (93 mg, 0.80 mmol) and 10-undecen-1-ol *p*-toluenesulfonate (155 mg, 0.50 mmol) were used. Solvent for chromatography: pentane. Colorless oil (PCyp₃: 80 mg, 59%, regioselectivity 95:5; [HPCyp₃]BF₄: 84 mg, 62%, regioselectivity 94:6).

¹H NMR (CDCl₃, 400 MHz): δ 7.39-7.35 (m, 2H), 7.29-7.25 (m, 1H), 7.20-7.18 (m, 2H), 5.90-5.80 (m, 1H), 5.56 (q, *J* = 6.9 Hz, 1H), 5.05-4.95 (m, 2H), 2.36 (t, *J* = 7.0 Hz,

2H), 2.24 (m, 2H), 1.59 (d, $J = 6.8$ Hz, 3H), 1.42-1.27 (m, 14H).

^{13}C NMR (CDCl_3 , 100 MHz): δ 142.4, 141.6, 139.7, 128.9, 128.4, 126.7, 121.3, 114.5, 39.6, 34.3, 30.0, 29.90, 29.86, 29.63, 29.56, 29.4, 28.6, 15.1.

IR (thin film): 2926, 2855, 1641, 1441 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{20}\text{H}_{30}$ (M) $^+$: 270.2342. Found: 270.2355.

Procedure F for Table 1.8. In a glove box, $\text{Pd}_2(\text{dba})_3$ (4.6 mg, 0.0050 mmol), PCyp_3 (5.0 μL , 4.8 mg, 0.020 mmol), and dry NMP (0.4 mL) were added to a vial. The reaction mixture was stirred for 3 min at r.t., and then the resulting yellow-green solution was treated with the phenyl- or *n*-butylzinc bromide (0.5 M in THF; 0.80 mL, 0.40 mmol), NMI (25 μL , 0.30 mmol), *n*-hexadecane (GC internal standard; 29 μL , 0.10 mmol), and the aryl halides/sulfonates (0.25 mmol). The vial was closed with a Teflon-coated screw cap, sealed with electrical tape, and taken out of the glove box. The reaction mixture was stirred in an 80 °C oil bath for 14 h and an aliquot was passed through silica gel and analyzed by gas chromatography.

Chapter 2.

Nickel-Catalyzed Negishi Cross-Coupling Reactions of Secondary Alkyl Electrophiles

2.1. Background

In Chapter 1, a Pd/PCyp₃ catalyst was developed for Negishi couplings of unactivated, primary alkyl electrophiles. Clearly, the full potential of these metal-catalyzed cross-coupling processes will only be realized when secondary electrophiles can also be employed. However, when the latter class of substrates were tested using the palladium catalyst, complex mixtures resulted without any desired products. With these more hindered electrophiles, the oxidative addition becomes even slower, and the problem of the β -hydride elimination is probably exacerbated (Figure 2.1).⁶

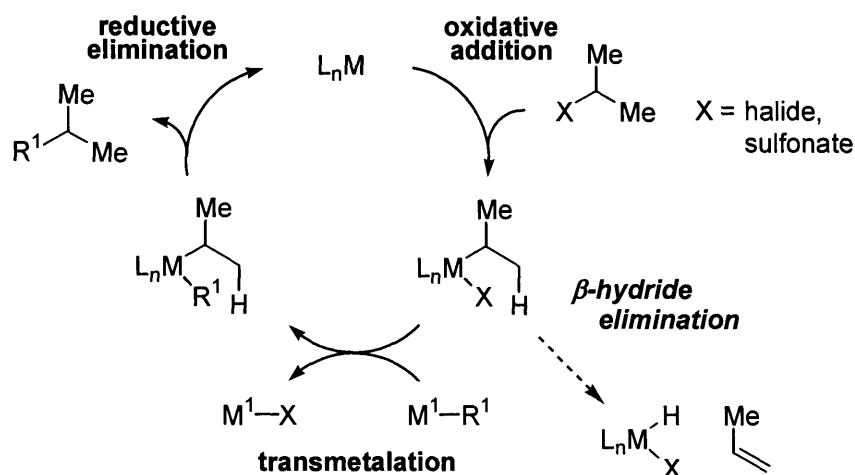


Figure 2.1. Difficulties in metal-catalyzed cross-coupling of secondary alkyl halides and sulfonates.

A careful survey of the literature, however, provides some optimism that nickel catalysts might be suitable for this transformation. It is well known that nickel(0) complexes are more reactive in oxidative addition than their palladium counterparts. As an illustration, $Ni(PPh_3)_4$ reacts with phenyl chloride at room temperature to produce *trans*- $(PPh_3)_2NiPhCl$,⁷¹ whereas the analogous reaction with $Pd(PPh_3)_4$ does not occur even at 135 °C.⁷² The first Kumada reactions actually used nickel catalysts and employed

⁷¹ Hidai, M.; Kashiwagi, T.; Ikeuchi, T.; Uchida, Y. *J. Organomet. Chem.* **1971**, *30*, 279–282.

⁷² Fitton, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287–291.

aryl or vinyl chlorides as their electrophilic components,^{2,73} while, for these substrates, generally useful, palladium-based methods were not existent until 1998 with the introduction of bulky, electron-rich phosphines and N-heterocyclic carbenes.⁷⁴ In fact, activation of aryl chlorides by nickel/bipy complexes in 1970 is considered as one of milestones in the genesis of the cross-coupling chemistry.⁷⁵

Furthermore, alkylnickel complexes are intrinsically less prone to undergo the β -hydride elimination. Through computational studies of $(\text{PH}_3)\text{PdEtH}$ and an analogous nickel model,⁷⁶ Morokuma suggested that the Ni(II) vacant d-orbitals have a higher energy level than their palladium counterparts, which will result in a weaker agostic interaction with β hydrogens on the ethyl group.⁷⁷ Such an agostic interaction is considered a prelude to the undesired β -elimination process.

The elimination process requires a vacant coordination site, and this problem, in principle, can be minimized by coordinative saturation of the nickel centers. Indeed, Grubbs and coworkers have examined thermolysis of some bis(phosphine)nickel metallocyclopentanes and concluded that the fate of these products was directly linked to the number of ligands on nickel (Eq 2.1 and 2.2). While direct reductive elimination to form carbon-carbon bonds was favored from bis(phosphine)nickel complexes, mono-ligated species with a free coordination site preferentially gave 1-butene, probably through a sequence of β -hydride elimination and subsequent reductive elimination. They have also noted that direct reductive elimination can be accelerated by the addition of oxidants or electron-deficient olefins.⁷⁸

⁷³ Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc. Chem. Comm.* **1972**, 144.

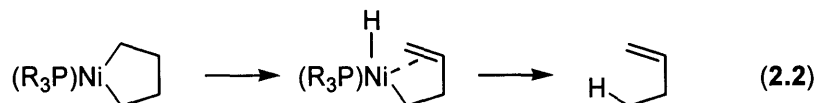
⁷⁴ For a review on palladium-catalyzed cross-coupling reactions of aryl chlorides, see: (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211. (b) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047–1062.

⁷⁵ Uchino, M.; Yamamoto, A.; Ikeda, S. *J. Organomet. Chem.* **1970**, *24*, C63.

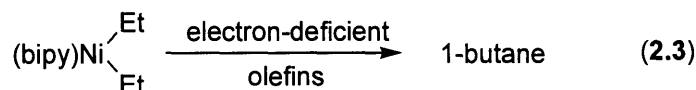
⁷⁶ Reductive elimination from $\text{ArNiMe}(\text{PEt}_3)_2$ complexed exhibited an inverse phosphine dependence of the rate, suggesting that this process proceeded via mono-ligated, three-coordinate intermediates: Smith, G.; Kochi, J. K. *J. Organomet. Chem.* **1980**, *198*, 199–214.

⁷⁷ Koga, N.; Obara, S.; Kitaura, K.; Morokuma, K. *J. Am. Chem. Soc.* **1985**, *107*, 7109–7116.

⁷⁸ Grubbs, R. H.; Miyashita, A.; Liu, M.; Burk, P. *J. Am. Chem. Soc.* **1978**, *100*, 2418–2425.



Despite these favorable features, one drawback with the nickel catalysis seems to be slow reductive elimination. As described in Chapter 1, for Knochel's nickel-catalyzed Negishi reaction of primary alkyl halides, π -acceptor additives were required to accelerate the catalysis.²³⁻²⁸ In fact, the use of these additives was inspired by Yamamoto's earlier findings that electron-deficient olefins accelerated reductive elimination from (bipy)dialkylnickel complexes (Eq 2.3).⁷⁹ Furthermore, Yamamoto et al. has shown that the same reductive elimination process could be accelerated by unactivated alkyl halides with concomitant production of (bipy)NiRX species.⁸⁰



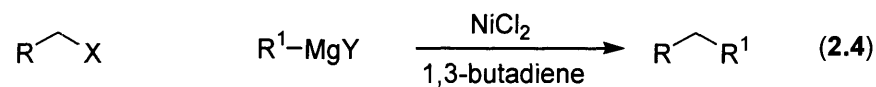
Recently, Kambe et al. published nickel-catalyzed cross-couplings of alkyl- and aryl-Grignard reagents with alkyl bromides, chlorides, tosylates, and even fluorides (Eq 2.4). The substrates were largely unfunctionalized because of the high reactivity of the Grignard reagents. Their ligands of choice were 1,3-butadienes and to account for the use of these rather uncommon ligands, cyclodimerization to generate bis- π -allylnickel intermediates have been proposed.⁸¹ This notion has been substantiated by their recent findings that tetraene additives were even more effective and successfully enabled diorganozinc compounds to be used in place of the Grignard reagents (Eq 2.5).⁸²

⁷⁹ Yamamoto, T.; Yamamoto, A.; Ikeda, S. *J. Am. Chem. Soc.* **1971**, *93*, 3350–3358.

⁸⁰ Yamamoto, T.; Kohara, T.; Osakada, K.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2147–2153.

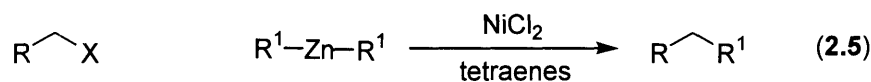
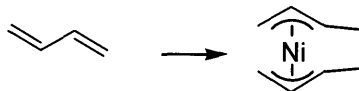
⁸¹ (a) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222–4223. (b) Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646–5647.

⁸² Terao, J.; Todo, H.; Watanabe, H.; Ikumi, A.; Kambe, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6180–6182.



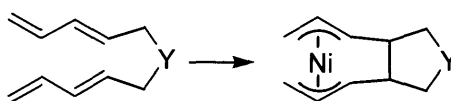
X = Br, Cl
OTs, F

R¹ = alkyl, aryl



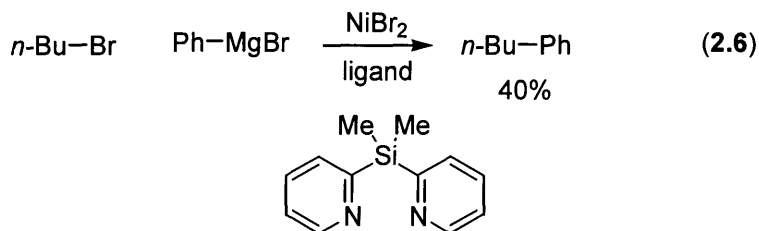
X = Br, OTs, F

R¹ = alkyl, aryl



Y = NBn
C(CO₂Me)₂

In fact, for the nickel-promoted Kumada couplings of primary alkyl bromides, there was an earlier, singular example using a bis(2-pyridyl)silane as the ligand (Eq 2.6).⁸³

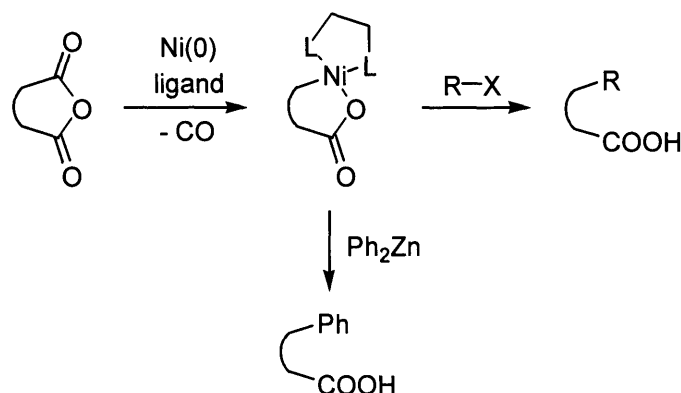


In addition, Ni(0) complexes with bipy-type ligands have been shown to insert into cyclic anhydrides, and, after decarbonylation, the resulting alkylnickel species can react with alkyl halides (even secondary ones) in a stoichiometric sense (Scheme 2.1).⁸⁴ Recently, Rovis has shown that these nickelacycle intermediates (some containing

⁸³ Wright, M. E.; Jin, M.-J. *J. Organomet. Chem.* **1990**, *387*, 373–379.

⁸⁴ (a) Schönecker, B.; Walther, D.; Fischer, R.; Nestler, B.; Bräunlich, G.; Eibisch, H.; Droscher, P. *Tetrahedron Lett.* **1990**, *31*, 1257–1260. (b) Fischer, R.; Walther, D.; Bräunlich, G.; Undeutsch, B.; Ludwig, W.; Bandmann, H. *J. Organomet. Chem.* **1992**, *427*, 395–407. (c) Castaño, A. M.; Echavarren, A. M. *Organometallics* **1994**, *13*, 2262–2268.

secondary alkyl-nickel bonds) can undergo stoichiometric couplings with diphenylzinc, too.⁸⁵



Scheme 2.1. Chemistry of nickelacycles for carbon-carbon bond formation.

Interestingly, back in 1967, in one of the earliest applications of organonickel complexes in organic synthesis, Corey et al. documented that π -allylnickel bromide can couple with various organic halides, including one example of cyclohexyl iodide.^{86,87} These precedents hint that nickel-based catalysts may be viable for cross-couplings of secondary alkyl electrophiles.

2.2. Results and Discussion

At the onset of our investigation, to our delight, we were presented with a long sought-after gift: an expeditious procedure for the preparation of alkylzinc bromides from common zinc powder.⁸⁸ Huo reported that in polar solvents this proceeded smoothly (Eq

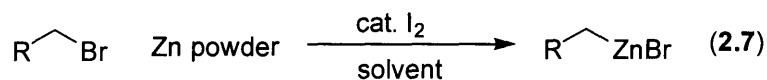
⁸⁵ O'Brien, E. M.; Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2003**, *125*, 10498–10499.

⁸⁶ Corey, E. J.; Semmelhack, M. F. *J. Am. Chem. Soc.* **1967**, *89*, 2755–2758.

⁸⁷ For reviews, see: (a) Billington, D. C. *Chem. Soc. Rev.* **1985**, *14*, 93–120. (b) Semmelhack, M. F. *Org. React.* **1972**, *19*, 115–198.

⁸⁸ During our studies of palladium-catalyzed Negishi couplings in Chapter 1, attempts were made to synthesize alkylzinc bromides from commercial Rieke zinc[®]. Even with a large excess, the zinc suspension in THF from Aldrich did not lead to high conversions of primary alkyl bromides. We have also made several attempts to prepare Rieke zinc[®] from Li/naphthalene according to the procedure described by Rieke et al., which led to no improvement: Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445–1453.

2.7). The key was the addition of a catalytic amount of iodine, which was claimed to have a dual role of both activating the zinc surface and converting alkyl bromides to more reactive iodides via halogen exchange. Thanks to the mild preparatory conditions, multiple polar functional groups now can be present in the organozinc reagents.⁸⁹ In our hands, quantitative conversions are usually observed by no-D NMR.⁹⁰ This method thus represents a significant advancement in the preparation of functionalized organozinc reagents.²⁹



solvent: DMF, DMA, NMP
DMPU, DMSO

⁸⁹ Huo, S. *Org. Lett.* **2003**, *5*, 423–425.

⁹⁰ Hoye, T. R.; Eklov, B. M.; Ryba, T. D.; Voloshin, M.; Yao, L. J. *Org. Lett.* **2004**, *6*, 953–956.

2.2.1. Achiral Cross-Couplings

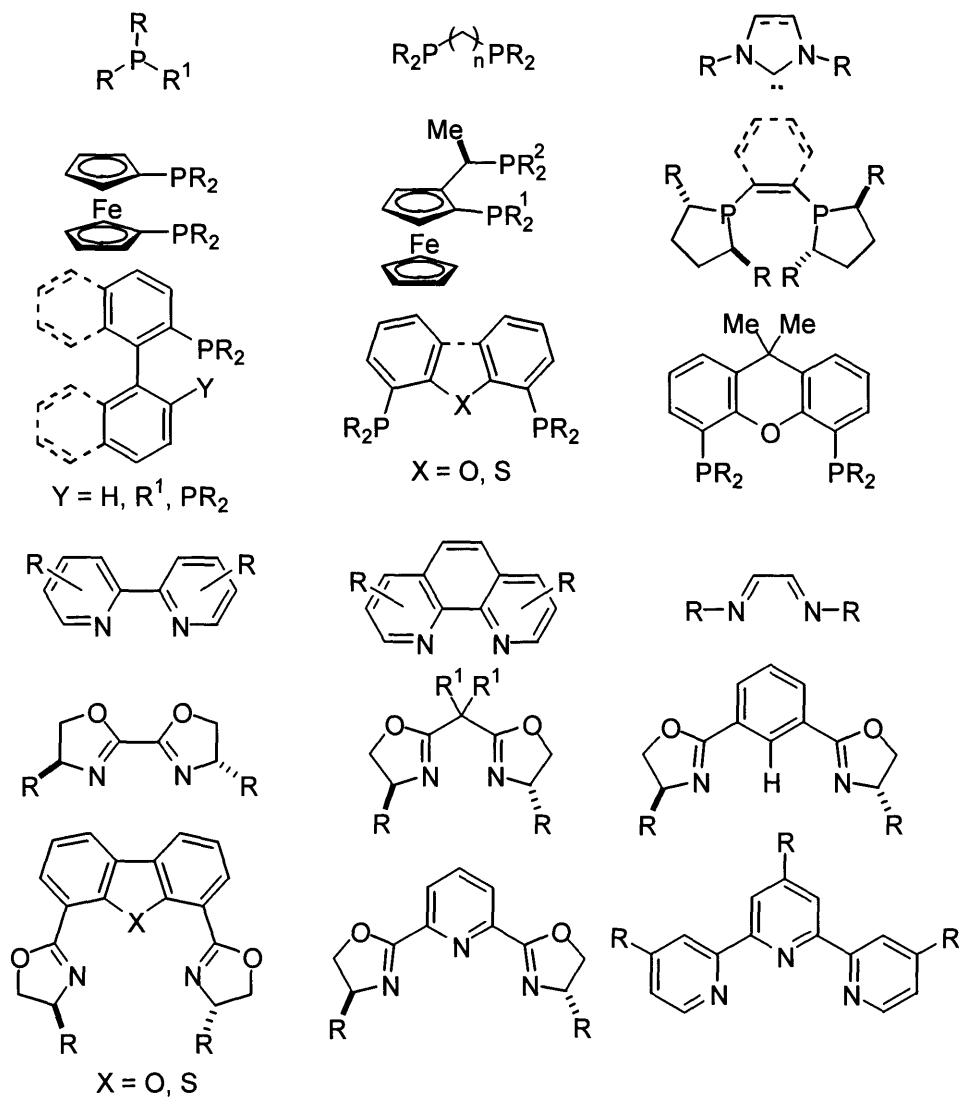
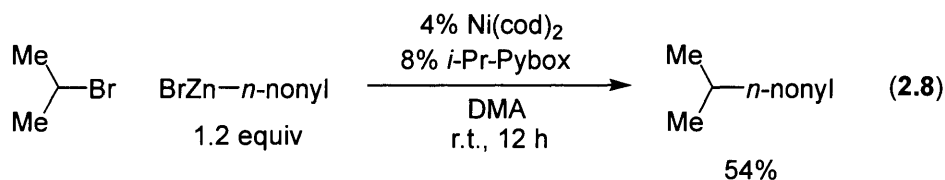


Figure 2.2. Ligands tested for Negishi cross-couplings.

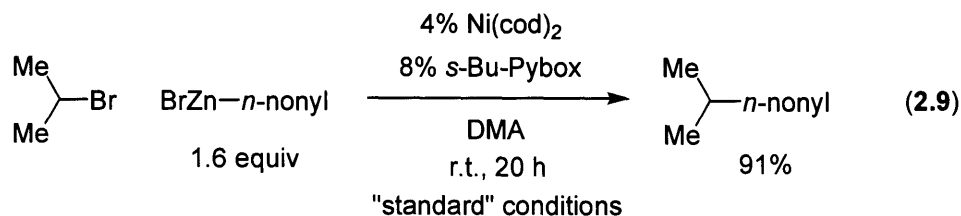
In the course of our methods development for cross-coupling reactions, we have accumulated about 150 ligands. Some of the structural motifs are depicted in Figure 2.2. With these ligands in hand, we carried out an extensive screening, targeting unactivated secondary electrophiles. Our model reaction consisted of isopropyl bromide and *n*-nonylzinc bromide in DMA. Within a month, we were gratified to find that a combination of Ni(cod)₂/*i*-Pr-Pybox⁹¹ can effect this coupling (Eq 2.8)!



Further fine-tuning of the ligands pointed to *s*-Bu-Pybox as the optimal. At room temperature, an excellent yield of the coupling product (91%) was obtained in the presence of 4% Ni(cod)₂/8% *s*-Bu-Pybox (Eq 2.9). Of equal importance, essentially no secondary-to-primary alkyl isomerization was detected. Table 2.1 illustrates the impact of a variety of reaction parameters on the course of the cross-coupling process. In the absence of Ni(cod)₂ (entry 2) or in the presence of other metal complexes (entries 3–4), the coupling was either ineffective or less effective than with Ni(cod)₂. Furthermore, a reduction in the quantity of *s*-Bu-Pybox led to a decrease in the efficiency of carbon–carbon bond formation (entries 5 and 6). The Negishi cross-coupling proceeded in somewhat diminished, but still useful, yields when less catalyst (entry 7) or less alkylzinc reagent (entry 8) was employed. Finally, a range of other types of ligands, including those that had proved useful in palladium-catalyzed couplings of *primary* alkyl electrophiles, were found to be ineffective (entries 9–15). We speculate that the unprecedented reactivity of the Pybox ligand may be attributable to its tridentate structure, which can occupy vacant coordination sites and thereby minimize β-hydride elimination.

⁹¹ For reviews of applications of oxazoline-based chiral ligands, including Pybox, in asymmetric catalysis, see: (a) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151–4202. (b) Nishiyama, H. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: Greenwich, CT, 1997; Volume 2, pp 153–188.

Table 2.1. Impact of Reaction Parameters on the Efficiency of a Negishi Cross-Coupling of a Secondary Alkyl Bromide



entry	change from the standard conditions	yield (%) ^a
1	none	91
2	no Ni(cod) ₂	0
3	NiBr ₂	44
4	Pd(OAc) ₂ or Pd ₂ (dba) ₃	0
5	no <i>s</i> -Bu-Pybox	0
6	4% <i>s</i> -Bu-Pybox	62
7	2% Ni(cod) ₂ , 4% <i>s</i> -Bu-Pybox	80
8	1.2 equiv BrZn- <i>n</i> -nonyl	70
9	PPh ₃	0
10	PCy ₃	0
11	P(<i>t</i> -Bu) ₃	0
12	P(<i>t</i> -Bu) ₂ Me	0
13	PCy(1-pyrrolidinyl) ₂	0
14	Cy ₂ CH ₂ CH ₂ Cy ₂	0
15	1,3-bis(1-adamantyl)imidazol-2-ylidene	1

^a Yield according to GC, versus a calibrated internal standard (average of two runs).

In Table 2.1, *s*-Bu-Pybox was shown to be uniquely active among several classes of ligands. Even within the Pybox class, the catalytic efficacy is profoundly influenced by the steric demand of the side chains. When the results are presented according to the steric demand of the substituents, a bell-shaped activity profile was unveiled (Figure 2.3). An increase in the size led to more efficient catalysts and the maximal activity was reached with *s*-Bu-Pybox. Then a further increase (*s*-Bu→*t*-Bu) resulted in an abrupt loss of catalytic reactivity. The bulky side chains on the ligands may facilitate reductive elimination by forcing the two organic groups closer to each other. Conversely, the bigger *t*-butyl groups probably shield the nickel center from the reactants. We have also perturbed the electronic property of *i*-Pr-Pybox and found *p*-chlorination offered a

slightly better catalyst,⁹² whereas a *p*-dimethylamino derivative had greatly diminished reactivity.⁹³ This seems to be consistent with the notion that reductive elimination usually contributes to the overall reaction rate in nickel catalysis and that it is impeded by an electron-rich metal center.

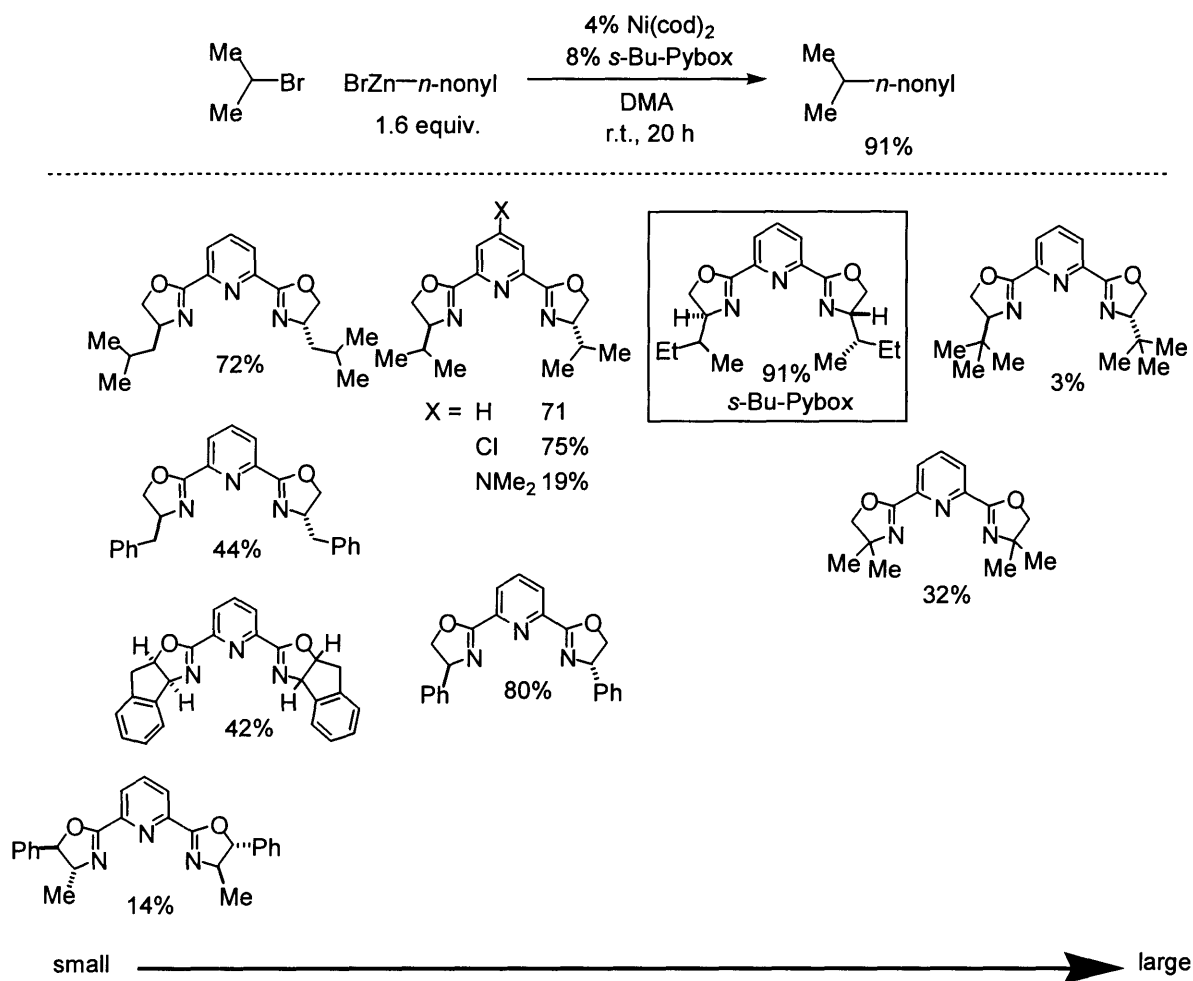


Figure 2.3. Relationship between the efficacy of Pybox ligands and the steric demand of their side chains.

The standard procedure (4% Ni(cod)₂/8% *s*-Bu-Pybox) can be applied to room-temperature Negishi reactions of not only acyclic (Table 2.2, entry 1), but also cyclic,

⁹² We have not determined whether the chlorinated ligand was alkylated in the course of catalysis.

⁹³ The *para*-substituted Pybox ligands were prepared according to a procedure: Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 4306–4309.

secondary alkyl bromides (entries 1–3). In addition to bromides, secondary alkyl iodides can be cross-coupled with this catalyst (entries 4–6). As illustrated in Table 2.1, the reaction conditions were compatible with functional groups such as sulfonamides, ethers, acetals, esters, and amides.

Table 2.2. Negishi Cross-Couplings of Secondary Alkyl Bromides and Iodides with Alkylzinc Reagents Under Standard Conditions

entry	R _{alkyl} -X	YZn-R ¹ _{alkyl}	yield (%)
1			66
2			62
3			68
4			62
5			78
6			88

All yields are isolated yields (average of two runs).

Ni(cod)₂/*s*-Bu-Pybox can also be employed as a catalyst for Negishi cross-couplings of *primary* alkyl halides (Table 2.3), reacting even with very hindered neopentyl iodide, which has been unsuccessful in our palladium catalysis (entry 3).⁹⁴ These examples

⁹⁴ Neopentyl iodides (without β hydrogens) have been effectively cross-coupled with diarylzinc reagents in the presence of a nickel catalyst: Park, K.; Yuan, K.; Scott, W. J. *J. Org. Chem.* **1993**, *58*, 4866–4870.

provide additional evidence for the high functional group tolerance of the method (e.g., imides and ketones).

Table 2.3. Negishi Cross-Couplings of Primary Alkyl Bromides and Iodides with Alkylzinc Reagents under Standard Conditions

entry	R _{alkyl} -X	BrZn-R ¹ _{alkyl}	yield (%)
1		BrZn-CH ₂ CH ₂ CH ₂ Ph	65
2		BrZn-CH ₂ CH ₂ CH ₂ CH ₂ OCH ₂ CH ₂ O	74
3		BrZn-CH ₂ CH ₂ CH ₂ Ph	73

All yields are isolated yields (average of two runs).

With respect to the scope of the reaction, we have also studied many other electrophiles (Figure 2.4):⁹⁵ (a) alkyl chlorides, alkyl tosylates, and tertiary alkyl bromides/iodides were not suitable substrates under the standard conditions; (b) three- and four-membered cyclic bromides were problematic; (c) 2,2-dihalopropanes were inert; (d) We have also defined the boundaries for sterically demanding halides, and in general, the iodides gave better yields than the bromides; (e) notably, some functionalized substrates were unsuccessful, including 4-bromocyclohexanone **2.1**, 4-bromopiperidine **2.2**, 2-bromotetrahydropyran **2.3**, 3-bromophthalide **2.4**, and a serine-derived iodide **1.2**; (f) the standard coupling conditions can also be applied to Negishi reactions of some activated alkyl halides. For example, *n*-nonylzinc bromide coupled with allyl bromide, benzyl bromide, and benzyl chloride in 60%, 89%, and 100% yields, respectively; on the other hand, α -bromo esters failed; (g) under our standard conditions, aryl bromides and iodides were suitable electrophiles, but not chlorides and tosylates.

⁹⁵ Some other examples will be presented later in the discussion of the reaction mechanism.

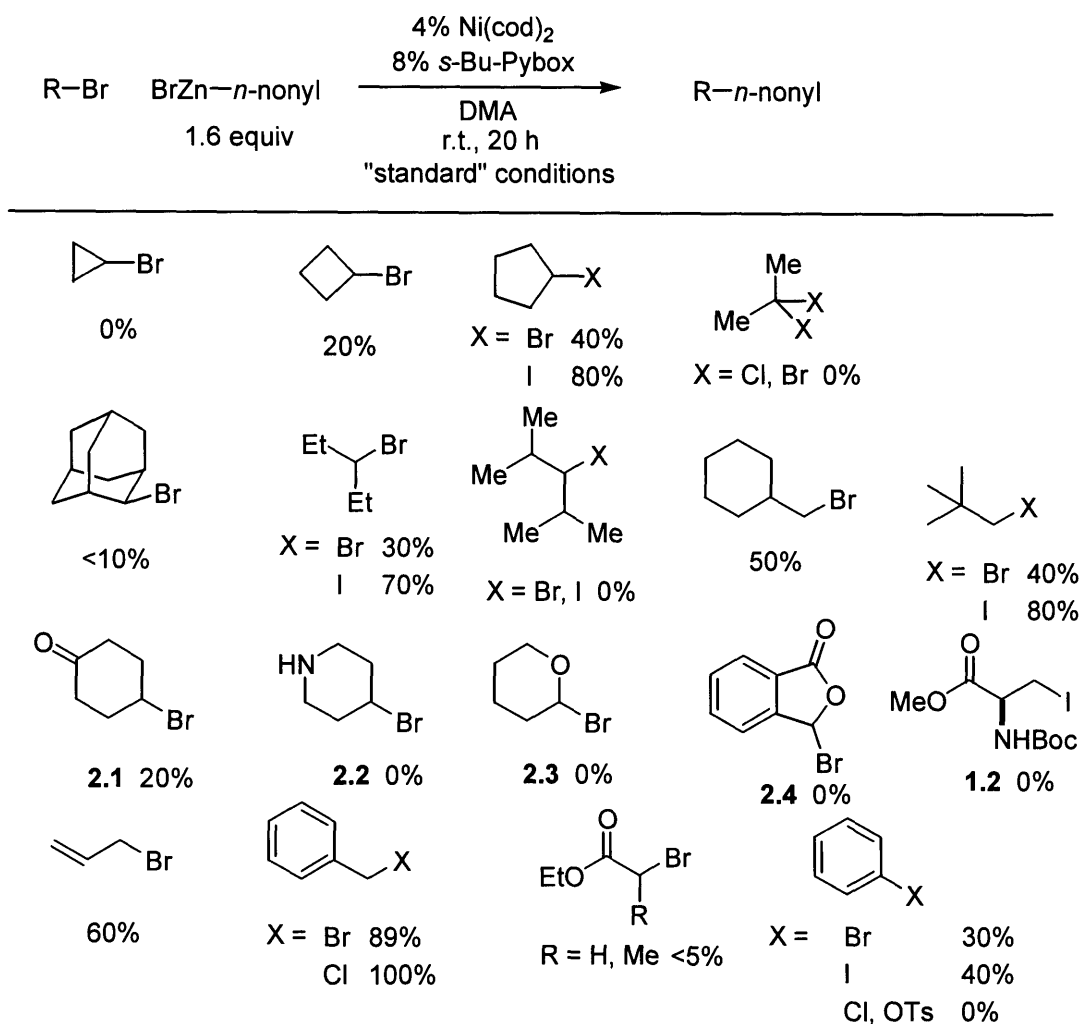


Figure 2.4. Scope of alkyl halides in nickel-catalyzed Negishi reactions.

We have also made some noteworthy observations with some organozinc reagents (Figure 2.5): (a) some functional groups, such as indole **2.5**, phthalamide **2.6**, and ester **1.7**⁸⁹ proximal to the coupling centers suppressed the catalysis; (b) with respect to steric concerns, β -branched alkylzinc reagents gave good yields; (c) primary alkylzinc halides, prepared from alkyl chlorides in the presence of LiBr or LiI, were not reactive under the standard conditions; (d) the use of secondary organozinc reagents led to <30% yield of products with primary alkyl halides (Br or I) and <10% with secondary halides; (e) aryl-, alkenyl-, allyl-, and benzylzinc species, and Reformatsky reagents were not suitable

coupling partners; (f) alkyl-, vinyl-, and aryl-Grignard reagents afforded no cross-coupling products.

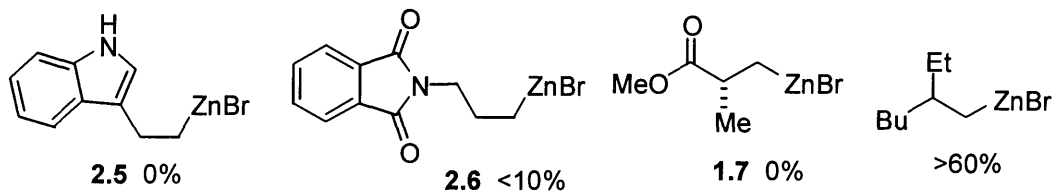


Figure 2.5. Unsuccessful alkylzinc reagents in nickel-catalyzed Negishi reactions.

2.2.2. Asymmetric Cross-Couplings

Since optically pure Pybox ligands were employed in the Negishi reactions, it is conceivable to test asymmetric couplings⁹⁶ with racemic secondary alkyl halides. In this regard, we have surveyed some alkyl bromides (Figure 2.6) under the standard conditions with either *i*-Pr- or *s*-Bu-Pybox and found measurable, but very low, enantioinduction (<10% ee). Although most substrates gave good chemical yields, there were a few exceptions. Some amides underwent complete elimination, whereas the presence of basic nitrogen functionalities suppressed the cross-couplings probably owing to their coordination to the nickel center.

⁹⁶ For examples of other types of metal-catalyzed asymmetric cross-coupling processes, see: (a) Hayashi, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 25. (b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051–12052. (c) Shimada, T.; Cho, Y.-H.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 13396–13397. (d) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261–1268. (e) Willis, M. C.; Powell, L. H. W.; Claverie, C. K.; Watson, S. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1249–1251.

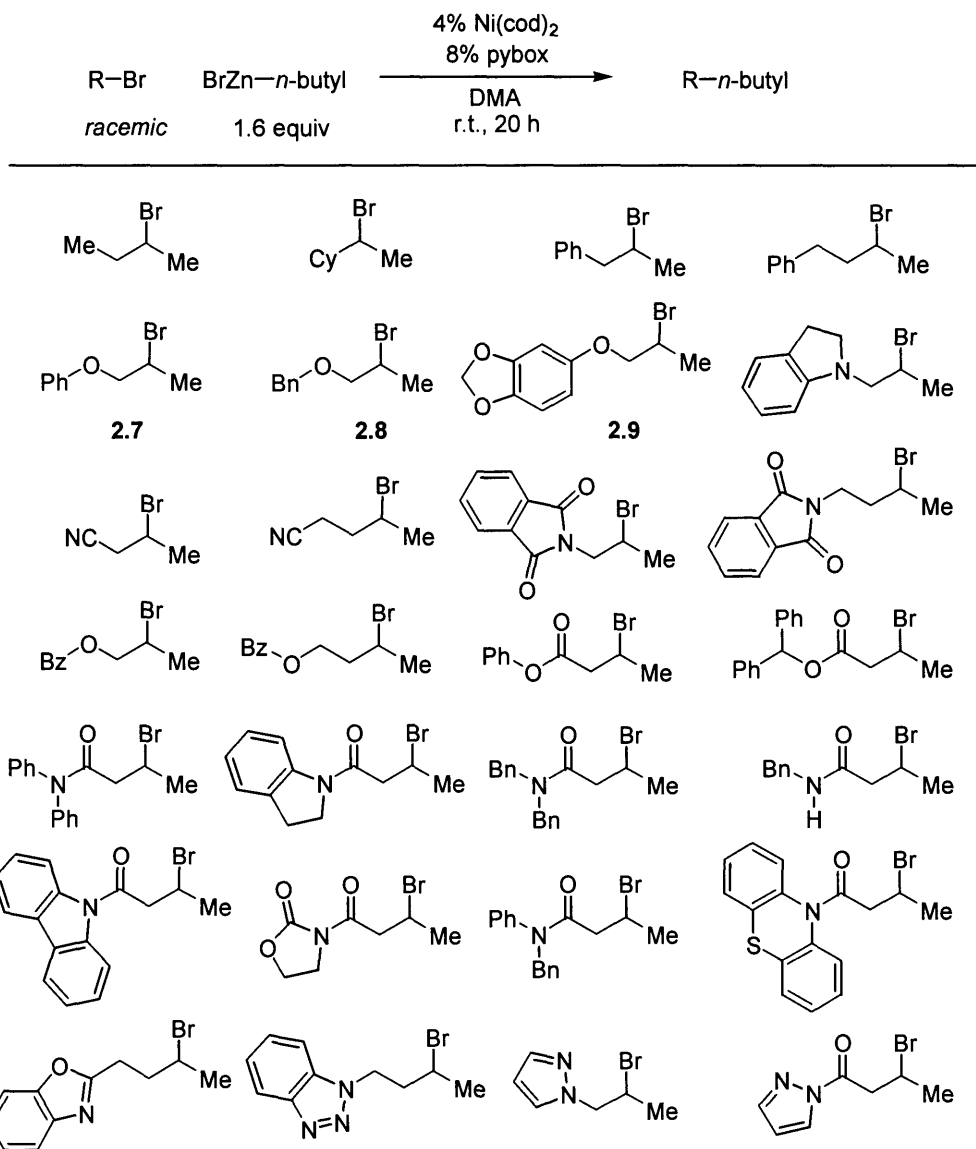


Figure 2.6. Racemic secondary alkyl bromides tested in asymmetric Negishi reactions.

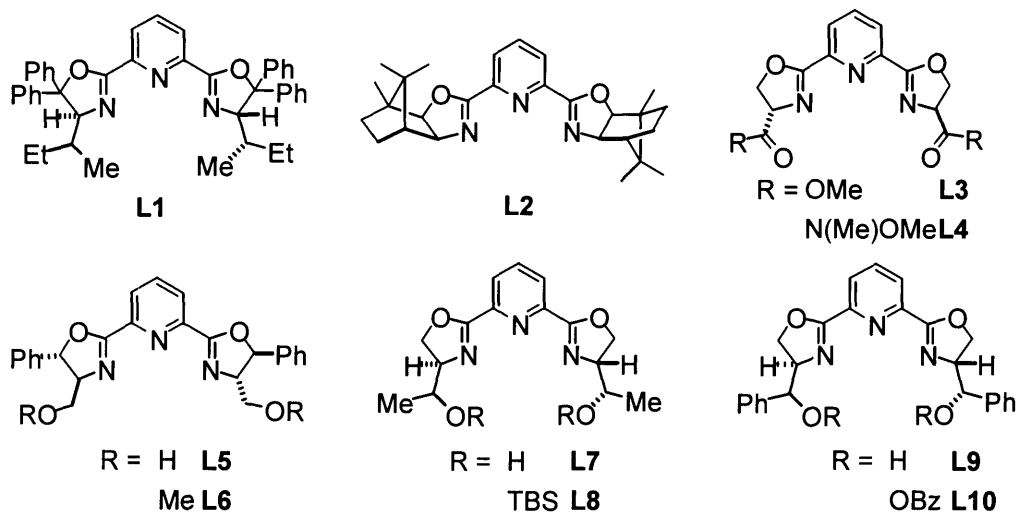
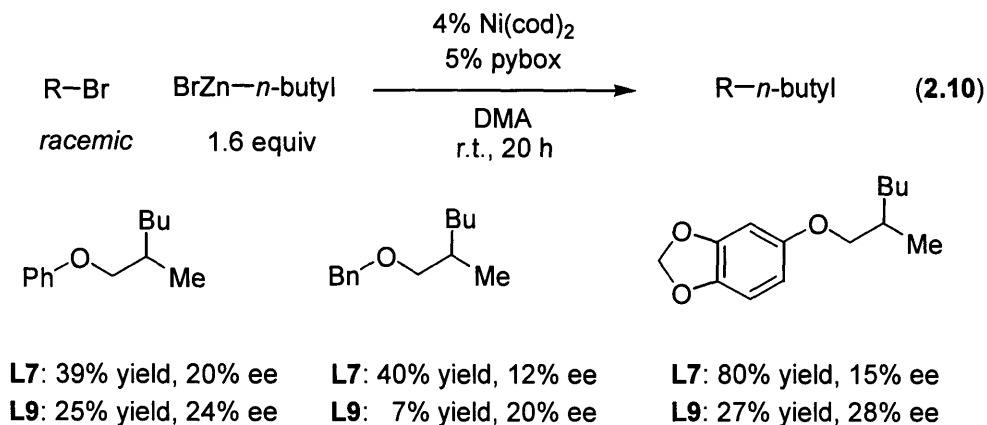


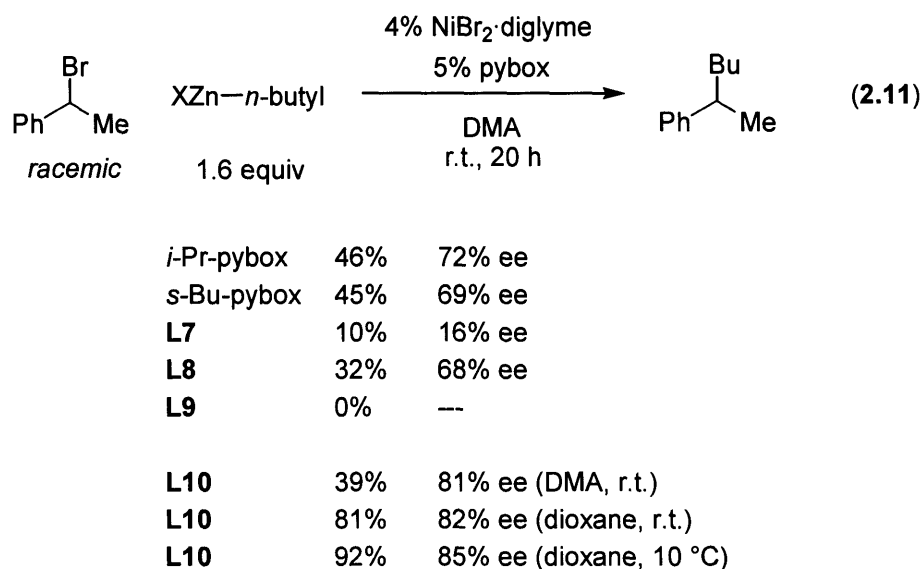
Figure 2.7. Additional Pybox ligands for asymmetric Negishi couplings.

We then synthesized some more elaborate Pybox ligands,⁹⁷ hoping to forge a more effective chiral environment (Figure 2.7). In the best cases, we obtained >20% ee with ligands **L7** and **L9** in the couplings of aryloxy bromides **2.7** and **2.9** (Eq 2.10). In these processes, no kinetic resolution of the starting material was operative since the unreacted alkyl bromides remained racemic. We believe that the hydroxyl groups on ligands **L7** and **L9** react with the alkylzinc bromide to generate zinc alkoxides which can help to dock the substrates on the catalyst through their aryloxy oxygens, and that the conformational flexibility of the docked substrates may be further reduced by π -interactions between the aromatic core of the ligands and the aryloxy groups.

⁹⁷ (a) **L1**, **L5**, and **L6** were prepared from pyridine-2,6-diimidate: Müller, P.; Boléa, C. *Helv. Chim. Acta* **2001**, *84*, 1093–1111. (b) **L2** was prepared from pyridine-2,6-dicarbonitrile with a catalytic amount of ZnCl₂ as described for the *s*-Bu-Pybox in the Experimental. (c) **L3** and **L4**: Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168. (d) **L7-L10**: Iwasa, S.; Tsushima, S.; Nishiyama, K.; Tsuchiya, Y.; Takezawa, F.; Nishiyama, H. *Tetrahedron: Asymmetry* **2003**, *14*, 855–865.



With activated benzylic bromides, we have observed high selectivities (Eq 2.11). In the presence of ligand **L10**, the coupling product was generated with 85% ee in almost quantitative yield.⁹⁸ Solvent switching to dioxane was necessary to suppress the formation of benzyl dimers as by-products.⁹⁹



As a continuation of this work, Forrest Arp in our group obtained excellent enantioselectivities in Negishi couplings with a subclass of benzylic halides, α -bromoindanes (Figure 2.8).¹⁰⁰ In an independent study, Dr. Christian Fischer also

⁹⁸ At 5 °C, the reaction mixture was frozen.

⁹⁹ In dioxane, the Negishi cross-couplings with unactivated secondary bromides did not occur.

¹⁰⁰ Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483.

discovered that some α -bromo amides can also afford $> 90\%$ ee in the coupling products.¹⁰¹

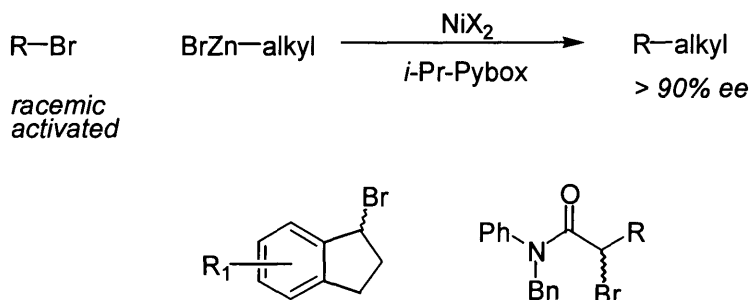


Figure 2.8. Highly enantioselective, asymmetric Negishi couplings with activated alkyl halides.

2.3. Mechanistic Aspects

We had been using isopropyl bromide in our model reactions. However, its by-products have very low boiling points and, thus, present a challenge for quantitative analysis of by-products. Therefore, we performed the nickel-catalyzed cross-coupling reactions with cyclohexyl bromide (Table 2.4). From this bromide, three major by-products were identified, including elimination and reduction products, and the cyclohexyl dimer. The appearance of the homodimer may suggest the presence of radical intermediates during the course of the reaction.

¹⁰¹ Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595.

Table 2.4. By-products from a Nickel-Catalyzed Negishi Reaction with Cyclohexyl Halides

X	y% catalyst	product (%)	(%)	(%)	(%)
Br	4	87	4	2	3
Br	20	69	16	4	3
→					
I	4	89	2	2	5
I	20	75	4	3	8

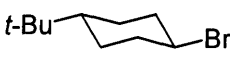
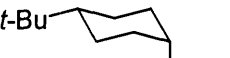
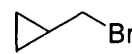
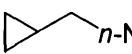
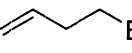
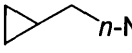
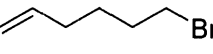
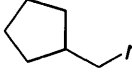
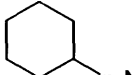
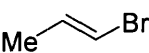
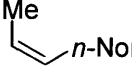
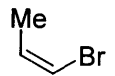
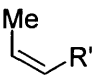
Yield according to GC, versus a calibrated internal standard.

To probe the intermediary of these organic radicals, we have conducted some additional experiments (Table 2.5). First, isomerically pure 4-*t*-butylcyclohexyl bromides (entries 1 and 2), regardless of their stereochemistry, gave the desired coupling product with almost identical ratios (*cis/trans* ~27:73). Second, cyclopropylmethyl bromide underwent significant ring opening during the course of the reaction (entry 3). Third, from 6-bromo-1-hexene we observed two cyclized products in addition to the linear one (entry 5).¹⁰² Fourth, when *cis*-1-propenyl bromide was subjected to the reaction conditions, the *trans* product was produced in substantial quantity (entries 6 and 7). Finally, unactivated alkyl chlorides and tosylates were inert under the standard conditions (entry 8). This contradicts the relative reactivity of electrophiles in a typical S_N2 reaction (I ≈ OTs > Br > Cl) and is most consistent with the trend in SET processes (I > Br > Cl > OTs).¹⁰³ In conclusion, all these data are in line with the generation of organic radicals during the oxidative addition of the electrophiles.

¹⁰² The rates of rearrangement of 5-hexenyl and cyclopropylmethyl radicals are on the order of 10⁵ s⁻¹ and 10⁸ s⁻¹ at room temperature, respectively: Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317–323.

¹⁰³ Ashby, E. C.; Park, B.; Patil, G. S.; Gadru, K.; Gurusurthy, R. *J. Org. Chem.* **1993**, *58*, 424–437.

Table 2.5. Substrate Probes for Radical Involvement in Nickel Catalysis.

$R-X$ $n\text{-Nonyl-ZnBr}$ 1.6 equiv		$\xrightarrow[\text{DMA}]{\text{4\% Ni(cod)}_2, \text{8\% s-Bu-Pybox}}$ r.t., 20 h	$R-R^1$	
entry	R-X	product	(%) ^a	
1		$\text{BrZn-}(\text{CH}_2)_4\text{-CN}$	44% ^b	(cis:trans 27:73)
2		$\text{BrZn-}(\text{CH}_2)_4\text{-CN}$	70% ^b	(cis:trans 29:71)
3		$\text{CH}_2=\text{CH-CH}_2\text{-}n\text{-Nonyl}$	48%	 6%
4		$\text{CH}_2=\text{CH-CH}_2\text{-}n\text{-Nonyl}$	25%	 0%
5		$\text{CH}_2=\text{CH-CH}_2\text{-}n\text{-Nonyl}$	29%	 7%  6%
6		$\text{Me-CH=CH-}n\text{-Nonyl}$	53%	 0%
7		$\text{Me-CH=CH-}n\text{-Nonyl}$	22%	 28%
8	R-Cl, OTs, or OTf	R- <i>n</i> -Nonyl	0%	

^a Yield according to GC, versus a calibrated internal standard.

^b 6-Cyanoethylzinc bromide was used instead of *n*-nonylzinc bromide. Isolated yields.

In 2004, Vicic et al. published some mechanistic studies with relevance to our nickel/Pybox catalysis (Figure 2.9). In his work, the ligand substitution of $\text{Me}_2\text{Ni}(\text{TMETA})$ with terpyridine (tpy) produced a discrete $\text{MeNi}(\text{tpy})$ complex, instead of the expected $\text{Me}_2\text{Ni}(\text{tpy})$. Then $\text{MeNi}(\text{tpy})$ was shown to react as a reagent with cyclohexyl iodide to afford the coupling product in good yield. It can also serve as a

(pre)catalyst in the coupling reactions between the iodide and alkylzinc bromides. Notably, a by-product, cyclohexyl homodimer, was produced during the catalysis. Combined with the intrinsic instability of dimethyl(tpy)Ni(II), they postulated a catalytic cycle featuring a direct combination of two organic radicals for the carbon-carbon bond formation.¹⁰⁴

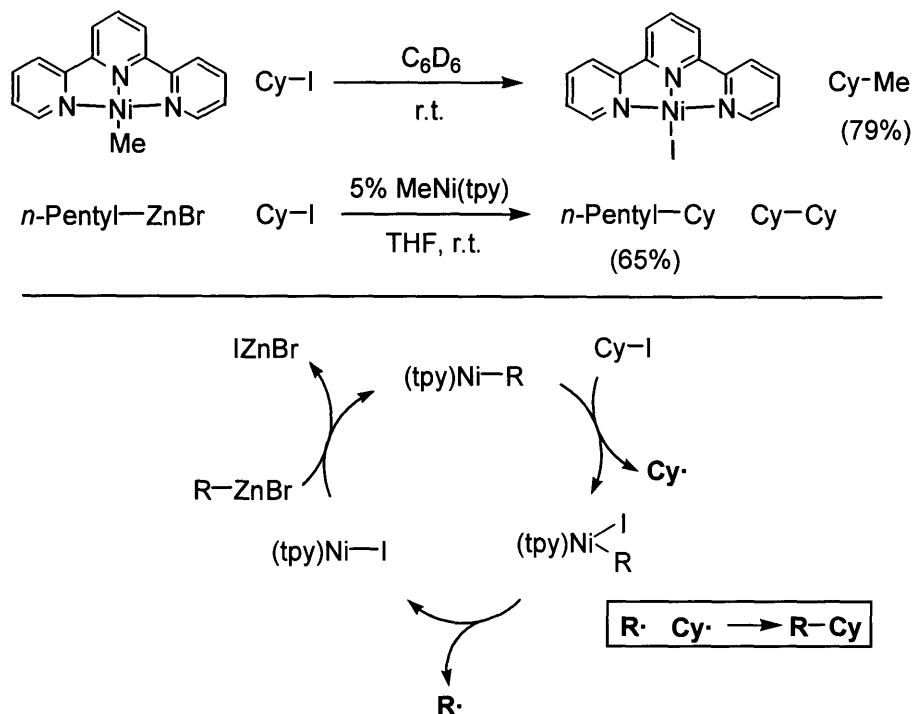


Figure 2.9. Mechanism of nickel-catalyzed Negishi reactions proposed by Vicic et al..

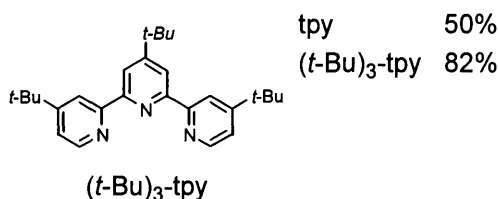
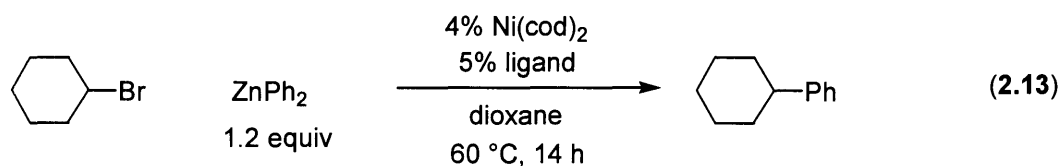
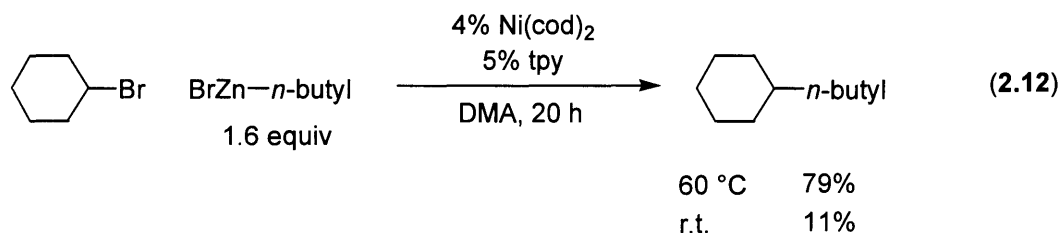
In our hands, $Ni(cod)_2$ -tpy was demonstrated to catalyze a smooth coupling between cyclohexyl bromide and *n*-butylzinc bromide at 60 °C (Eq 2.12). In addition, we have shown that the reaction can be extended to diphenylzinc (Eq 2.13).¹⁰⁵ While it is possible to selectively perform the cross-couplings at the expense of homocouplings in radical chemistry,¹⁰⁶ it is difficult to rationalize the enantioselectivity we have observed in our asymmetric Ni/Pybox-mediated reactions (in Section 2.2.2). We suggest that reductive

¹⁰⁴ Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100–8101.

¹⁰⁵ Zhou, J.; Fu, G. C. Unpublished results.

¹⁰⁶ For reviews on the persistent radical effect, see: (a) Studer, A. *Chem.–Eur. J.* **2001**, *7*, 1159–1164. (b) Fischer, H. *Chem. Rev.* **2001**, *101*, 3581–3610.

elimination from diorganonickel(III) should be considered as an alternative for the carbon-carbon bond formation step.



In addition, Espenson and Castro have independently studied the reactions of Nickel(I) complexes of cyclams or isobacteriochlorin with alkyl halides, and concluded that they proceeded via radical pathways.¹⁰⁷ Furthermore, Espenson and colleagues have established that the generation of organic radicals involved an inner-sphere electron transfer process, rather than an outer-sphere mechanism (Figure 2.10).¹⁰⁸ In terms of their applications, electrogenerated Ni^I(cyclam) complexes have been shown to effect homocouplings of alkyl halides.¹⁰⁹

¹⁰⁷ (a) Bakac, A.; Espenson, J. H. *J. Am. Chem. Soc.* **1986**, *108*, 713–719. (b) Helvenston, M. C.; Castro, C. E. *J. Am. Chem. Soc.* **1992**, *114*, 8490–8496.

¹⁰⁸ (a) Ram, M. S.; Bakac, A.; Espenson, J. H. *Inorg. Chem.* **1988**, *27*, 4231–4235. (b) Sadler, N.; Scott, S. L.; Bakac, A.; Espenson, J. H.; Ram, M. S. *Inorg. Chem.* **1989**, *28*, 3951–3954.

¹⁰⁹ (a) Gosden, C.; Healy, K. P.; Pletcher, D. *J. Chem. Soc., Dalton Trans.* **1978**, 972–976. (b) Becker, J. Y.; Kerr, J. B.; Pletcher, D.; Rosas, R. *J. Electroanal. Chem.* **1981**, *117*, 87–99.

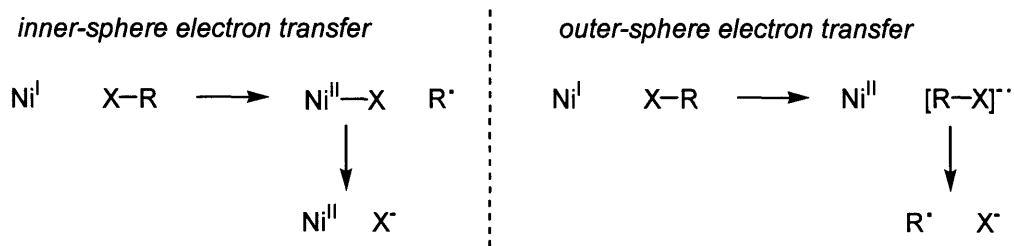
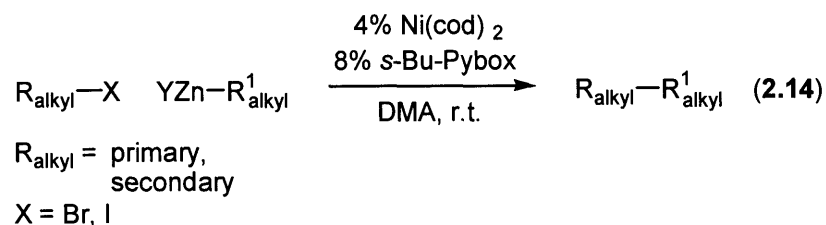


Figure 2.10. Inner- and outer-sphere electron transfer processes (ligands and charges on nickel are omitted for clarity).

In an attempt to unravel the mechanism of our nickel catalysis, Ivory Hills has isolated a (*s*-Bu-Pybox)Ni(I)Br complex when Ni(cod)₂ and the ligand were treated with 3-bromo-1-cyclohexene.¹¹⁰ Unfortunately, no further progress has been achieved ever since.¹¹¹

2.4. Conclusion

In summary, we have established that Ni(cod)₂/*s*-Bu-Pybox can catalyze Negishi reactions of an array of functionalized alkyl bromides and iodides at room temperature. To the best of our knowledge, this is the first nickel-catalyzed method for cross-coupling β -hydrogen-containing, unactivated secondary alkyl halides (Eq 2.14).¹¹² We have also obtained some preliminary evidence to support the existence of organic radicals in the course of nickel catalysis. Furthermore, the use of optically pure Pybox ligands enabled high level of stereinduction in cross-coupling of certain activated halides.



¹¹⁰ Hills, I. D. Ph.D. Thesis, Massachusetts Institute of Technology, Massachusetts, 2004.

¹¹¹ Broad peaks were observed in the model reactions by ¹H NMR due to the presence of paramagnetic nickel species.

¹¹² Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726–14727.

2.5. Experimental

I. General

The following reagents were purchased: pyridine-2,6-dinitrile (Aldrich), (2*S*,3*S*)-isoleucinol (TCI), ZnCl₂ (anhydrous; Cerac), chlorobenzene (anhydrous; Aldrich), Ni(cod)₂ (Strem), *N,N*-dimethylacetamide (DMA; anhydrous; Aldrich), 4-bromopiperidine hydrobromide (Aldrich), pentan-3-ol (Aldrich), 4-chlorobutyrophenone (92%; Aldrich), zinc powder (-140+325 mesh, 99.9%; Alfa-Aesar), iodine (chips, 99+%; Aldrich), *n*-nonyl bromide (Avocado), cycloheptyl bromide (Lancaster), cyclooctyl bromide (Lancaster), cyclopentyl iodide (Aldrich), cyclohexyl iodide (Lancaster), 1-bromo-4-phthalimidobutane (Avocado), neopentyl iodide (Aldrich), isoamyl iodide (Aldrich), 3-phenoxypropyl bromide (Aldrich), 2-(2-bromoethyl)-1,3-dioxolane (Avocado), ethyl 5-bromovalerate (Avocado), and 3-phenylpropyl bromide (Aldrich). The liquid alkyl halides were purged with argon prior to use. All reactions were conducted in oven-dried glassware under an inert atmosphere with magnetic stirring.

II. Preparation of Substrates and Reagents

The yields have not been optimized.

***s*-Bu-Pybox (2,6-bis[(4*S*, 6*S*)-*sec*-butyl-2-oxazolin-2-yl]pyridine) [118949-62-5].**¹¹³
In a glove box, pyridine-2,6-dinitrile (367 mg, 2.85 mmol), (2*S*,3*S*)-isoleucinol (1.00 g, 8.5 mmol), anhydrous ZnCl₂ (39 mg, 0.29 mmol), and anhydrous chlorobenzene (10.0 mL) were added to a vial. The reaction mixture was stirred at 110 °C for 40 h, and then it was passed through a short pad of silica gel (CH₂Cl₂ washings). The filtrate was then concentrated, and the residue was crystallized from hot hexane/EtOAc (10:1). The resulting white powder was collected by filtration to give 740 mg (79%) of the desired product.

¹¹³ (a) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500–508. (b) Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173–1180. (c) Chelucci, G.; Deriu, S.; Pinna, G. A.; Saba, A.; Valenti, R. *Tetrahedron: Asymmetry* **1999**, *10*, 3803–3809.

¹H NMR (CDCl₃, 400 MHz): δ 8.22 (d, *J* = 7.8 Hz, 2H), 7.85 (t, *J* = 7.8 Hz, 1H), 4.55-4.48 (m, 2H), 4.30-4.21 (m, 4H), 1.76-1.60 (m, 4H), 1.31-1.20 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 6H), 0.88 (d, *J* = 6.7 Hz, 6H).

¹³C NMR (CDCl₃, 400 MHz): δ 162.4, 147.2, 137.3, 125.9, 71.7, 70.7, 39.3, 26.4, 14.7, 11.7.

4-Bromo-*N*-(*p*-toluenesulfonyl)piperidine [347885-68-1]. 4-Bromopiperidine hydrobromide (1.15 g, 4.7 mmol), *p*-toluenesulfonyl chloride (1.16 g, 6.1 mmol), and pyridine (10 mL) were added to a flask, and the resulting mixture was stirred at r.t. for 18 h. The product was then extracted (CH₂Cl₂/1 N HCl), and the organic layer was concentrated. The residue was dissolved in CH₂Cl₂ and precipitated with hexane to give a white solid (1.15 g, 77%).

¹H NMR (CDCl₃, 400 MHz): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 4.28-4.23 (m, 1H), 3.23-3.17 (m, 2H), 3.13-3.07 (m, 2H), 2.46 (s, 3H), 2.24-2.17 (m, 2H), 2.10-2.03 (m, 2H).

¹³C NMR (CDCl₃, 400 MHz): δ 143.9, 133.3, 130.0, 127.8, 48.0, 44.0, 34.8, 21.7.

3-Iodopentane [1809-05-8].¹¹⁴ Imidazole (4.76 g, 70 mmol) and PPh₃ (18.3 g, 70 mmol) were added to a Schlenk tube equipped with a stir bar. The air was removed by evacuating/refilling with argon (three times), and then CH₂Cl₂ (100 mL) was added. The resulting solution was cooled to 0 °C, and iodine chips (17.8 g, 70 mmol) were introduced portion-wise. Pentan-3-ol (4.41 g, 50 mmol) was added dropwise to the 0 °C mixture (brown solution with yellow solids), which was then allowed to warm to r.t. overnight. Hexane was added, and the solids were removed by passing the mixture through silica gel (hexane washings). The resulting solution was concentrated, and the residue was purified by flash chromatography (hexane), which furnished the desired product as a pink oil (3.09 g; 31% yield).

¹H NMR (CDCl₃, 400 MHz): δ 4.10-4.04 (hept, *J* = 4.7 Hz, 1H), 1.93-1.72 (m, 4H), 1.04 (t, *J* = 7.2 Hz, 6H).

¹³C NMR (CDCl₃, 400 MHz): δ 44.8, 33.6, 14.3.

¹¹⁴ Prepared according to: Lange, G. L.; Gottardo, C. *Synth. Commun.* **1990**, *20*, 1473–1479.

4-Iodobutyrophenone [65488-05-3]. 4-Chlorobutyrophenone (1.96 g, 9.9 mmol) and NaI (7.50 g, 50 mmol) were refluxed in acetone (40 mL) for 10 h. The solvent was then removed, and the residue was passed through silica gel (CH₂Cl₂ washings). The filtrate was concentrated, and the residue was purified by flash chromatography (hexane/EtOAc), which provided a colorless oil (2.42 g, 88%) that quickly turned red (and solidified during storage in a refrigerator).

¹H NMR (CDCl₃, 400 MHz): δ 8.02-8.00 (m, 2H), 7.63-7.59 (m, 1H), 7.52-7.49 (m, 2H), 3.36 (t, *J* = 6.6 Hz, 2H), 3.17 (t, *J* = 7.0 Hz, 2H), 2.29 (apparent quintet, *J* = 6.7 Hz, 2H).

¹³C NMR (CDCl₃, 400 MHz): δ 199.0, 137.1, 133.7, 129.1, 128.4, 39.3, 27.9, 7.3.

Preparation of alkylzinc bromide solutions: Representative procedure. Zinc powder (0.980 g, 15.0 mmol) was added to a 25-mL Schlenk tube, and the air was removed by evacuating/refilling with argon (three times). Iodine chips (127 mg, 0.50 mmol) and *N,N*-dimethylacetamide (DMA; 10.0 mL) were then added, and the resulting mixture was stirred for 2 min at r.t., during which time the solution changed from dark-brown to colorless (zinc powder remained). *n*-Nonyl bromide (2.07 g, 10.0 mmol) was added by syringe, and the reaction mixture was stirred at 80 °C for 3 h, at which time all of the starting material had been consumed (monitored by GC). The purity of the solution was >90%, and the concentration in DMA was ~0.75 M.

Preparation of isoamylzinc iodide. Zinc powder (0.980 g, 15.0 mmol) was added to a 25-mL Schlenk tube, and the air was removed by evacuating/refilling with argon (three times). Iodine chips (127 mg, 0.50 mmol) and DMA (10.0 mL) were then added, and the resulting mixture was stirred for 2 min at r.t., during which time the solution changed from dark-brown to colorless (zinc powder remained). Isoamyl iodide (1.98 g, 10.0 mmol) was added by syringe, and the reaction mixture was stirred at r.t. for 3 h, at which time all of the starting material had been consumed (monitored by GC). The purity of the solution was >95% and the concentration in DMA was ~0.75 M.

III. Negishi Cross-Coupling Reactions

Procedure for Table 2.1. In a glove box, yellow Ni(cod)₂ crystals (2.8 mg, 0.010 mmol), *s*-Bu-Pybox (6.6 mg, 0.020 mmol), and DMA (0.40 mL) were added to a vial. The resulting mixture was stirred for 20 min at r.t., and then the resulting deep-blue solution was treated in turn with *n*-C₁₆H₃₄ (internal standard for GC analysis; 29 μL, 0.10 mmol), a solution of *n*-nonylzinc bromide (0.75 M in DMA; 0.53 mL, 0.40 mmol) and *i*-propyl bromide (24 μL, 31 mg, 0.25 mmol). The reaction mixture was stirred for 20 h at r.t., and then it was quenched with ethanol (~0.5 mL). The resulting mixture was stirred at r.t. for 10 min, and then an aliquot was passed through silica gel and analyzed by GC.

Procedure for Tables 2.2 and 2.3 (with a glove box). In a glove box, yellow Ni(cod)₂ crystals (5.6 mg, 0.020 mmol), *s*-Bu-Pybox (13.2 mg, 0.040 mmol), and DMA (0.80 mL) were added to a vial. The resulting mixture was stirred for 20 min at r.t., and then the resulting deep-blue solution was treated in turn with a solution of the alkylzinc halide (0.75 M in DMA; 1.06 mL, 0.80 mmol) and the alkyl halide (0.50 mmol). The reaction mixture was stirred for 20 h at r.t., and then the excess organozinc reagent was quenched with iodine chips (~100 mg). After stirring at r.t. for 10 min, the dark-brown mixture was passed through a short pad of silica gel (to remove DMA, inorganic salts, and iodine). The filtrate was then concentrated, and the residue was purified by flash chromatography.

Procedure for Tables 2.2 and 2.3 (without a glove box). Yellow Ni(cod)₂ crystals (5.6 mg, 0.020 mmol) and *s*-Bu-Pybox (13.2 mg, 0.040 mmol) were added to a vial. The air was removed by evacuating/refilling with argon (three times), and then DMA (0.80 mL) was added. The resulting mixture was stirred for 20 min at r.t., and then the resulting deep-blue solution was treated in turn with a solution of the alkylzinc halide (0.75 M in DMA; 1.06 mL, 0.80 mmol) and the alkyl halide (0.50 mmol). The reaction mixture was stirred for 20 h at r.t., and then the excess organozinc reagent was quenched with iodine chips (~100 mg). After stirring at r.t. for 10 min, the dark-brown mixture was passed through a short pad of silica gel (to remove DMA, inorganic salts, and iodine). The filtrate was then concentrated, and the residue was purified by flash chromatography. [Note: Electrophiles that are solids (4-bromo-*N*-(*p*-toluenesulfonyl)piperidine, 1-bromo-4-phthalimidobutane, and 4-iodobutyrophenone) were added before DMA.]

Table 2.2, entry 1. 4-Bromo-*N*-(*p*-toluenesulfonyl)piperidine (159 mg, 0.50 mmol) and isoamylzinc iodide (0.75 M in DMA; 1.06 mL, 0.80 mmol) were used. Solvent for chromatography: hexane/EtOAc 100:10. White powder (glove box: 102 mg, 66%; no glove box: 100 mg, 65%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.63 (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.2$ Hz, 2H), 3.75 (d, $J = 11.6$ Hz, 2H), 2.42 (s, 3H), 2.18 (td, $J = 11.9, 2.1$ Hz, 2H), 1.70 (d, $J = 11.5$ Hz, 2H), 1.44 (hept, $J = 6.6$ Hz, 1H), 1.31-1.24 (m, 2H), 1.25-1.16 (m, 2H), 1.13-1.08 (m, 3H), 0.83 (d, $J = 6.6$ Hz, 6H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 143.4, 133.2, 129.6, 127.8, 46.7, 35.9, 35.5, 33.9, 31.7, 28.1, 22.7, 21.6.

IR (KBr pellet): 2945, 2844, 1598, 1466, 1338, 1168 cm^{-1} .

HRMS (ESI): Calcd for $\text{C}_{17}\text{H}_{27}\text{NNaO}_2\text{S}$ ($\text{M}+\text{Na}$) $^+$ 332.1655. Found: 332.1650.

Table 2.2, entry 2. Cycloheptyl bromide (90 mg, 0.50 mmol) and 3-phenoxypropylzinc bromide (0.75 M in DMA; 1.06 mL, 0.80 mmol) were used. Solvent for chromatography: hexane/ Et_2O 100:3. Colorless oil (glove box: 70 mg, 60%; no glove box: 74 mg, 64%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.35-7.29 (m, 2H), 6.99-6.92 (m, 3H), 3.98 (t, $J = 6.7$ Hz, 2H), 1.87-1.39 (m, 15H), 1.29-1.20 (m, 2H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 159.3, 129.6, 120.6, 114.7, 68.4, 39.2, 34.7, 34.6, 28.7, 27.4, 26.7.

IR (thin film): 2922, 2852, 1601, 1497, 1245 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{16}\text{H}_{24}\text{O}$ ($\text{M}+\text{Na}$) $^+$ 232.1822. Found: 232.1818.

Table 2.2, entry 3. Cyclooctyl bromide (96 mg, 0.50 mmol) and 2-(1,3-dioxolan-2-yl)ethylzinc bromide (0.75 M in DMA; 1.06 mL, 0.80 mmol) were used. Solvent for chromatography: hexane/ Et_2O 100:3. Colorless oil (glove box: 74 mg, 70%; no glove box: 69 mg, 65%).

^1H NMR (CDCl_3 , 400 MHz): δ 4.84 (t, $J = 4.8$ Hz, 1H), 3.99-3.93 (m, 2H), 3.90-3.84 (m, 2H), 1.70-1.42 (m, 15H), 1.36-1.24 (m, 4H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 105.2, 65.0, 37.4, 32.5, 32.4, 32.1, 27.5, 26.5, 25.7.

IR (thin film): 2910, 2856, 1728, 1474, 1447, 1145 cm^{-1} .

HRMS (EI): Calcd for $C_{13}H_{23}O_2$ (M-H)⁺: 211.1693. Found: 211.1701.

Table 2.2, entry 4. 3-Iodopentane (99 mg, 0.50 mmol) and 4-ethoxycarbonylbutylzinc bromide (0.75 M in DMA; 1.06 mL, 0.80 mmol) were used. Solvent for chromatography: hexane/Et₂O 100:3. Colorless oil (glove box: 61 mg, 61%; no glove box: 62 mg, 62%).

¹H NMR (CDCl₃, 400 MHz): δ 4.12 (q, *J* = 7.1 Hz, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 1.61 (quintet, *J* = 7.5 Hz, 2H), 1.33-1.13 (m, 12H), 0.83 (t, *J* = 7.5 Hz, 6H).

¹³C NMR (CDCl₃, 400 MHz): δ 174.2, 60.4, 40.4, 34.6, 32.5, 26.5, 25.6, 25.5, 14.5, 11.1.

IR (thin film): 2962, 2934, 1739, 1462, 1167 cm⁻¹.

HRMS (ESI): Calcd for $C_{12}H_{24}NaO_2$ (M+Na)⁺ 223.1669. Found: 223.1677.

Table 2.2, entry 5. Cyclopentyl iodide (98 mg, 0.50 mmol) and 5-diethylaminocarbonylpentylzinc bromide (0.75 M in DMA; 1.06 mL, 0.80 mmol) were used. Solvent for chromatography: hexane/EtOAc 100:15. Colorless oil (glove box: 92 mg, 77%; no glove box: 94 mg, 79%).

¹H NMR (CDCl₃, 400 MHz): δ 3.39-3.27 (m, 4H), 2.28 (t, *J* = 7.1 Hz, 2H), 1.72-1.47 (m, 9H), 1.30 (br s, 6H), 1.18-1.05 (m, 8H).

¹³C NMR (CDCl₃, 400 MHz): δ 172.5, 42.1, 40.3, 40.2, 36.2, 33.3, 32.9, 30.0, 28.8, 25.7, 25.3, 14.6, 13.3.

IR (thin film): 2934, 2857, 1644, 1461, 1428, 1266 cm⁻¹.

HRMS (ESI): Calcd for $C_{15}H_{29}NNaO$ (M+Na)⁺ 262.2141. Found: 262.2139.

Table 2.2, entry 6. [170661-44-6] Cyclohexyl iodide (106 mg, 0.50 mmol) and 3-phenylpropylzinc bromide (0.75 M in DMA; 1.06 mL, 0.80 mmol) were used. Solvent for chromatography: hexane. Colorless oil (glove box: 88 mg, 87%; no glove box: 89 mg, 88%).

¹H NMR (CDCl₃, 400 MHz): δ 7.32-7.28 (m, 2H), 7.22-7.18 (m, 3H), 2.61 (t, *J* = 7.9 Hz, 2H), 1.75-1.62 (m, 7H), 1.30-1.25 (m, 6H), 0.94-0.85 (m, 2H).

¹³C NMR (CDCl₃, 400 MHz): δ 143.2, 128.6, 128.4, 125.8, 37.8, 27.4, 36.5, 33.6, 29.0, 27.0, 26.7.

Table 2.3, entry 1 [151921-82-3]. 1-Bromo-4-phthalimidobutane (141 mg, 0.50 mmol) and 3-phenylpropylzinc bromide (0.75 M in DMA; 1.06 mL, 0.80 mmol) were used. Solvent for chromatography: hexane/EtOAc 100:7. Colorless oil (glove box: 99 mg, 64%; no glove box: 102 mg, 66%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.87-7.84 (m, 2H), 7.74-7.70 (m, 2H), 7.31-7.27 (m, 2H), 7.28-7.20 (m, 3H), 3.70 (t, $J = 7.3$ Hz, 2H), 2.61 (t, $J = 7.8$ Hz, 2H), 1.73-1.61 (m, 4H), 1.38 (br s, 6H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 168.6, 142.9, 134.0, 132.3, 128.5, 128.4, 125.7, 123.3, 38.2, 36.0, 31.5, 29.3, 29.2, 28.7, 26.9.

Table 2.3, entry 2. 4-Iodobutyrophenone (137 mg, 0.50 mmol) and 2-(1,3-dioxolan-2-yl)ethylzinc bromide (0.75 M in DMA; 1.06 mL, 0.80 mmol) were used. Solvent for chromatography: hexane/EtOAc 100:10. White solid (glove box: 93 mg, 75%; no glove box: 91 mg, 73%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.97-7.95 (m, 2H), 7.57-7.53 (m, 1H), 7.48-7.44 (m, 2H), 4.85 (t, $J = 4.8$ Hz, 1H), 3.98-3.92 (m, 2H), 3.89-3.83 (m, 2H), 2.98 (t, $J = 7.5$ Hz, 2H), 1.80-1.73 (m, 2H), 1.71-1.66 (m, 2H), 1.53-1.41 (m, 4H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 200.5, 137.1, 133.0, 128.7, 128.2, 104.7, 65.0, 38.6, 33.9, 29.4, 24.3, 24.0.

IR (KBr pellet): 2940, 2894, 2860, 1684, 1449, 1231 cm^{-1} .

HRMS (ESI): Calcd for $\text{C}_{15}\text{H}_{20}\text{NaO}_3$ ($\text{M}+\text{Na}$) $^+$ 271.1305. Found: 271.1305.

Table 2.3, entry 3 [130986-02-6]. Neopentyl iodide (99 mg, 0.50 mmol) and 3-phenylpropylzinc bromide (0.75 M in DMA; 1.06 mL, 0.80 mmol) were used. Solvent for chromatography: hexane. Colorless oil (glove box: 68 mg, 72%; no glove box: 70 mg, 74%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.38-7.34 (m, 2H), 7.28-7.24 (m, 3H), 2.70 (t, $J = 7.7$ Hz, 2H), 1.68 (quintet, $J = 7.0$ Hz, 2H), 1.44-1.36 (m, 2H), 1.32-1.27 (m, 2H), 0.96 (s, 9H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 143.2, 128.6, 128.4, 125.7, 44.2, 36.3, 32.7, 30.5, 29.6, 24.6.

Asymmetric cross-couplings with racemic alkyl bromides. In a glove box, yellow Ni(cod)₂ (2.8 mg, 0.010 mmol), ligand **L9** (5.5 mg, 0.012 mmol), and DMA (0.25 mL) were added to a vial. The resulting mixture was stirred for 20 min at r.t., and then the resulting deep-blue solution was treated in turn a solution of *n*-butylzinc bromide (1.6 M in DMA; 0.25 mL, 0.40 mmol) and alkyl bromide (0.25 mmol). The reaction mixture was stirred for 20 h at r.t., and then it was quenched with ethanol (~0.5 mL). The resulting mixture was stirred with *n*-C₁₄H₃₀ (internal standard for GC analysis; 26 μL, 0.10 mmol) at r.t. for 10 min, and then an aliquot was passed through silica gel and analyzed by GC.

2-Methyl-1-phenoxyhexane. 25% GC yield. Chiral HPLC analysis: 24 % ee [Daicel CHIRALPAK OD-H; solvent: 100% hexanes; flow rate: 1.0 mL/min; retention times: 21.5 min (minor), 28.0 min (major)].

¹H NMR (CDCl₃, 400 MHz): δ 7.33-7.28 (m, 2H), 6.98-6.93 (m, 3H), 3.87-3.84 (m, 1H), 3.77-3.73 (m, 1H), 2.01-1.94 (m, 1H), 1.59-1.52 (m, 1H), 1.45-1.23 (m, 5H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.95 (t, *J* = 6.8 Hz, 3H).

¹³C NMR (CDCl₃, 400 MHz): δ 159.5, 129.6, 120.6, 114.7, 73.3, 33.4, 33.3, 29.4, 23.2, 17.3, 14.3.

IR (thin film): 2957, 2928, 2873, 2859, 1602, 1497, 1468, 1244 cm⁻¹.

HRMS (EI): Calcd for C₁₃H₂₀O (M)⁺: 192.1509. Found: 192.1506.

2-Methyl-1-benzyloxyhexane. 7% GC yield. Chiral HPLC analysis: 20% ee [Daicel CHIRALPAK OD-H; solvent: 100% hexanes; flow rate: 1.0 mL/min; retention times: 23.8 min (major), 27.7 min (minor)].

¹H NMR (CDCl₃, 400 MHz): δ 7.36-7.29 (m, 5H), 4.52 (s, 2H), 3.36-3.33 (m, 1H), 3.27-3.23 (m, 1H), 1.79-1.75 (m, 1H), 1.47-1.43 (m, 1H), 1.31-1.24 (m, 4H), 1.16-1.09 (m, 1H), 0.95-0.89 (m, 6H).

¹³C NMR (CDCl₃, 400 MHz): δ 139.1, 128.5, 127.7, 127.6, 76.3, 73.2, 33.7, 33.6, 29.4, 23.2, 17.4, 14.3.

IR (thin film): 2957, 2928, 2857, 1454, 1362, 1099 cm⁻¹.

HRMS (ESI): Calcd for C₁₄H₂₂NaO (M+Na)⁺: 229.1563. Found: 229.1567.

2-Methyl-1-(3,4-methylenedioxyphenoxy)hexane. 27% GC yield. Chiral HPLC analysis: 28% ee [Daicel CHIRALPAK OJ-H; solvent: 100% hexanes; flow rate: 1.0 mL/min; retention times: 12.8 min (major), 14.2 min (minor).

^1H NMR (CDCl_3 , 400 MHz): δ 6.72 (d, $J = 8.5$ Hz, 1H), 6.52 (d, $J = 2.5$ Hz, 1H), 6.35 (dd, $J = 8.5, 2.5$ Hz, 1H), 5.93 (s, 2H), 3.76 (dd, $J = 8.9, 5.8$ Hz, 1H), 3.66 (dd, $J = 8.9, 6.7$ Hz, 1H), 1.95-1.87 (m, 1H), 1.56-1.48 (m, 1H), 1.42-1.18 (m, 6H), 1.02 (d, $J = 6.7$ Hz, 3H), 0.93 (t, $J = 6.8$ Hz, 3H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 155.1, 148.4, 141.6, 108.1, 105.8, 101.2, 98.3, 74.4, 33.39, 33.35, 29.4, 23.2, 17.3, 14.3.

IR (thin film): 2958, 2928, 2873, 2860, 1504, 1489, 1472, 1185, 1039 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{14}\text{H}_{20}\text{O}_3$ (M) $^+$: 236.1407. Found: 236.1414.

2-Phenylhexane [6031-02-3]. In a glove box, yellow $\text{NiBr}_2 \cdot \text{diglymediyne}$ (3.5 mg, 0.010 mmol), ligand L10 (7.6 mg, 0.012 mmol), and DMA (0.25 mL) were added to a vial. The resulting mixture was stirred for 20 min at r.t., and then the resulting deep-blue solution was treated in turn a solution of *n*-butylzinc bromide (1.6 M in DMA; 0.25 mL, 0.40 mmol) and 1-phenylethyl bromide (47 mg, 0.25 mmol). The reaction mixture was stirred for 20 h at r.t., and then it was quenched with ethanol (~0.5 mL). The resulting mixture was stirred with *n*- $\text{C}_{14}\text{H}_{30}$ (internal standard for GC analysis; 26 μL , 0.10 mmol) at r.t. for 10 min, and then an aliquot was passed through silica gel and analyzed by GC. The calibrated GC yield was determined to be 39%.

Chiral GC analysis: 81% ee [Chrompack chiralsil-Dex CB; temperature gradient: 80-120 $^\circ\text{C}$; carrier gas: helium; flow rate: 1.0 mL/min; retention times: 20.7 min (minor), 21.2 min (major).

^1H NMR (CDCl_3 , 400 MHz): δ 7.28-7.23 (m, 2H), 7.17-7.13 (m, 3H), 2.64 (m, 1H), 1.57-1.50 (m, 2H), 1.29-1.09 (m, 7H), 0.82 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 148.2, 128.5, 127.2, 125.9, 40.1, 38.4, 30.2, 23.0, 22.6, 14.3.

Chapter 3.

Nickel-Catalyzed Suzuki Reactions of Secondary Alkyl Halides

3.1. Background

In Chapter 2, we have made new advances in cross-coupling chemistry of alkyl electrophiles. Thus, through the use of a Ni/pybox catalyst, we succeeded in performing the reactions between secondary alkyl halides and organozinc reagents. Naturally, we became interested in applying this newly discovered catalysis to other types of organometallic nucleophiles. Among those prominent coupling partners (Figure 1.1), organoboronic acids are particularly appealing owing to several desirable attributes. In general, they are nontoxic and stable to air, water, and heat. Another attractive feature is that boron-containing by-products of coupling reactions are innocuous and readily separable from the desired coupling products. These features, combined with often mild coupling conditions, render Suzuki reactions applicable to large-scale synthesis.¹¹⁵

Traditionally, these reagents have been prepared by transmetalation from Grignard or organolithium reagents. Nowadays, many functionalized, elaborated boronic acids can be accessed indirectly from palladium-catalyzed cross-couplings between aryl/vinyl halides and bis(pinacolato)diboron¹¹⁶ or pinacolborane¹¹⁷ (Eq 3.1). In addition, direct¹¹⁸ or catalyzed¹¹⁹ hydroborations of acetylenes readily provide stereochemically defined, 1,2-

¹¹⁵ Examples of the Suzuki reactions in large-scale synthesis: (a) Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151–8156. (b) Kawada, K.; Arimura, A.; Tsuru, T.; Fuji, M.; Komurasaki, T.; Yonezawa, S.; Kugimiya, A.; Haga, N.; Mitsumori, S.; Inagaki, M.; Nakatani, T.; Tamura, Y.; Takechi, S.; Taishi, T.; Kishino, J.; Ohtani, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 973–975. (c) Ennis, D. S.; McManus, J.; Wood-Kaczmar, W.; Richardson, J.; Smith, G. E.; Carstairs, A. *Org. Process Res. Dev.* **1999**, *3*, 248–252. (d) Jacks, T. E.; Belmont, D. T.; Briggs, C. A.; Horne, N. M.; Kanter, G. D.; Karrick, G. L.; Krikke, J. J.; McCabe, R. J.; Mustakis, J. G.; Nanninga, T. N.; Risedorph, G. S.; Seamans, R. E.; Skeenan, R. E.; Winkle, D. D.; Zennie, T. M. *Org. Process Res. Dev.* **2004**, *8*, 201–212. (e) Jensen, M. S.; Hoerrner, R. S.; Li, W.; Nelson, D. P.; Javadi, G. J.; Dormer, P. G.; Cai, D.; Larsen, R. D. *J. Org. Chem.* **2005**, *70*, 6034–6039. (f) For a recent review, see: King, A. O.; Yasuda, N. *Top. Organomet. Chem.* **2004**, *6*, 205–245.

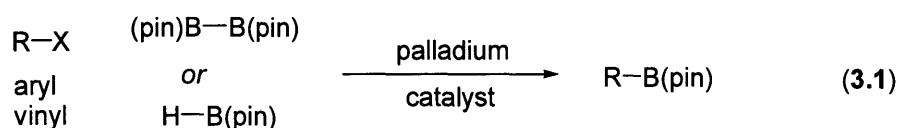
¹¹⁶ (a) Ma, Y.; Song, C.; Jiang, W.; Xue, G.; Cannon, J. F.; Wang, X.; Andrus, M. B. *Org. Lett.* **2003**, *5*, 635–638. (b) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 8001–8006. (c) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813–9816. (d) Willis, D. M.; Strongin, R. M. *Tetrahedron Lett.* **2000**, *41*, 8683–8686. (e) Takahashi, K.; Takagi, J.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 126–127. (f) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447–3450. (g) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 508–510.

¹¹⁷ (a) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164–168. (b) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *Synthesis* **2000**, 778–780. (c) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458–6459.

¹¹⁸ Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482–3485.

¹¹⁹ (a) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127–3128. (b) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc.* **2000**, *122*, 4990–4991. (c) Josyula, K. V. B.; Gao, P.; Hewitt, C.

disubstituted alkenylboronates. Supplementing these methods, ruthenium-catalyzed olefin metathesis can furnish tri-substituted vinyl boronates with excellent regioselectivity.¹²⁰ Recently, arylboronates with defined substitution pattern on the arene rings have been synthesized through iridium-catalyzed borylation of arenes, via position-selective, direct C-H_{aryl} activation processes.¹²¹ Furthermore, a large collection of organoboronic acids are now available from commercial sources.¹²² The ready availability of these compounds renders them particularly popular in library synthesis, especially of biaryls, an important subclass of pharmacophores.¹²³



Today, a host of palladium-based catalysts are available for the Suzuki couplings of aryl or vinyl electrophiles, including even less reactive chlorides and tosylates. This topic has been extensively covered by several recent reviews.¹²⁴ As for nickel-catalyzed reactions with organoboronic acids, aryl chlorides have been popular substrates historically.¹²⁵ In the past decade, several nickel-catalyzed protocols have evolved for

Tetrahedron Lett. **2003**, *44*, 7789–7792. (d) For a review in this area, see: Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957–5026.

¹²⁰ Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733–7736.

¹²¹ Chotana, G. A.; Rak, M. A.; Smith, M. R. III *J. Am. Chem. Soc.* **2005**, *127*, 10539–10544 and references cited therein.

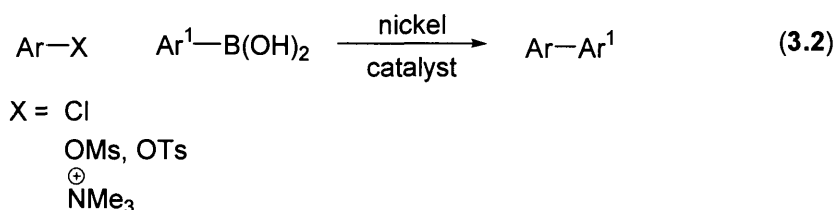
¹²² (a) Over 230 organoboronic acids and about 100 of related esters are now available from Frontier Scientific: Frontier Scientific Home Page. <http://frontiersci.com> (accessed July 2005). (b) About 500 entities of organoboronic acids and their ester derivatives are sold through Aldrich: Sigma-Aldrich Home Page. <http://www.sigmaaldrich.com> (accessed July 2005).

¹²³ The biaryl motif has been shown to be a privileged substructure for protein binding and exists in 4.3% of all known drugs: Hajduk, P.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443–3447.

¹²⁴ For reviews of the Suzuki reactions, see: (a) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440. (b) Suzuki, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; Wiley Interscience: New York, 2002; pp 249–262. (c) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11–59. (d) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695. (e) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 2. (f) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168. (g) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303. (h) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.

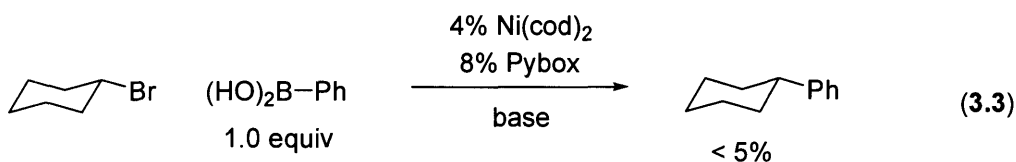
¹²⁵ (a) Ackermann, L.; Born, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 2444–2447. (b) Lipshutz, B. H.; Sclafani, J. A.; Blomgren, P. A. *Tetrahedron* **2000**, *56*, 2139–2144. (c) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024–8030. (d) Saito, S.; Sakai, M.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 993–996.

other classes of aryl electrophiles, including mesylates,¹²⁶ tosylates,¹²⁷ and trimethylammonium salts¹²⁸ (Eq 3.2). The capacity of the nickel catalysts to activate these challenging substrates is a powerful testament to their high intrinsic nucleophilicity, may the oxidative addition be defined by an S_NAr-type displacement, templated by nickel-haloarene pre-association, or triggered by electron transfer. Very recently, two palladium-catalyzed processes have emerged to effect Suzuki couplings with primary alkyl electrophiles.^{13,21} However, at the onset of our investigation, no such palladium or nickel catalysts existed for the secondary substrates. Clearly, to fully exploit the exciting potential of the Suzuki reactions, a breakthrough in this area was highly desirable.



3.2. Results and Discussion

Prompted by the success of Pybox ligands in our Negishi cross-couplings, we eagerly tested them under Suzuki conditions using phenylboronic acid as the coupling partner. Unfortunately, it did not take long for us to realize that these ligands were not productive (<5% yield) (Eq 3.3).



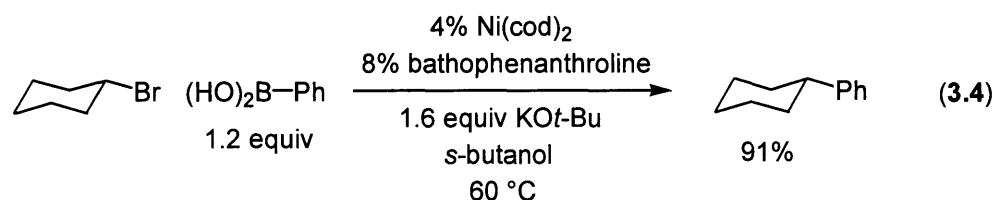
Not being thwarted by this initial disappointment, we made persistent attacks on this new frontier. Organoboronic acids are stable compounds and can be easily handled, but

¹²⁶ Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1060–1065.

¹²⁷ (a) Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *124*, 3058–3059. (b) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049–3051.

¹²⁸ Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046–6047.

they require appropriate bases or inorganic fluorides for activation.¹²⁹ This means an additional parameter to study during our method development. After exploring a wide array of ligands and conditions, we finally achieved the coupling between cyclohexyl bromide and phenylboronic acid in 91% yield. The key to this success is the combination of Ni(cod)₂ and bathophenanthroline, as well as the use of KO^t-Bu in an alcoholic solvent, *s*-BuOH (Eq 3.4).



In fact, the decisive breakthrough was made with phenanthroline and 2,2'-bipyridine (65% and 43% yields, respectively), as shown in Figure 3.1.^{130,131} Subsequent ligand fine-tuning led to bathophenanthroline as the best ligand. We surmise that its extended π -conjugation may facilitate reductive elimination by decreasing electron density on nickel through back-bonding. In addition, the catalytic potency was very sensitive to *ortho*-substitution on these ligands, exemplified by completely inactive neocuproine and 2,2'-bis(quinoline); even 6-methylation on bipy led to a much inferior ligand. Interestingly, the newly established catalytic ability seems to be a privilege of nitrogen-based bidentates since the tridentate ligands (e.g., Pybox or terpyridine) failed completely in the catalysis. Additionally, di(2-picryl)amines also gave the desired coupling product in moderate yields, and at this stage we are not certain whether they bind to nickel as tridentates or bidentates.

¹²⁹ For an overview on the role of the bases in the transmetalation step of the Suzuki reactions, see: Braga, A. A.; Morgon, N. H.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2005**, *127*, 9298–9307 and references cited therein.

¹³⁰ The bipy ligand has been used previously in nickel-catalyzed couplings of aryl halides: (a) with phenyl boronic acids: Leadbeater, N. E.; Resouly, S. M. *Tetrahedron* **1999**, *55*, 11889–11894. (b) With dialkylaluminum reagents: Gelman, D.; Dechert, S.; Schumann, H.; Blum, J. *Inorg. Chim. Acta* **2002**, *334*, 149–158. (c) Homocouplings of aryl chlorides in the presence of zinc powder: Colon, I.; Kelsey, D. R. *J. Org. Chem.* **1986**, *51*, 2627–2637.

¹³¹ Ni/bipy has also been shown to catalyze reductive homocouplings of primary alkyl bromides under electrochemical conditions: Marbrouk, S.; Pellegrini, S.; Folest, J.-C.; Rollin, Y.; Perichon, J. *J. Organomet. Chem.* **1986**, *301*, 391–400.

Table 3.1 illustrates the impact of other parameters on the efficiency of the model reaction. Although Ni(acac)₂ displayed some activity (entry 3), other nickel and palladium complexes gave essentially no desired adduct (entries 4 and 5). In place of bathophenanthroline, the use of phosphines and N-heterocyclic carbenes did not generate active catalysts (entries 6-7). The choice of the activator was also crucial. We found that potassium *t*-butoxide can only be replaced by potassium ethoxide or methoxide, but not potassium hydroxide (entries 10-12). The potassium counterion was critical to the success of the reaction, too. With the sodium or lithium salt, little coupling adduct was formed (entries 13 and 14). Also, the use of secondary or tertiary alcoholic solvents was necessary for a smooth coupling. Other common organic solvents, including ethanol, did not work well (entries 17-19). We have also determined that the model reaction can tolerate up to 1.6 equiv of added water (entries 20-21). More water (3.0 equiv), however, was detrimental to product formation (entry 22). Thus, the studies of bases, solvents, and water addition suggest that the most effective activators of the boronic acid are potassium secondary/tertiary alkoxides, instead of the hydroxide. The alcohol solvents probably help to solubilize the boronic acids and, thereby, accelerate the coupling process. In order to achieve a reasonable reaction rate, heating was required (entry 23). Finally, a reduction in the ligand or catalyst loading led to lower yields (entries 24 and 25).

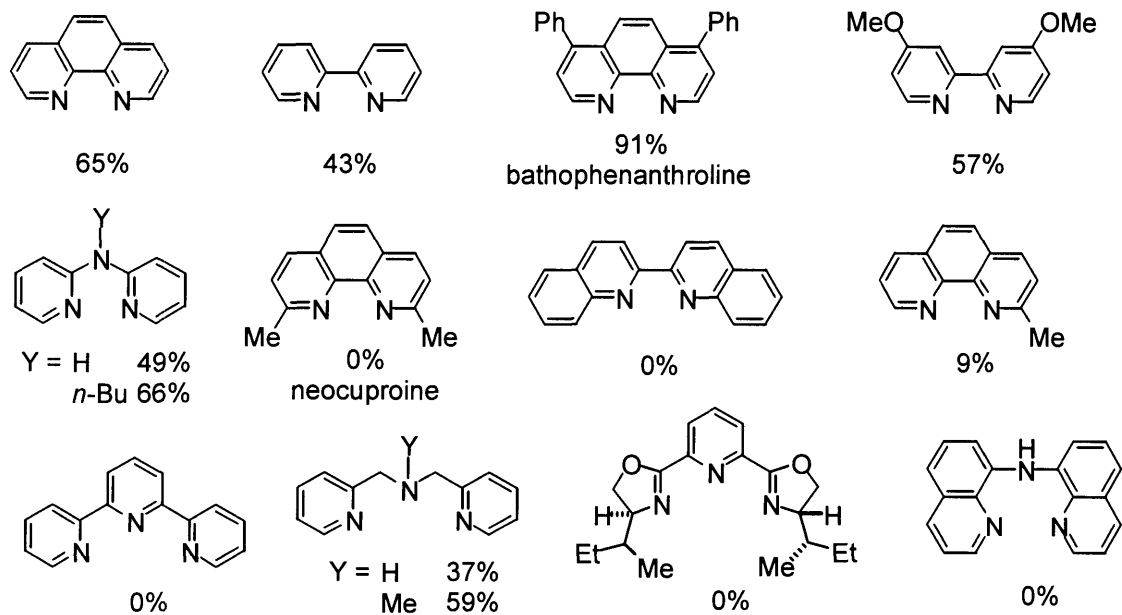
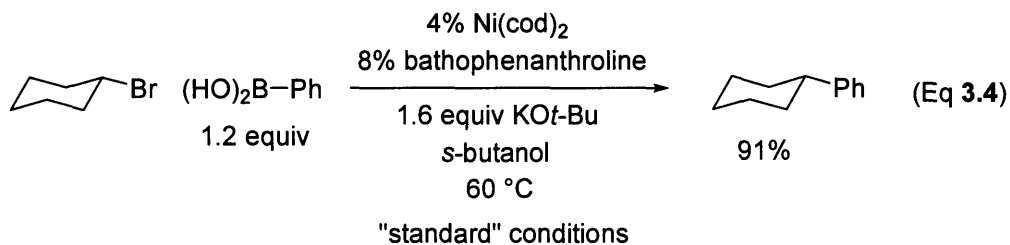


Figure 3.1. Ligands tested in the Suzuki reactions.

Table 3.1. Impact of Reaction Parameters on the Efficiency of the Model Suzuki Cross-Coupling (Eq 3.4)



entry	deviation from the "standard" conditions	yield (%) ^a
1	none	91
2	no Ni(cod) ₂	0
3	Ni(acac) ₂	24
4	NiCl ₂ or NiBr ₂	0
5	Pd(OAc) ₂ or Pd ₂ (dba) ₃	0
6	PPh ₃ or P(<i>t</i> -Bu) ₂ Me	2
7	1,3-bis(1-adamantyl)imidazol-2-ylidene	2
8	no bathophenanthroline	0
9	1.2 equiv KO ^t -Bu	73
10	KOEt	83
11	KOMe	63
12	KOH	9
13	NaO ^t -Bu	0
14	LiO ^t -Bu	7
15	<i>t</i> -BuOH	58
16	<i>i</i> -PrOH	84
17	EtOH	0
18	THF	7
18	acetone	2
19	DMA	0
20	addition of H ₂ O 1.0 equiv	74
21	1.6 equiv	61
22	3.0 equiv	5
23	r.t.	8
24	2% Ni(cod) ₂ , 4% bathophenanthroline	76
25	4% Ni(cod) ₂ , 4% bathophenanthroline	49

^a Yield according to GC, versus a calibrated internal standard (average of two runs).

Our optimized procedure can be applied directly to Suzuki cross-couplings of a range of secondary alkyl bromides (Table 3.2). Both electron-rich (entries 1-2) and electron-poor (entries 3-4) arylboronic acids can be coupled, along with certain heteroaryl boronic acids (entries 5-6). Interestingly, for the substrate illustrated in entry 7, the reaction occurs selectively at the secondary C(sp³)-Br, rather than the Ar-Cl, bond.

Table 3.2. Suzuki Cross-Couplings of Unactivated Secondary Alkyl Bromides (Eq 3.4)

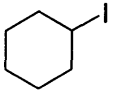
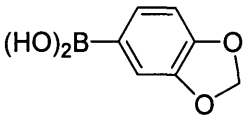
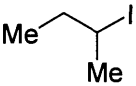
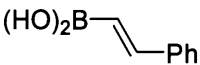
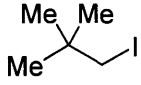
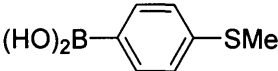
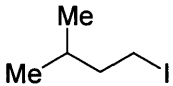
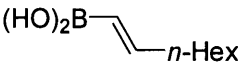
entry	R _{alkyl} -Br	(HO) ₂ B-R	yield (%)
1			90
2			68
3			44
4			63 ^a
5			63
6			67
7			75

^a The trans product was formed with >50:1 selectivity.

The method that we have developed for cross-coupling alkyl bromides can also be employed for Suzuki reactions of alkyl iodides (Table 3.3). Thus, without re-optimizing the conditions, we have determined that 4% Ni(cod)₂/8% bathophenanthroline catalyzed

couplings of secondary (entries 1-2) and primary (entries 3-4) alkyl iodides with aryl- and alkenylboronic acids in satisfactory yields.

Table 3.3. Suzuki Cross-Couplings of Unactivated Alkyl Iodides (Eq 3.4)

entry	R _{alkyl} -I	(HO) ₂ B-R	yield (%)
1			62
2			65
3			75
4			63

To determine the scope of the new method, we have also studied many other electrophiles under the standard conditions (Figure 3.2): (a) as in our nickel-mediated Negishi reactions, alkyl chlorides, alkyl tosylates, and tertiary alkyl bromides/iodides were inert; (b) again, 2,2-dihalopropanes did not react; (c) surprisingly, primary alkyl bromides were poor substrates (< 20% yield); (d) to our delight, 2-bromoadamantane and 2-bromohexane gave good yields; (e) the behavior of cyclic substrates was very different from the Negishi couplings; for instance, three- and four-membered cyclic bromides were suitable substrates, whereas the seven- and eight-membered were not; (f) notably, no desired products were isolated from 4-bromocyclohexanone **2.1** or 4-bromopiperidine **2.2**; (g) the standard coupling conditions can also be applied to some activated alkyl halides, for example, allyl bromide, benzyl bromide, and benzyl chloride yielded ~64% of products. Unfortunately, no desired product was generated from 1-phenylethyl bromide; (h) one more major disparity of the current method from the nickel-catalyzed Negishi reactions was the low-yielding reactions with aryl or vinyl halides.

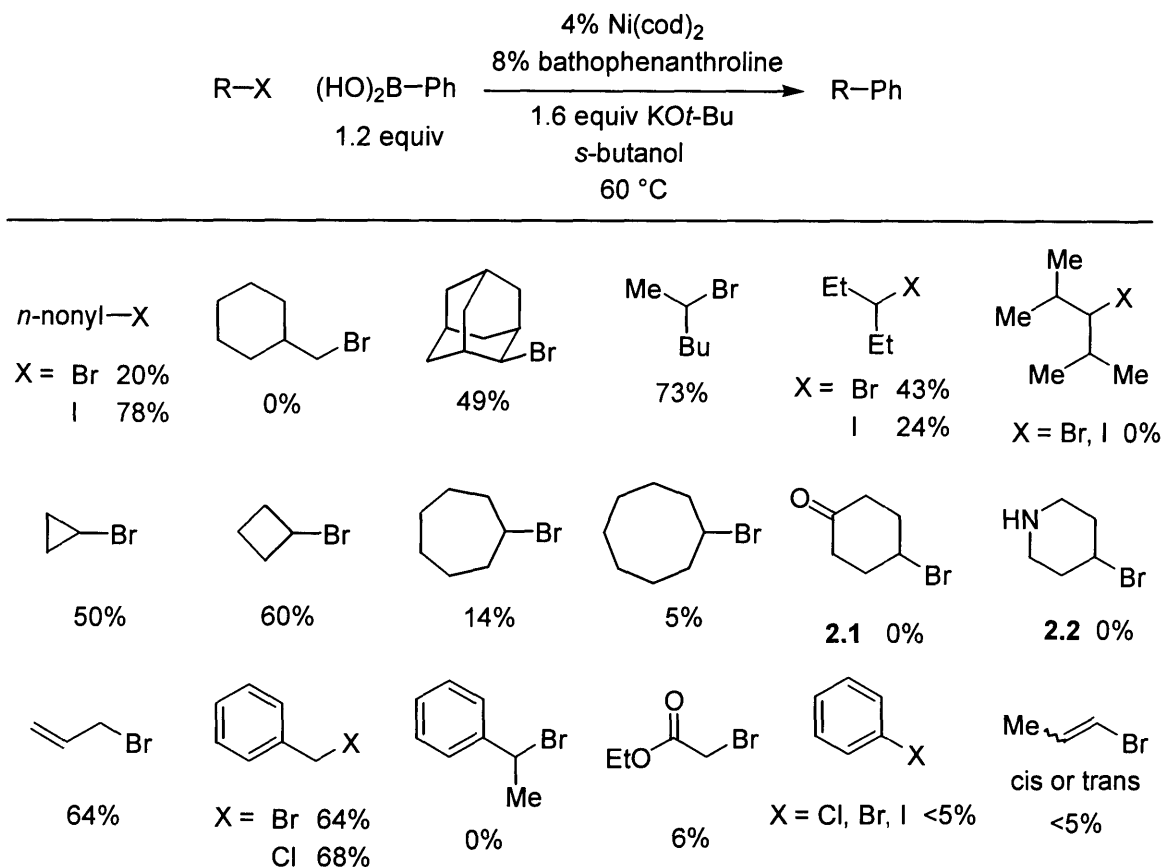
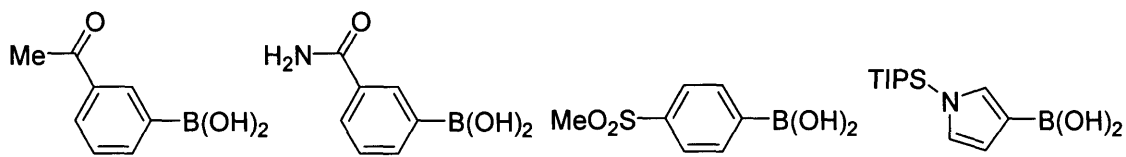


Figure 3.2. Organic halides tested under the standard conditions.

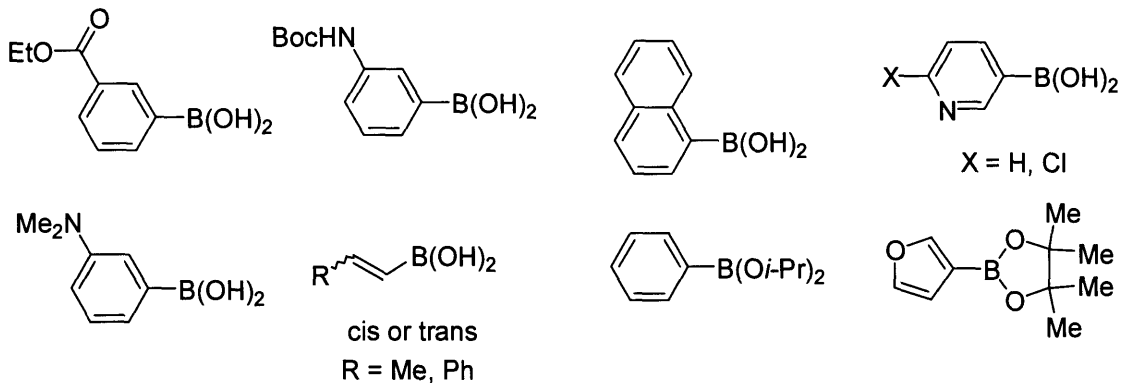
Concerning the scope of the organoboronic acids,¹³² we have a few comments (Figure 3.3): (a) in addition to the functionalities showcased in Tables 3.2 and 3.3, ketones, amides, esters, carbamates, anilines, and sulfones on the arylboronic acids can be tolerated with certain success, but not aldehydes, nitro groups, and aryl halides; (b) in terms of steric influence, *ortho*-substitution on the arylboronic acids severely impeded the reaction; (c) we found that acidic hydrogens of phenols, alcohols, carboxylic acids, and indoles were also problematic, even in the presence of extra base; (d) 3-heteroaryl boronic acids were reasonably reactive, including protected pyrrole, furan, and thiophene rings. In contrast, more challenging 2-heteroaromatic ones did not form any cross-coupling adducts in our reactions; (e) some vinylboronic acids were proven to be good coupling partners, but not alkylboronic acids; (f) other organoboron reagents (isopropyl esters and pinacol esters) were moderately reactive, whereas catecholboronates and trifluoroborates did not furnish any desired products.

¹³² We thank Frontier Scientific for free samples of organoboronic acids.

good yield (>50%)



modest yield (10-50%)



poor yield (<10%)

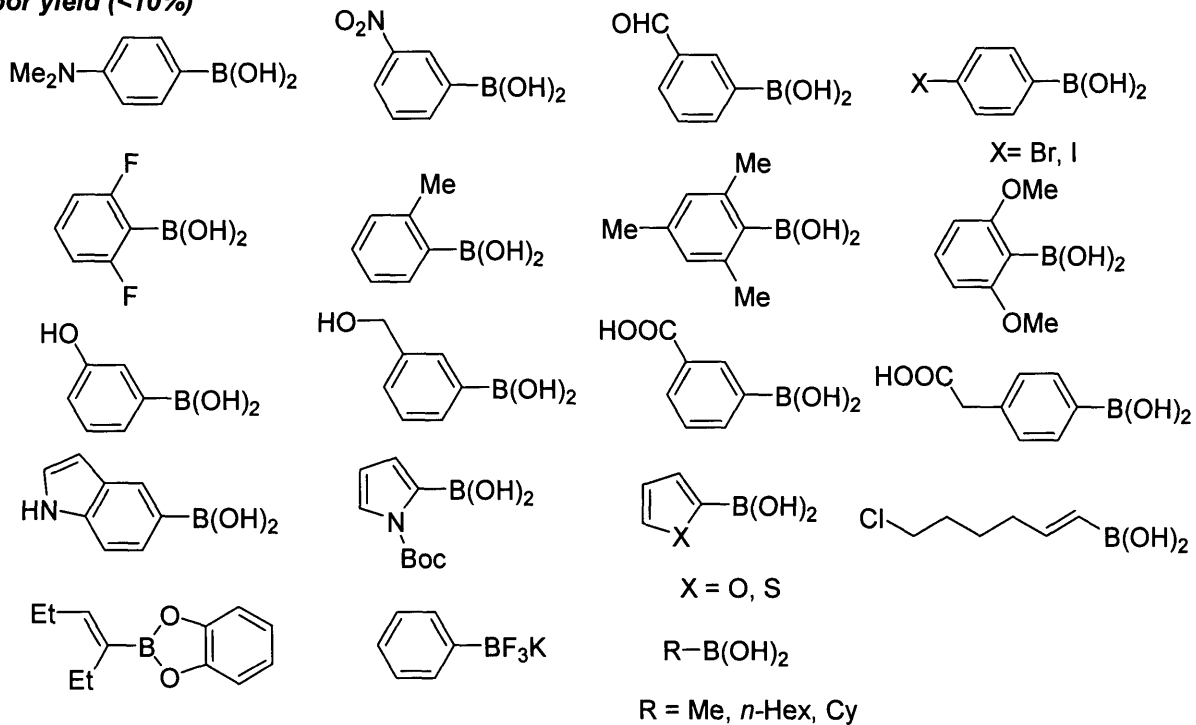
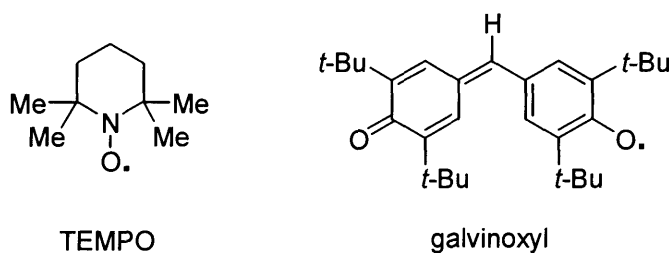


Figure 3.3. Results from organoboronic acids and related reagents under the standard conditions.

3.3. Mechanistic Considerations

It is noteworthy that in entry 4 of Table 3.2, the *trans* bromide yielded almost exclusively the *trans* adduct. This stereochemical outcome is governed by sterics, and cannot fit into the pathway of an S_N2-type oxidative addition with configurational inversion, followed by stereochemistry-preserving reductive elimination. The data are consistent with an organic radical being produced during the oxidative addition, and then an incipient nickel-carbon bond being formed on the less shielded side of the indane framework.

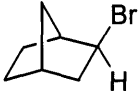
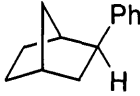
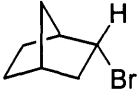
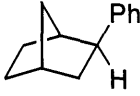
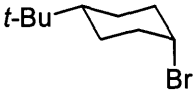
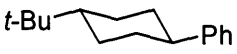
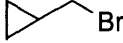
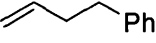
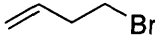
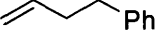
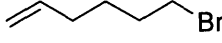
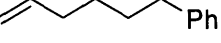
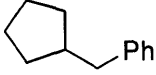
To test this hypothesis, we included radical traps (0.25 or 1.0 equiv) in the model reaction. The radical traps, TEMPO or galvinoxyl, dramatically altered the course of the reaction, and as a result no desired adduct was formed. However, this result alone should not be interpreted as the ultimate proof for the radical mechanism, since there is a caveat that these radical scavengers may not only react with organic radicals, but also interfere with the transition metal catalysts.¹³³



In addition, the proposed radical pathway has received substantiation from couplings of some substrate-based probes (Table 3.4). First, 2-bromonorbornanes (entries 1 and 2), regardless of their stereochemistry, gave exclusively the more stable, *exo* adduct. Second, *cis*-4-*t*-butylcyclohexyl bromide provided two products with a *trans/cis* ratio of 12:1 (entry 3). Third, cyclopropylmethyl bromide underwent complete ring opening before the carbon-carbon bond formation (entries 4 and 5). Fourth, from 6-bromo-1-hexene we observed a 5-*exo*-cyclized product in addition to the linear one (entry 6). All these data are consistent with the involvement of organic radicals during the oxidative addition step.

¹³³ Albéniz, A. C.; Espinet, P.; López-Fernández, R.; Sen, A. *J. Am. Chem. Soc.* **2002**, *124*, 11278–11279.

Table 3.4. Suzuki Cross-Couplings of Substrate-Based Mechanistic Probes (Eq 3.4)

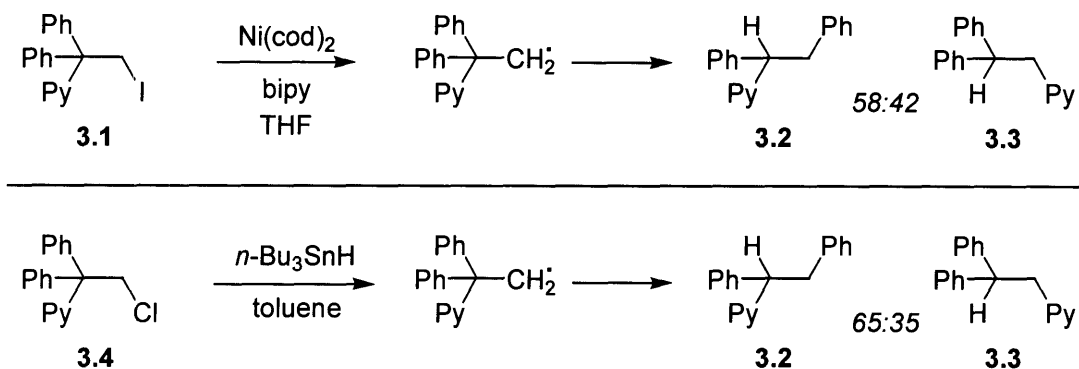
		$\begin{array}{c} \text{R-Br} \quad (\text{HO})_2\text{B-Ph} \\ \xrightarrow[\text{1.2 equiv}]{\begin{array}{c} 4\% \text{ Ni(cod)}_2 \\ 8\% \text{ bathophenanthroline} \\ 1.6 \text{ equiv KO}t\text{-Bu} \\ \text{s-butanol} \\ 60^\circ\text{C} \end{array}} \text{R-Ph} \end{array}$	
entry	R-X	product	(%) ^a
1			74% ^b
2			71% ^b
3			82% trans/cis 12:1
4			25%
5			4%
6			14%  6%

^a Yield according to GC, versus a calibrated internal standard.

^b The exo product was formed in >50:1 selectivity. Isolated yields.

In fact, some evidence already exists in literature supporting such a radical pathway. When Ni(cod)_2 and bipy were treated with 2,2-diphenyl-2-(2-pyridyl)ethyl iodide **3.1** in THF, a mixture of reduction products **3.2** and **3.3** were produced, after competitive [1,2]-phenyl and pyridyl shifts. When D_2O was added during workup, no deuterium was incorporated into the products, indicating the absence of carbanionic species. Furthermore, the corresponding chloride **3.4**, when subjected to $n\text{-Bu}_3\text{SnH}$, also yielded **3.2** and **3.3** in a similar ratio. The latter process is well known to involve radical intermediates. Since the relative migratory aptitude of the aryl groups is diagnostic of

reaction intermediates, the reaction of the (bipy)Ni complex, also of keen interest in our studies, most likely shares a common radical pathway.¹³⁴



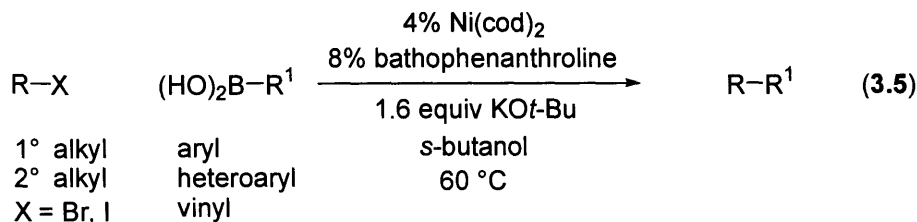
To date, many other important questions related to the reaction mechanism still remain unanswered, for example, whether the catalysis follows a conventional Ni(0)/Ni(II) cycle, which nickel species is directly responsible for the electron transfer, and whether the radicals later formally combine with the nickel center.

3.4. Conclusion and Outlook

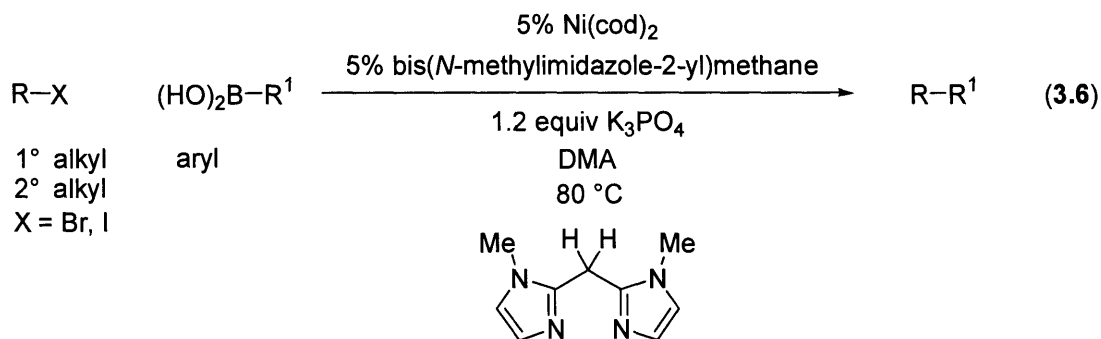
In conclusion, we have developed a catalyst system that achieves the first Suzuki reactions of unactivated secondary alkyl bromides and iodides (Eq 3.5).¹³⁵ The ability to couple readily available, user-friendly organoboronic acids is an attractive feature of this process. We have also charted the boundaries of both the electrophilic and nucleophilic components in these reactions; some rather hindered halides are reasonably successful. With respect to a mechanistic understanding, we have accumulated some evidence in support of a radical mechanism during the oxidative addition.

¹³⁴ Eisch, J. J.; Kovacs, C. A.; Chobe, P.; Boleslawski, M. P. *J. Org. Chem.* **1987**, *52*, 4427–4437.

¹³⁵ Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340–1341. This paper is ranked the third most requested document under the category of chemistry and related science in 2004 via CAS online services: CAS Science Spotlight. <http://www.cas.org/spotlight/request.html> (accessed July 2005).



Soon after we disclosed the nickel-catalyzed Negishi and Suzuki cross-couplings,¹³⁶ patents by Itahashi and Kamikawa at Sumitomo Chemical were released, claiming nickel-catalyzed couplings between arylboronic acids and alkyl halides. In one patent, phenanthroline was employed and the scope was limited to primary alkyl halides,¹³⁷ while in the other document, they managed to incorporate secondary bromides and iodides as the coupling electrophiles with a different ligand, bis(*N*-methylimidazole-2-yl)methane (Eq 3.6).¹³⁸



Our work has also served as a stepping stone for the development of similar cross-coupling processes using other coupling partners. Using nickel catalysts, Dr. David Powell and Dr. Toshihide Maki in our group successfully expanded the reactions to Hiyama and Stille couplings (Eqs 3.7 and 3.8).¹³⁹ As with Suzuki reactions, effective

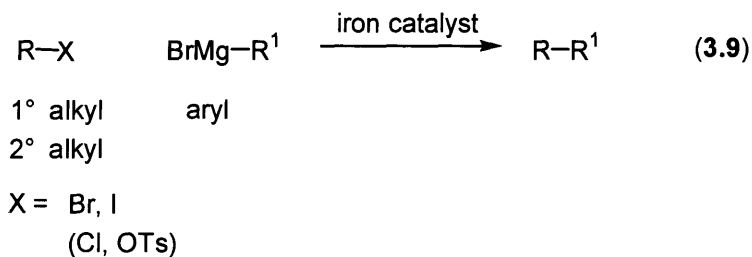
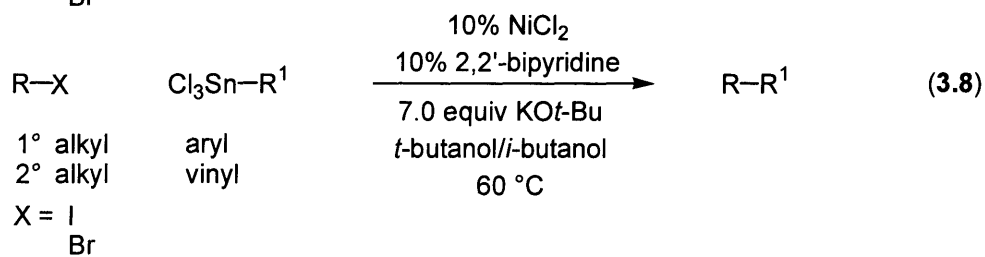
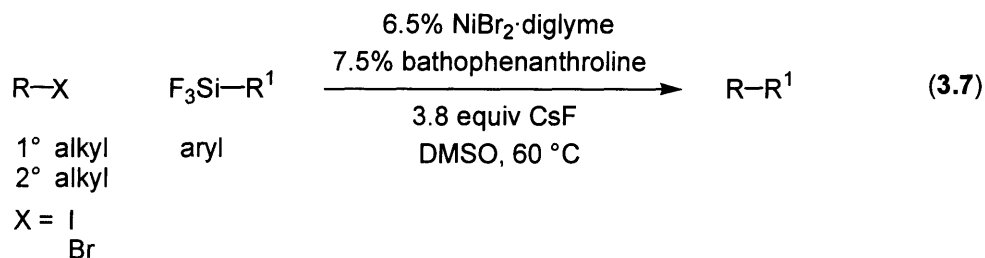
¹³⁶ For reviews on this topic, see: (a) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532. (b) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688.

¹³⁷ (a) Itahashi, T.; Kamikawa, T. Production Method of a Coupling Compound. U.S. Patent 2004167364, Aug. 26, 2004. (b) Itahashi, T.; Kamikawa, T. Production Method of a Cross-Coupling Compound from an Alkyl Halide and an Organoboron Compound. Eur. Pat. Appl. 1449580, Aug. 25, 2004.

¹³⁸ (a) Itahashi, T.; Kamikawa, T. Method for Producing Coupling Compound. U.S. Patent 2004161404, Aug. 19, 2004. (b) Itahashi, T.; Kamikawa, T. Method for Preparing Suzuki Coupling Compounds, in Particular Alkylarenes, in the Presence of a Base and a Catalytic System Comprising a Ni Compound and a Bisimidazolium Derivative. Eur. Pat. Appl. 1439157, July 21, 2004.

¹³⁹ (a) Powell, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 7788–7789. (b) Powell, D. A.; Maki, T.; Fu,

activation was necessary for these arylsilicon and organotin reagents. Based on similarities among these three systems, we suspect that they probably share a similar catalytic cycle.



Another remarkable advance in this field is the development of iron-catalyzed Kumada-type reactions of secondary alkyl bromides, iodides, and occasionally chlorides and tosylates (Eq 3.9).^{140,141} However, the reactivity was confined to aryl Grignard reagents, which are incompatible with many functional groups. To solve this problem, Nakamura et al. recently expanded the iron-catalyzed reactions to arylzinc reagents.¹⁴² Fe/Mg clusters of the formal composition $[\text{Fe}(\text{MgX})_2]_n$ have been postulated to account

G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510–511.

¹⁴⁰ (a) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297–1299. (b) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686–3687. (c) Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955–3957.

¹⁴¹ The seed for iron-promoted Kumada reactions of alkyl halides has been planted much earlier: Tamura, M.; Kochi, J. *J. Organomet. Chem.* **1971**, *31*, 289–309.

¹⁴² Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, 1794–1798.

for the unusual reactivity. Interestingly, these reactions also display the traits of radical intermediates.

The discussion on displacement of alkyl electrophiles for carbon-carbon bond formation will not be complete without mentioning organocuprates. They are mostly derived from Grignard or organolithium reagents, and are well known to couple with unactivated, secondary alkyl halides and sulfonates.¹⁴³ Besides the problem with functional group tolerance, these reactions often require large excess of organocopper reagents and low reaction temperature. Over years, several copper catalysts have also emerged to effect alkyl couplings using Grignard reagents.¹⁴⁴

So far, we have provided some proof-of-principle examples for cross-couplings of secondary alkyl electrophiles. Nevertheless, these methods are not yet versatile and further improvement in the substrate scope is imperative so that they can become generally useful tools for carbon-carbon bond formation. Another obvious direction in the future will be catalytic, asymmetric cross-couplings employing chiral ligands. The use of readily available, racemic secondary electrophiles for the production of optically pure compounds can be an attractive potential advantage of this approach.

¹⁴³ For reviews, see: (a) Posner, G. H. *Org. React.* **1972**, *19*, 1–113. (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005–5038. (c) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135–631. (d) Lipshutz, B. H. *Adv. Metal-Organic Chemistry* **1995**, *4*, 1–64.

¹⁴⁴ (a) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303–305. (b) Burns, D. H.; Miller, J. D.; Chan, H.-K.; Delaney, M. O. *J. Am. Chem. Soc.* **1997**, *119*, 2125–2133. (c) Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* **2000**, *56*, 2733–2737.

3.5. Experimental

I. General

The following reagents were purchased: Ni(cod)₂ (Strem), bathophenanthroline (Lancaster), KO^t-Bu (Strem), *s*-butanol (anhydrous; Aldrich), *exo*-2-bromonorbornane (*exo*:*endo* 115:1; Aldrich), 1-bromobenzocyclobutane (Aldrich), isopropyl bromide (Alfa-Aesar), cyclopentyl bromide (Alfa-Aesar), *trans*-2-bromo-1-hydroxylindane (Lancaster), cyclohexyl bromide (Alfa-Aesar), cyclohexyl iodide (Lancaster), *s*-butyl iodide (TCI), neopentyl iodide (Aldrich), 1-iodo-3-methylbutane (Aldrich), phenylboronic acid (Frontier Scientific), *p*-tolylboronic acid (Frontier Scientific), 4-methoxyphenylboronic acid (Frontier Scientific), 4-cyanophenylboronic acid (Frontier Scientific), 4-trifluoromethylphenylboronic acid (Frontier Scientific), 3-thiopheneboronic acid (Aldrich), *N*-methylindole-5-boronic acid (Frontier Scientific), 3-chlorophenylboronic acid (Frontier Scientific), 3,4-methylenedioxyphenylboronic acid (Frontier Scientific), *trans*- β -styreneboronic acid (Frontier Scientific), 4-methylthiophenylboronic acid (Frontier Scientific), (*E*)-1-octen-1-ylboronic acid (Aldrich). *endo*-2-Bromonorbornane [13237-87-1] (*endo*:*exo* 32:1) was prepared according to a literature procedure.¹⁴⁵ The liquid alkyl halides were purged with argon prior to use. Other reagents were used as received.

All reactions were conducted in oven-dried glassware under an inert atmosphere with magnetic stirring.

II. Preparation of Substrates

***trans*-2-Bromo-1-(*t*-butyldimethylsiloxy)indane.** Imidazole (0.96 g, 14 mmol) was added to a solution of *trans*-2-bromo-1-hydroxylindane (2.00 g, 9.4 mmol) and TBSCl (1.83 g, 12.2 mmol) in CH₂Cl₂ (50 mL) at r.t. This reaction mixture was stirred

¹⁴⁵ (a) Tamao, K.; Yoshida, J.-i.; Takahashi, M.; Yamamoto, H.; Kakui, T.; Matsumoto, H.; Kurita, A.; Kumada, M. *J. Am. Chem. Soc.* **1978**, *100*, 290–292. (b) Tamao, K.; Yoshida, J.-i.; Murata, M.; Kumada, M. *J. Am. Chem. Soc.* **1980**, *102*, 3267–3269. (c) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887–9888. (d) Uozumi, Y.; Lee, S.-Y.; Hayashi, T. *Tetrahedron Lett.* **1992**, *33*, 7185–7188.

overnight, and then the resulting yellow suspension was filtered through a pad of silica gel (washed with 10:1 hexane/EtOAc). The filtrate was concentrated, and the residue was purified by flash chromatography (hexane), which provided 2.72 g (88%) of the desired product as a yellow oil.

^1H NMR (400 MHz, CDCl_3): δ 7.33-7.22 (m, 4H), 5.33 (d, $J = 5.7$ Hz, 1H), 4.27 (dd, $J = 13.8, 7.4$ Hz, 1H), 3.58 (dd, $J = 16.1, 7.4$ Hz, 1H), 3.22 (dd, $J = 16.1, 7.5$ Hz, 1H), 0.99 (s, 9H), 0.29 (s, 3H), 0.26 (s, 3H).

^{13}C NMR (400 MHz, CDCl_3): δ 143.2, 139.7, 128.6, 127.5, 124.6, 124.3, 84.0, 55.0, 40.9, 26.1, 18.4, -3.6, -4.1.

IR (thin film): 2956, 2929, 2894, 2857, 1471, 1462, 1362, 1257 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{15}\text{H}_{22}\text{BrSiO}$ (M-H) $^+$: 325.0623. Found: 325.0628.

III. Suzuki Cross-Coupling Reactions (Tables 3.2 and 3.3)

Procedure for Table 3.1 and Table 3.4 (except entries 1 and 2). In a glove box, $\text{Ni}(\text{cod})_2$ (2.8 mg, 0.010 mmol), bathophenanthroline (6.6 mg, 0.020 mmol), phenyl boronic acid (37 mg, 0.30 mmol), $\text{KO}t\text{-Bu}$ (45 mg, 0.40 mmol), and *s*-butanol (1.5 mL) were added to a vial equipped with a stir bar. The mixture was stirred at r.t. for 10 min, and to the resulting deep-purple solution was added the cyclohexyl bromide (41 mg, 0.25 mmol). The vial was removed from the glove box, and the reaction mixture was stirred at 60 °C for 5 h. Then, it was mixed with *n*- $\text{C}_{14}\text{H}_{30}$ (internal standard for GC analysis; 26 μL , 0.10 mmol), and an aliquot was passed through silica gel and analyzed by GC.

Procedure for Table 3.2, 3.3, 3.4 (entries 1 and 2): no glove box. $\text{Ni}(\text{cod})_2$ (5.6 mg, 0.020 mmol), bathophenanthroline (13.2 mg, 0.040 mmol), the arylboronic acid (0.60 mmol), and $\text{KO}t\text{-Bu}$ (90 mg, 0.80 mmol) were added to a vial equipped with a stir bar. The vial was evacuated/refilled with argon three times, and then *s*-butanol (3.0 mL) was added. The mixture was stirred at r.t. for 10 min, and to the resulting deep-purple solution was added the alkyl halide (0.50 mmol). The reaction mixture was stirred at 60 °C for 5 h, and then it was passed through a short pad of silica gel (to remove *s*-butanol and polar compounds). The filtrate was concentrated, and the residue was purified by flash chromatography.

Procedure for Table 3.2, 3.3, 3.4 (entries 1 and 2): with a glove box. In a glove box, Ni(cod)₂ (5.6 mg, 0.020 mmol), bathophenanthroline (13.2 mg, 0.040 mmol), the arylboronic acid (0.60 mmol), KO^t-Bu (90 mg, 0.80 mmol), and *s*-butanol (3.0 mL) were added to a vial equipped with a stir bar. The mixture was stirred at r.t. for 10 min, and to the resulting deep-purple solution was added the alkyl halide (0.50 mmol). The vial was removed from the glove box, and the reaction mixture was stirred at 60 °C for 5 h. Then, it was passed through a short pad of silica gel (to remove *s*-butanol and polar compounds), and the filtrate was concentrated. The residue was purified by flash chromatography.

1-*p*-Tolylbenzocyclobutene (Table 3.2, entry 1). 1-Bromobenzocyclobutane (92 mg, 0.50 mmol) and *p*-tolylboronic acid (81 mg, 0.60 mmol) were used. Solvent for chromatography: hexane. Colorless oil (no glove box: 87 mg, 90%; glove box: 82 mg, 84%).

¹H NMR (400 MHz, CDCl₃): δ 7.36-7.31 (m, 2H), 7.24-7.17 (m, 6H), 4.73 (dd, *J* = 5.5, 2.6 Hz, 1H), 3.77 (dd, *J* = 13.9, 5.6 Hz, 1H), 3.13 (dd, *J* = 13.9, 2.6 Hz, 1H), 2.40 (s, 3H).

¹³C NMR (400 MHz, CDCl₃): δ 148.1, 144.4, 140.0, 136.1, 129.3, 127.7, 127.3, 127.0, 123.4, 122.9, 47.4, 40.3, 21.3.

IR (thin film): 3021, 2921, 1661, 1513, 1459 cm⁻¹.

HRMS (EI): Calcd for C₁₅H₁₄ (M⁺): 194.1090. Found: 194.1090.

4-Isopropylanisole [4132-48-3] (Table 3.2, entry 2). Isopropyl bromide (62 mg, 0.50 mmol) and 4-methoxyphenylboronic acid (99 mg, 0.60 mmol) were used. Solvent for chromatography: hexane/ethyl ether 100:1. Colorless oil (no glove box: 51 mg, 68%; glove box: 50 mg, 67%).

¹H NMR (400 MHz, CDCl₃): δ 7.25-7.21 (m, 2H), 6.94-6.90 (m, 2H), 3.87 (s, 3H), 2.94 (heptet, *J* = 6.9 Hz, 1H), 1.30 (d, *J* = 6.9 Hz, 6H).

¹³C NMR (400 MHz, CDCl₃): δ 157.8, 141.3, 127.5, 113.9, 55.5, 33.5, 24.4.

3-Cyclopentylbenzotrile (Table 3.2, entry 3). Cyclopentyl bromide (76 mg, 0.50 mmol) and 3-cyanophenylboronic acid (89 mg, 0.60 mmol) were used. Solvent for chromatography: hexane/ethyl ether 100:1. Colorless oil (no glove box: 38 mg, 44%; glove box: 40 mg, 47%).

^1H NMR (400 MHz, CDCl_3): δ 7.54 (s, 1H), 7.50-7.48 (m, 2H), 7.41-7.37 (m, 1H), 3.03 (m, 1H), 2.15-2.08 (m, 2H), 1.88-1.80 (m, 2H), 1.78-1.69 (m, 2H), 1.63-1.53 (m, 2H).

^{13}C NMR (400 MHz, CDCl_3): δ 148.1, 132.0, 130.9, 129.6, 129.2, 119.4, 112.3, 45.6, 34.6, 25.6.

IR (thin film): 2955, 2869, 2228, 1483 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{12}\text{H}_{13}\text{N}$ (M^+): 171.1043. Found: 171.1035.

***trans*-1-*t*-Butyldimethylsiloxy-2-(4-trifluoromethylphenyl)indane (Table 3.2, entry 4).** *trans*-2-Bromo-1-*t*-butyldimethylsiloxyindane (164 mg, 0.50 mmol) and 4-trifluoromethylphenylboronic acid (114 mg, 0.60 mmol) were used. Solvent for chromatography: hexane/ethyl ether 100:1. Colorless oil (no glove box: 123 mg, 63%; glove box: 118 mg, 60%). ^1H NMR revealed a product *trans*:*cis* ratio of >50:1.¹⁴⁶

^1H NMR (400 MHz, CDCl_3): δ 7.62 (d, $J = 8.1$ Hz, 2H), 7.47 (d, $J = 8.1$ Hz, 2H), 7.33-7.25 (m, 4H), 5.29 (d, $J = 7.7$ Hz, 1H), 3.50 (dd, $J = 17.8, 8.2$ Hz, 1H), 3.36 (dd, $J = 15.7, 8.2$ Hz, 1H), 3.08 (dd, $J = 15.6, 9.9$ Hz, 1H), 0.89 (s, 9H), 0.04 (s, 3H), -0.35 (s, 3H).

^{13}C NMR (400 MHz, CDCl_3): δ 147.2, 144.7, 140.5, 129.1, 128.7, 128.3, 127.3, 125.61, 125.57, 124.8, 124.1, 83.9, 57.3, 38.3, 25.9, 18.2, -4.3, -4.7.

^{19}F NMR (400 MHz, CDCl_3): δ -62.6.

IR (thin film): 2955, 2930, 2858, 1620, 1326 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{18}\text{H}_{18}\text{SiOF}_3$ ($\text{M}-\text{C}_4\text{H}_9$)⁺: 335.1074. Found: 335.1075.

3-Cyclohexylthiophene [120659-34-9] (Table 3.2, entry 5). Cyclohexyl bromide (82 mg, 0.50 mmol) and 3-thiopheneboronic acid (77 mg, 0.60 mmol) were used. Solvent for chromatography: hexane. Colorless oil (no glove box: 52 mg, 63%; glove box: 51 mg, 61%).

^1H NMR (400 MHz, CDCl_3): δ 7.27 (dd, $J = 5.7, 3.7$ Hz, 1H), 7.02 (d, $J = 4.9$ Hz, 1H), 6.96 (d, $J = 2.1$ Hz, 1H), 2.67-2.62 (m, 1H), 2.05-2.00 (m, 2H), 1.86-1.84 (m, 2H), 1.81-1.74 (m, 1H), 1.47-1.35 (m, 4H), 1.32-1.24 (m, 1H).

¹⁴⁶ *trans*-1-*t*-Butyldimethylsiloxy-2-phenylindane was synthesized via hydroboration/oxidation of commercially available 2-phenylindene, followed by silylation of the secondary alcohol. The coupling patterns for the protons at C_2 and C_3 are essentially identical to those for the reaction product of Table 3.2, entry 4.

^{13}C NMR (400 MHz, CDCl_3): δ 149.3, 127.2, 125.1, 118.5, 39.7, 34.4, 26.8, 26.4.

***N*-Methyl-5-cyclohexylindole (Table 3.2, entry 6).** Cyclohexyl bromide (82 mg, 0.50 mmol) and *N*-methylindole-5-boronic acid (105 mg, 0.60 mmol) were used. Solvent for chromatography: hexane/ethyl ether 100:1. Yellow solid (no glove box: 71 mg, 67%; glove box: 69 mg, 65%).

^1H NMR (400 MHz, CDCl_3): δ 7.51 (t, $J = 0.8$ Hz, 1H), 7.29 (d, $J = 11.3$ Hz, 1H), 7.16 (dd, $J = 8.4, 1.6$ Hz, 1H), 7.06 (d, $J = 3.1$ Hz, 1H), 6.48 (d, $J = 3.1$ Hz, 1H), 3.81 (s, 3H), 2.68-2.61 (m, 1H), 1.98 (d, $J = 11.9$ Hz, 2H), 1.91 (d, $J = 12.2$ Hz, 2H), 1.84-1.80 (m, 1H), 1.60-1.42 (m, 4H), 1.39-1.32 (m, 1H).

^{13}C NMR (400 MHz, CDCl_3): δ 139.5, 135.6, 129.0, 128.7, 121.4, 118.4, 109.1, 100.7, 44.9, 35.4, 33.0, 27.4, 26.5.

IR (KBr pellet): 2921, 2849, 1511, 1490, 1446, 1424 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{15}\text{H}_{19}\text{N}$ (M^+): 213.1512. Found: 213.1509.

3-Cyclohexyl-1-chlorobenzene [27163-66-2] (Table 3.2, entry 7). Cyclohexyl bromide (82 mg, 0.50 mmol) and 3-chlorophenylboronic acid (94 mg, 0.60 mmol) were used. Solvent for chromatography: hexane. Colorless oil (no glove box: 71 mg, 75%; glove box: 68 mg, 70%).

^1H NMR (400 MHz, CDCl_3): δ 7.26-7.22 (m, 2H), 7.19-7.16 (m, 1H), 7.12-7.10 (m, 1H), 2.54-2.48 (m, 1H), 1.89-1.86 (m, 4H), 1.80-1.76 (m, 1H), 1.47-1.35 (m, 4H), 1.31-1.25 (m, 1H).

^{13}C NMR (400 MHz, CDCl_3): δ 150.3, 134.2, 129.7, 127.2, 126.1, 125.3, 44.5, 34.5, 27.0, 26.2.

Formaldehyde 4-cyclohexyl-1,2-catechol acetal (Table 3.3, entry 1). Cyclohexyl iodide (106 mg, 0.50 mmol) and 3,4-methylenedioxyphenylboronic acid (100 mg, 0.60 mmol) were used. Solvent for chromatography: hexane/ethyl ether 100:1. Colorless oil (no glove box: 63 mg, 62%; glove box: 61 mg, 60%).

^1H NMR (400 MHz, CDCl_3): δ 6.77-6.75 (m, 2H), 6.68 (dd, $J = 8.0, 1.6$ Hz, 1H), 5.94 (s, 2H), 2.48-2.43 (m, 1H), 1.87-1.85 (m, 4H), 1.81-1.75 (m, 1H), 1.45-1.33 (m, 4H), 1.30-1.23 (m, 1H).

^{13}C NMR (400 MHz, CDCl_3): δ 147.6, 145.6, 142.5, 119.7, 108.2, 107.5, 100.9, 44.6, 35.0, 27.1, 26.3.

IR (thin film): 2925, 2851, 1503, 1490, 1441, 1247 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_2$ (M^+): 204.1145. Found: 204.1143.

(E)-3-Methyl-1-phenyl-1-pentene [15325-63-0] (Table 3.3, entry 2). *s*-Butyl iodide (92 mg, 0.50 mmol) and *trans*- β -styreneboronic acid (89 mg, 0.60 mmol) were used. Solvent for chromatography: hexane. Colorless oil (no glove box: 52 mg, 65%; glove box: 49 mg, 61%).

^1H NMR (400 MHz, CDCl_3): δ 7.39-7.37 (m, 2H), 7.33-7.29 (m, 2H), 7.23-7.19 (m, 1H), 6.36 (d, J = 15.9 Hz, 1H), 6.12 (dd, J = 15.9, 7.9 Hz, 1H), 2.22 (m, 1H), 1.43 (quintet, J = 8.2 Hz, 2H), 1.10 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H).

^{13}C NMR (400 MHz, CDCl_3): δ 138.2, 137.0, 128.7, 128.3, 126.9, 126.2, 39.1, 30.0, 20.4, 12.1.

Methyl 4-neopentylphenyl thioether (Table 3.3, entry 3). Neopentyl iodide (100 mg, 0.50 mmol) and 4-methylthiophenylboronic acid (101 mg, 0.60 mmol) were used. Solvent for chromatography: hexane/ethyl ether 100:3. Colorless oil (no glove box: 73 mg, 75%; glove box: 68 mg, 70%).

^1H NMR (400 MHz, CDCl_3): δ 7.21-7.19 (m, 2H), 7.08-7.06 (m, 2H), 2.50 (s, 3H), 2.47 (s, 2H), 0.91 (s, 9H).

^{13}C NMR (400 MHz, CDCl_3): δ 137.1, 135.3, 131.2, 126.5, 49.9, 32.0, 29.5, 16.4.

IR (thin film): 2920, 2864, 1495, 1476, 1363 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{12}\text{H}_{18}\text{S}$ (M^+): 194.1124. Found: 194.1119.

(E)-2-Methyl-5-dodecene [112197-48-5] (Table 3.3, entry 4). 1-Iodo-3-methylbutane (100 mg, 0.50 mmol) and (*E*)-1-octen-1-ylboronic acid (94 mg, 0.60 mmol) were used. Solvent for chromatography: hexane. Colorless oil (no glove box: 57 mg, 63%; glove box: 56 mg, 61%).

^1H NMR (400 MHz, CDCl_3): δ 5.42-5.40 (m, 2H), 1.20 (br s, 4H), 1.57 (heptet, J = 6.6 Hz, 1H), 1.35-1.22 (m, 10H), 0.92-0.89 (m, 9H).

^{13}C NMR (400 MHz, CDCl_3): δ 130.7, 130.4, 39.1, 32.9, 32.0, 30.7, 29.9, 29.1, 27.7, 22.9, 22.7, 14.3.

***exo*-2-Phenylnorbornane [52752-81-5] (Table 3.4, entry 1).** *exo*-2-Bromonorbornane (88 mg, 0.50 mmol; *exo*:*endo* 115:1) and phenylboronic acid (74 mg, 0.60 mmol) were used. Solvent for chromatography: hexane. Colorless oil (no glove box: 64 mg, 74%; glove box: 63 mg, 73%). ¹H NMR revealed a product *exo*:*endo* ratio of >50:1. The assignment of product stereochemistry is based on comparison with reported ¹H and ¹³C NMR spectra.¹⁴⁷

¹H NMR (400 MHz, CDCl₃): δ 7.34-7.31 (m, 2H), 7.28-7.26 (m, 2H), 7.21-7.18 (m, 1H), 2.79 (dd, *J* = 8.7, 5.8 Hz, 1H), 2.40 (d, *J* = 3.1 Hz, 2H), 1.85-1.79 (m, 1H), 1.74-1.68 (m, 1H), 1.65-1.57 (m, 3H), 1.43-1.30 (m, 2H), 1.23 (dd, *J* = 8.2 Hz, 1.5 Hz, 1H).

¹³C NMR (400 MHz, CDCl₃): δ 147.8, 128.4, 127.3, 125.6, 47.5, 43.1, 39.3, 37.0, 36.3, 30.8, 29.1.

***exo*-2-Phenylnorbornane [52752-81-5] (Table 3.4, entry 2).** *endo*-2-Bromonorbornane (88 mg, 0.50 mmol; *endo*:*exo* 32:1) and phenylboronic acid (74 mg, 0.60 mmol) were used. Solvent for chromatography: hexane. Colorless oil (no glove box: 62 mg, 71%; glove box: 64 mg, 74%). ¹H NMR revealed a product *exo*:*endo* ratio of >50:1. The assignment of product stereochemistry is based on comparison with reported ¹H and ¹³C NMR spectra.

¹⁴⁷ (a) *exo*-2-Phenylnorbornane: Brunel, J. M.; Heumann, A.; Buono, G. *Angew. Chem., Int. Ed.* 2000, 39, 1946–1949; Namyslo, J. C.; Kaufmann, D. E. *Chem. Ber.* 1997, 130, 1327–1331. (b) *endo*-2-Phenylnorbornane: Tateiwa, J.-i., Aoki, I.; Suama, M.; Uemura, S. *Bull. Chem. Soc. Jpn.* 1994, 67, 1170–1177.

Education

Ph.D., Organic Chemistry, Massachusetts Institute of Technology, MA, August, 2005

Thesis title: "Cross-Coupling Reactions of Unactivated Alkyl Halides"

Advisor: Professor Gregory C. Fu

M. Sc., Organic Chemistry, National University of Singapore, Singapore, July, 2000

Thesis title: "Enantioselective Allylation Reactions of Carbonyl Compounds"

Advisor: Professor Teck-Peng Loh

B. Sc., Honors (first-class), Chemistry, National University of Singapore, Singapore, July, 1998

Awards and Scholarships

2001 **Synlett-Journals Award** Massachusetts Institute of Technology

1998-2000 **Research Scholarship** National University of Singapore

1996-1997 **Dean's List** National University of Singapore

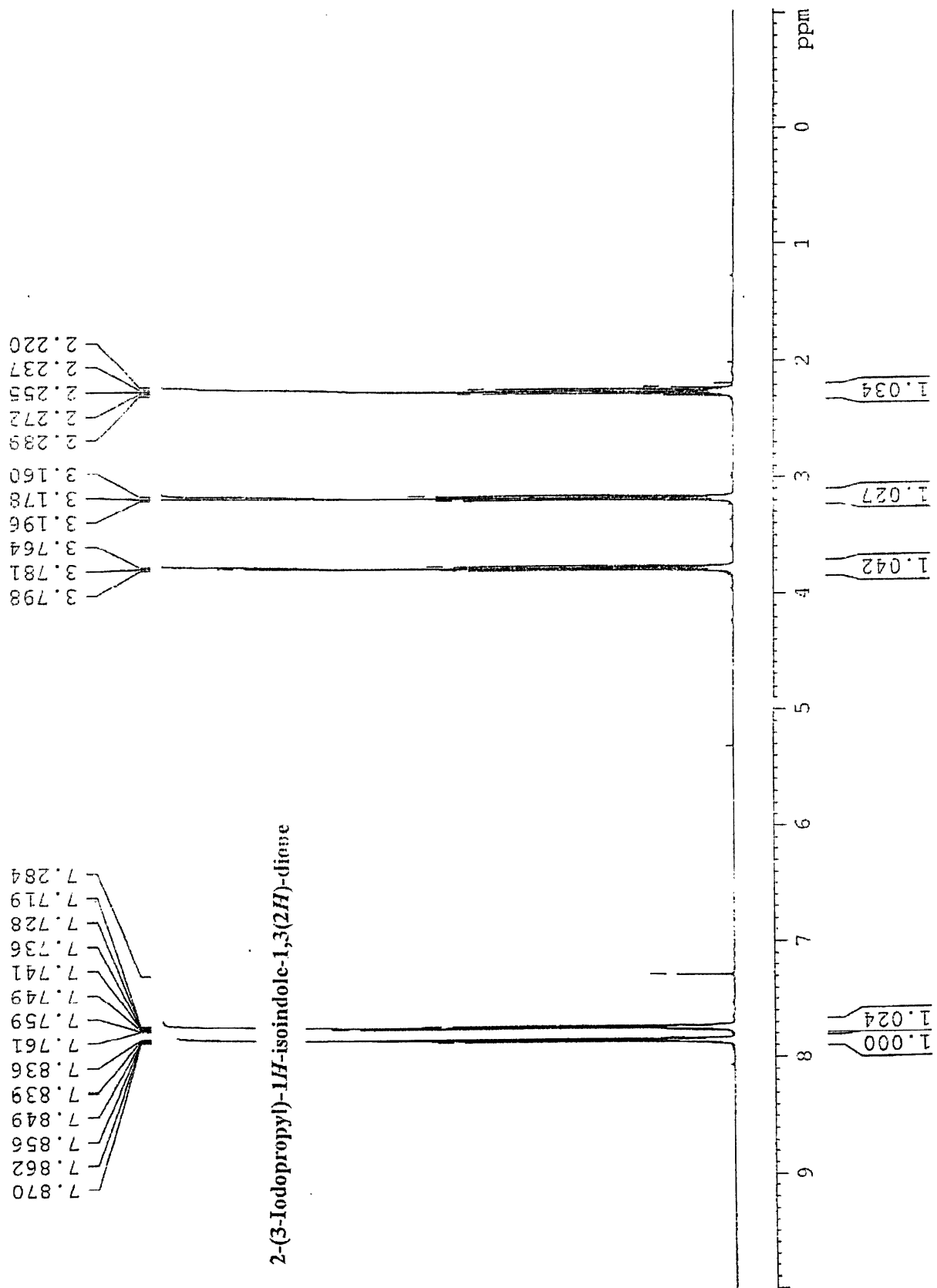
1995-1996 **Dean's List** National University of Singapore

Publications

- (8) **Suzuki Cross-Couplings of Unactivated Secondary Alkyl Halides**
J. Am. Chem. Soc. **2004**, *126*, 1340-1341.
Zhou, J.; Fu, G. C.
- (7) **Cross-Couplings of Unactivated Secondary Alkyl Halides: Room-Temperature Nickel-Catalyzed Negishi Reactions of Alkyl Bromides and Iodides**
J. Am. Chem. Soc. **2003**, *125*, 14726-14727.
Zhou, J.; Fu, G. C.
- (6) **Palladium-Catalyzed Negishi Cross-Coupling Reactions of Unactivated Alkyl Iodides, Bromides, Chlorides, and Tosylates**
J. Am. Chem. Soc. **2003**, *125*, 12527-12530.
Zhou, J.; Fu, G. C.
- (5) **A Highly Enantioselective Indium-Mediated Allylation Reaction of Aldehydes**
Org. Lett. **2000**, *1*, 1855-1857.
Loh, T.-P.; Zhou, J.-R.; Yin, Z.
- (4) **A Catalytic Enantioselective Allylation Reaction of Aldehydes in an Aqueous Medium**
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Loh, T.-P.; Zhou, J.-R.
- (3) **An Enantioselective Indium-Mediated Allylation Reaction of Aldehydes and Ketones in Dichloromethane**
Tetrahedron Lett. **1999**, *40*, 9333-9336.
Loh, T.-P.; Zhou, J.-R.; Li, X.-R.
- (2) **An Enantioselective Allylation Reaction of Aldehydes in an Aqueous Medium**
Tetrahedron Lett. **1999**, *40*, 9115-9118.
Loh, T.-P.; Zhou, J.-R.
- (1) **A Novel Reductive Aminocyclization for the Syntheses of Chiral Pyrrolidines: Stereoselective Syntheses of (*S*)-Nornicotine and 2-(2'-Pyrrolidyl)pyridines**
Tetrahedron Lett. **1999**, *40*, 7847-7850.
Loh, T.-P.; Zhou, J.-R.; Li, X.-R.; Sim, K.-Y.

Appendix: Selected ^1H Spectra

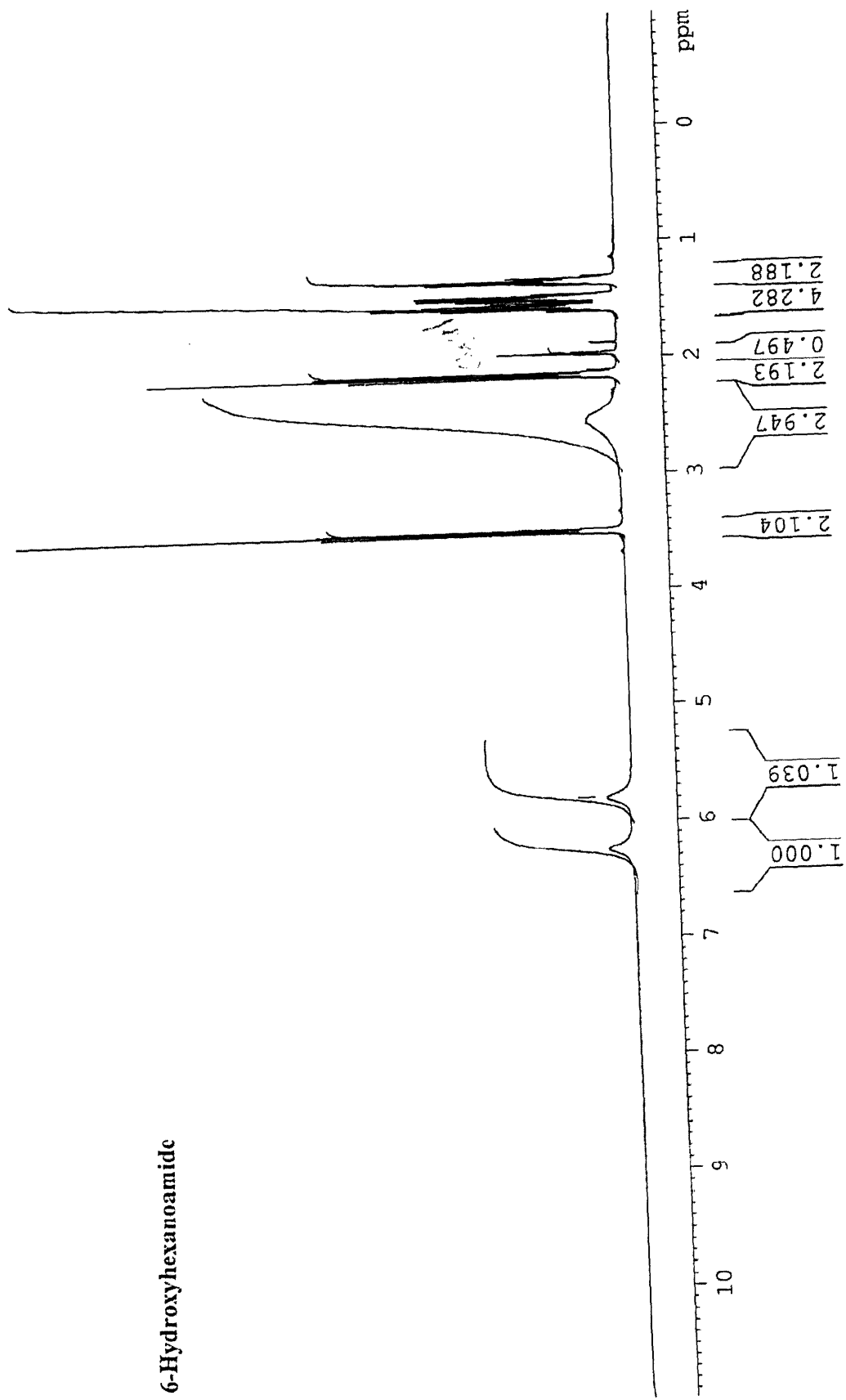
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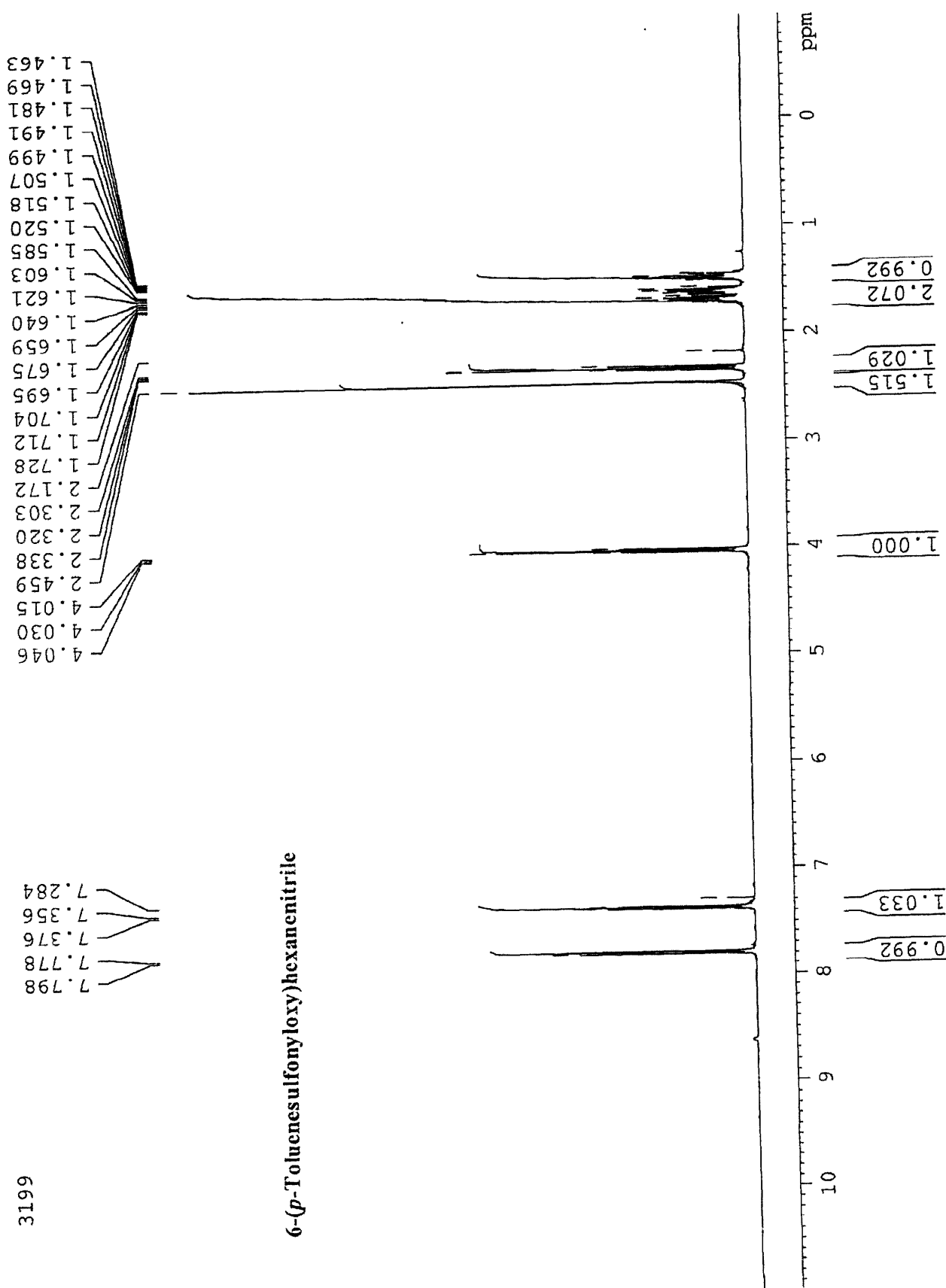


3191 in CH3CN

5.794

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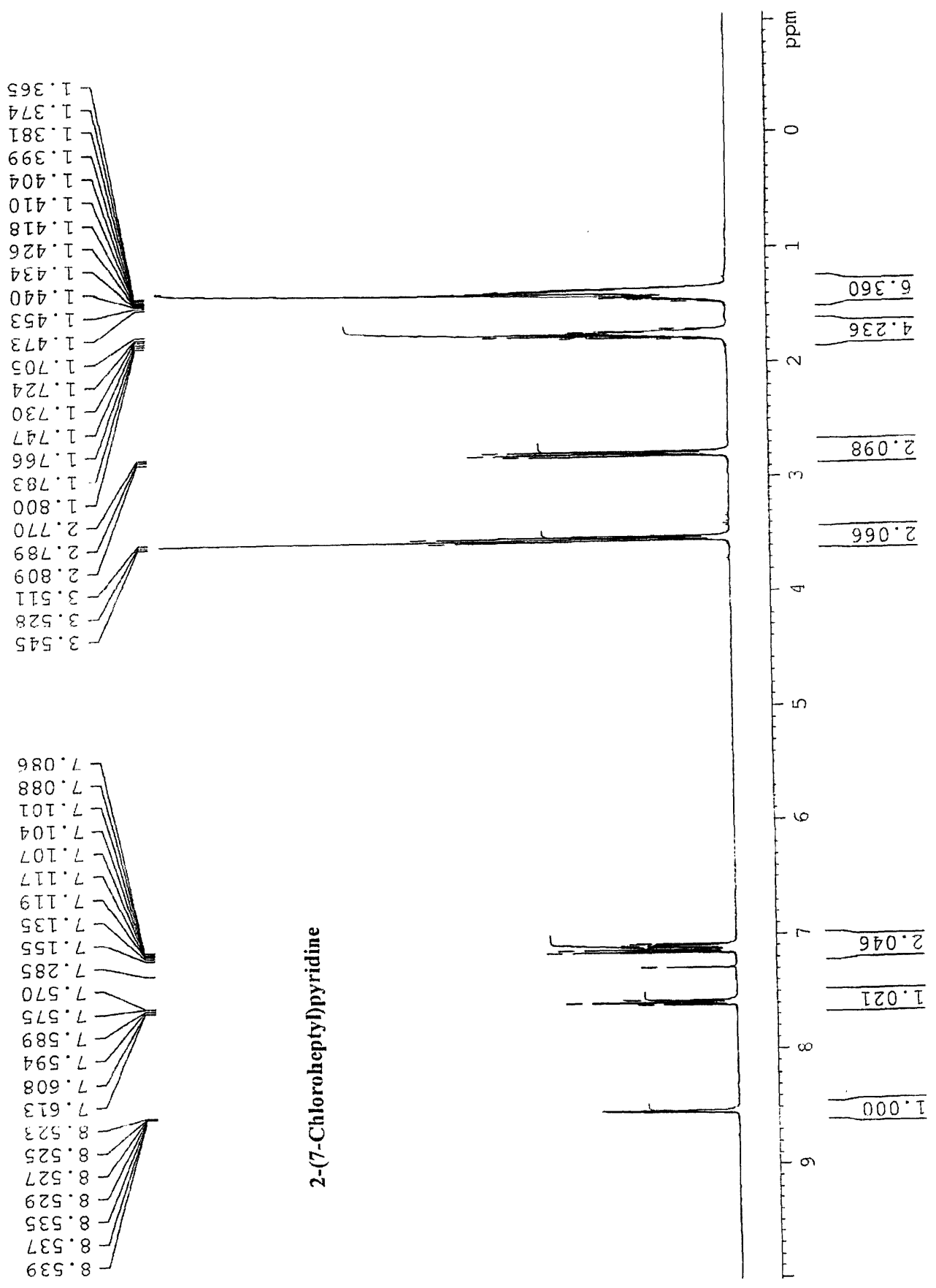




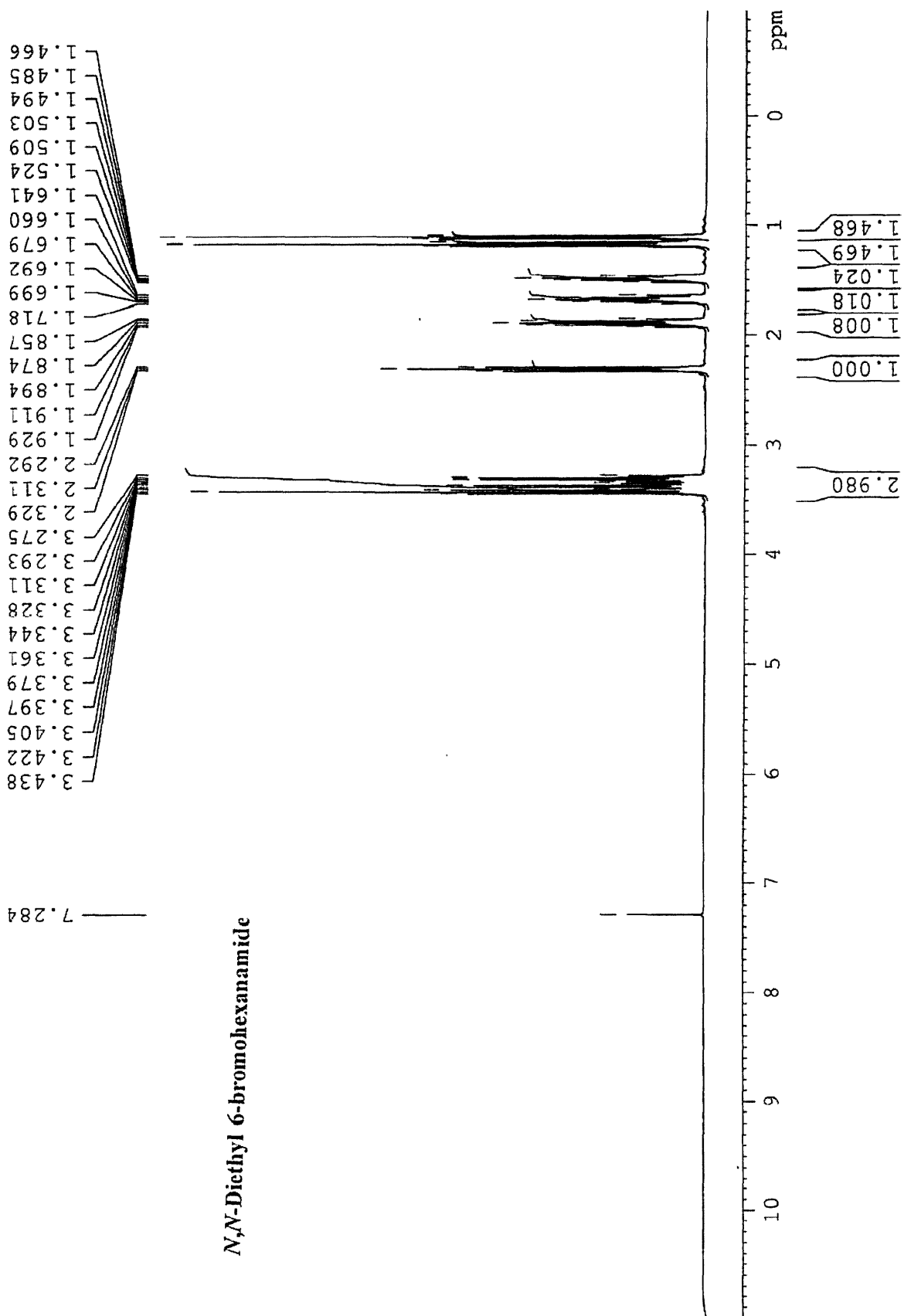
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3199

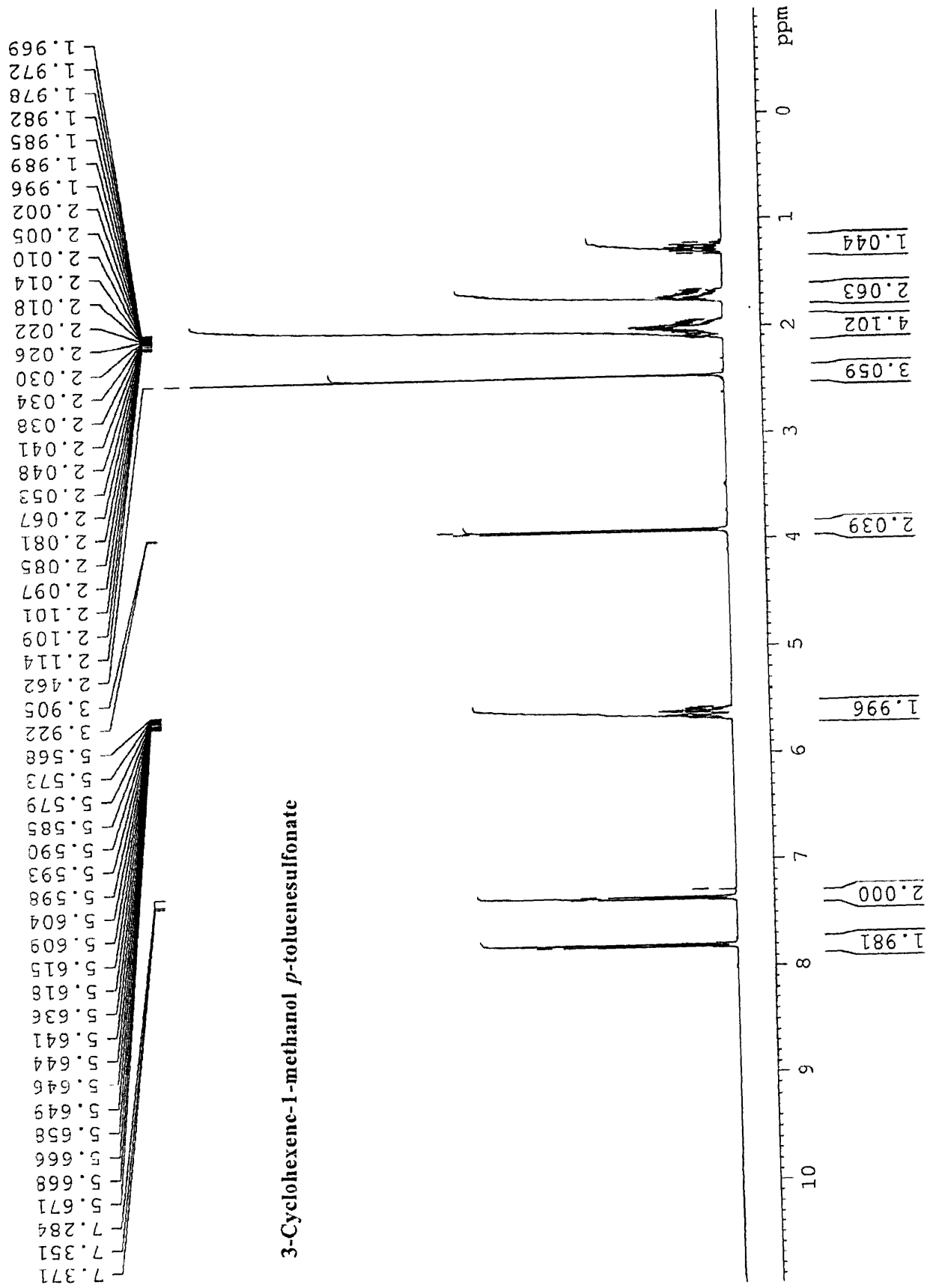
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32772



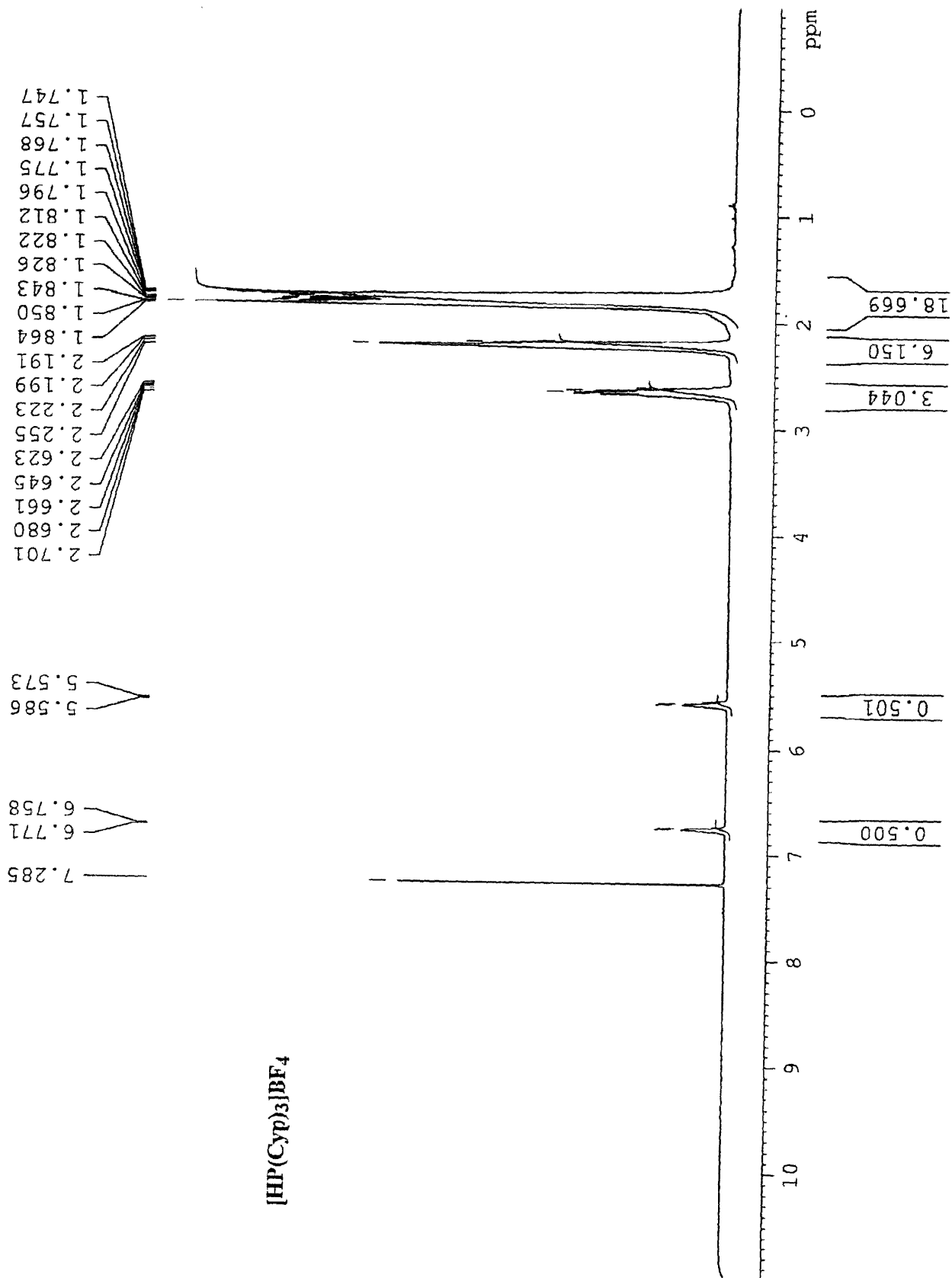
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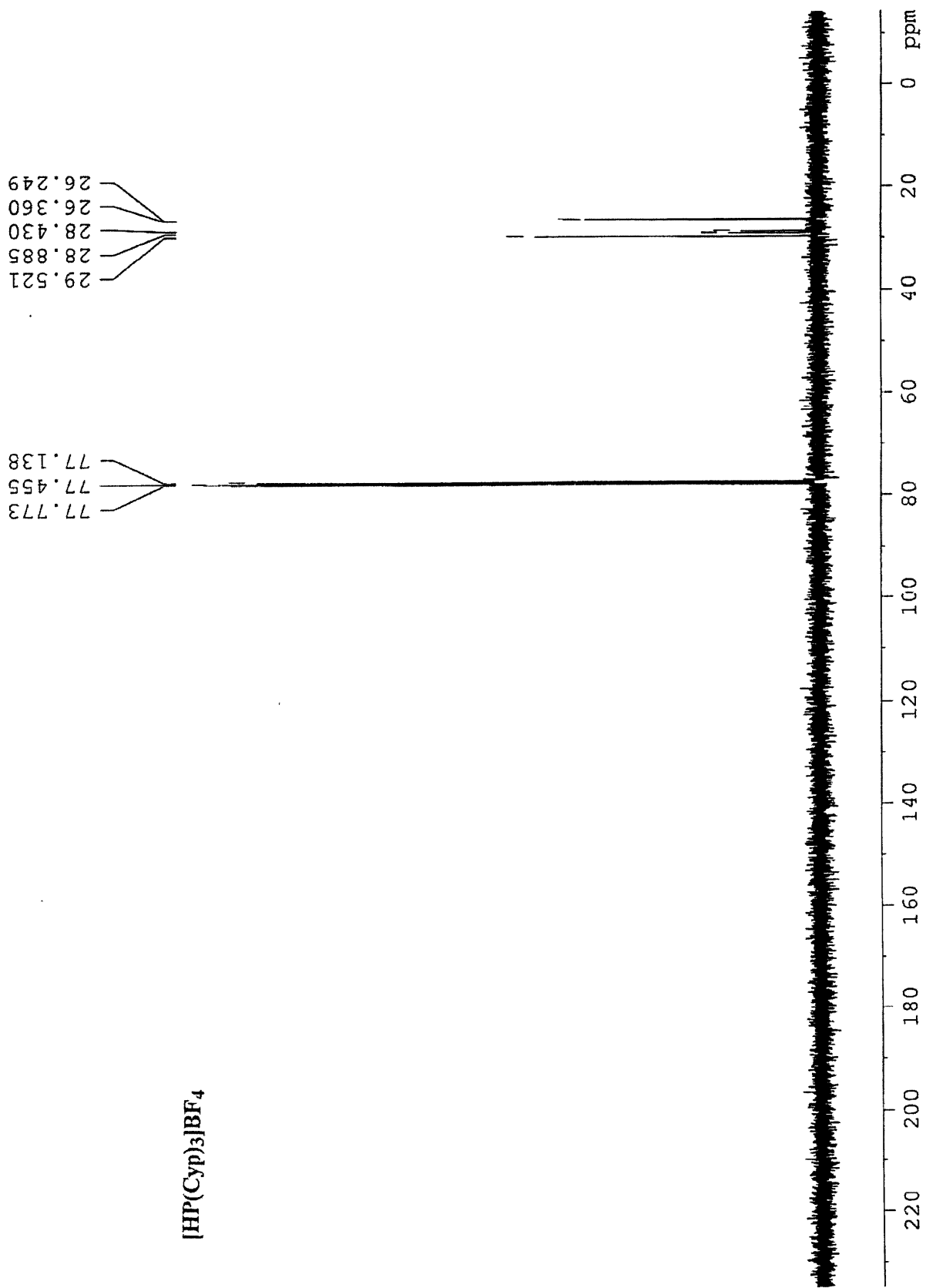


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3203

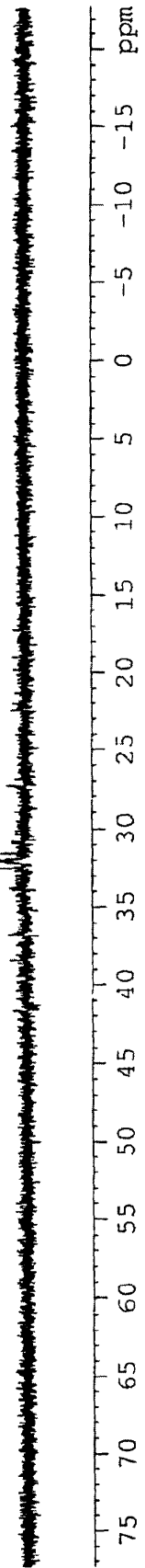
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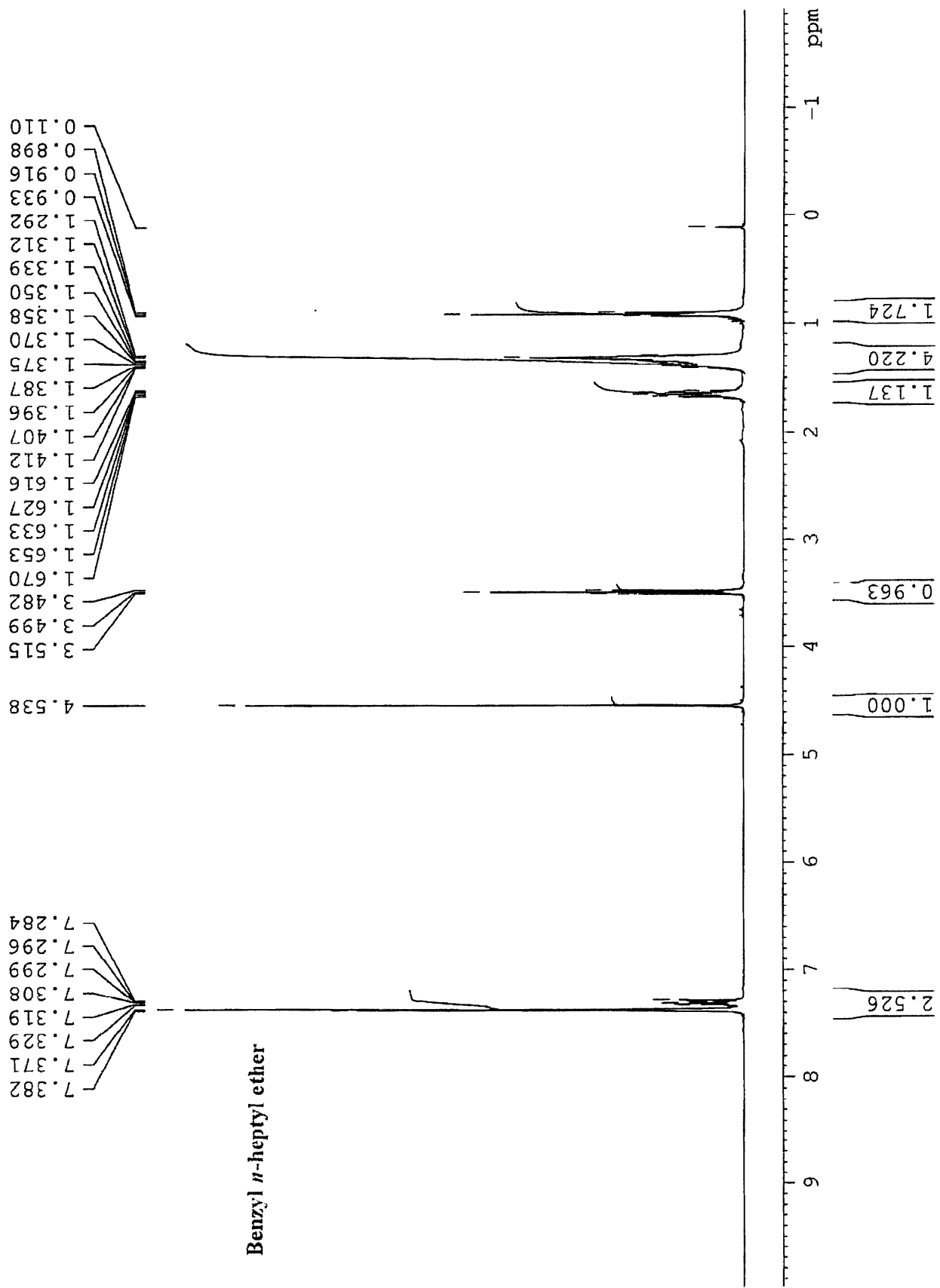
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32.022

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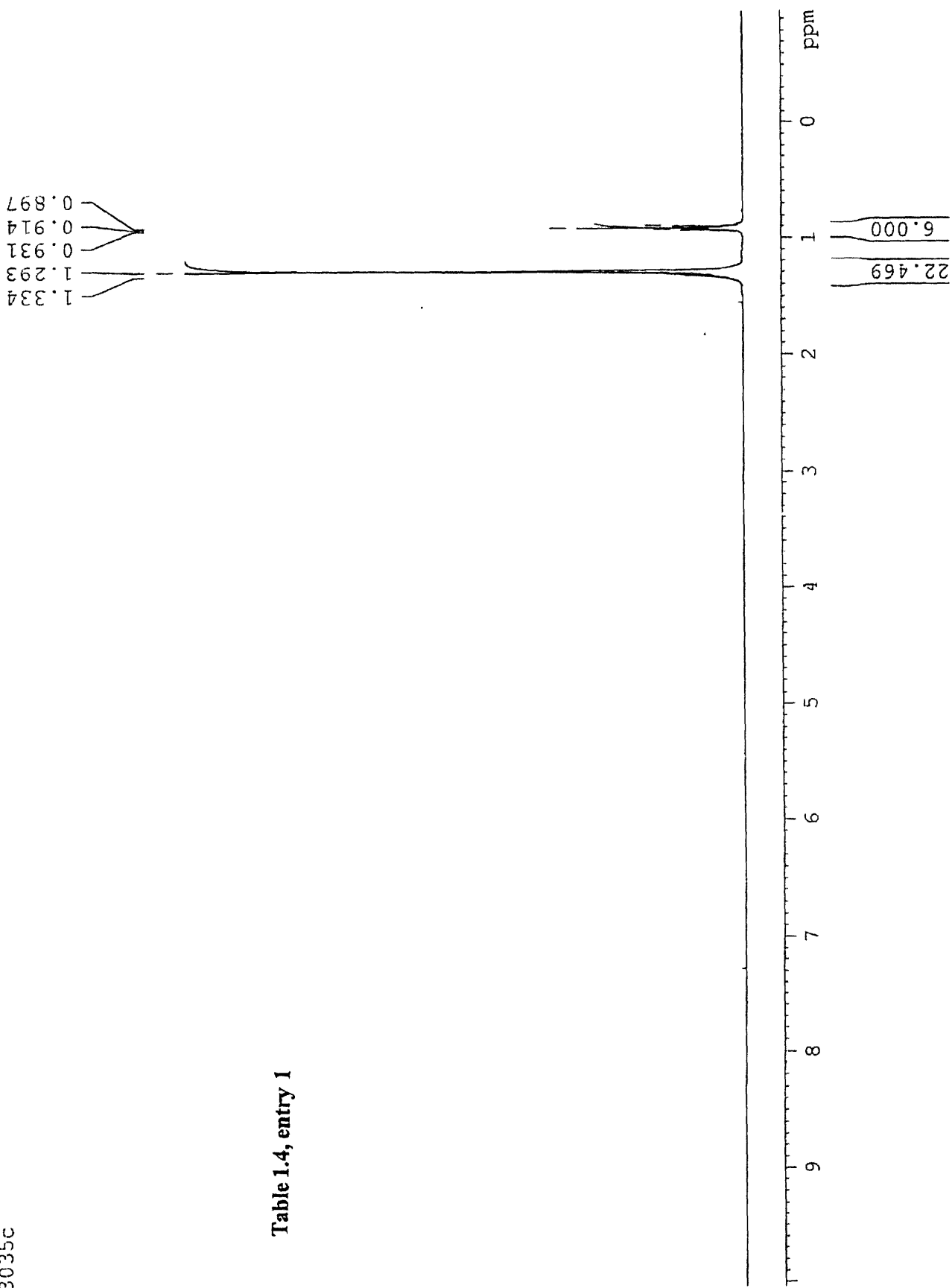


2245b



3035c

Table 1.4, entry 1



3053b

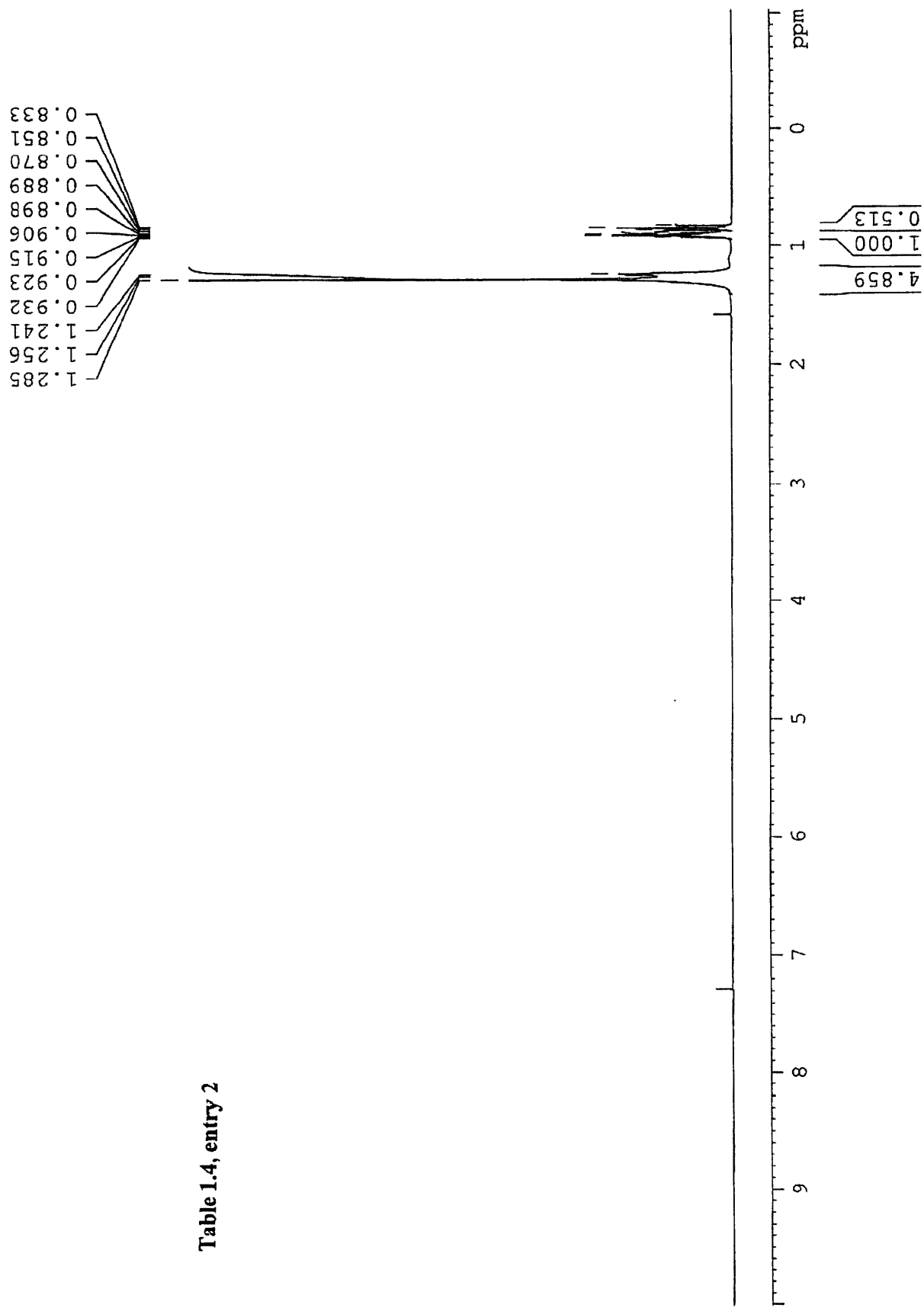


Table 1.4, entry 2

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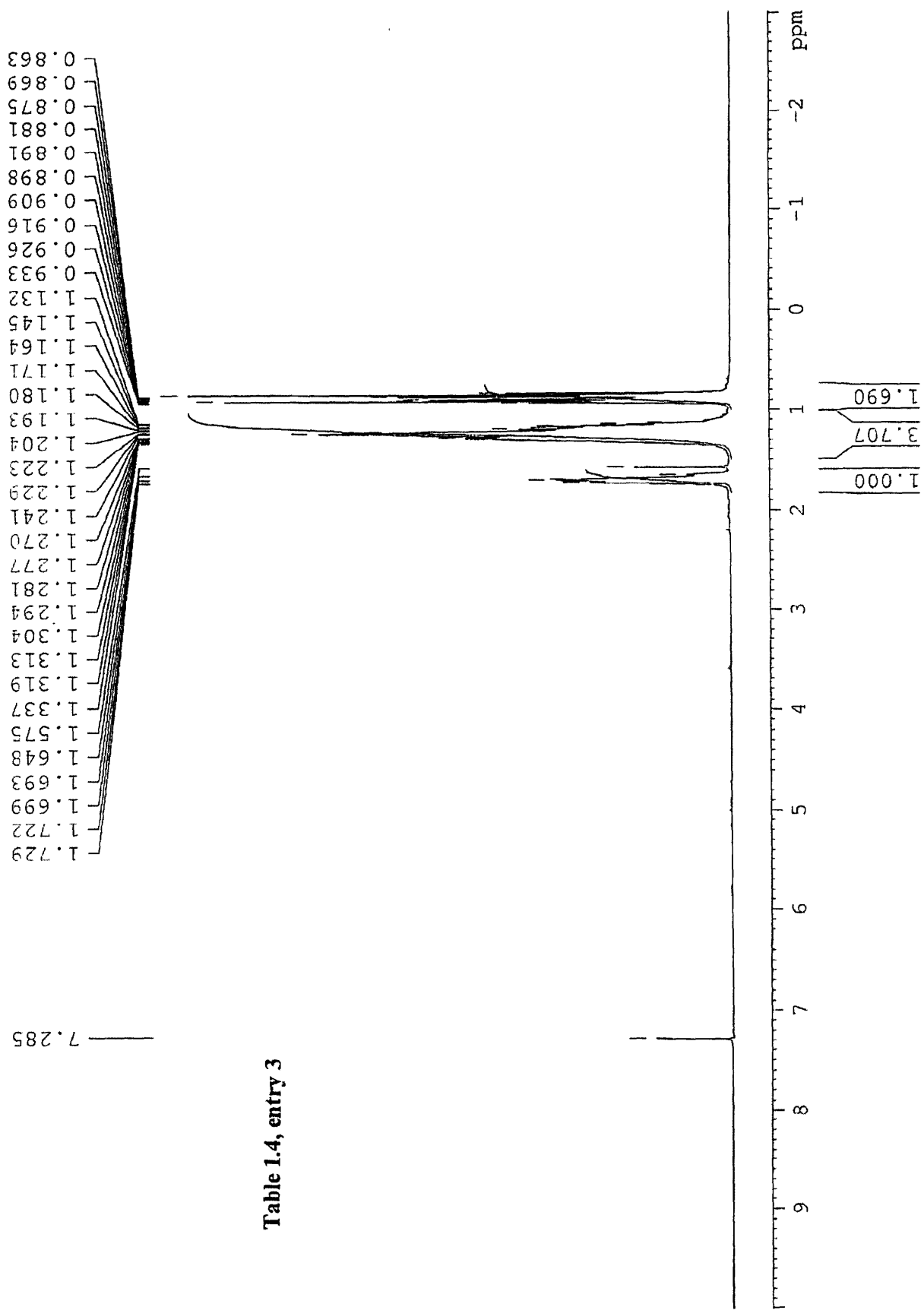


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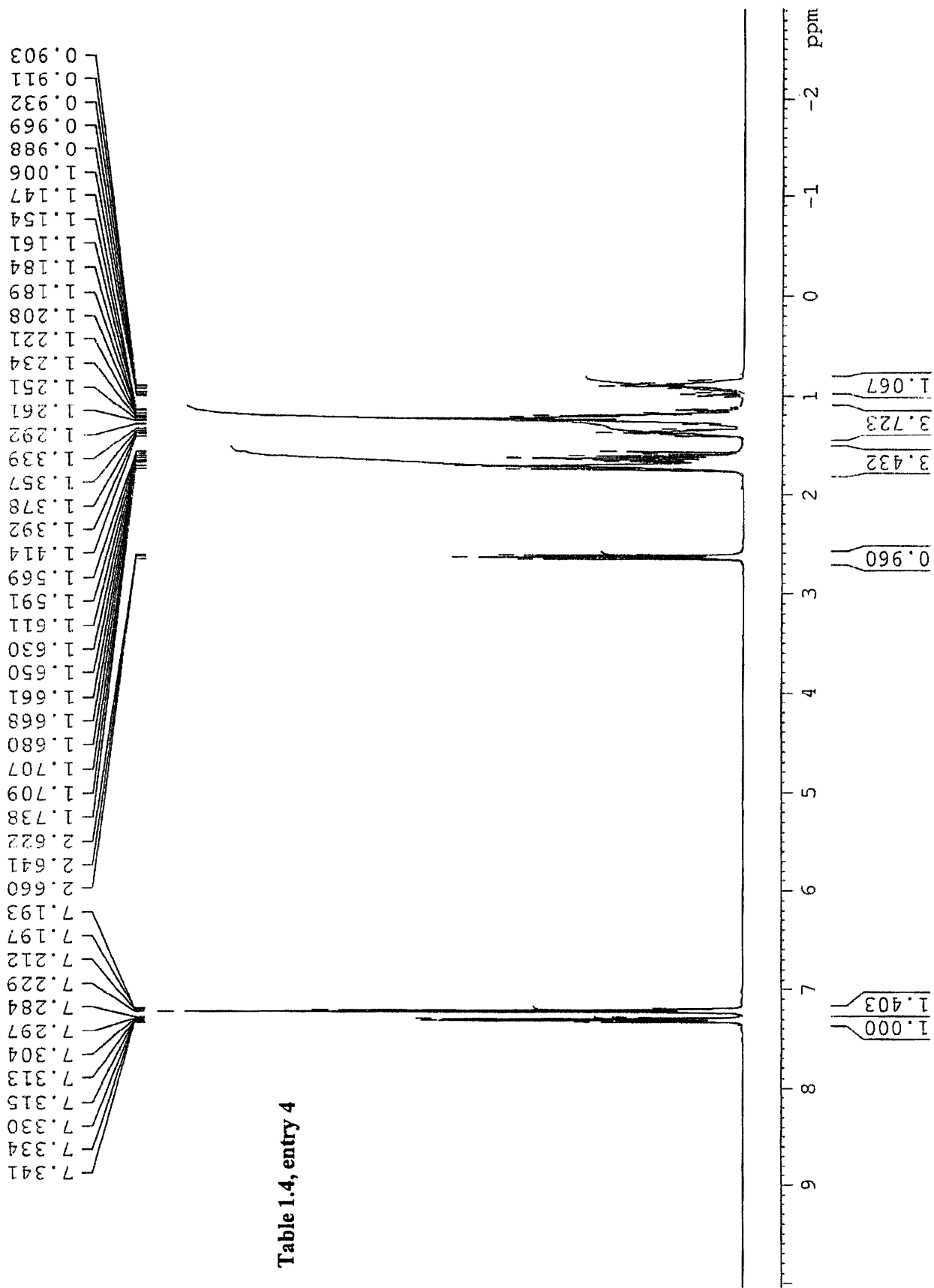


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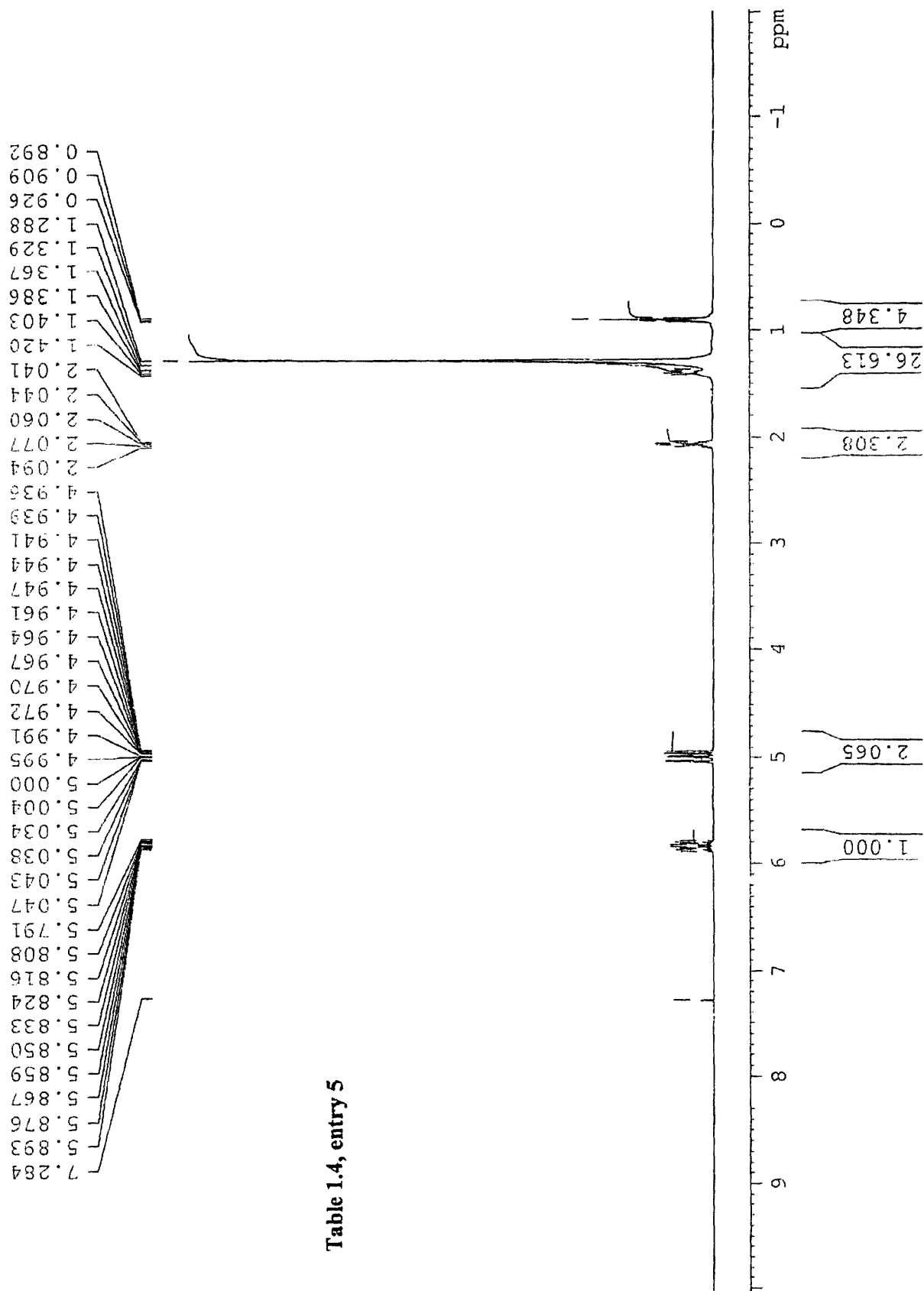
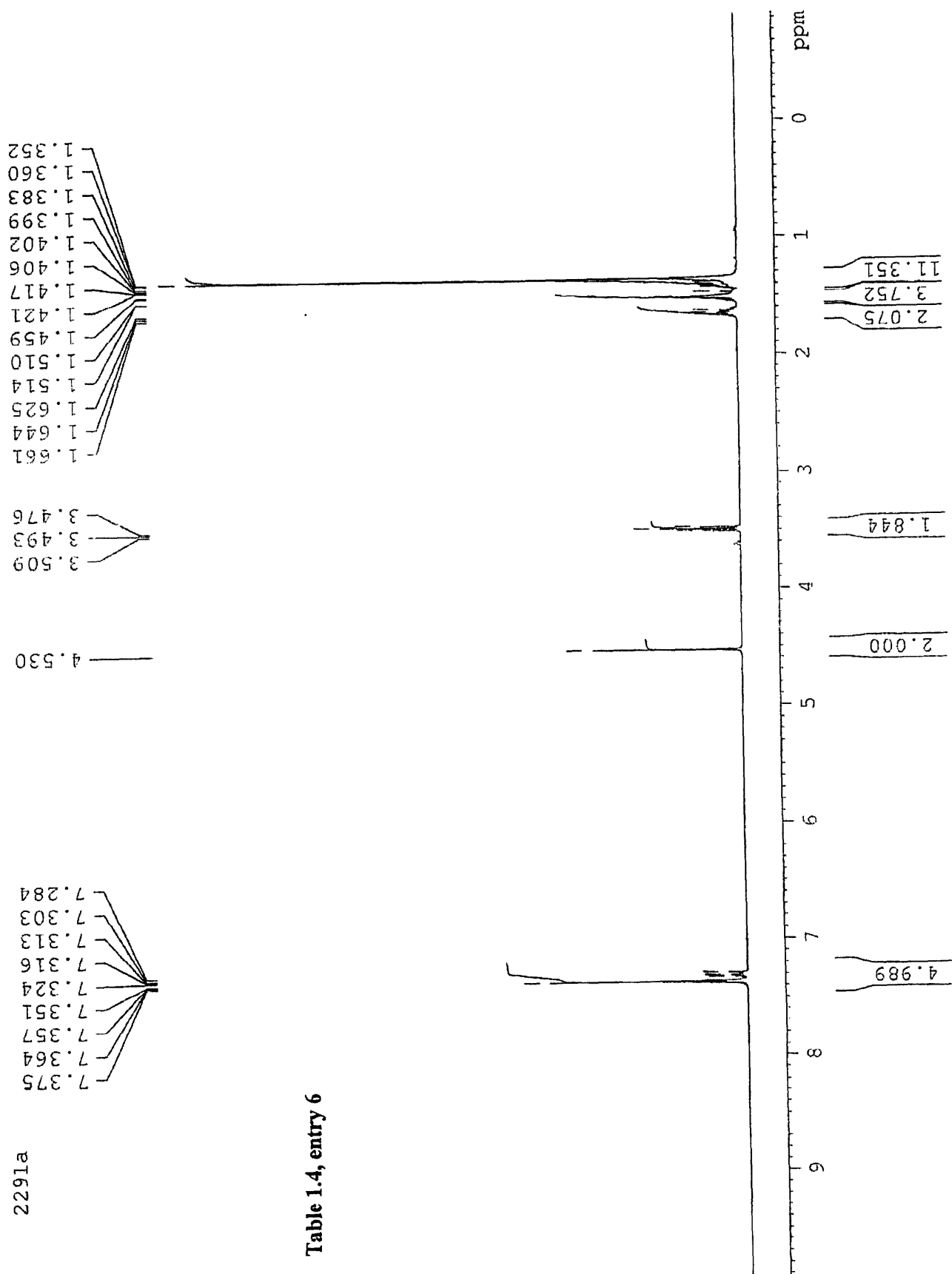


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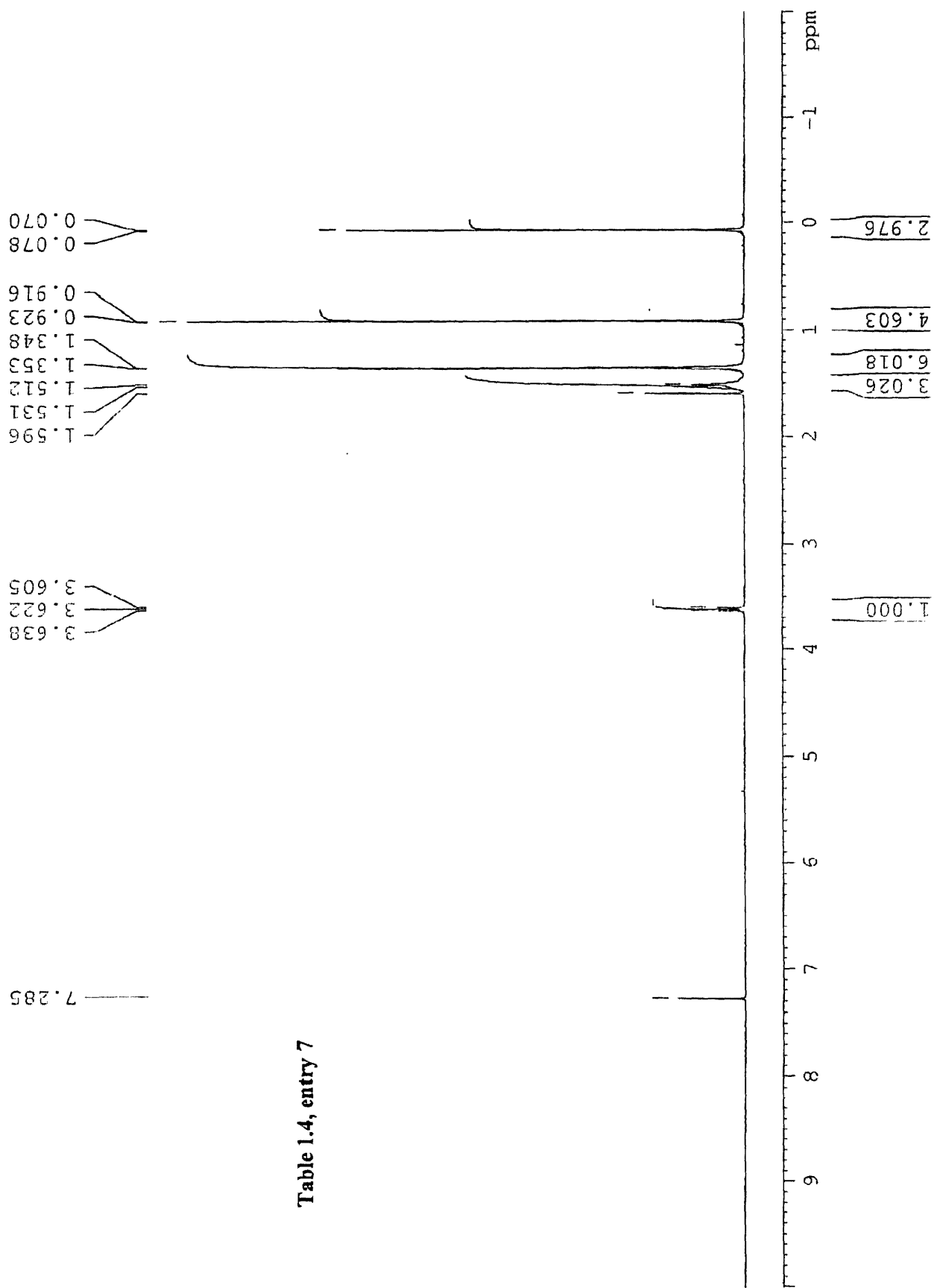


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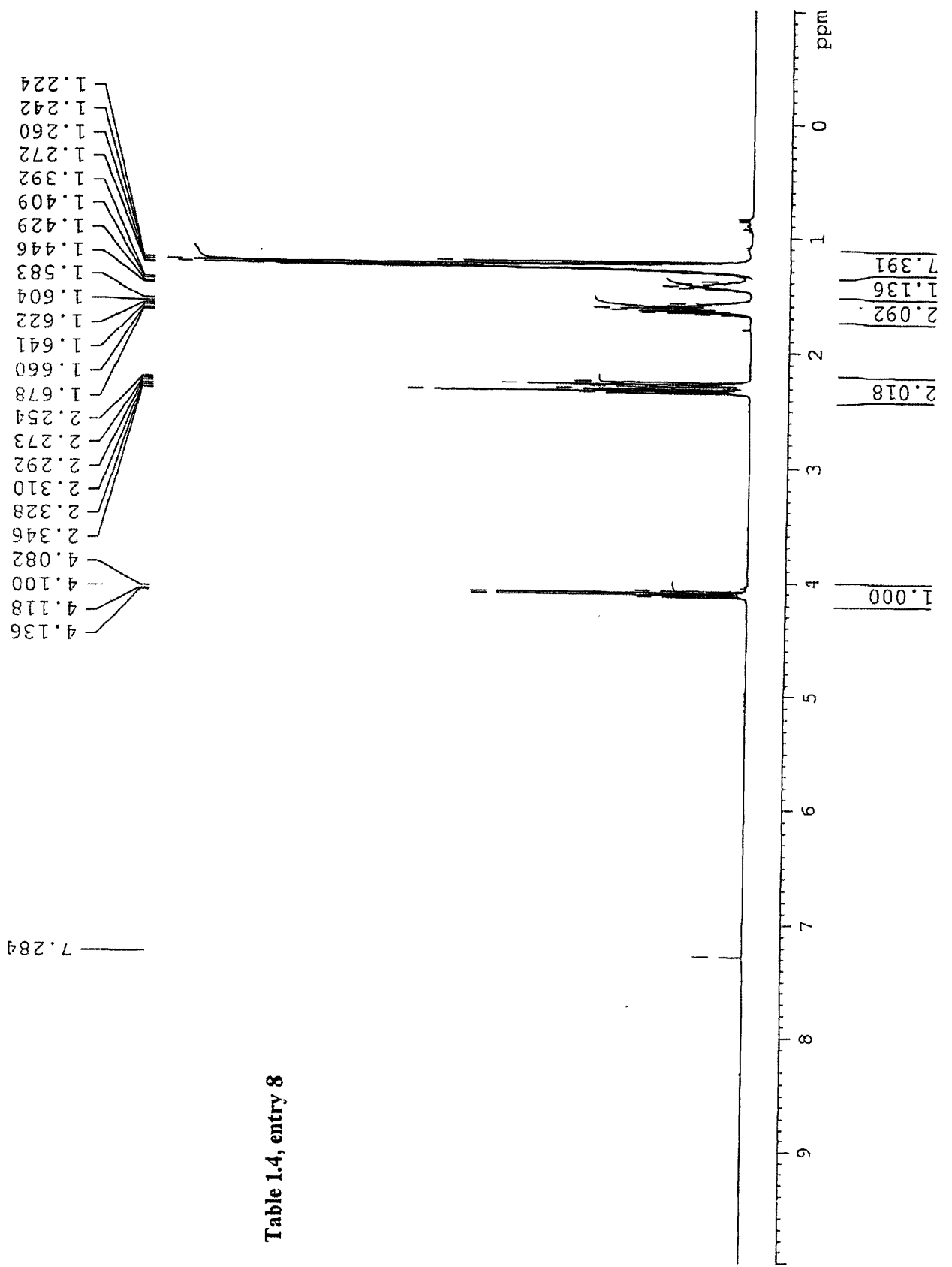
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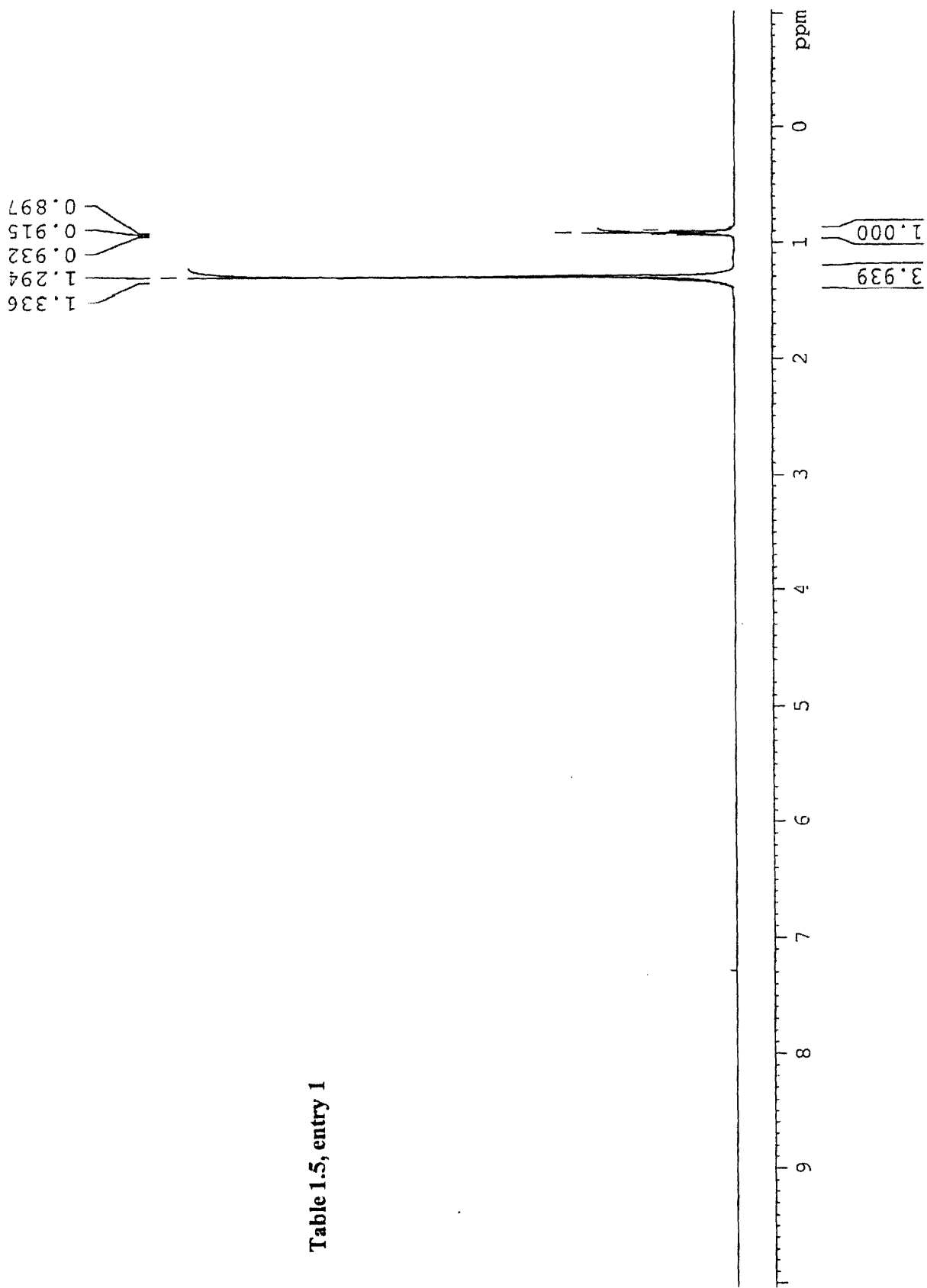
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Table 1.4, entry 8



2289a

Table 1.5, entry 1

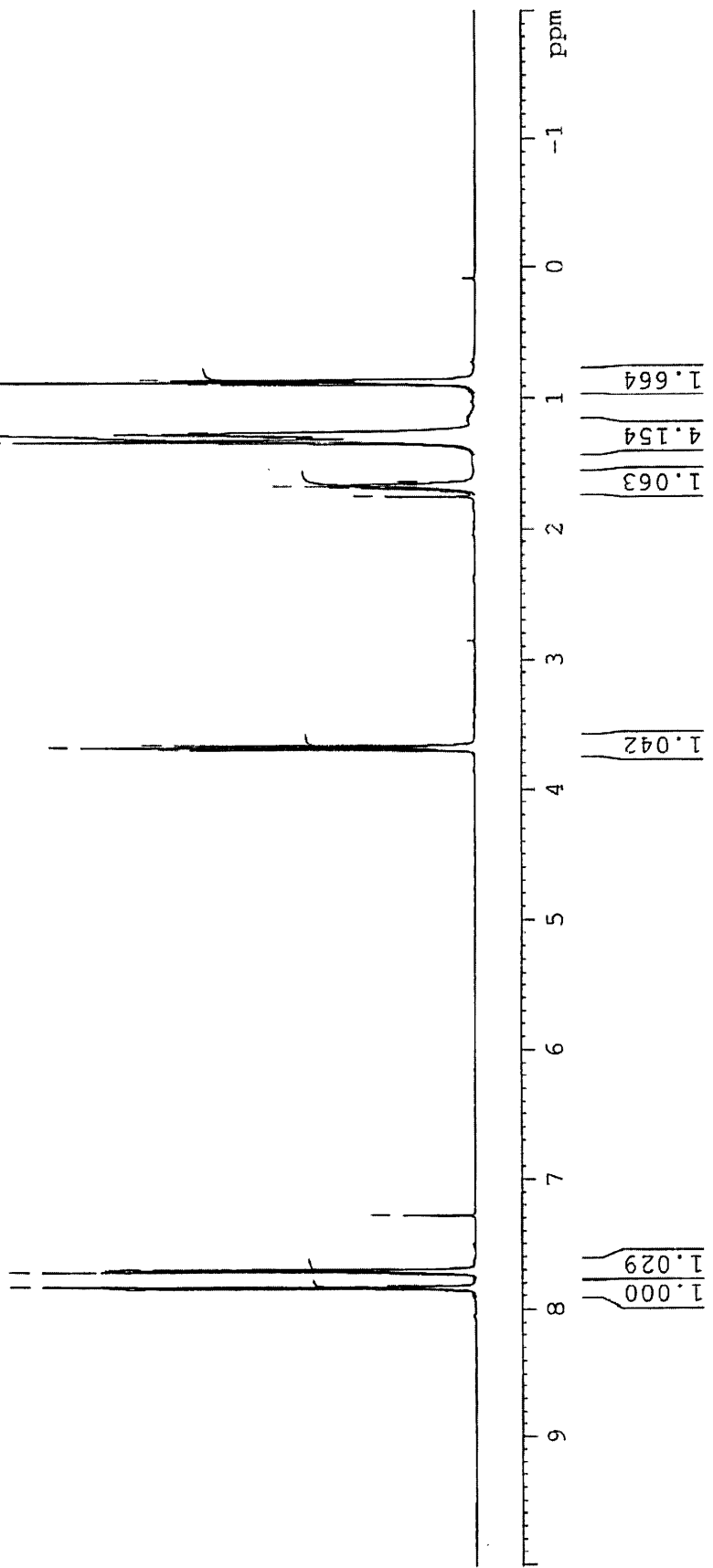


3039d

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7.704
7.284

3.699
3.681
3.663
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1.675
1.656
1.638
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1.333
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Table 1.5, entry 2



3035d

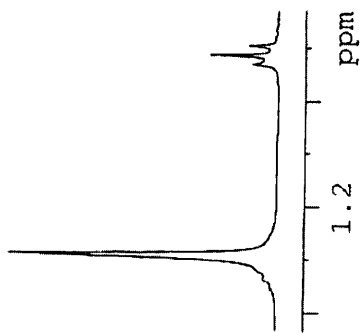
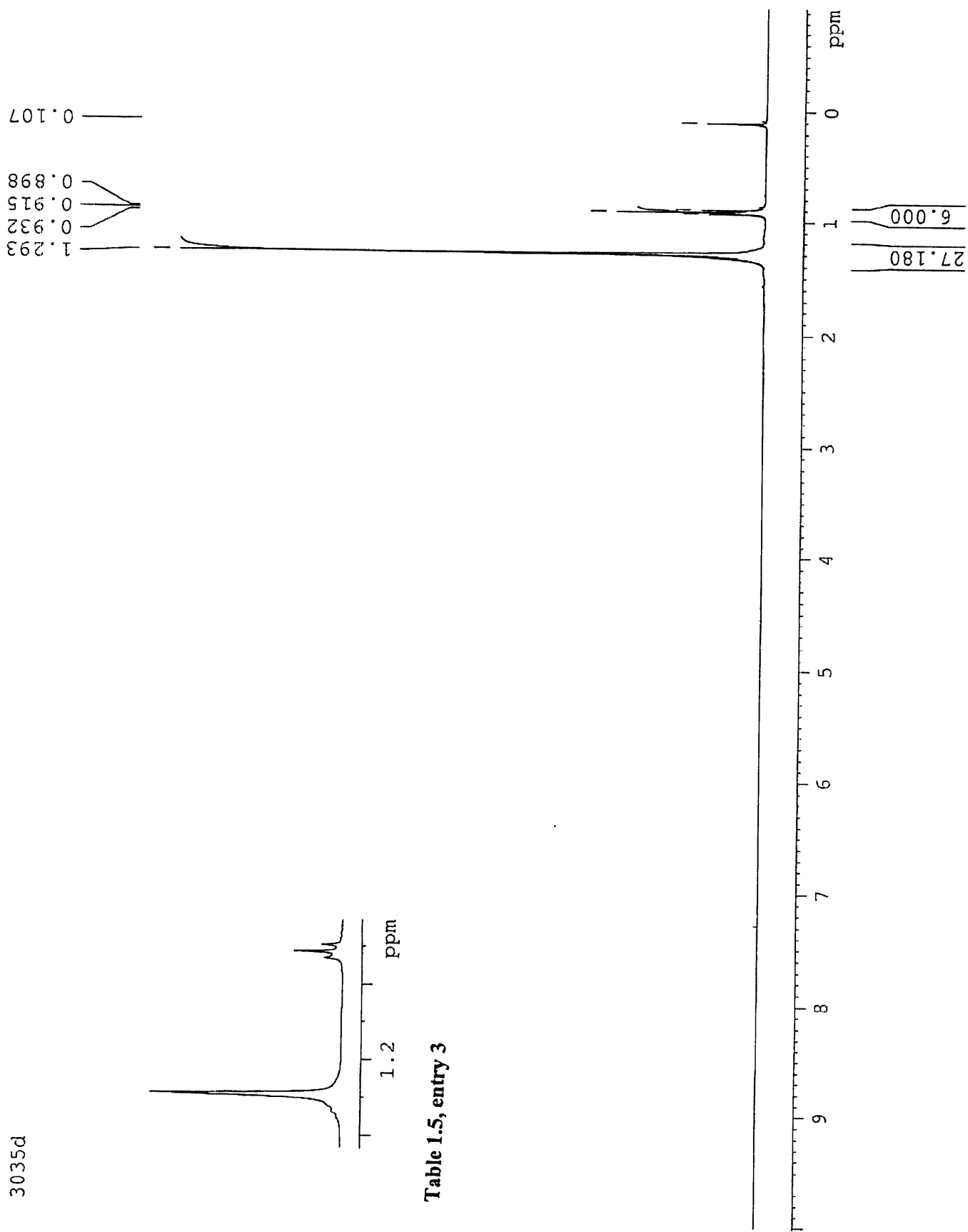


Table 1.5, entry 3



3197c2

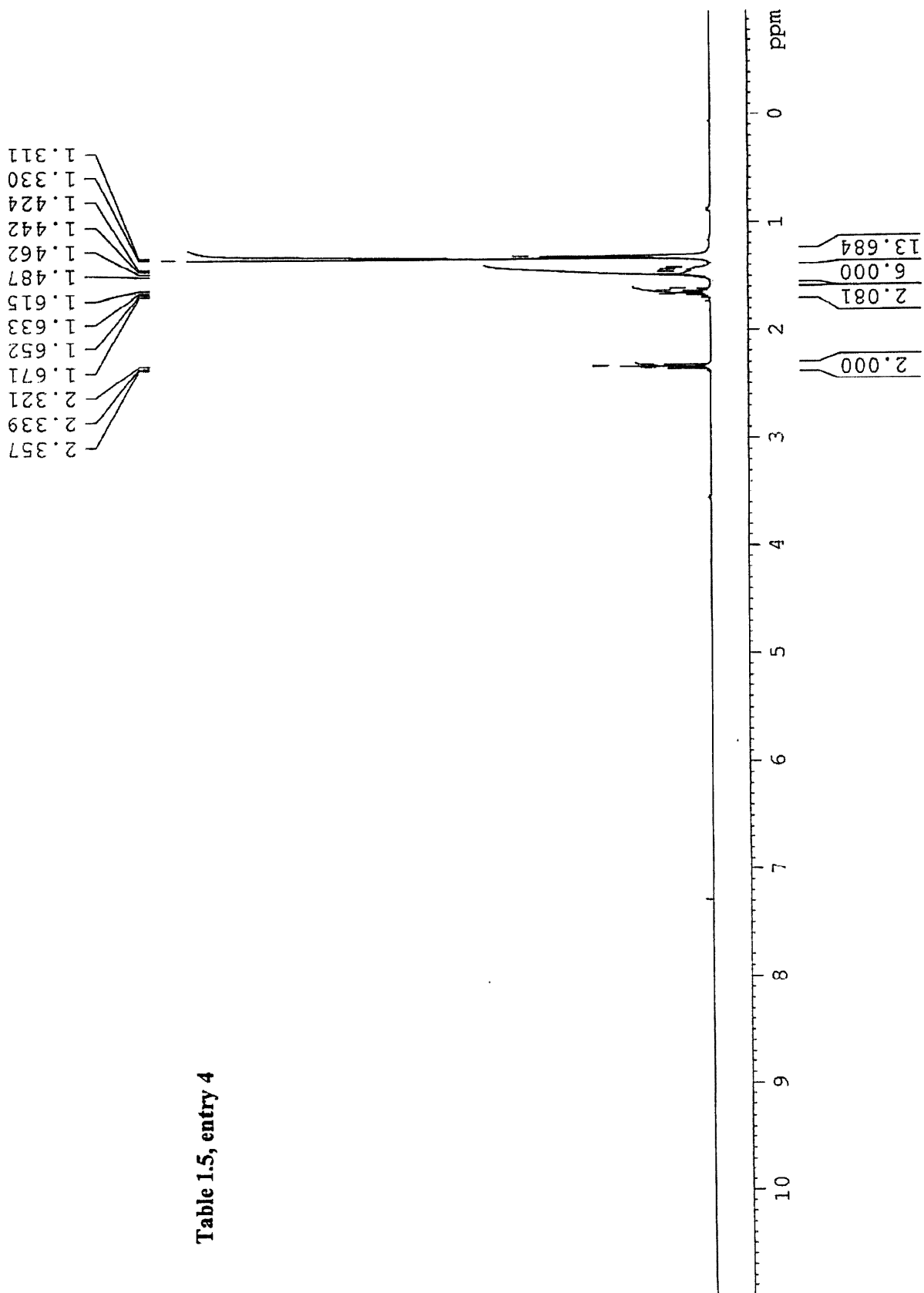
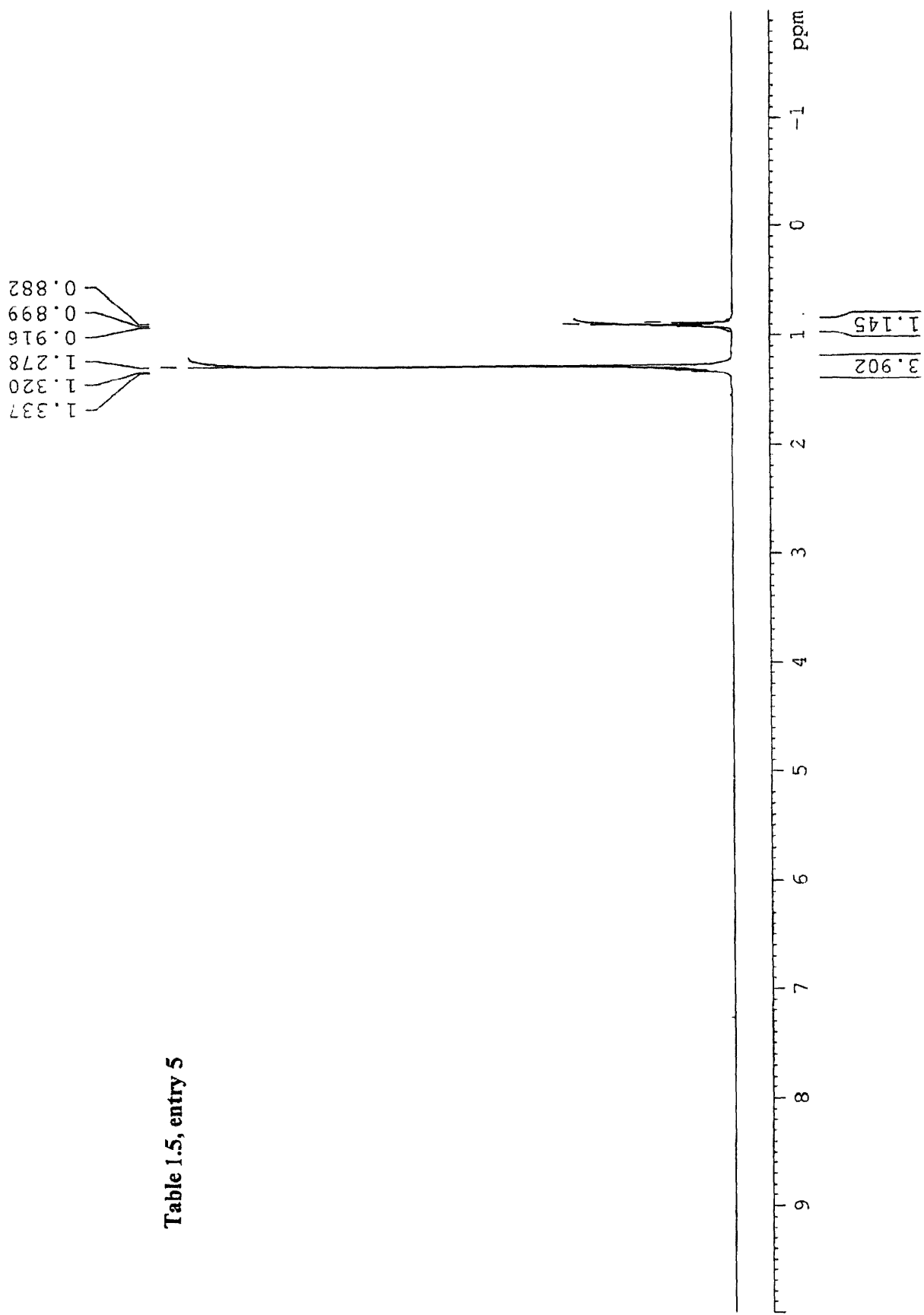


Table 1.5, entry 4

3025a1

Table 1.5, entry 5



3067g

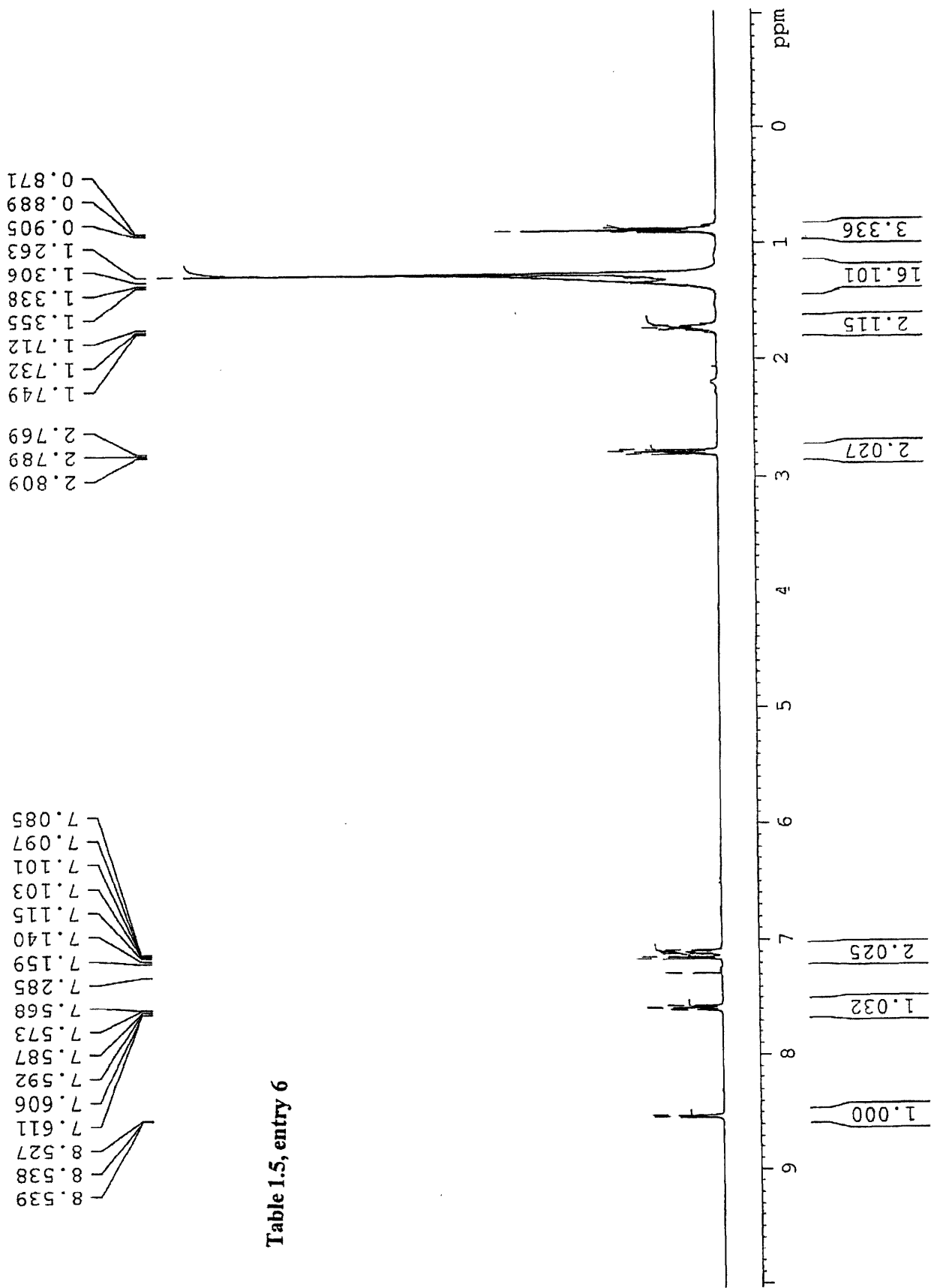
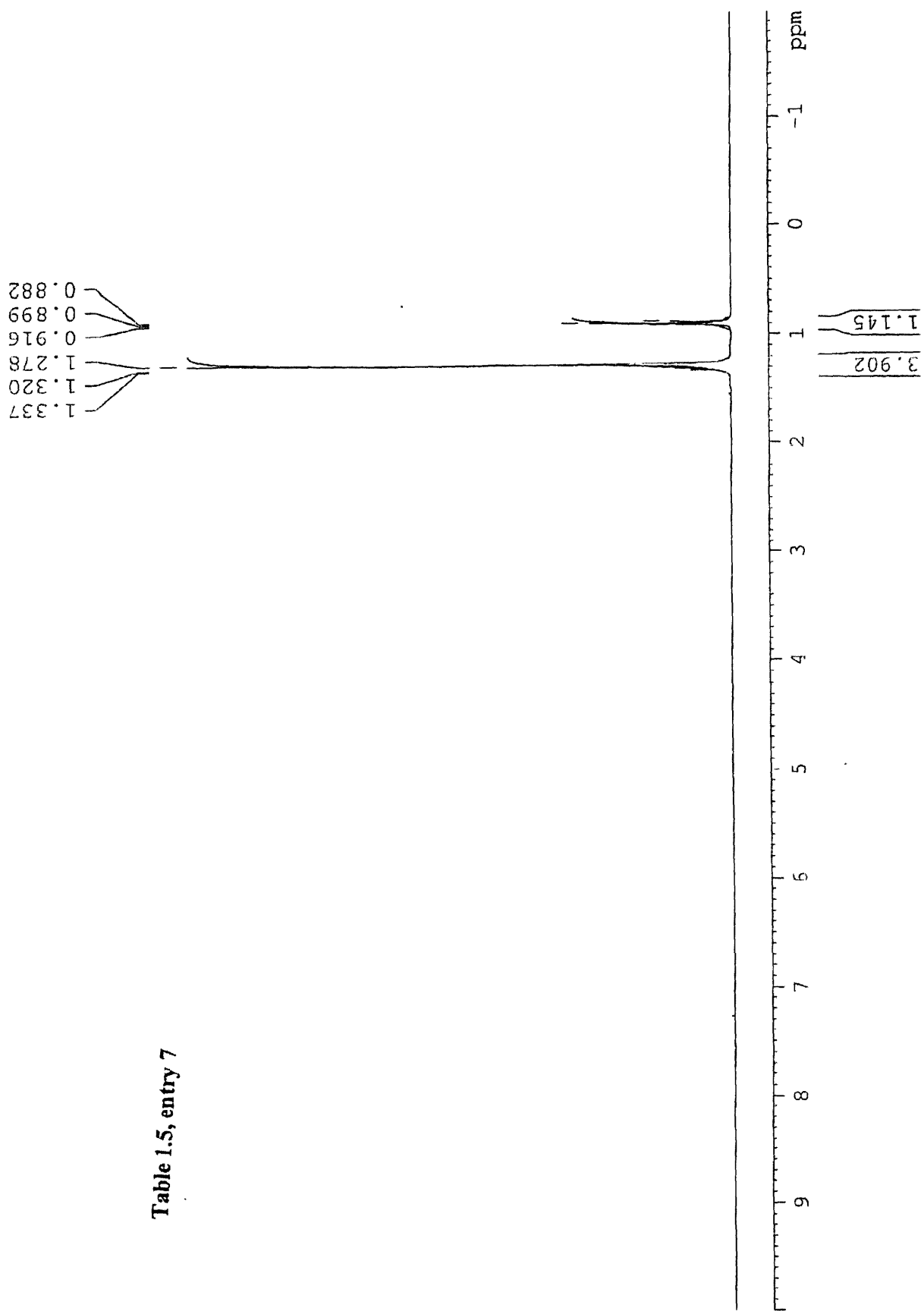


Table 1.5, entry 6

3025a1

Table 1.5, entry 7



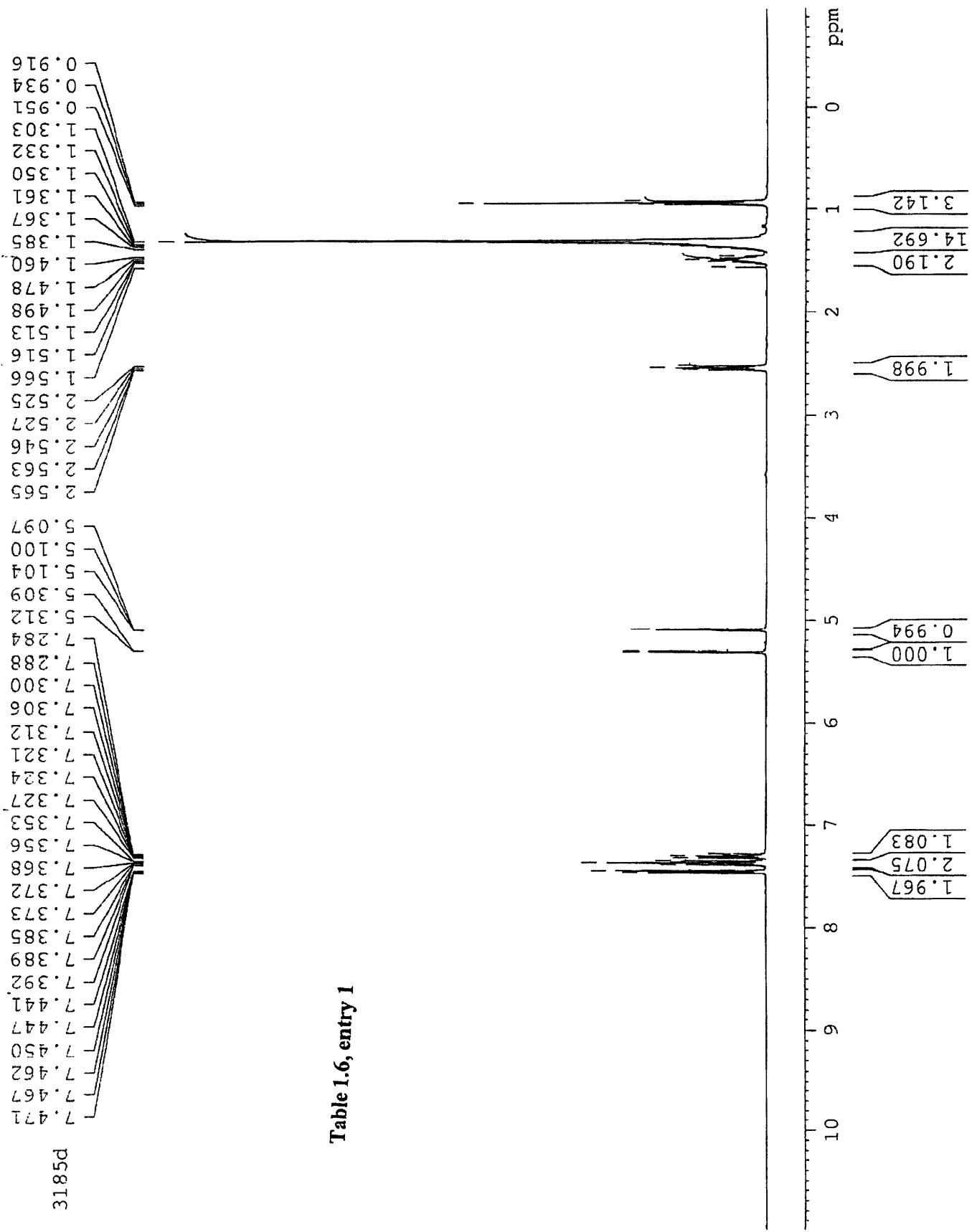
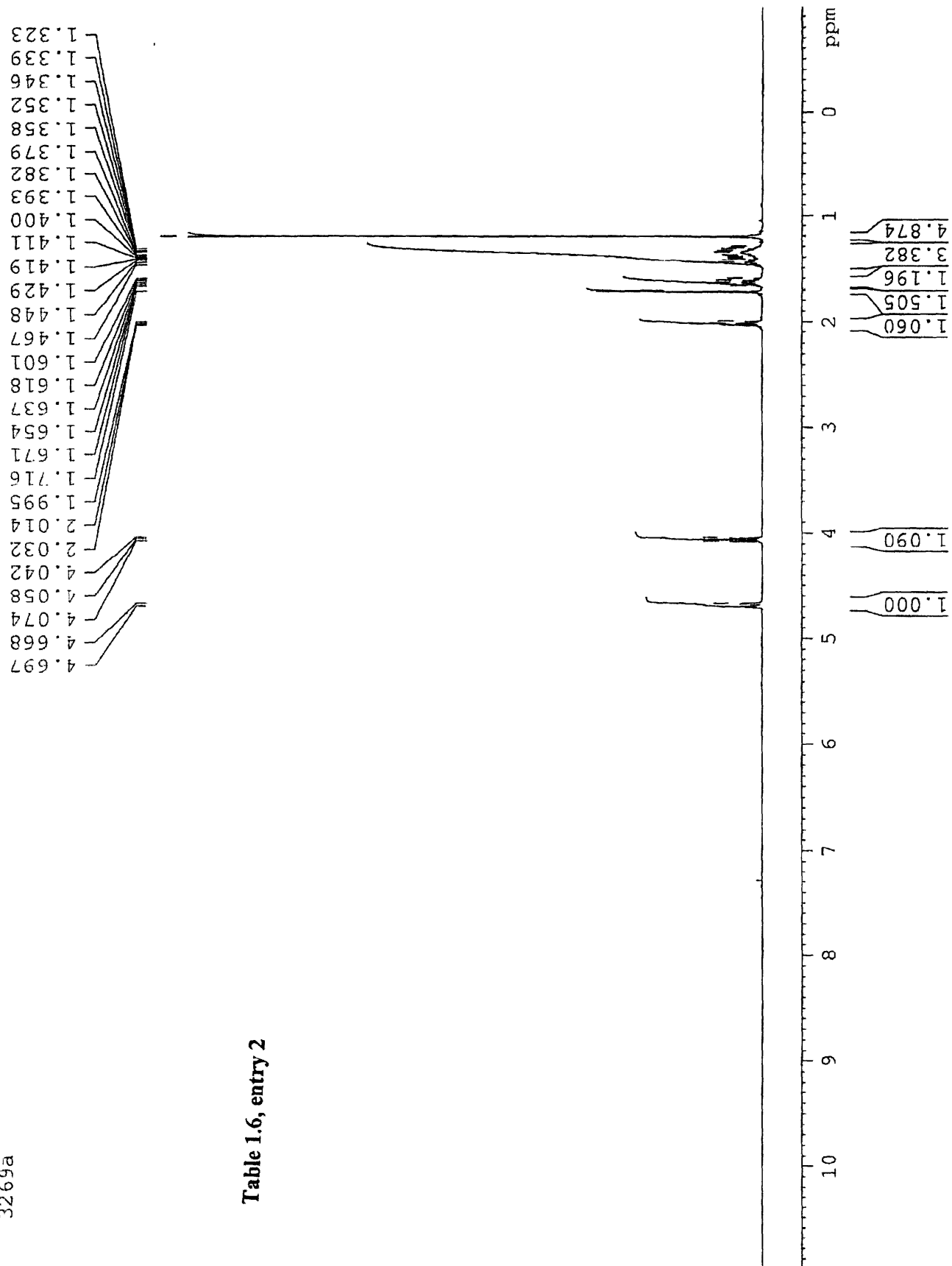


Table 1.6, entry 1

3269a

Table 1.6, entry 2



3269b

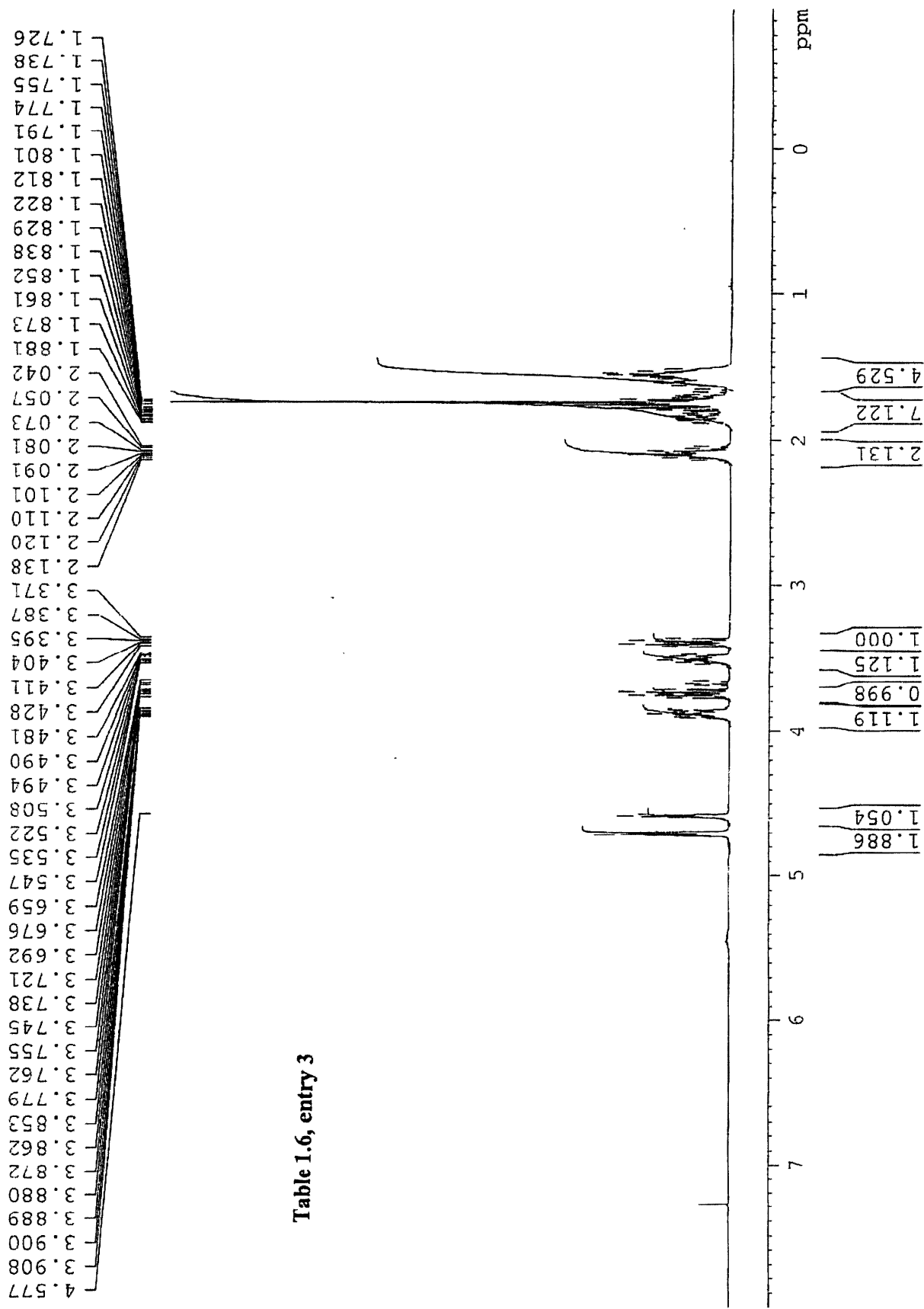
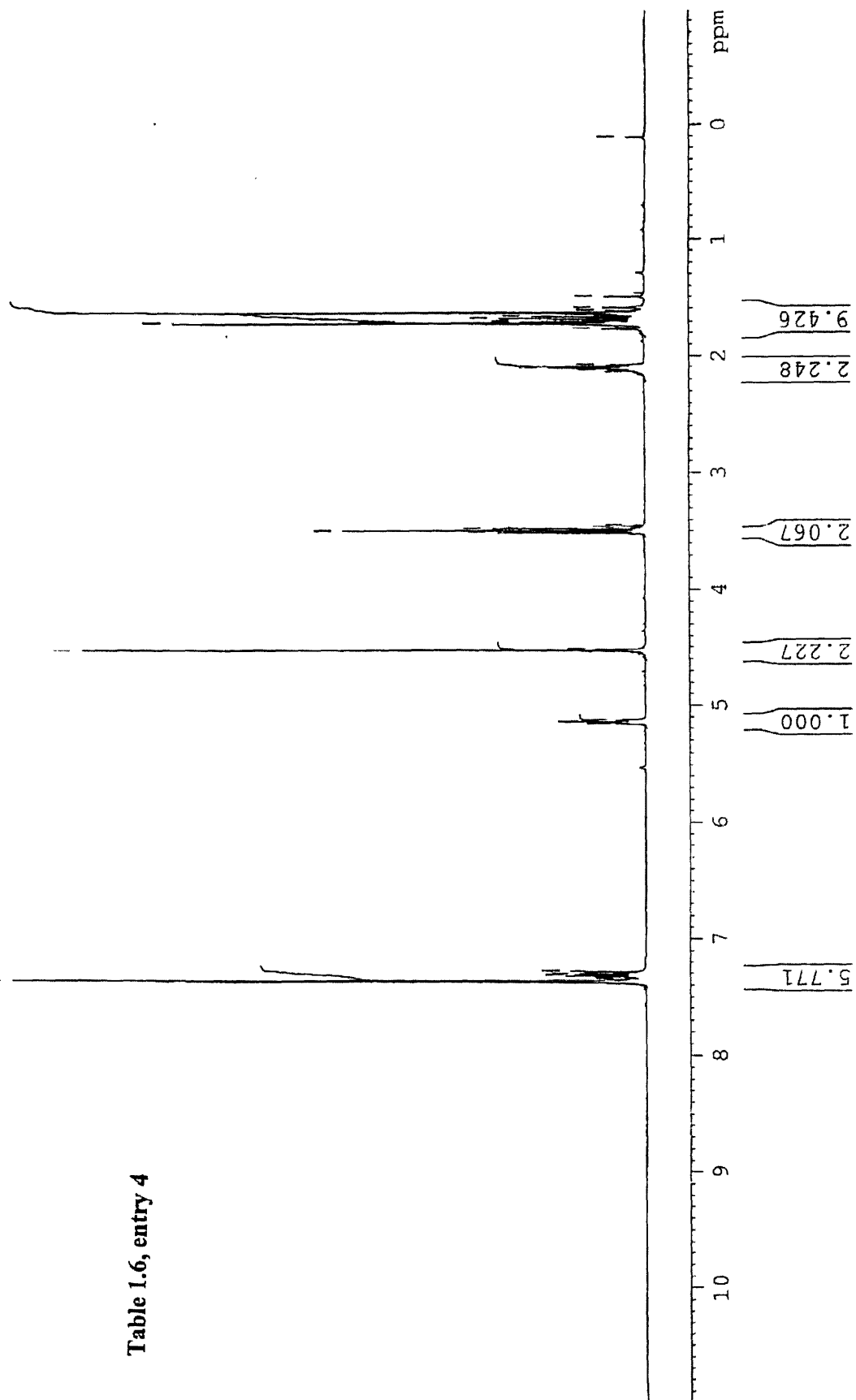


Table 1.6, entry 3

4145a1

7.381
7.370
7.352
7.349
7.339
7.329
7.319
7.308
7.298
7.295
7.284
5.163
5.159
5.148
5.144
5.141
5.130
5.127
4.533
4.521
3.517
3.500
3.484
3.475
3.458
3.442
2.147
2.131
2.114
2.095
2.077
1.770
1.722
1.706
1.687
1.670
1.653
1.639
1.616
1.594
1.500
0.110

Table 1.6, entry 4



4063b2

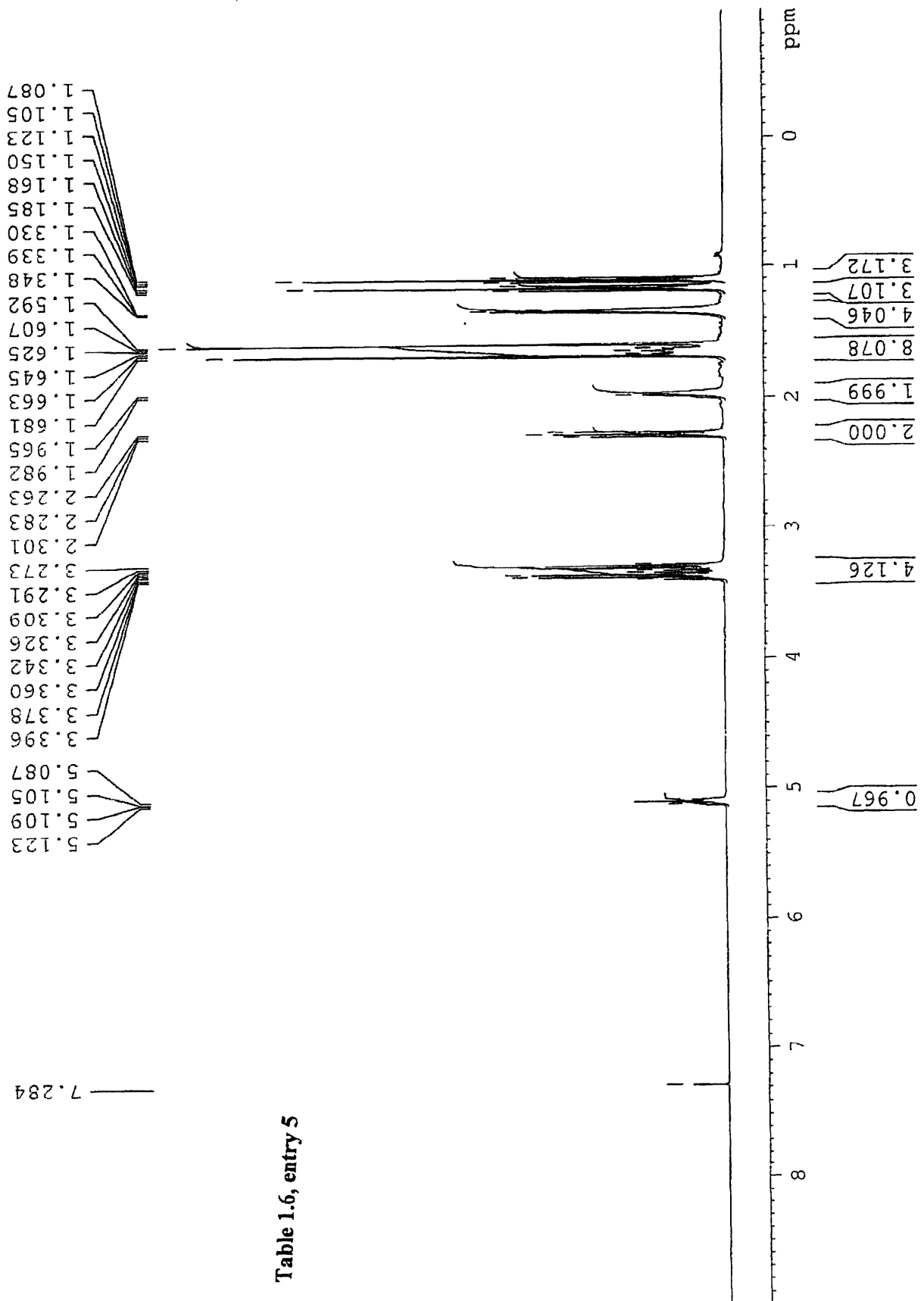
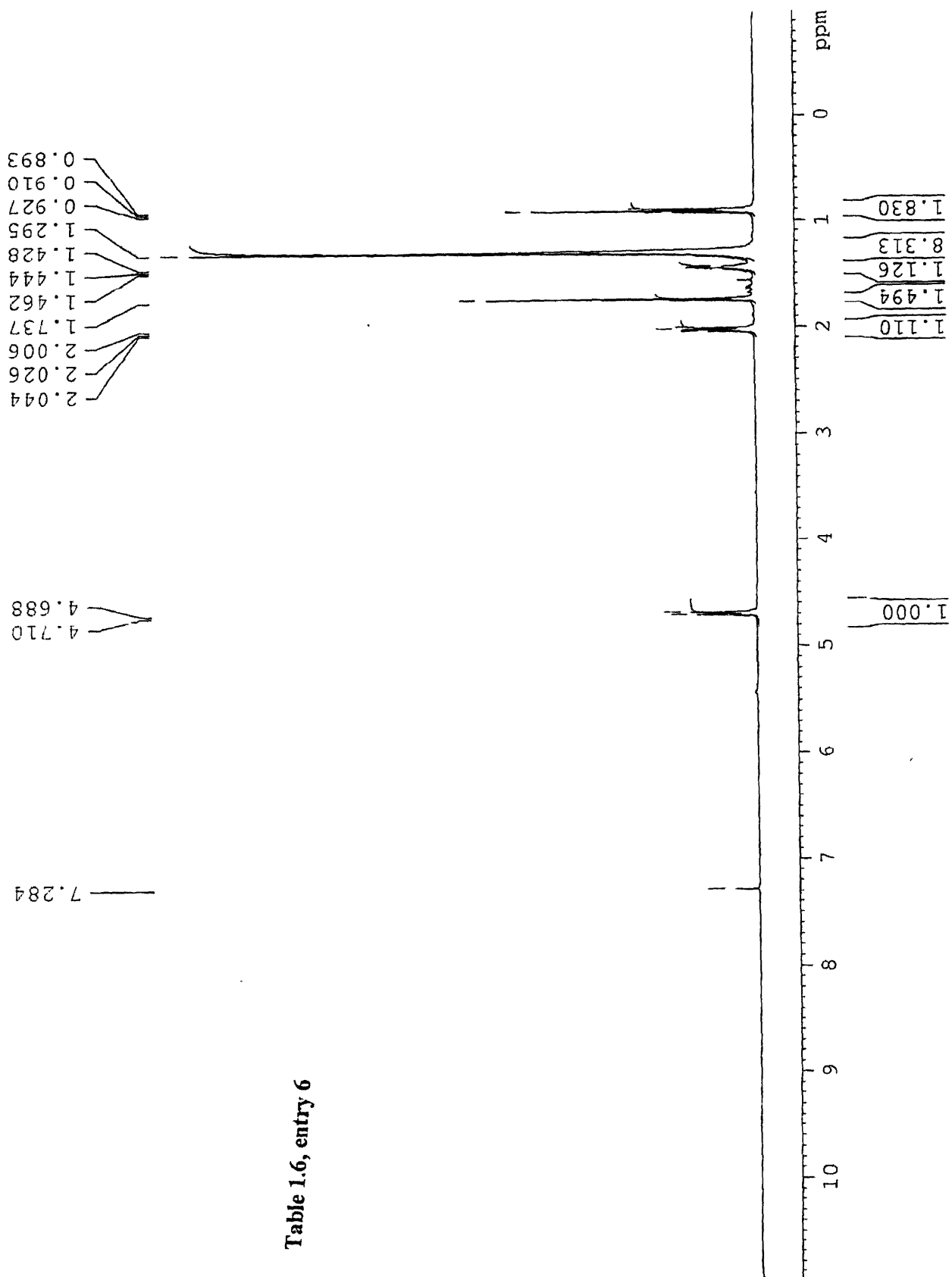


Table 1.6, entry 5

3261b

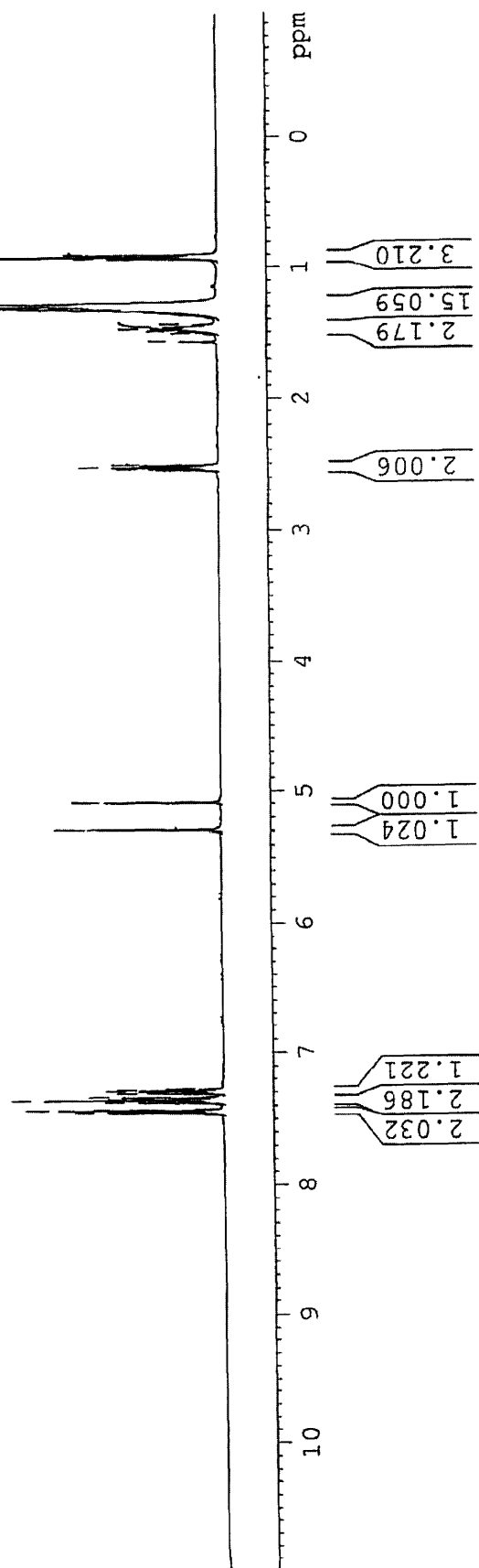
Table 1.6, entry 6



3205a2

7.455
7.450
7.446
7.432
7.431
7.378
7.375
7.371
7.358
7.354
7.342
7.338
7.313
7.310
7.307
7.298
7.292
7.285
7.277
7.274
7.271
5.293
5.290
5.085
5.083
2.545
2.527
2.507
1.572
1.514
1.496
1.478
1.459
1.440
1.330
1.312
1.283
0.931
0.915
0.897

Table 1.6, entry 7



4075ar1

7.844
7.836
7.826
7.823
7.739
7.736
7.726
7.719
7.713
7.705
7.412
7.408
7.403
7.391
7.388
7.353
7.350
7.345
7.333
7.329
7.314
7.296
7.292
7.288
7.284
7.281
7.274
7.267
7.260
7.256
5.314
5.132
5.129
3.773
3.755
3.736
2.613
2.594
2.575
1.927
1.908
1.889
1.871
1.852

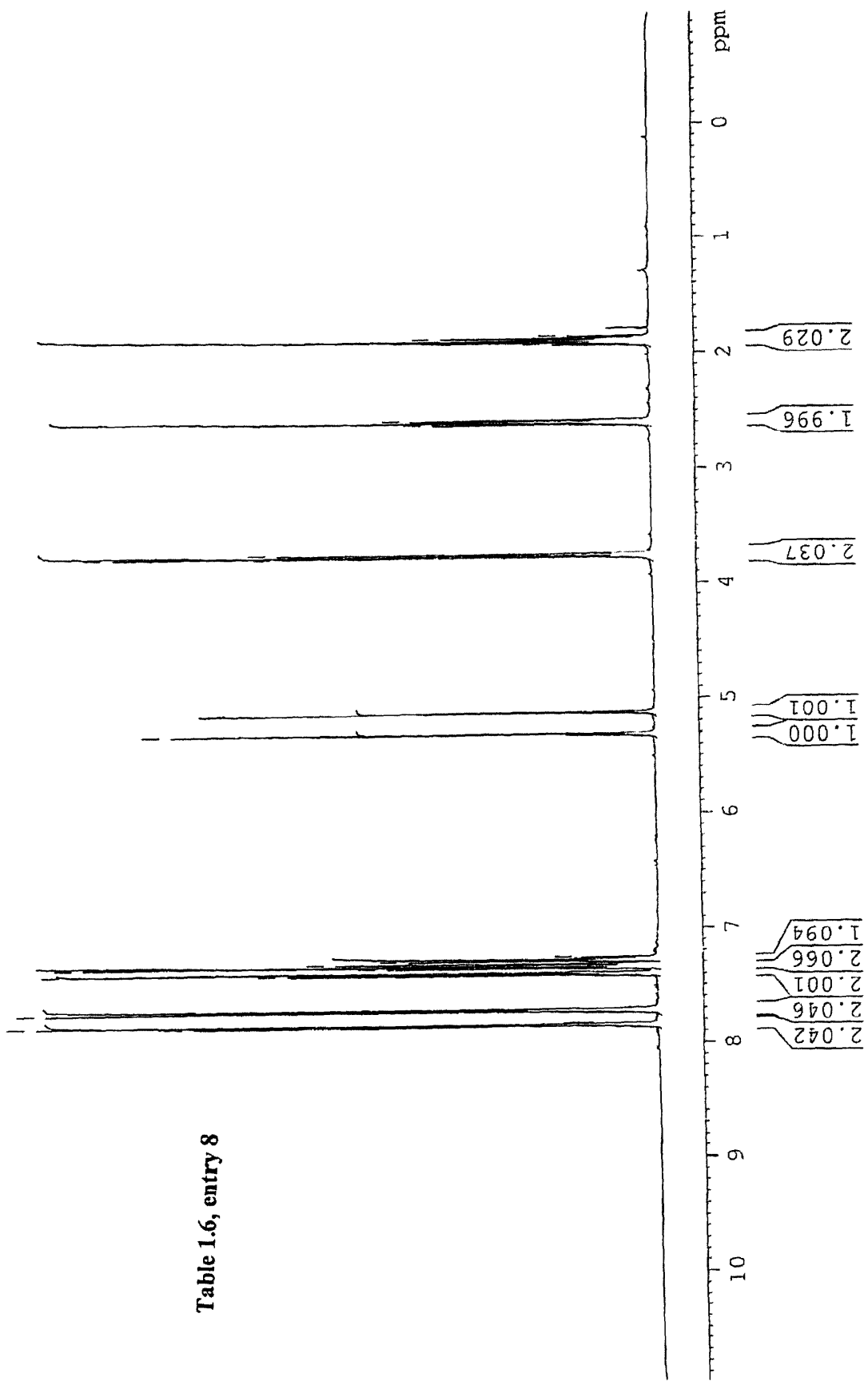
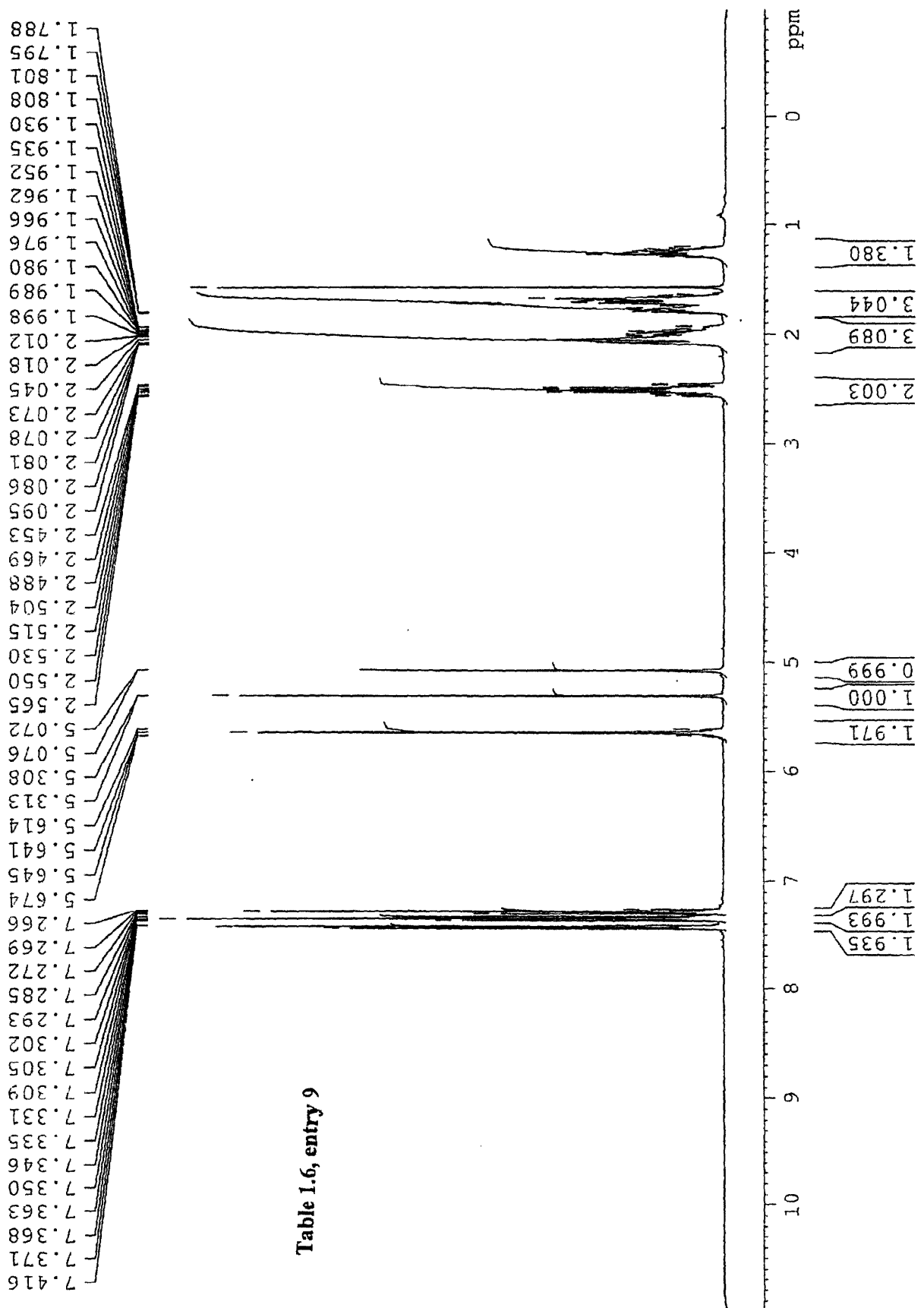


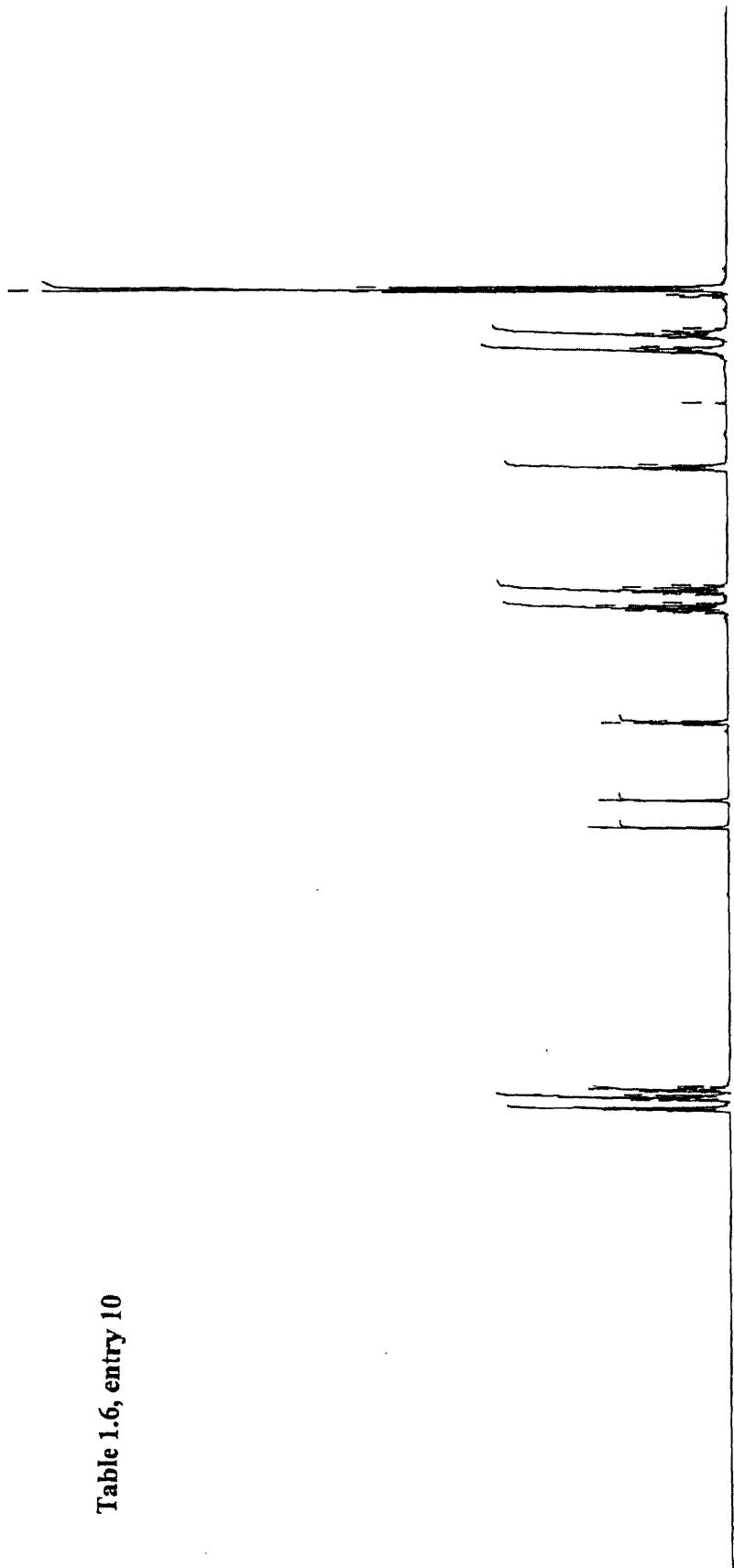
Table 1.6, entry 8

4095er



40952r

7.420
7.417
7.366
7.361
7.348
7.344
7.332
7.329
7.306
7.303
7.299
7.291
7.285
7.278
7.270
7.267
7.263
5.306
5.303
5.094
5.091
4.511
4.497
4.482
3.660
3.643
3.637
3.625
3.619
3.607
3.602
3.584
3.518
3.501
3.495
3.483
3.477
3.466
3.460
3.442
2.576
2.558
2.539
2.071
1.704
1.701
1.686
1.672
1.668
1.663
1.649
1.589



6.159
2.122
2.220
2.012
2.081
2.033
0.999
1.008
1.000
2.014
2.114
1.247

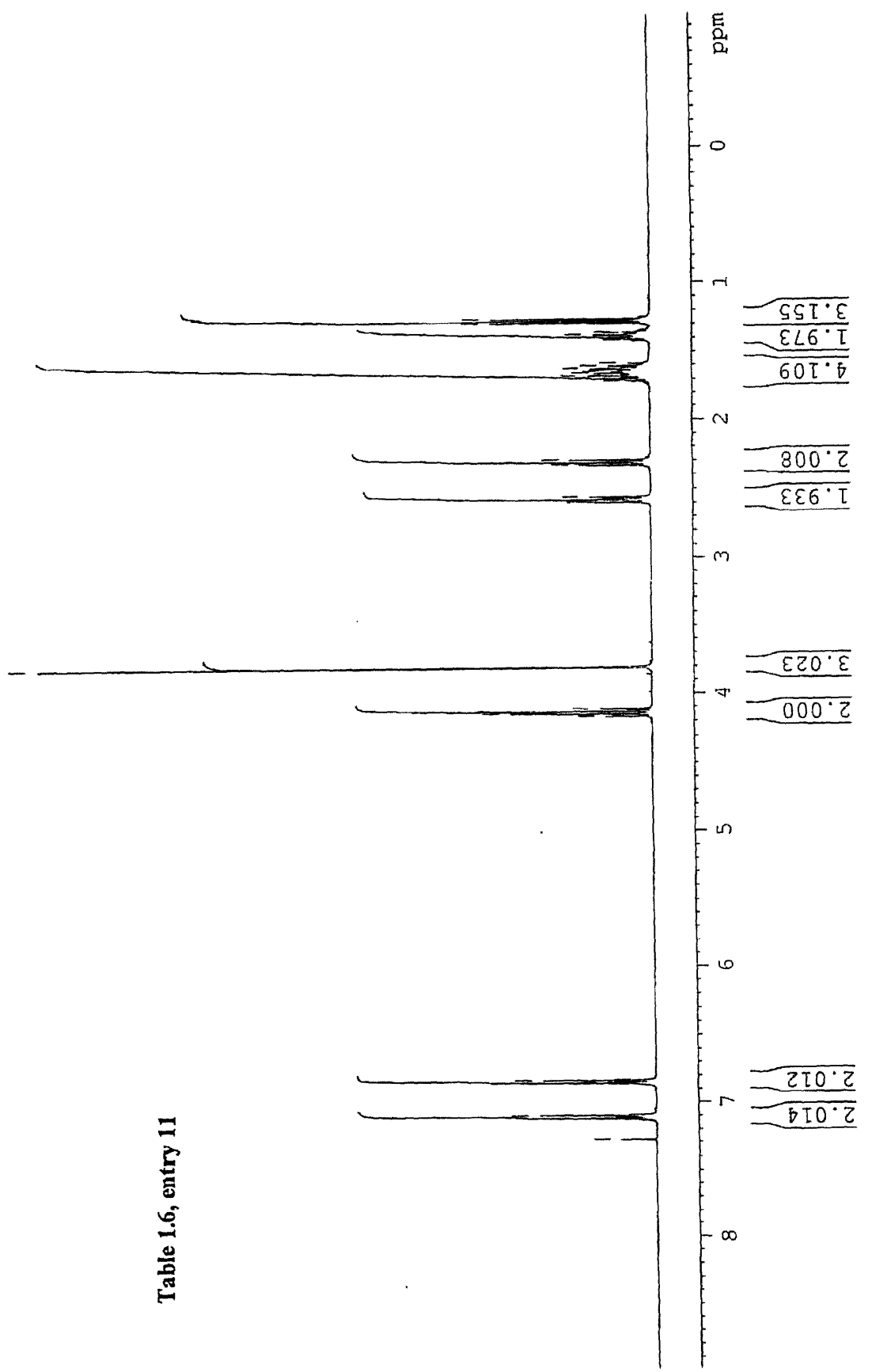
Table 1.6, entry 10

40931

7.284
7.128
7.121
7.099
6.865
6.858
6.852
6.841
6.836
6.829

4.171
4.153
4.135
4.117
3.810
2.596
2.577
2.557
2.331
2.313
2.293
1.714
1.696
1.677
1.665
1.657
1.646
1.639
1.627
1.608
1.589
1.414
1.400
1.394
1.384
1.376
1.362
1.356
1.290
1.272
1.261
1.254

Table 1.6, entry 11

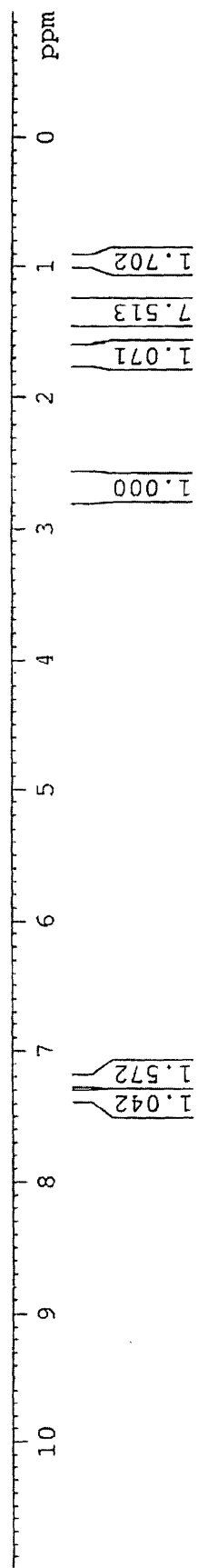


4137c

2.691
2.672
2.652
2.112
1.721
1.702
1.684
1.665
1.647
1.381
1.337
1.313
1.296
0.975
0.959
0.941
0.912
0.901

7.361
7.340
7.330
7.324
7.285
7.257
7.239
7.221

Table 1.6, entry 12

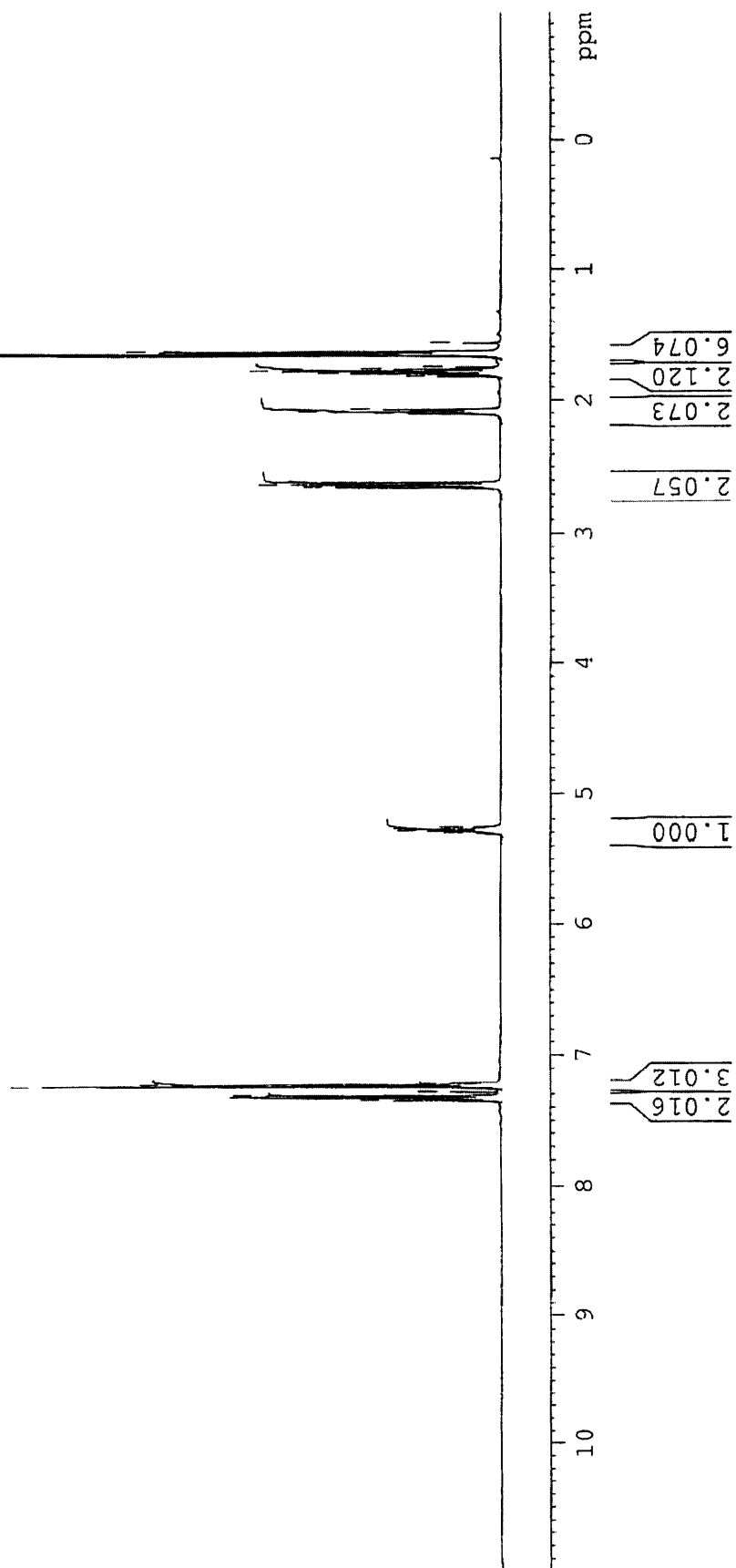


40231

1.568
1.633
1.635
1.657
1.660
1.741
1.760
1.765
1.775
1.780
1.786
1.798
1.803
1.818
2.068
2.088
2.106
2.613
2.633
2.652

5.262
5.265
5.276
5.279
5.292
5.295
5.309
5.311
7.213
7.232
7.250
7.285
7.315
7.322
7.332
7.334
7.348
7.353

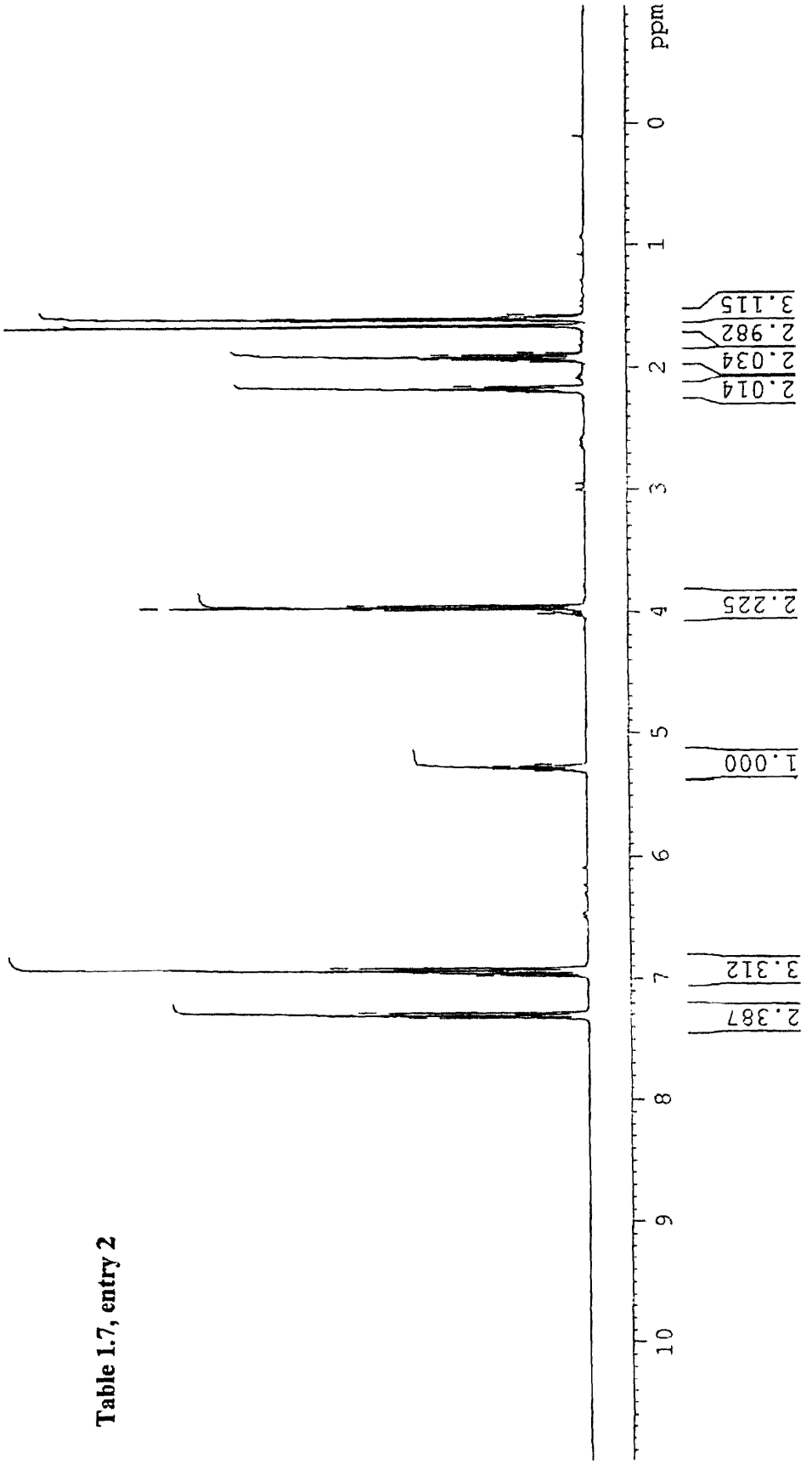
Table 1.7, entry 1



4071a1

7.334
7.328
7.322
7.309
7.306
7.300
7.293
7.288
7.285
6.979
6.976
6.960
6.940
6.938
6.918
6.916
5.312
5.309
5.298
5.295
5.292
5.289
5.282
5.279
5.275
5.272
5.262
5.259
4.016
3.978
3.962
3.945
2.199
2.180
2.161
1.950
1.934
1.918
1.913
1.902
1.896
1.879
1.664
1.619
1.617
1.603
1.600
1.579

Table 1.7, entry 2



4067b3

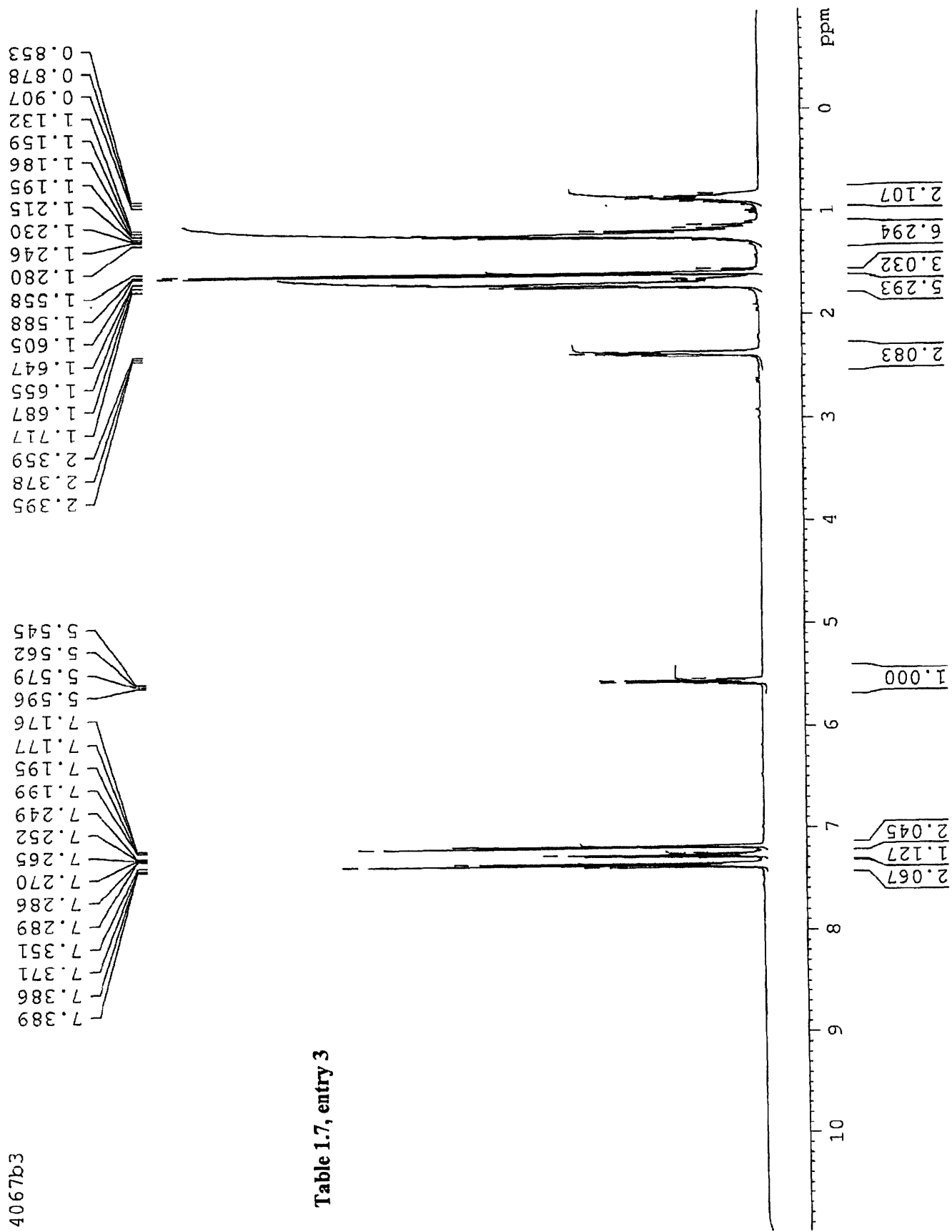
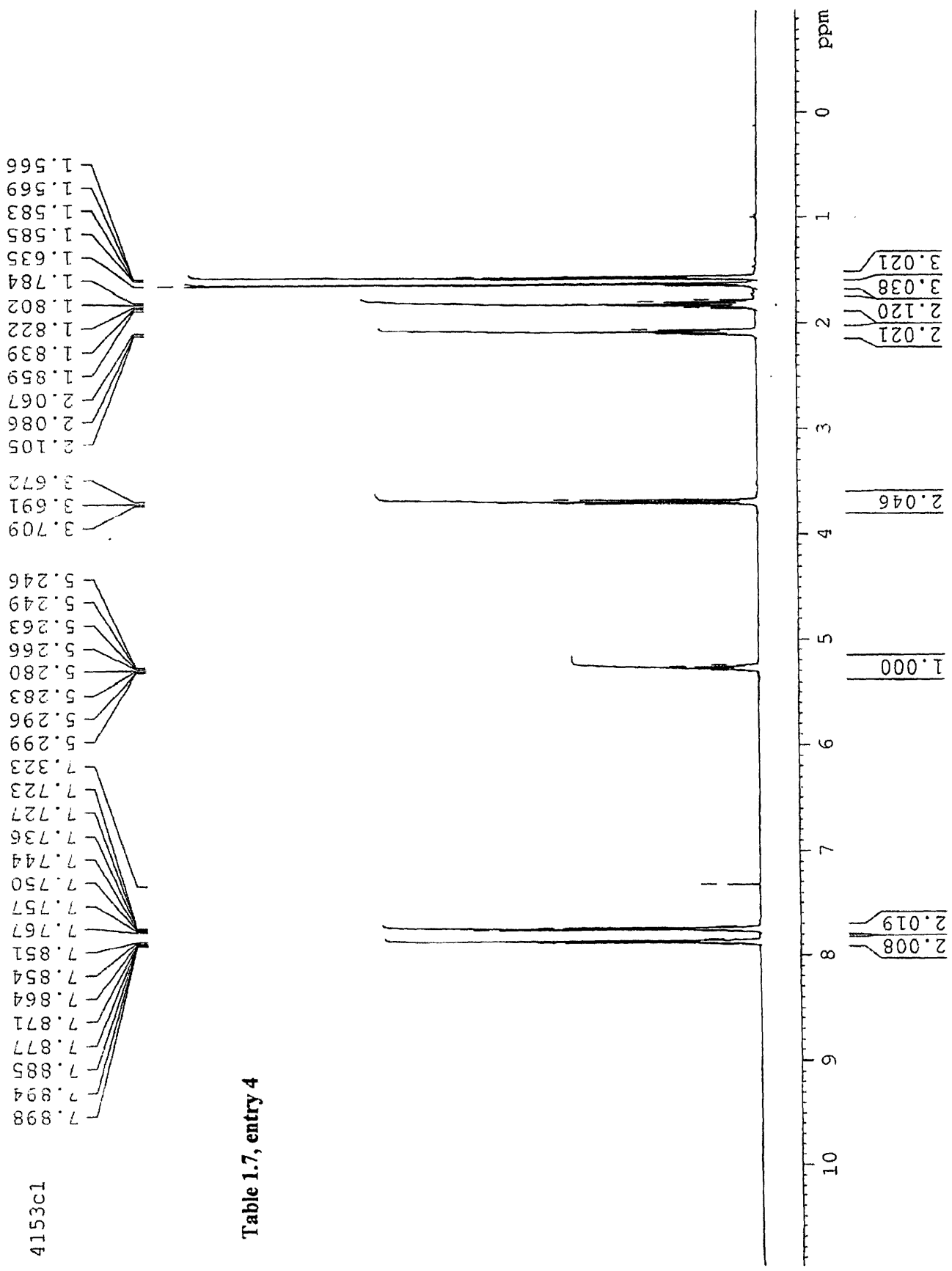


Table 1.7, entry 3



4153c1

Table 1.7, entry 4

4137c1

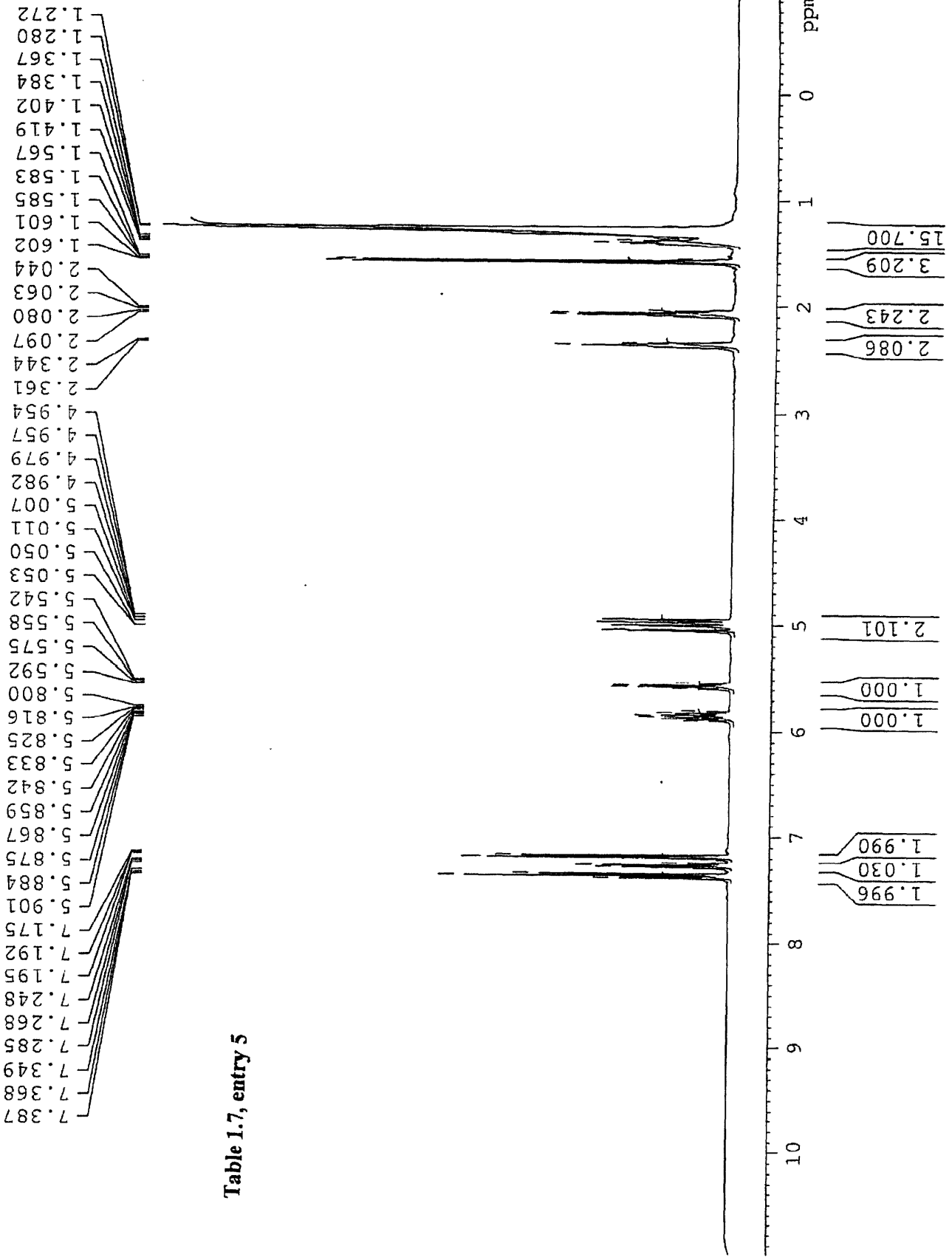
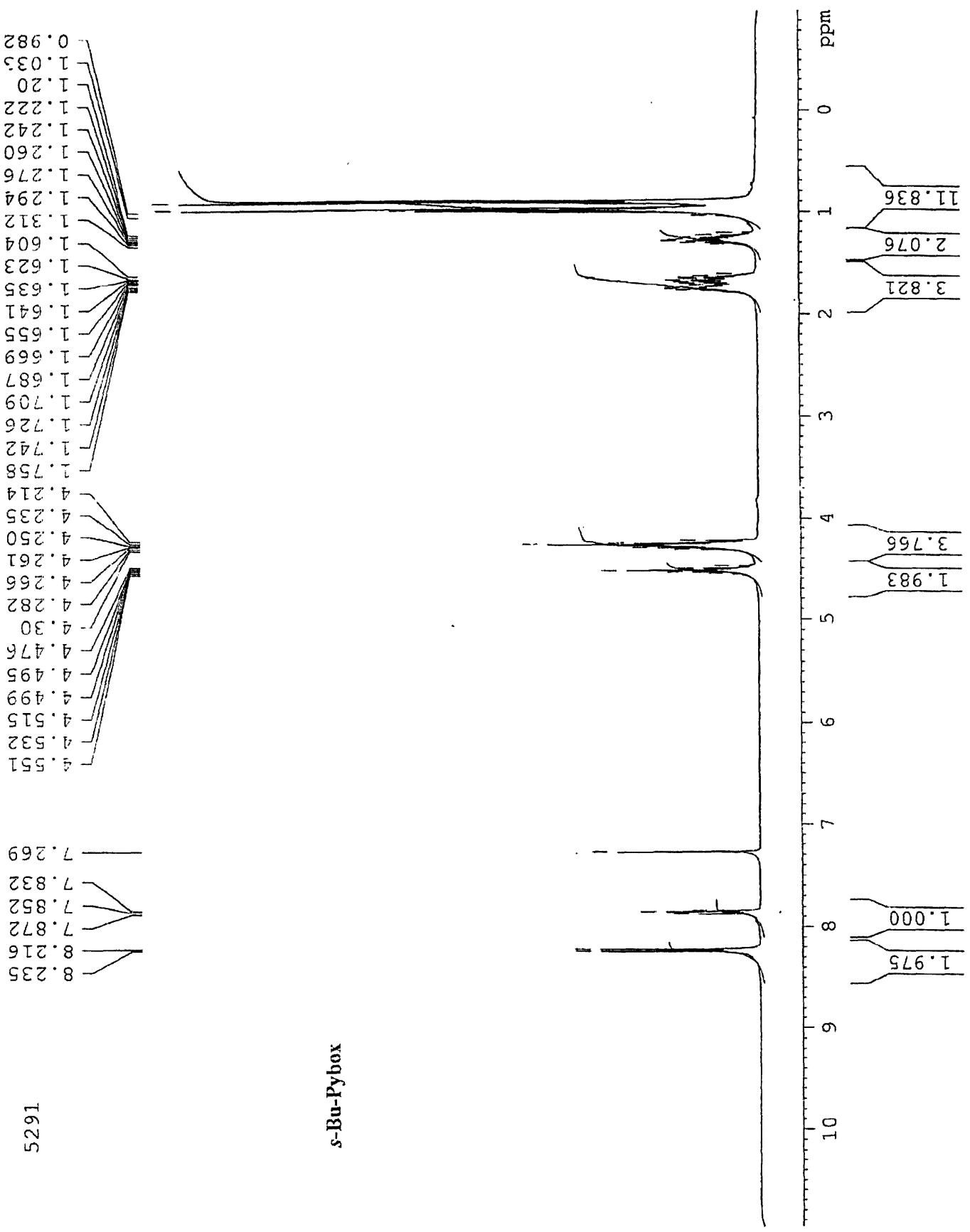


Table 1.7, entry 5

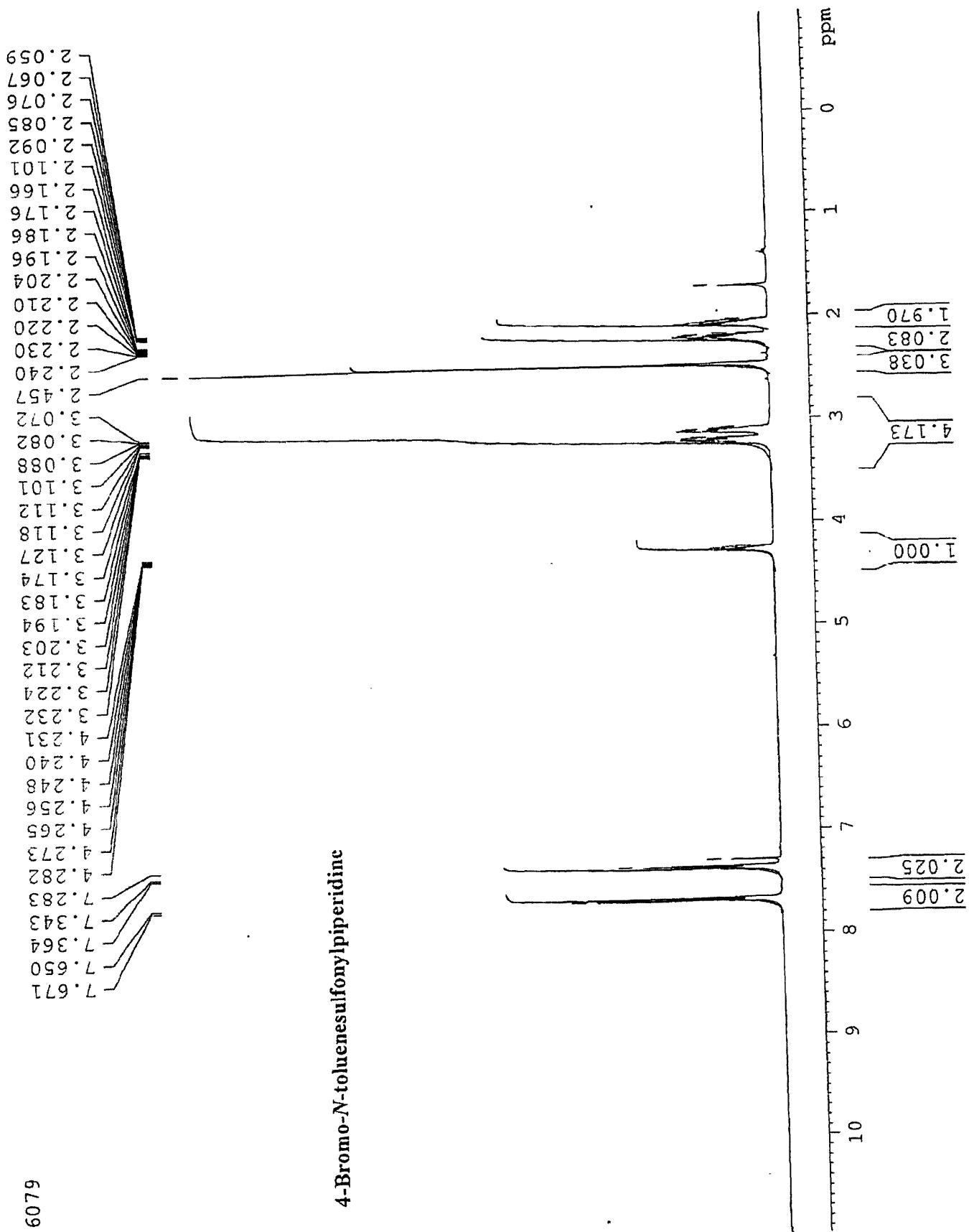


s-Bu-Pybox

5291

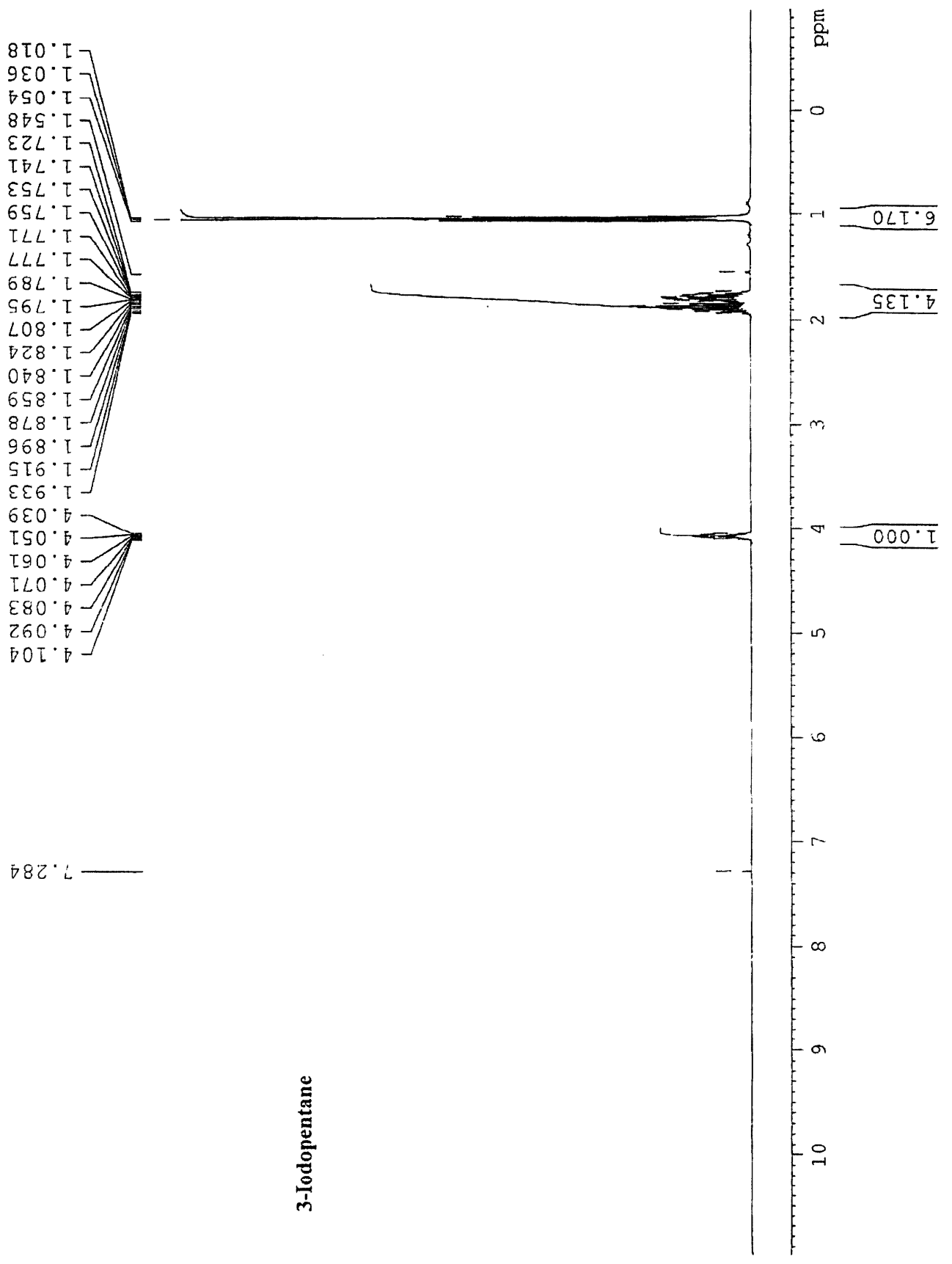
6079

4-Bromo-N-toluenesulfonylpiperidine

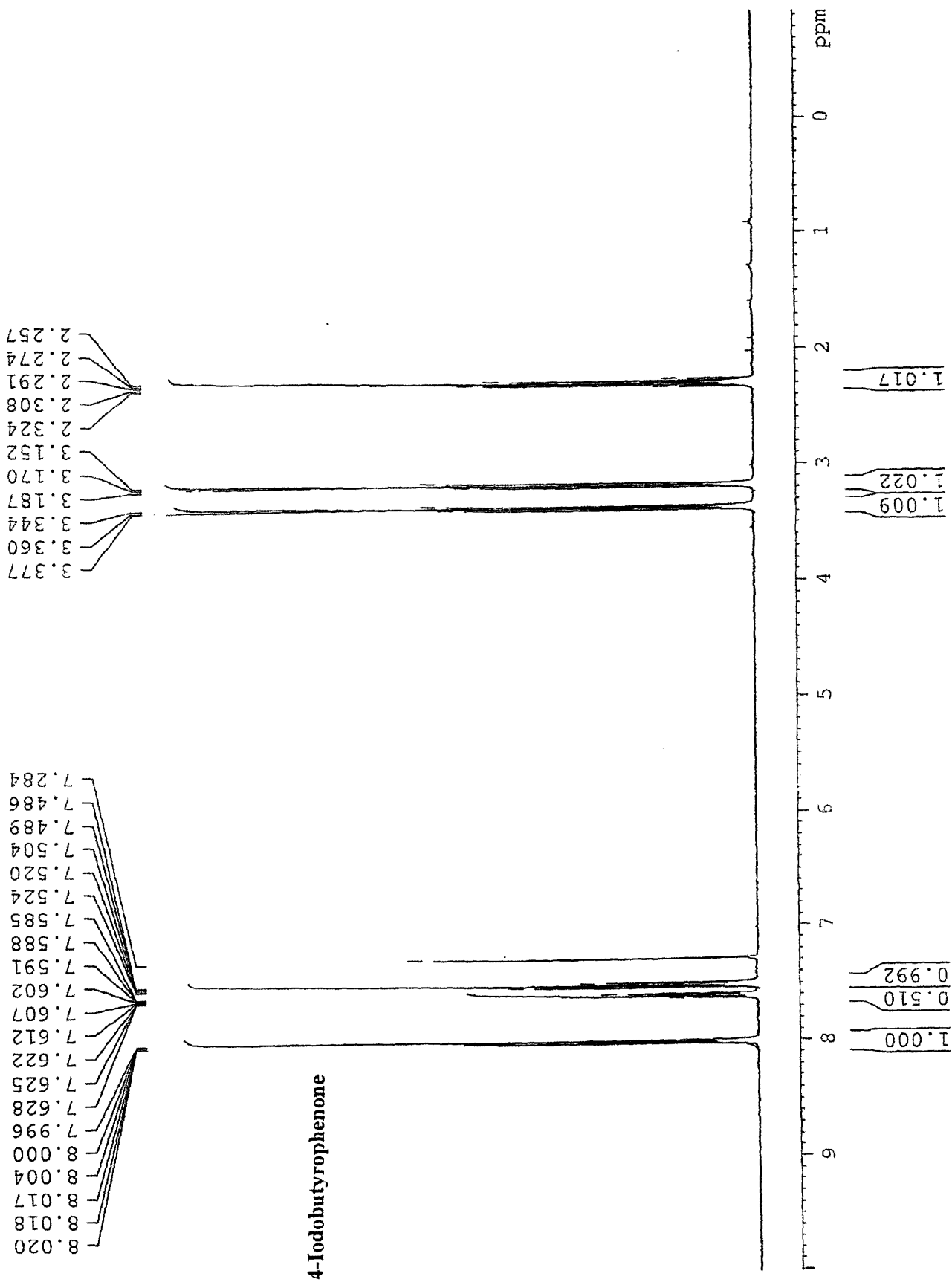


6073a

3-Iodopentane



2029



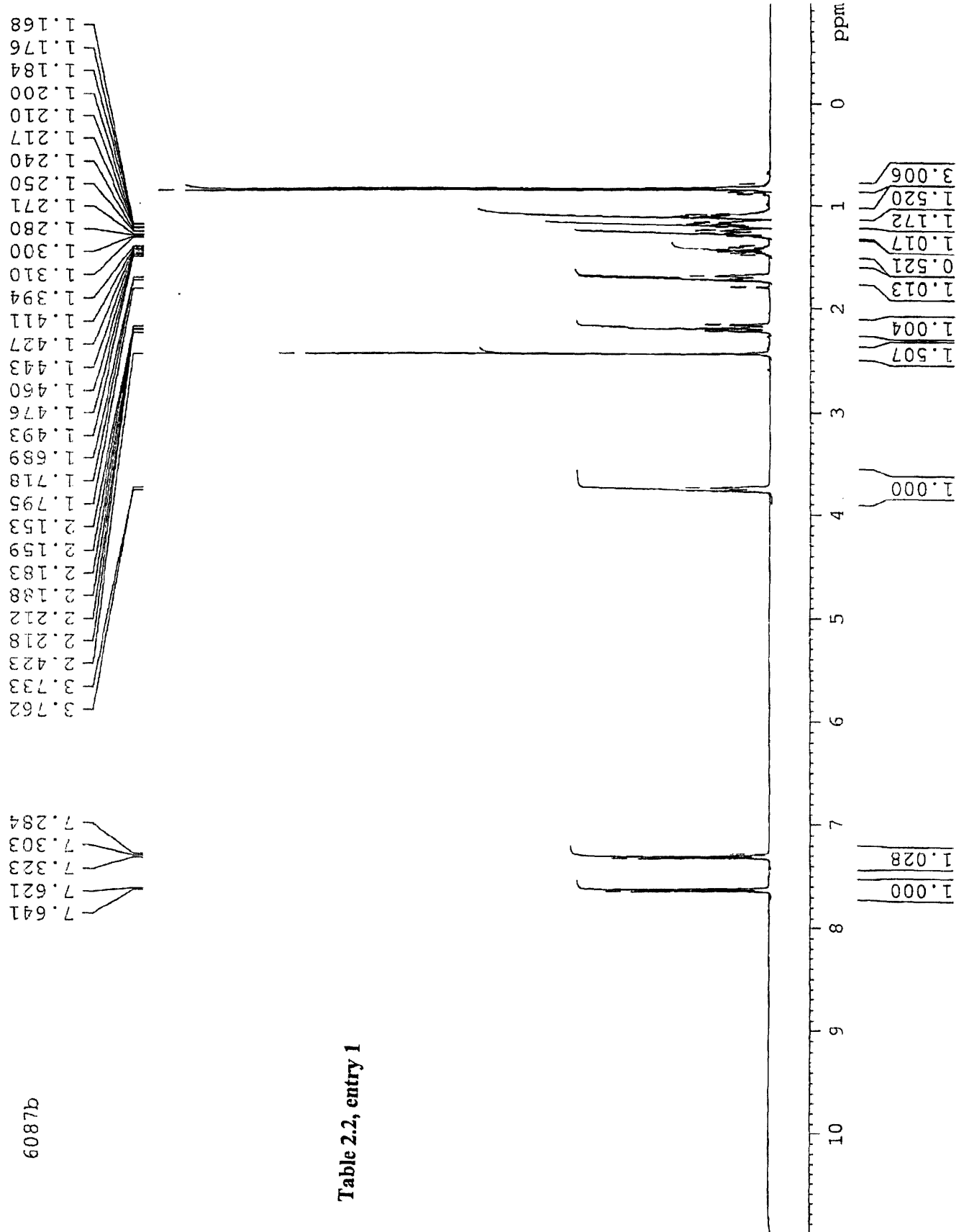


Table 2.2, entry 1

6087b

6099a

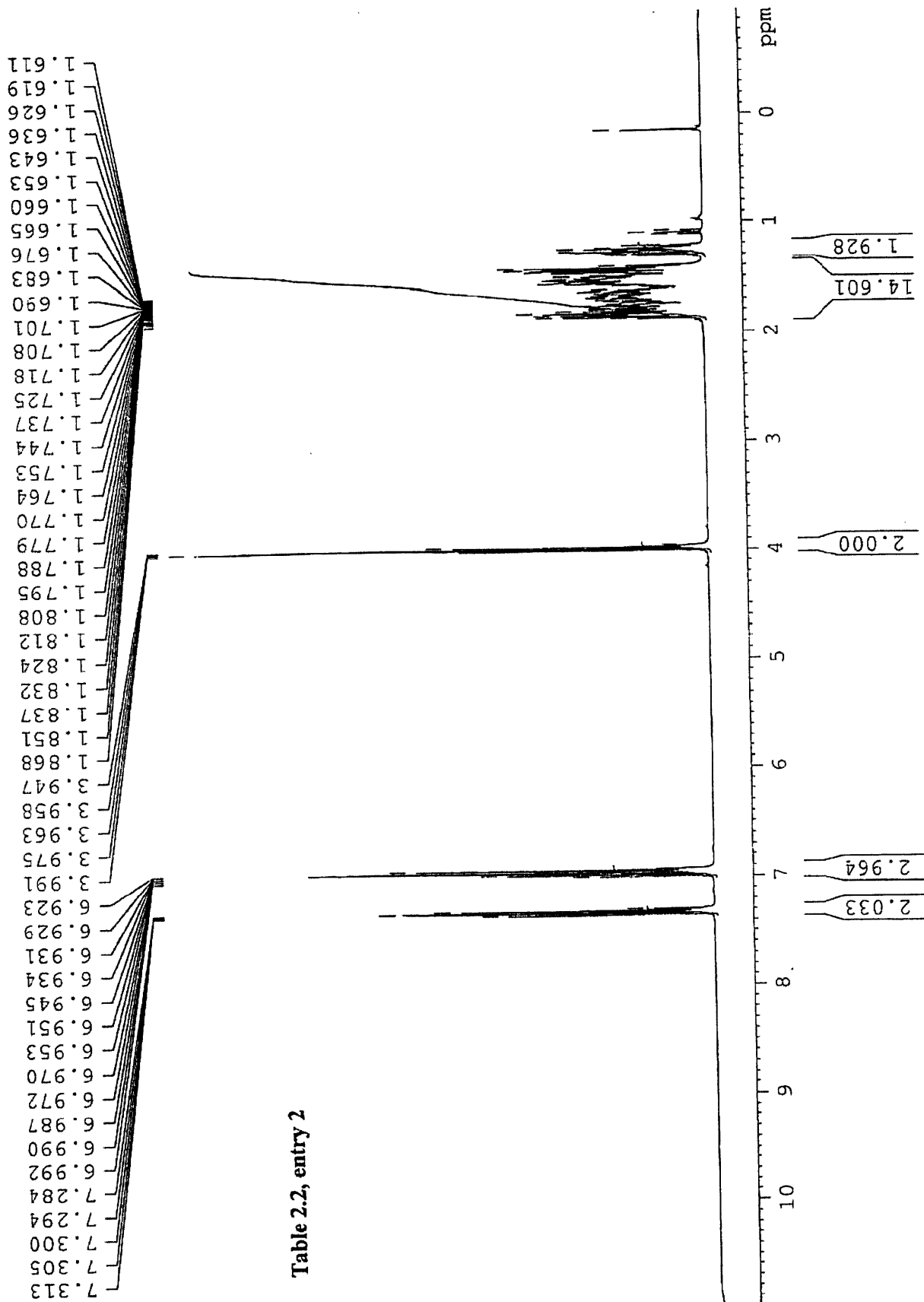
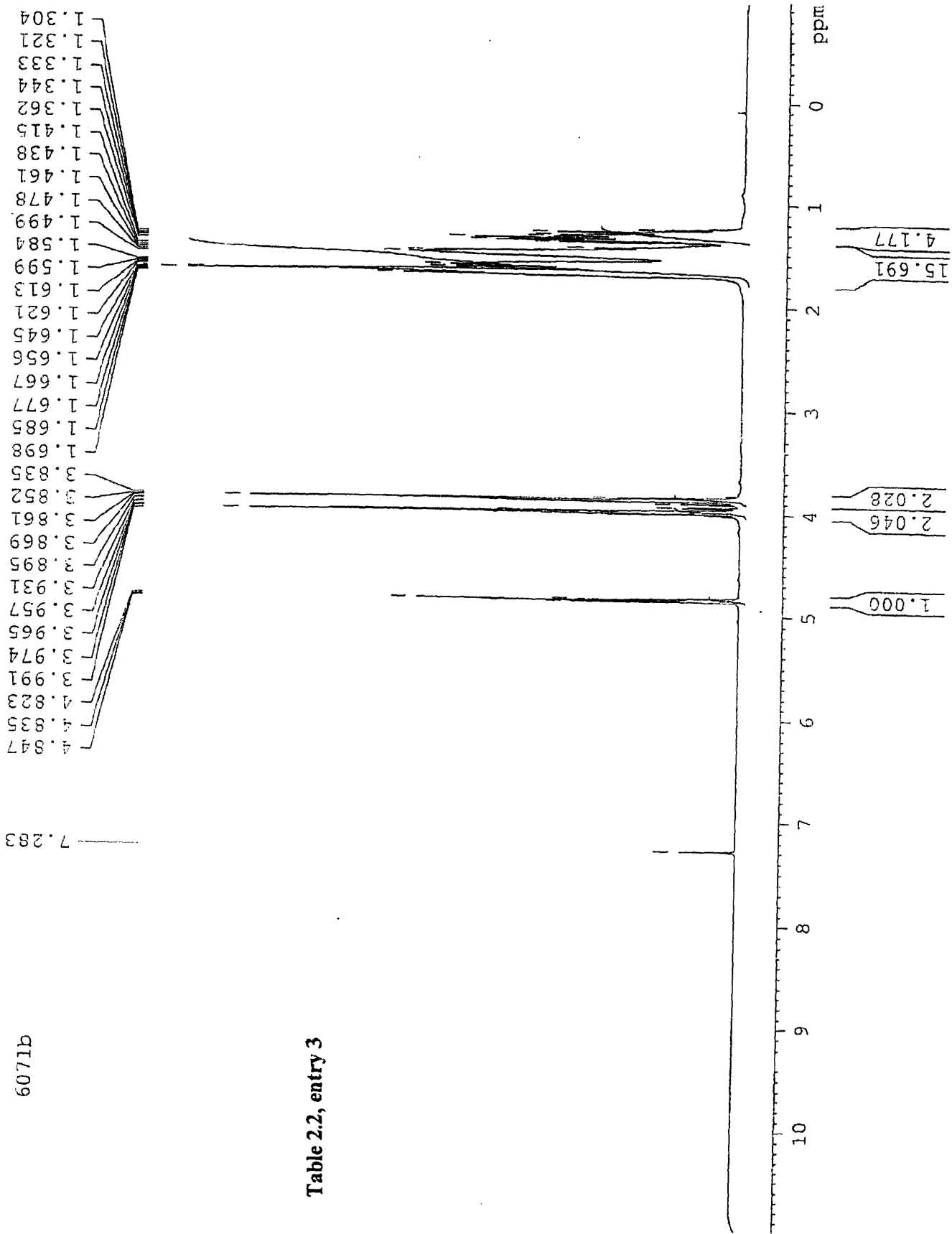


Table 2.2, entry 2



6071b

Table 2.2, entry 3

6081a

7.284

4.154
4.136
4.118
4.100
2.317
2.298
2.279
1.645
1.627
1.609
1.590
1.571
1.331
1.326
1.315
1.304
1.298
1.286
1.274
1.272
1.256
1.239
1.226
1.214
1.209
1.201
1.188
1.172

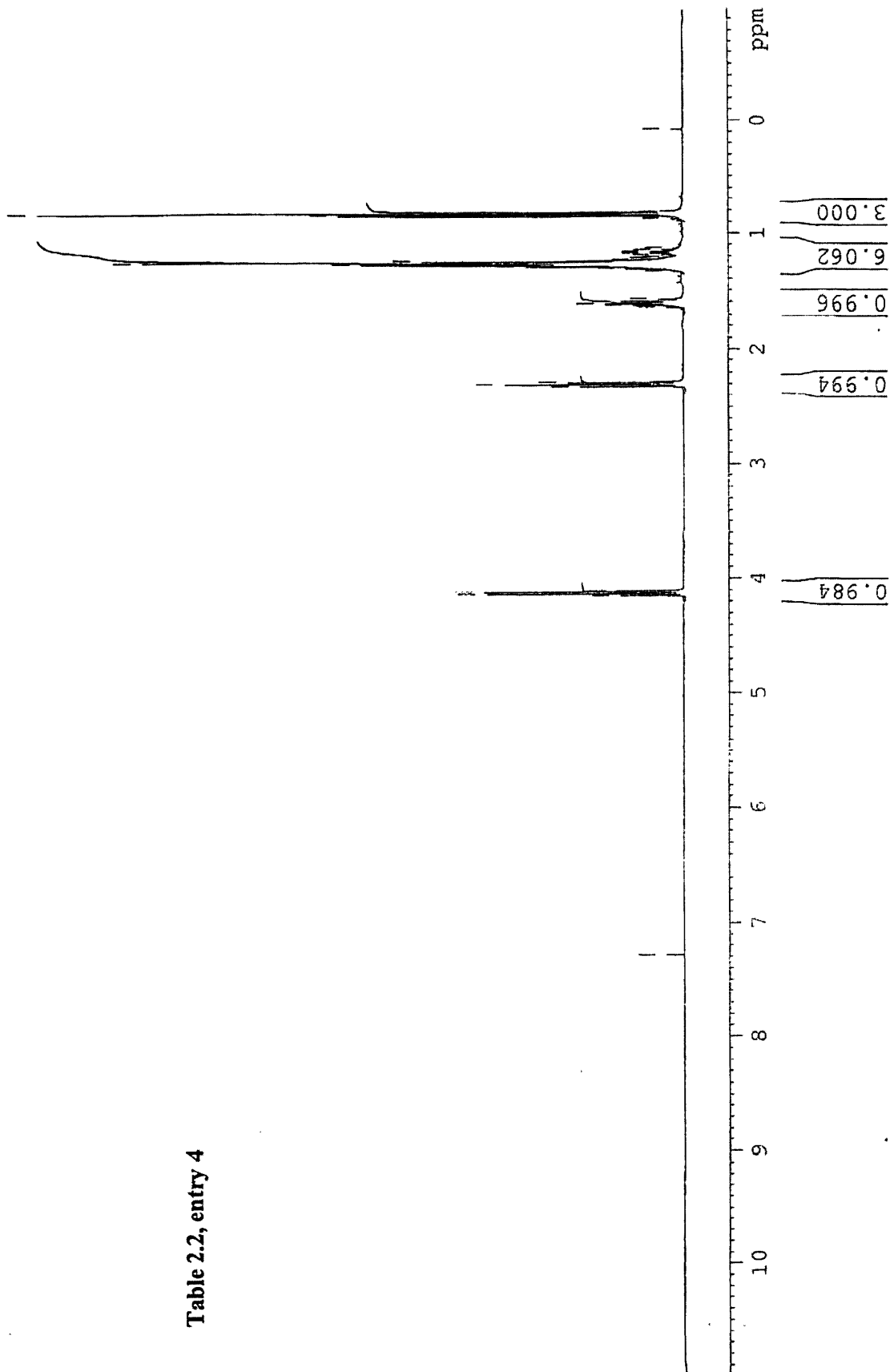


Table 2.2, entry 4

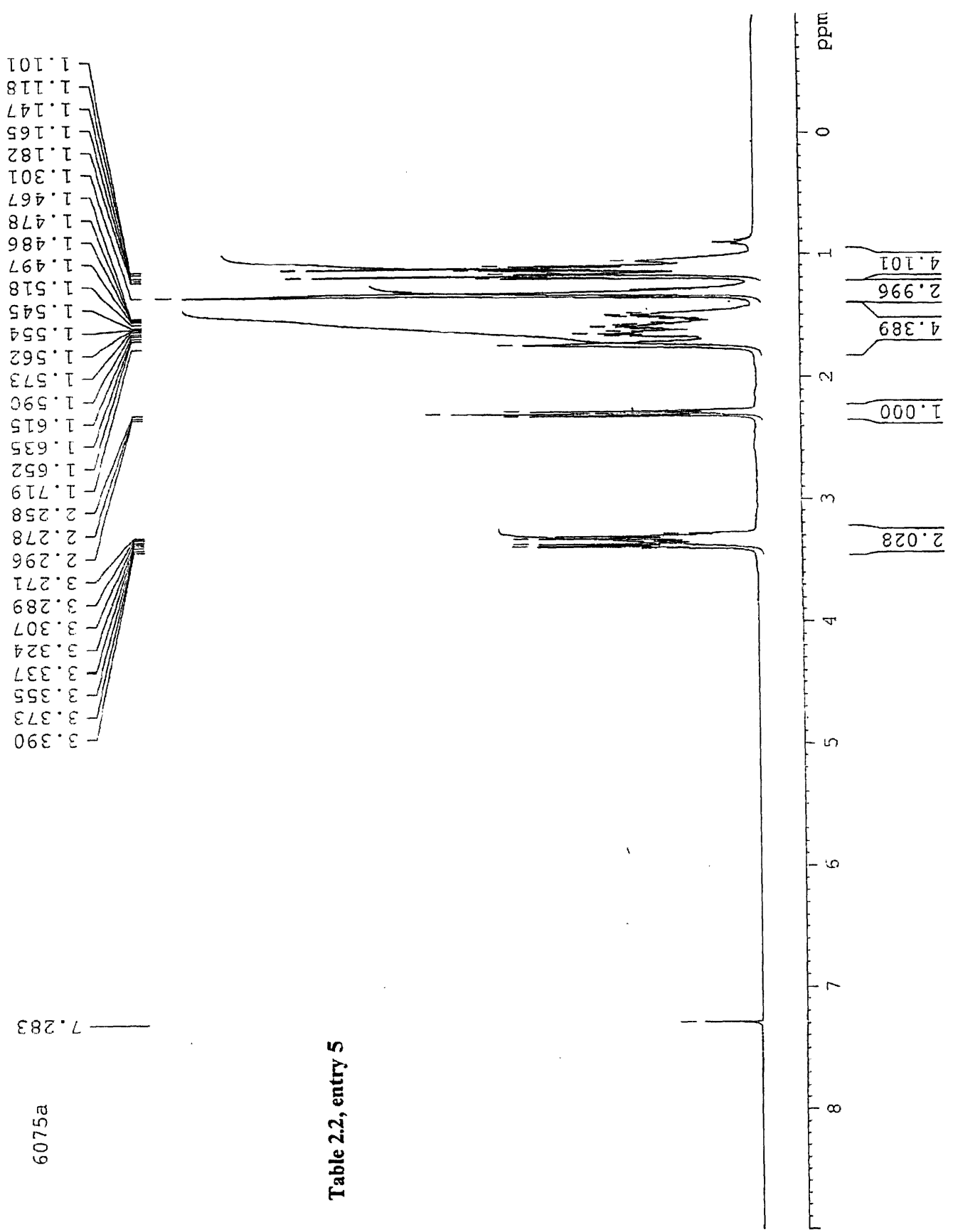


Table 2.2, entry 5

6047e

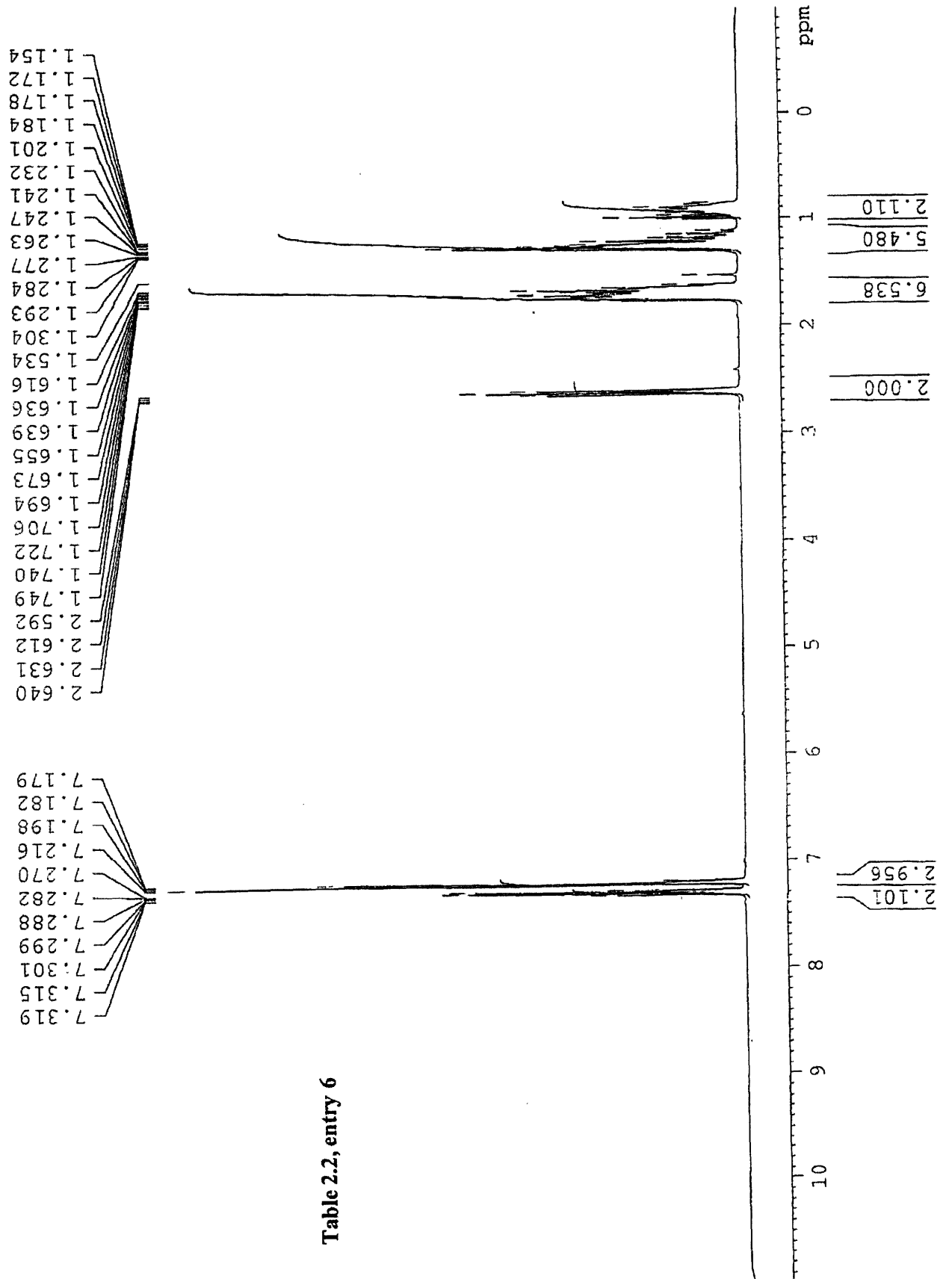


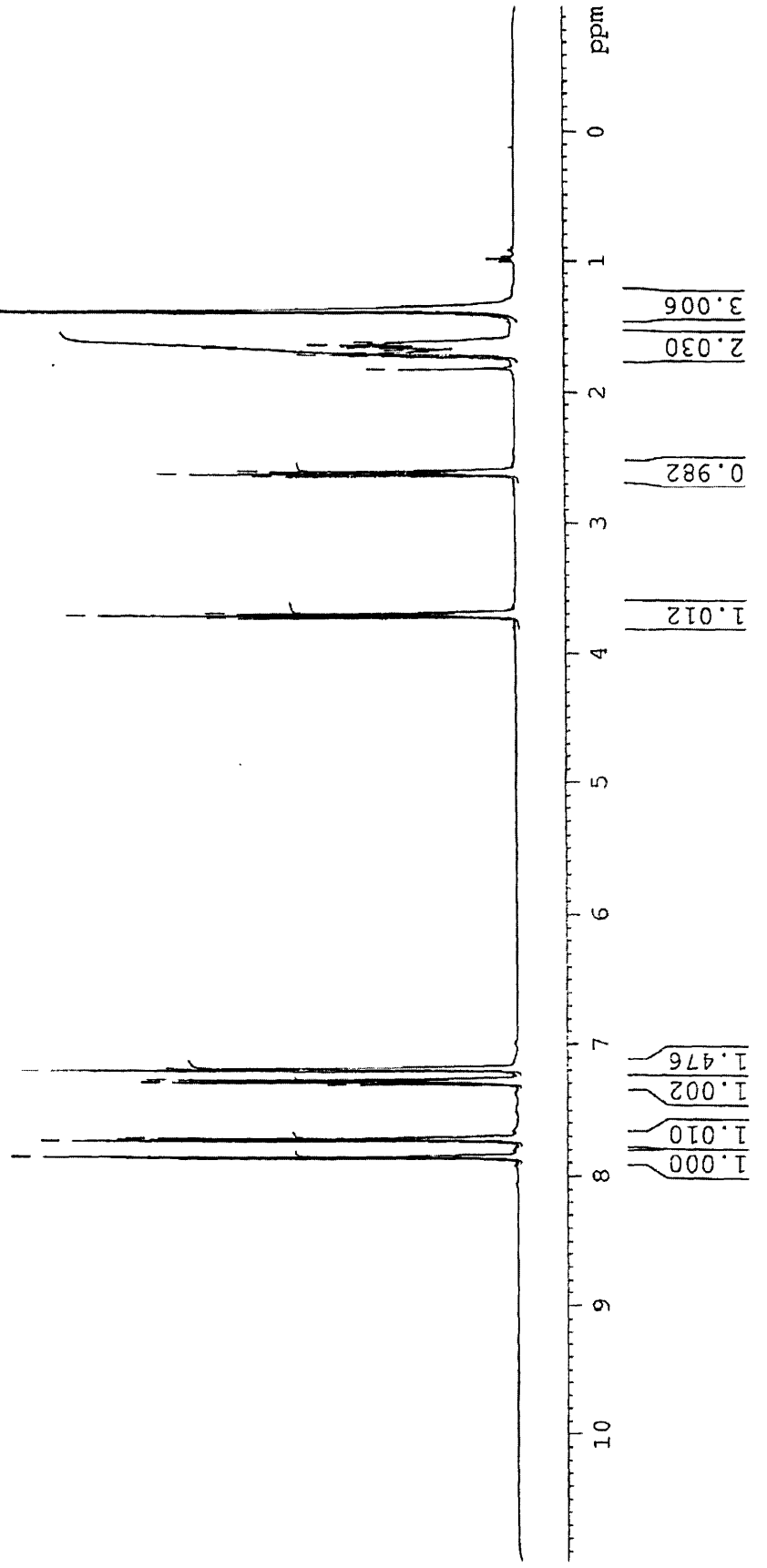
Table 2.2, entry 6

6103dl

3.717
3.699
3.681
2.632
2.612
2.593
1.815
1.732
1.713
1.696
1.679
1.666
1.646
1.628
1.611
1.376

7.870
7.863
7.857
7.849
7.839
7.742
7.732
7.724
7.719
7.711
7.702
7.307
7.288
7.269
7.198
7.185
7.178

Table 2.3, entry 1



61131

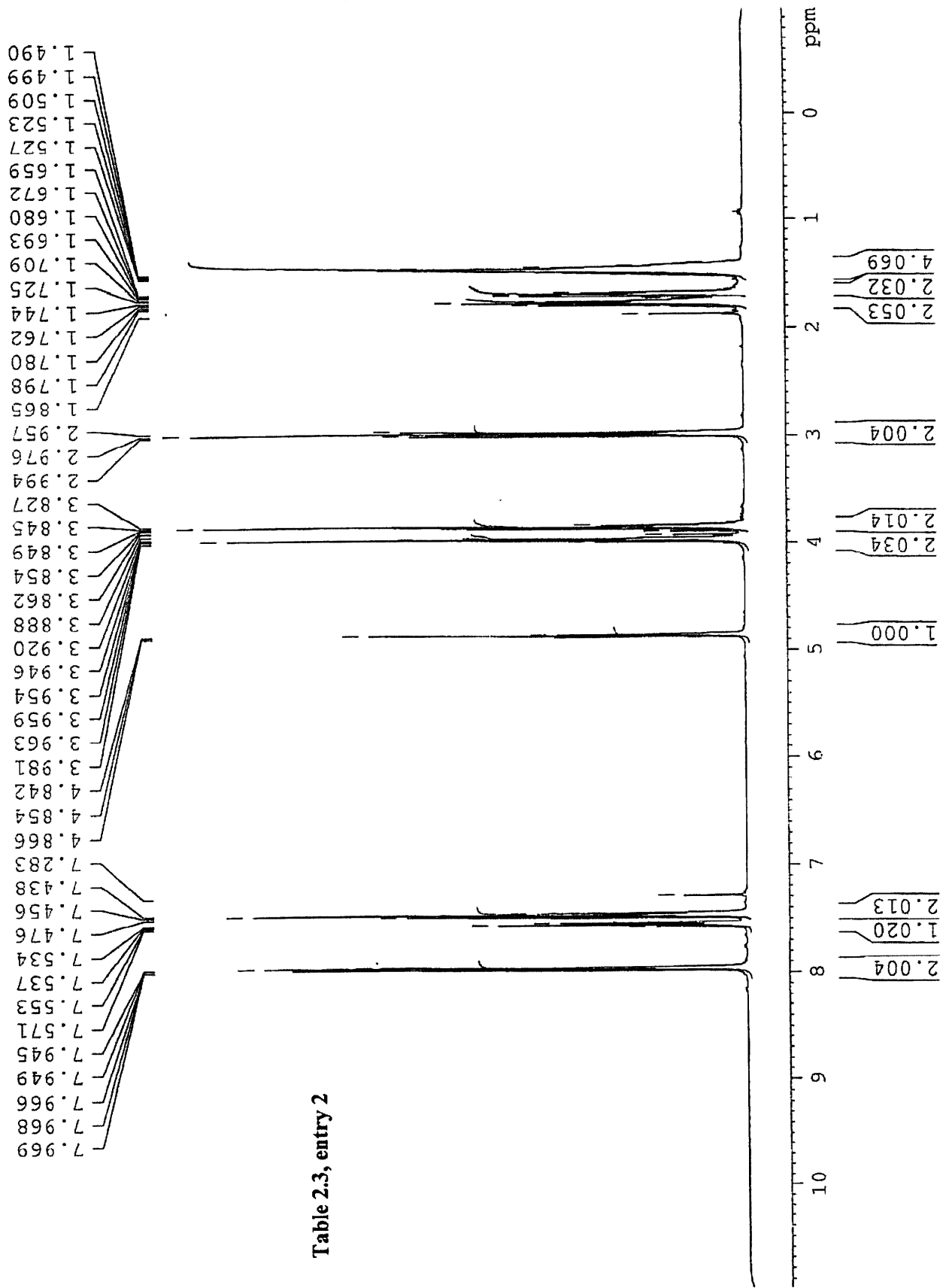
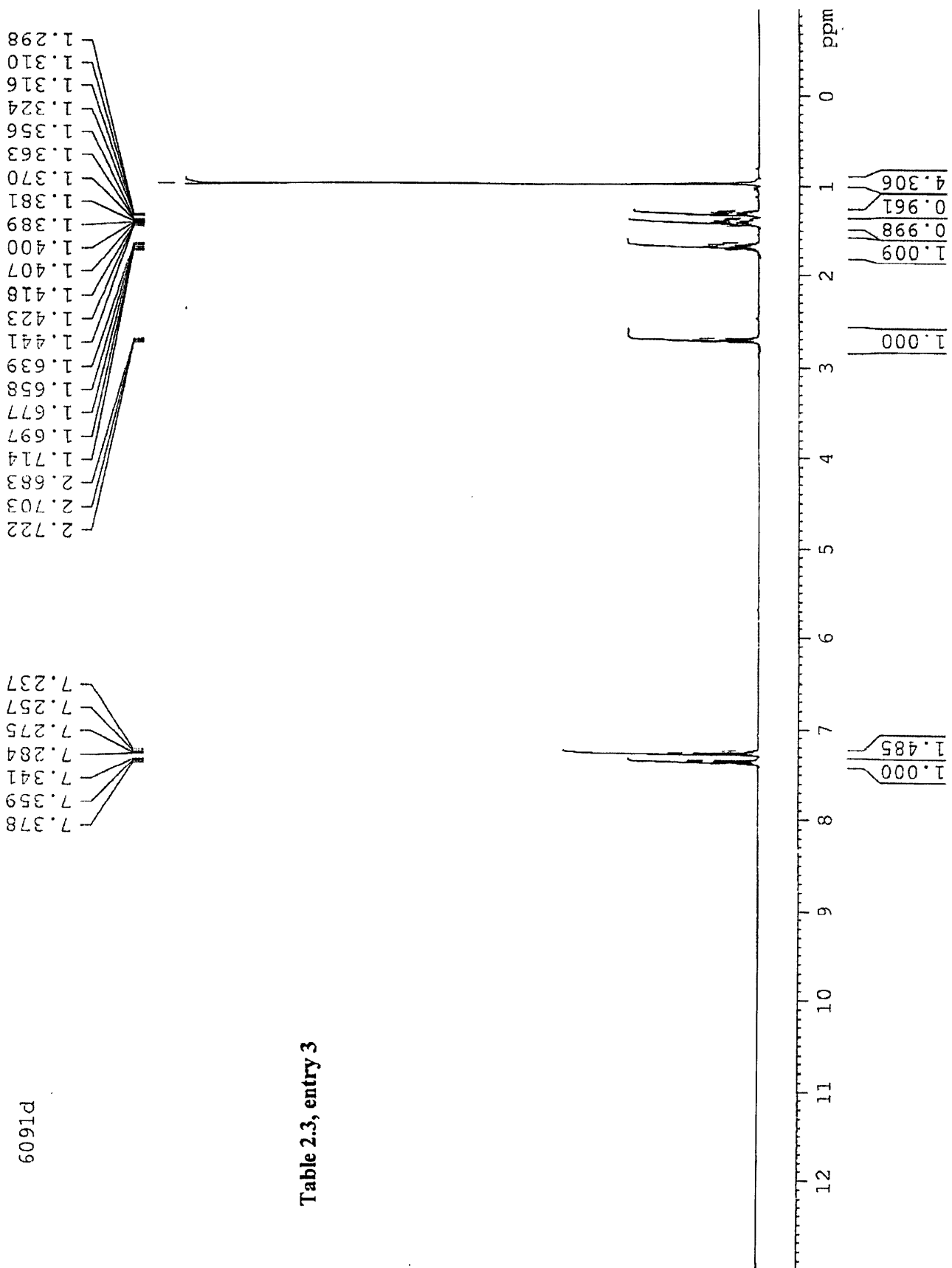


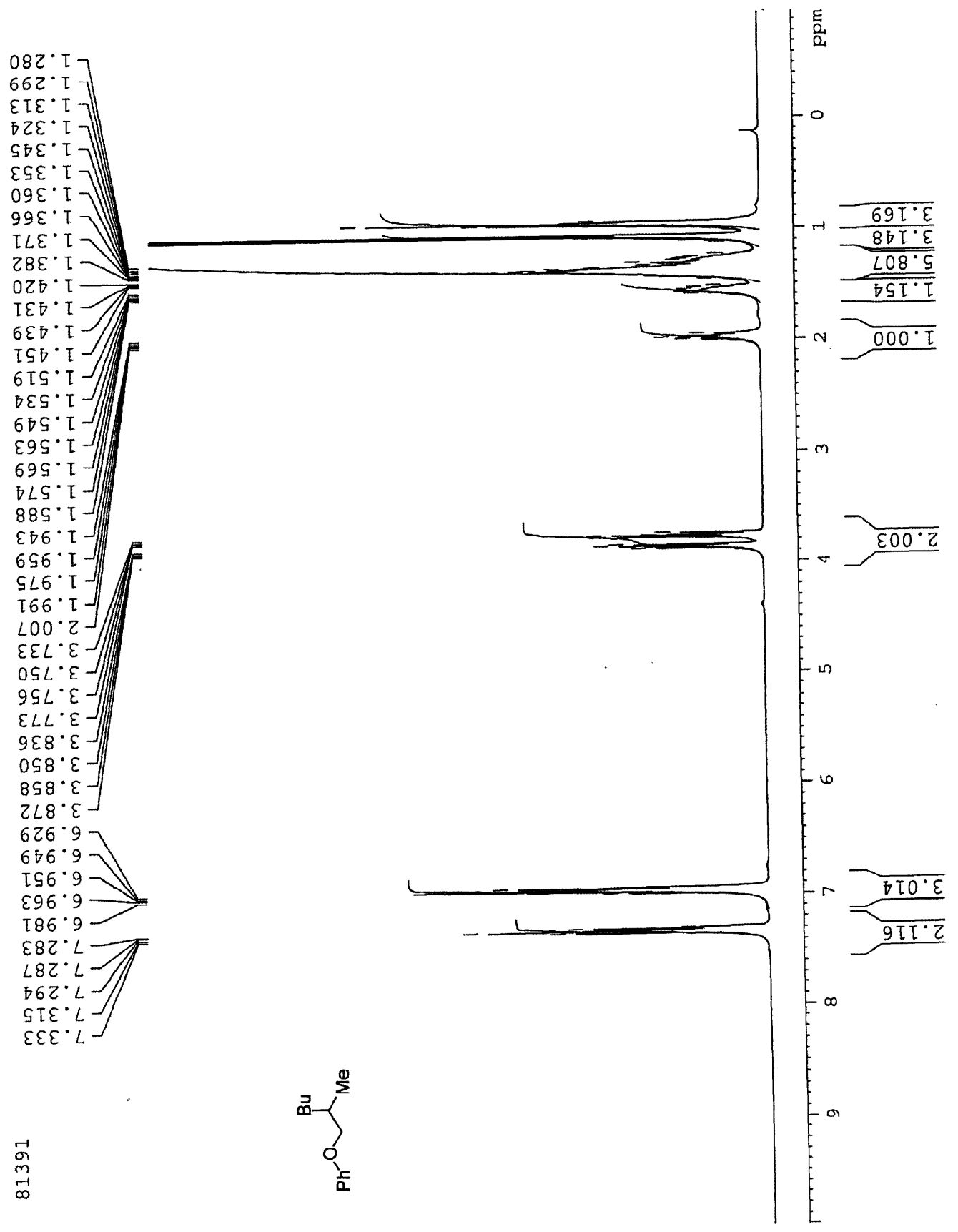
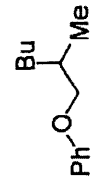
Table 2.3, entry 2

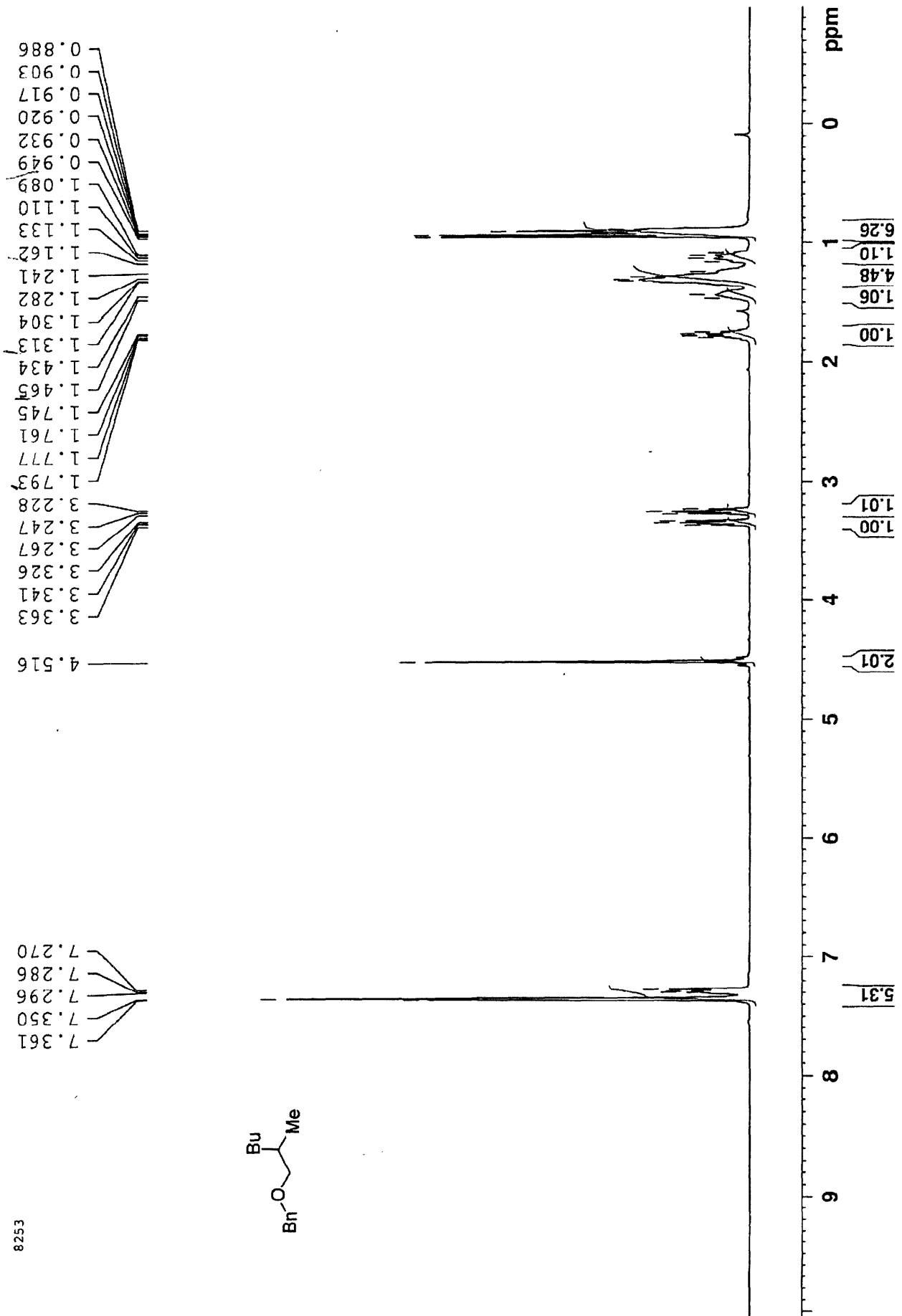


601d

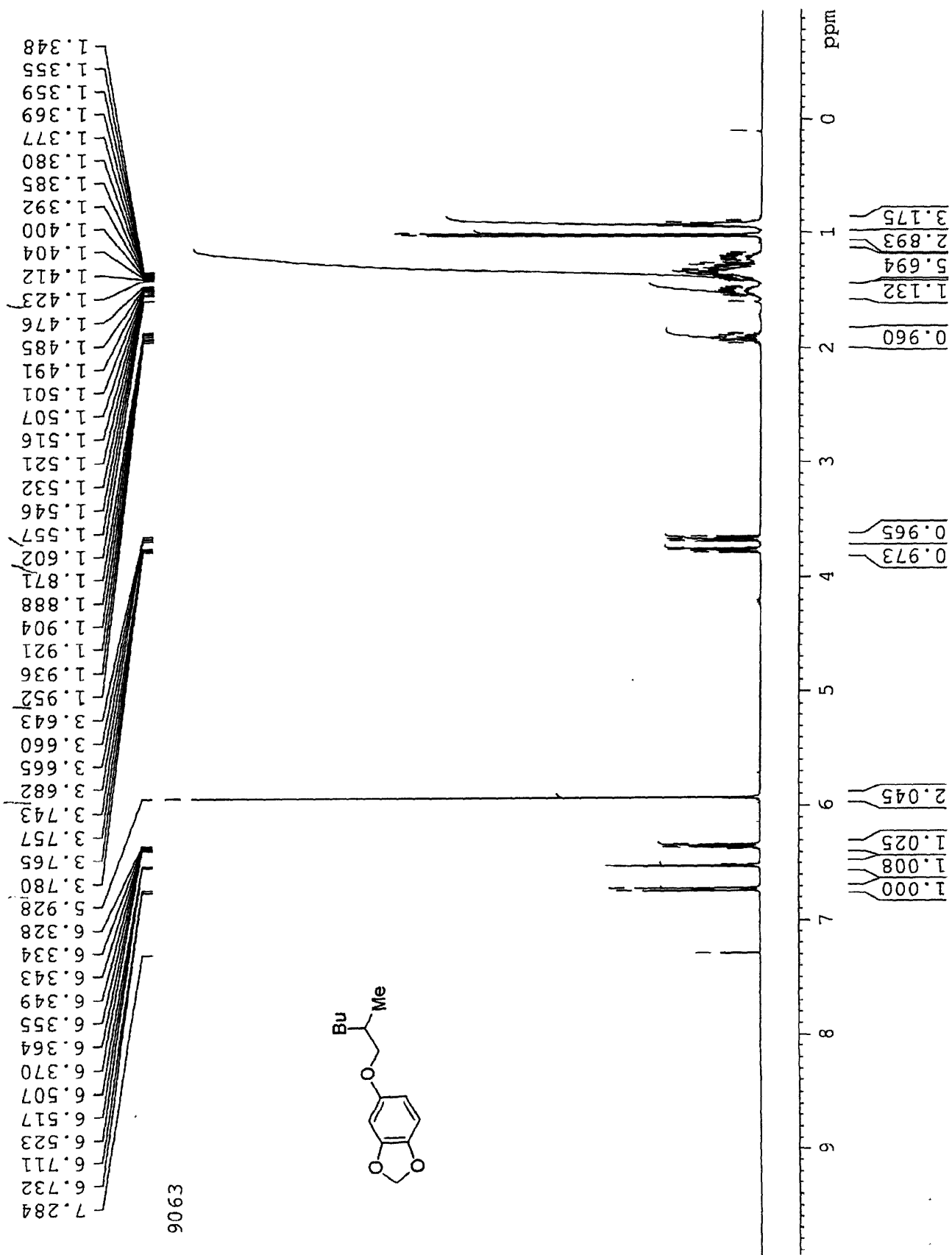
Table 2.3, entry 3

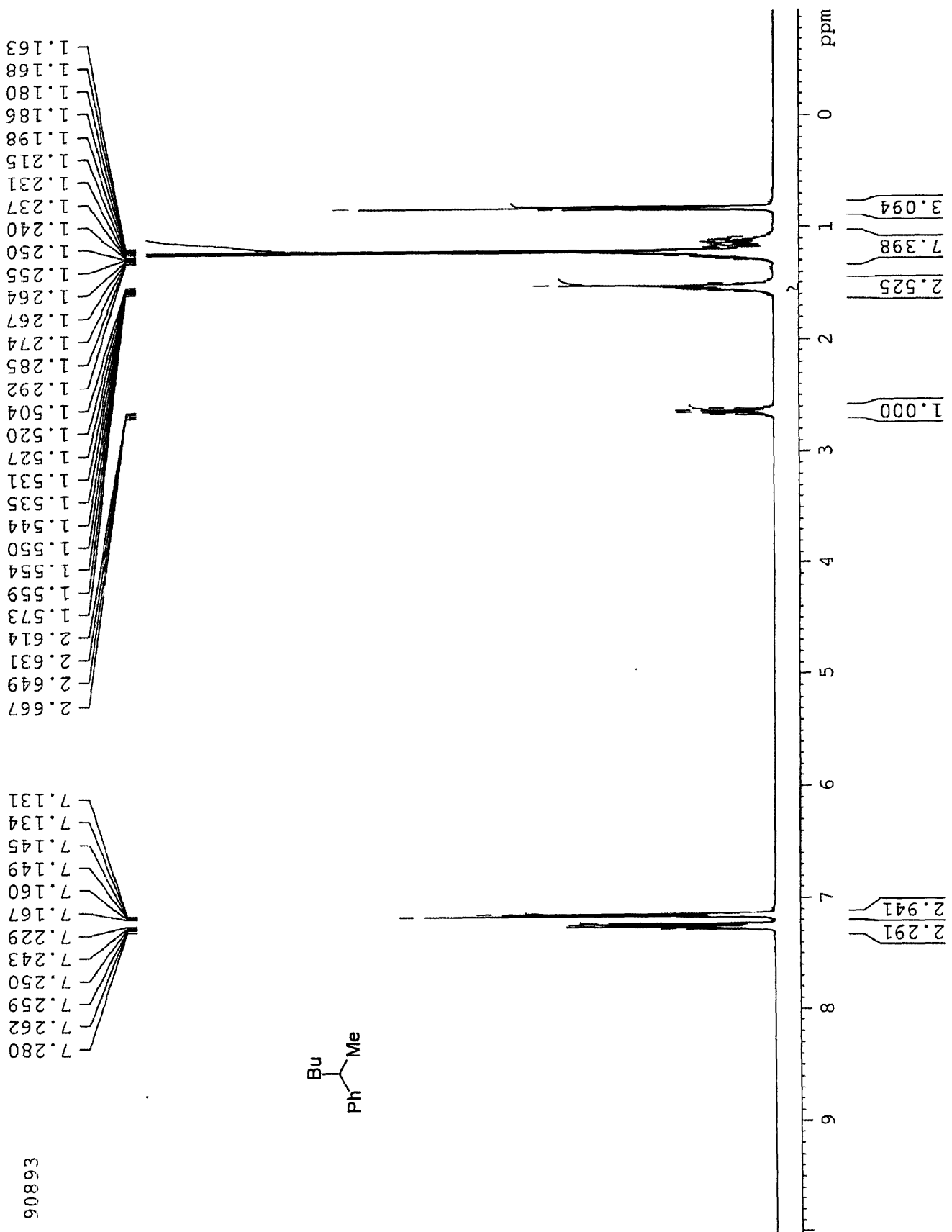
81391





8253

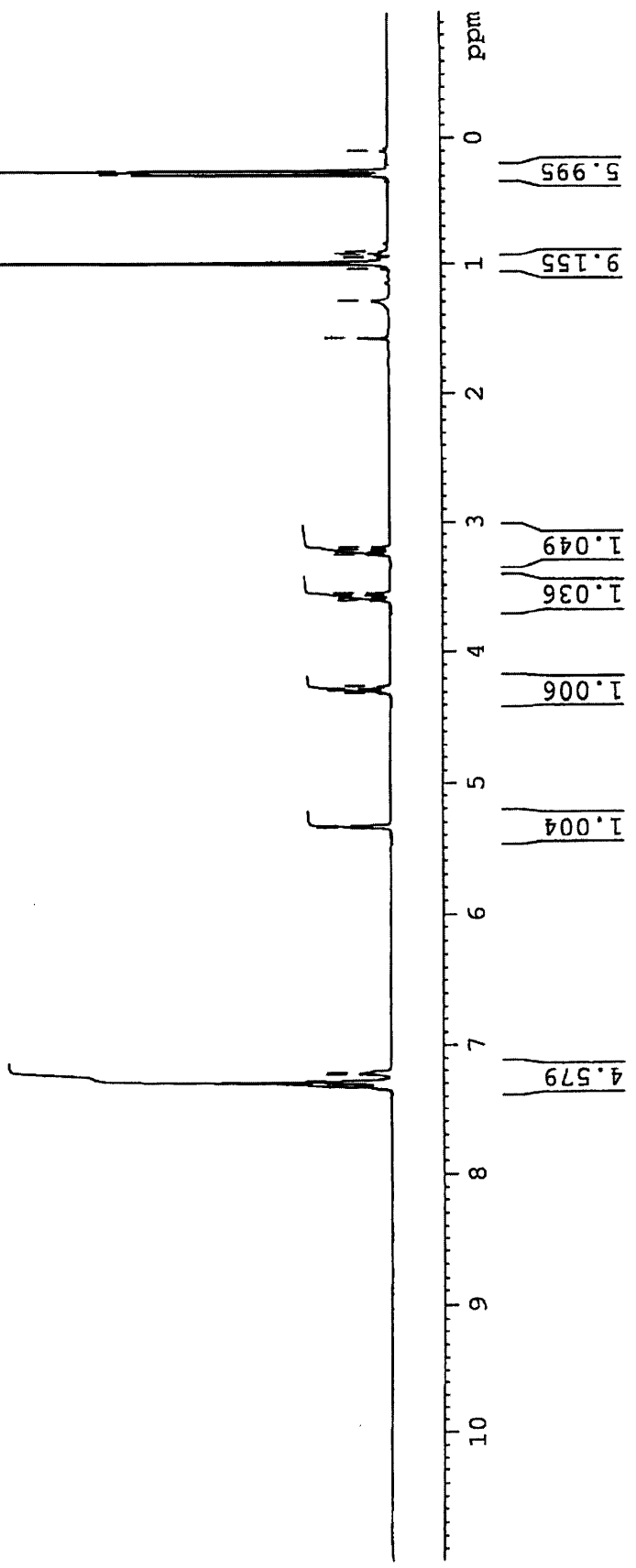




61312

trans-2-Bromo-1-*t*-butyldimethylsiloxyindane

- 7.327
- 7.318
- 7.305
- 7.296
- 7.286
- 7.283
- 7.277
- 7.226
- 7.217
- 5.336
- 5.321
- 4.307
- 4.281
- 4.284
- 4.269
- 4.250
- 3.612
- 3.593
- 3.571
- 3.553
- 3.254
- 3.235
- 3.213
- 3.194
- 1.568
- 1.291
- 1.037
- 0.991
- 0.987
- 0.945
- 0.919
- 0.909
- 0.893
- 0.287
- 0.255
- 0.091



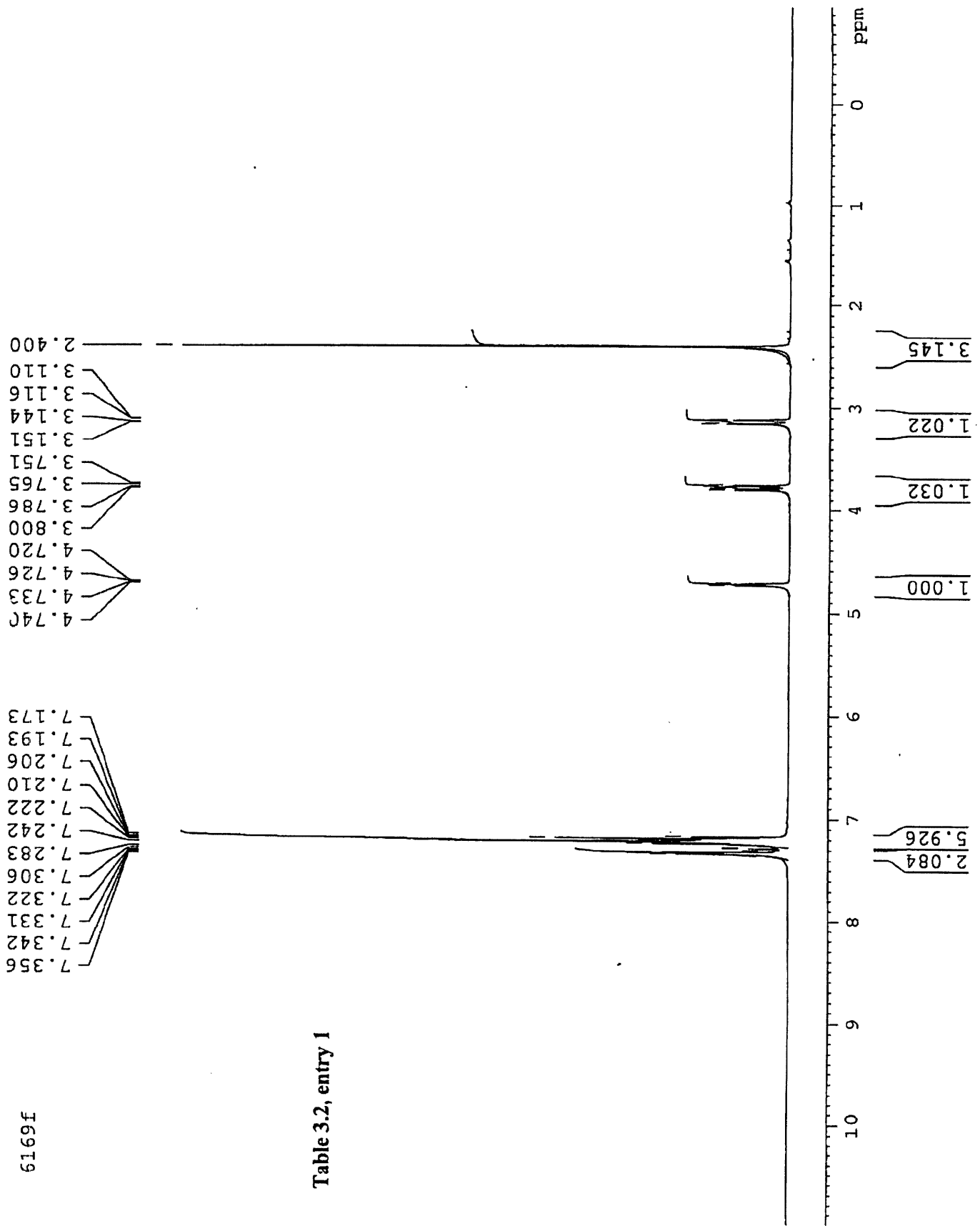
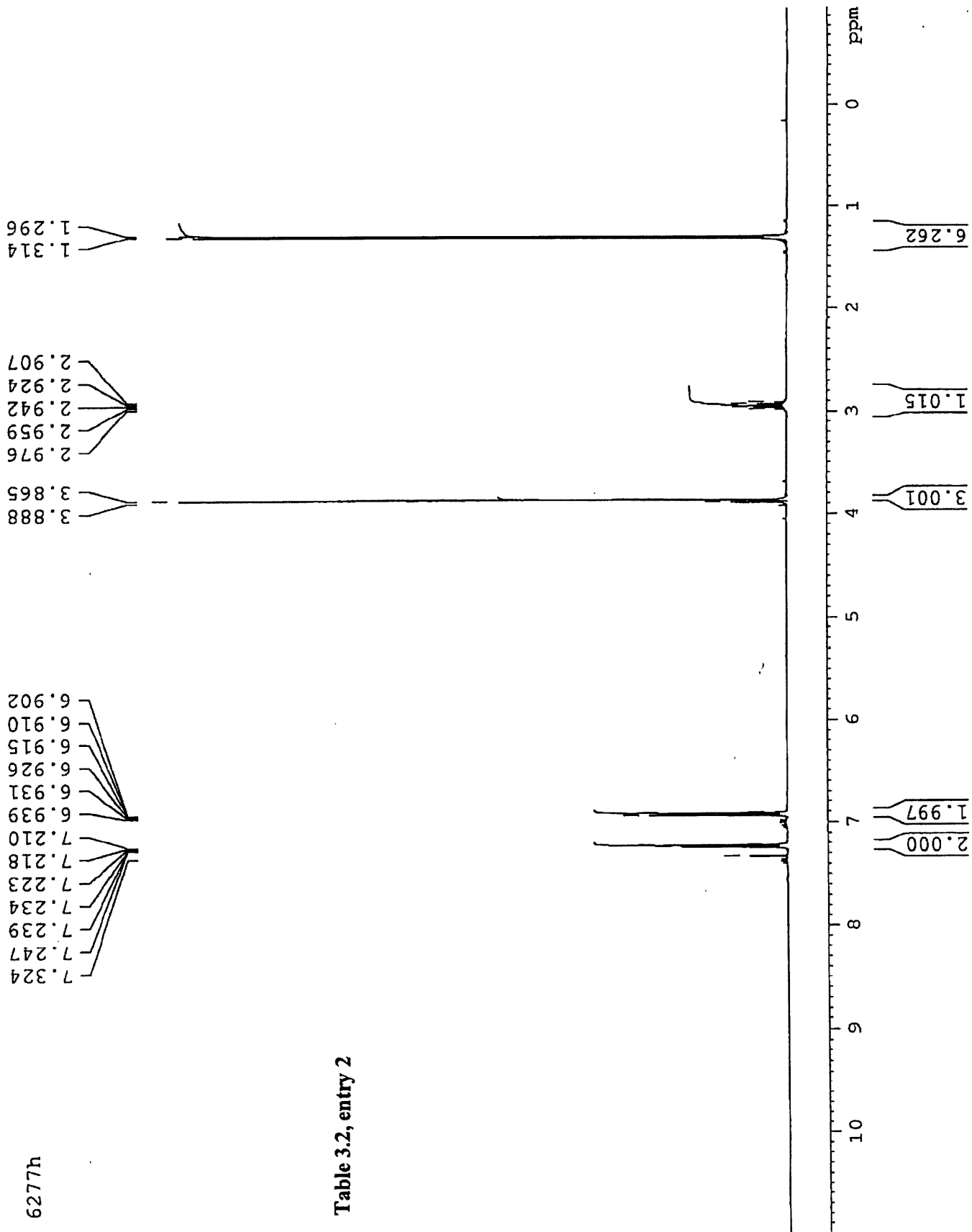


Table 3.2, entry 1

6169f



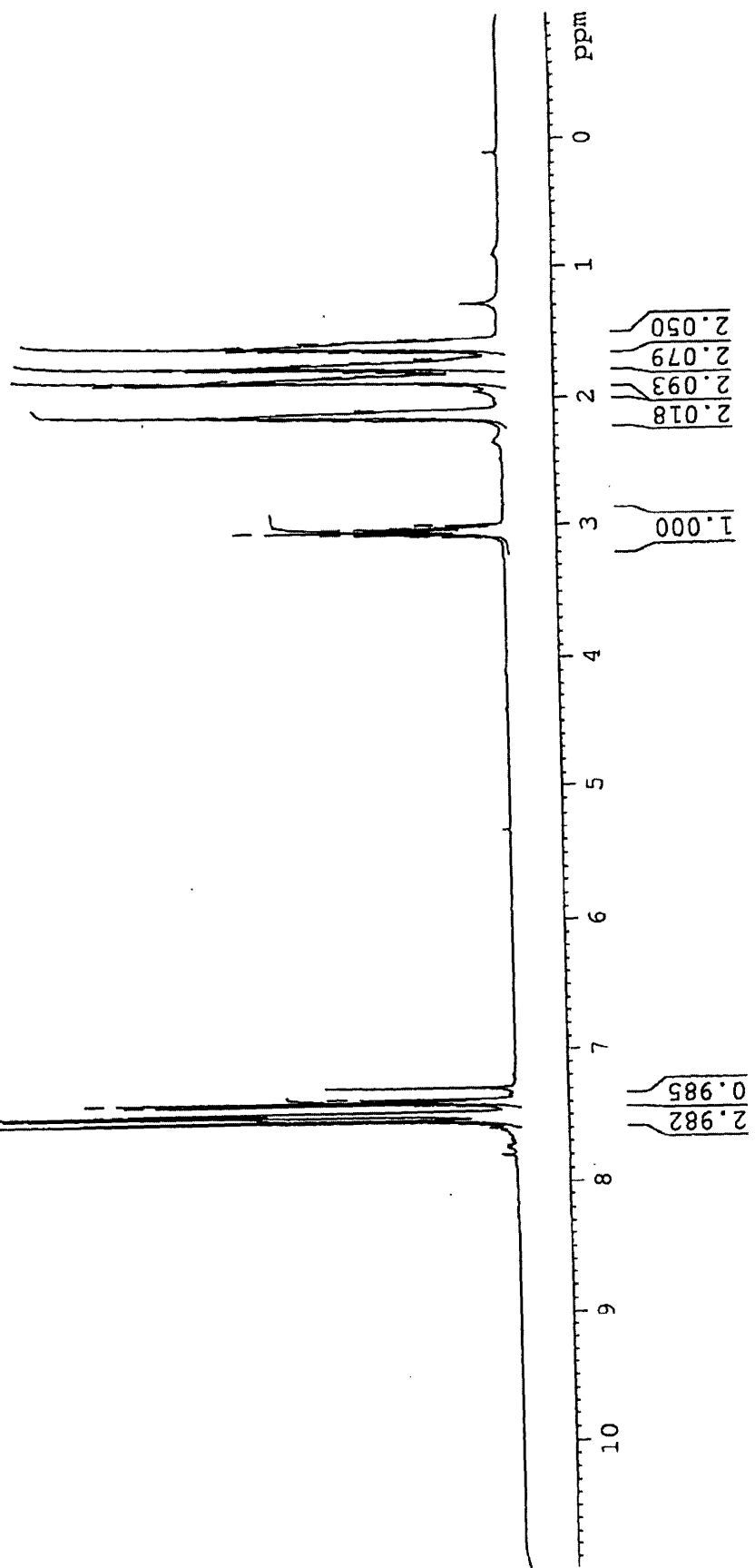
6277h

Table 3.2, entry 2

6277dr

7.538
7.498
7.495
7.492
7.487
7.478
7.475
7.410
7.391
7.372
7.286
7.283
3.077
3.056
3.033
3.013
2.990
2.149
2.131
2.124
2.121
2.118
2.112
2.109
2.105
2.077
1.882
1.864
1.854
1.845
1.835
1.827
1.819
1.812
1.803
1.778
1.772
1.767
1.759
1.752
1.739
1.732
1.721
1.712

Table 3.2, entry 3



6271e2

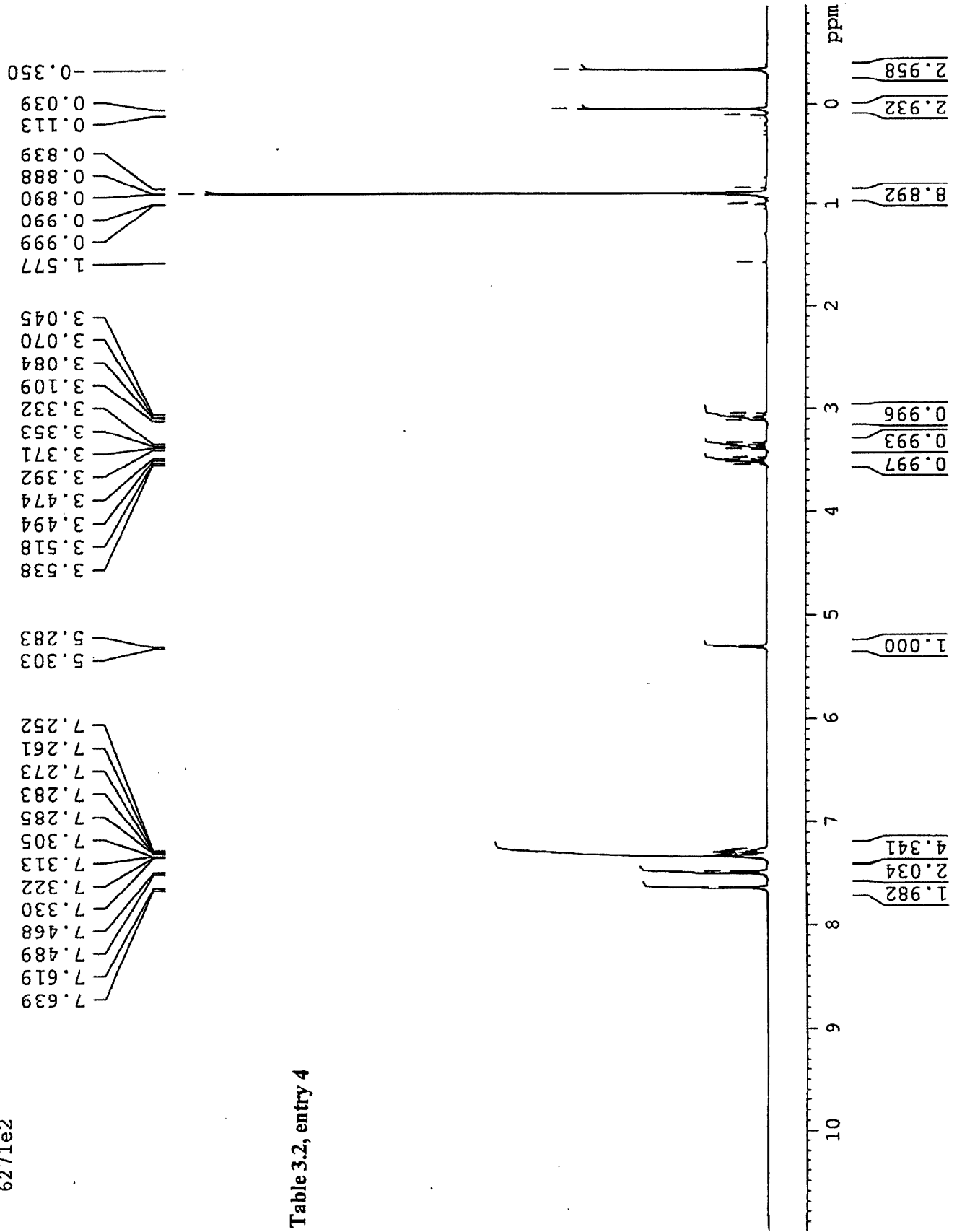
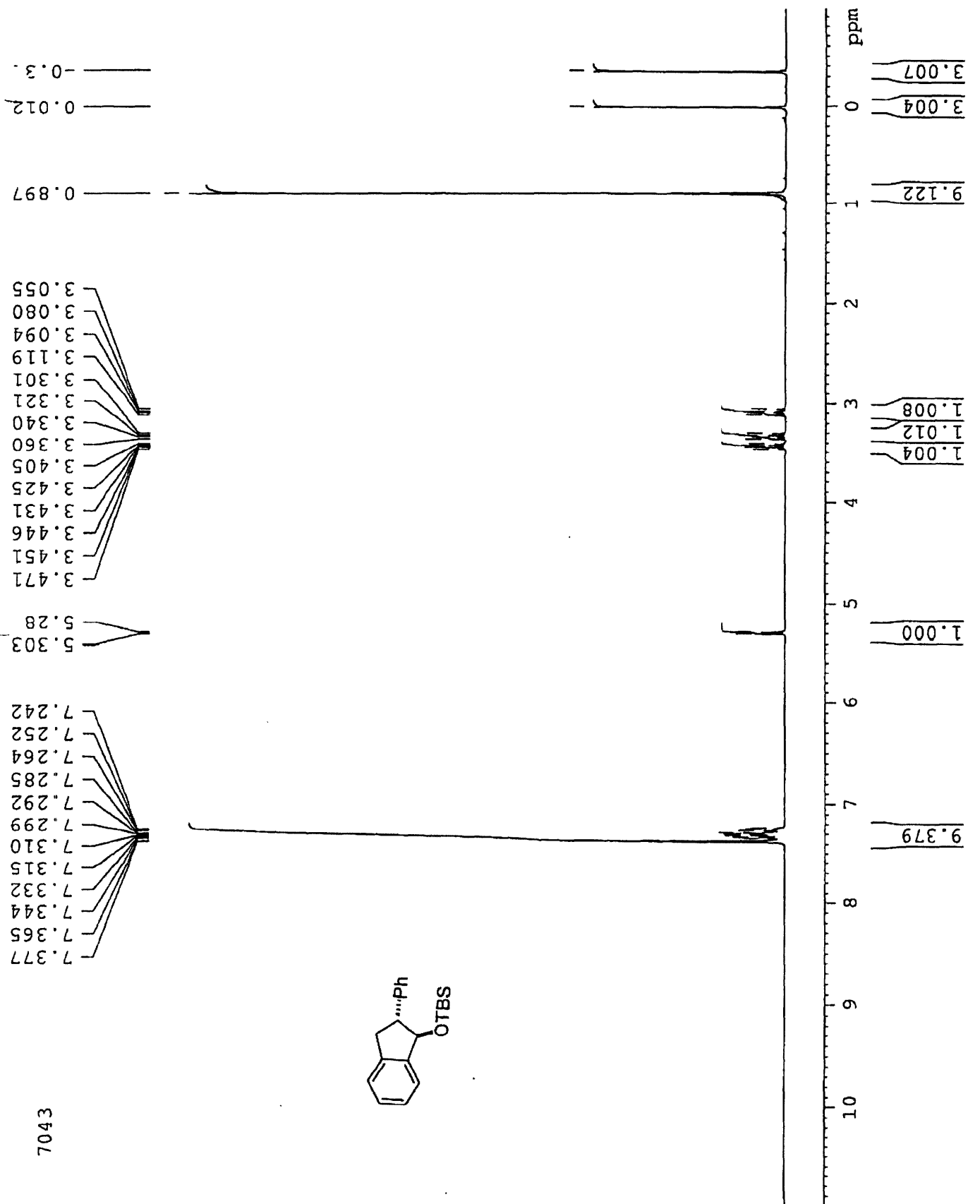
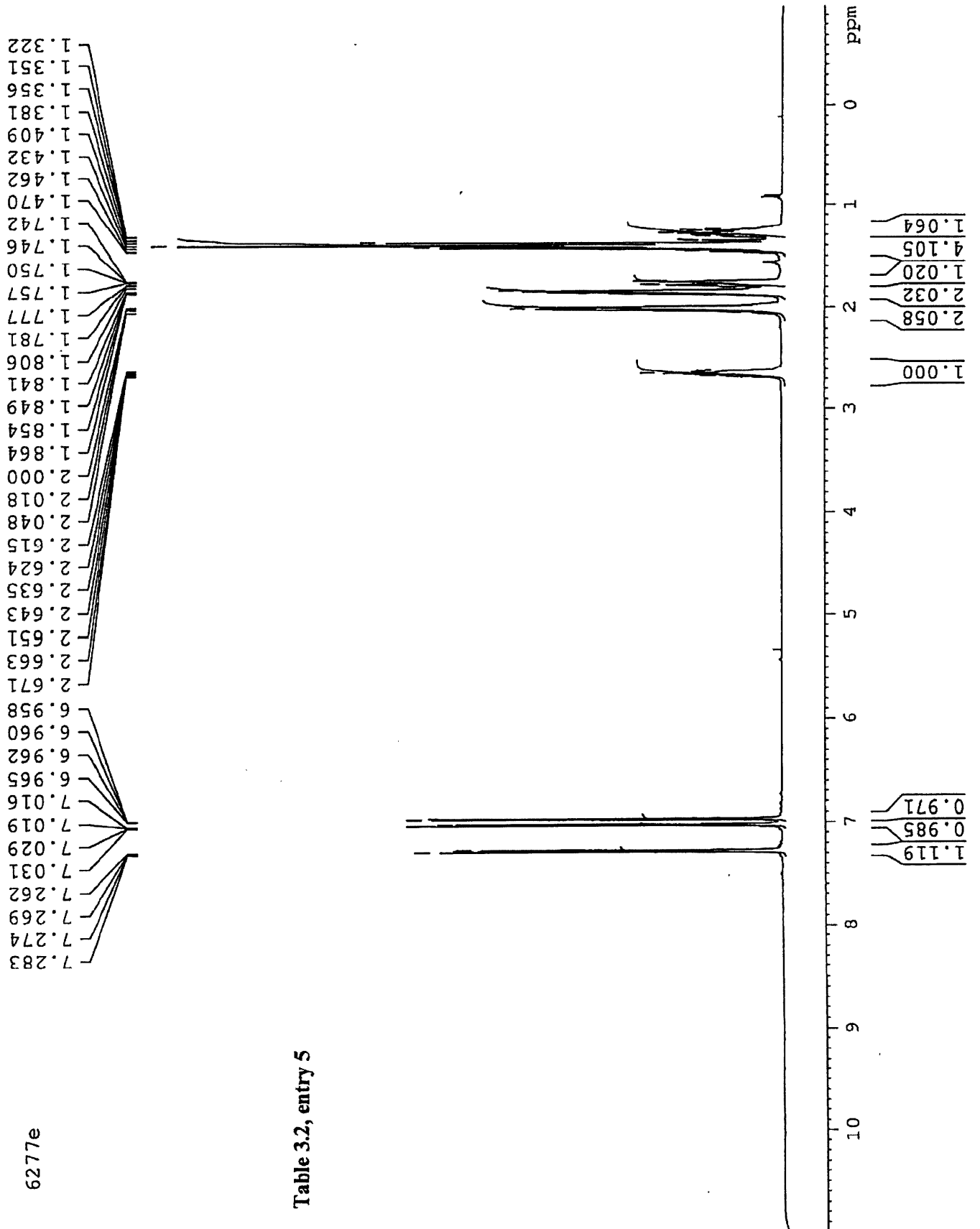


Table 3.2, entry 4



7043



6277e

Table 3.2, entry 5

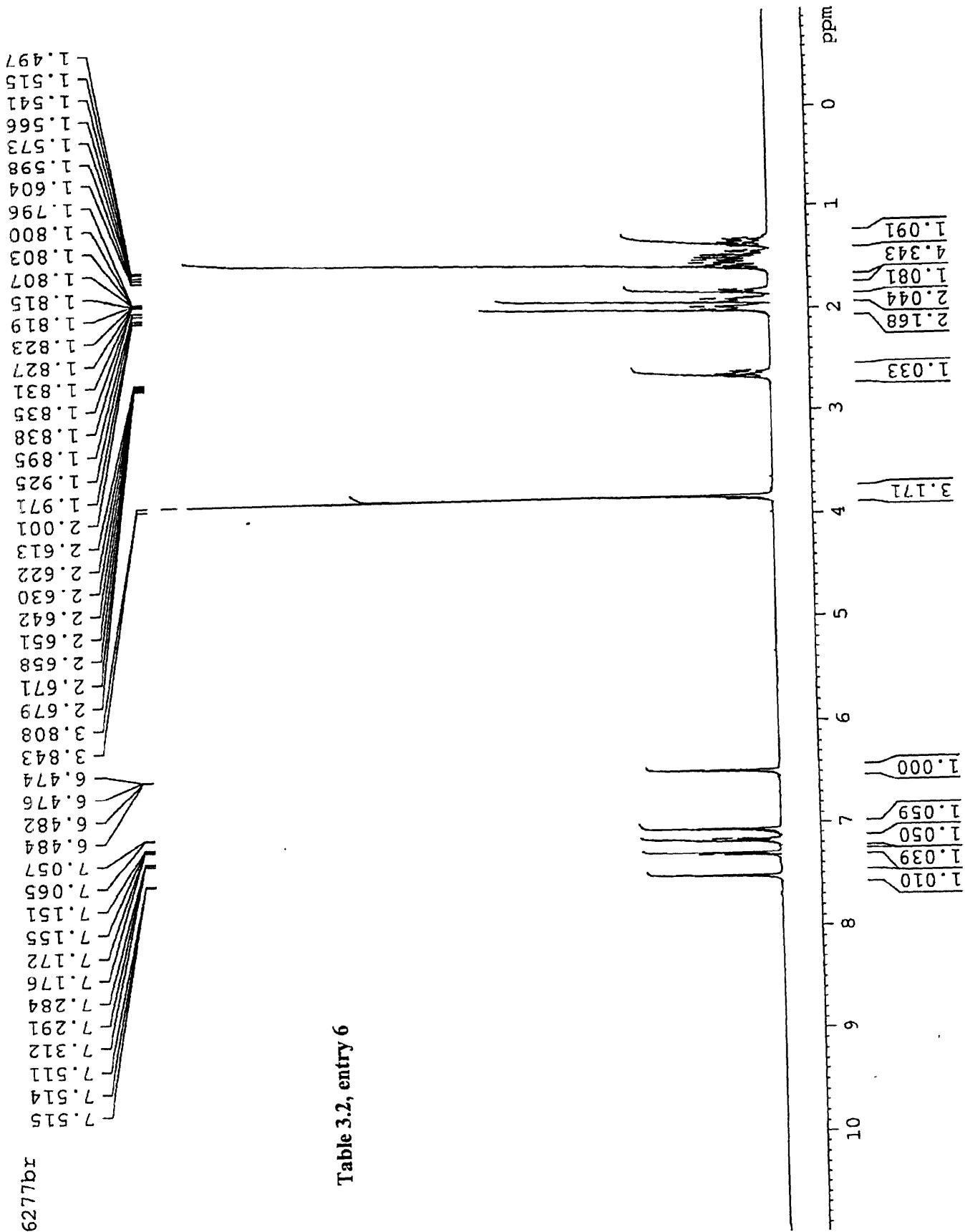


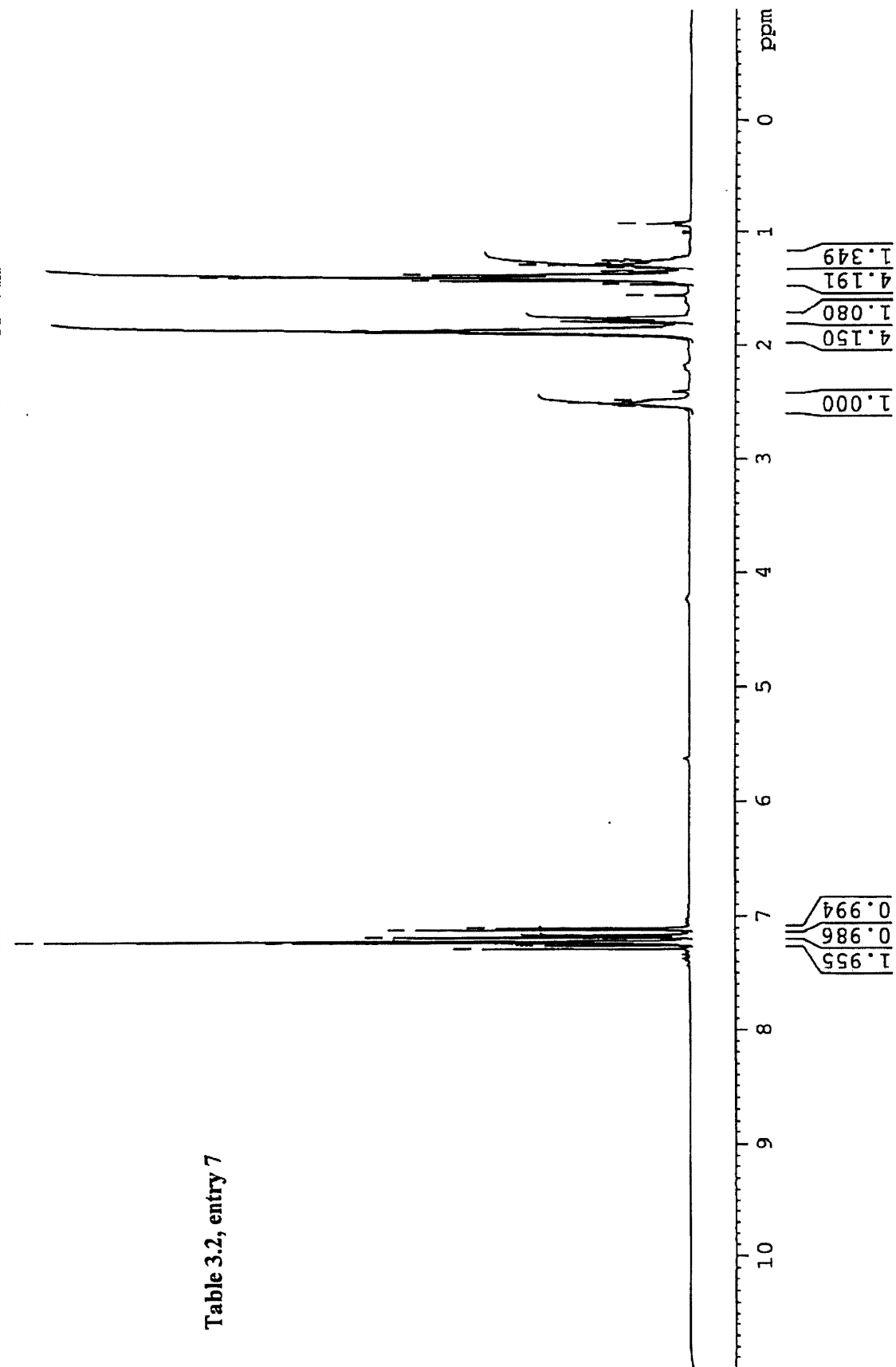
Table 3.2, entry 6

6277br

6277F

7.284
7.256
7.236
7.227
7.223
7.218
7.189
7.186
7.170
7.165
7.162
7.118
7.103
7.100
2.535
2.528
2.515
2.507
2.499
2.485
2.478
1.894
1.879
1.872
1.865
1.857
1.801
1.797
1.794
1.790
1.783
1.763
1.759
1.564
1.474
1.444
1.420
1.413
1.403
1.390
1.359
1.352
1.317

Table 3.2, entry 7



6277c1r

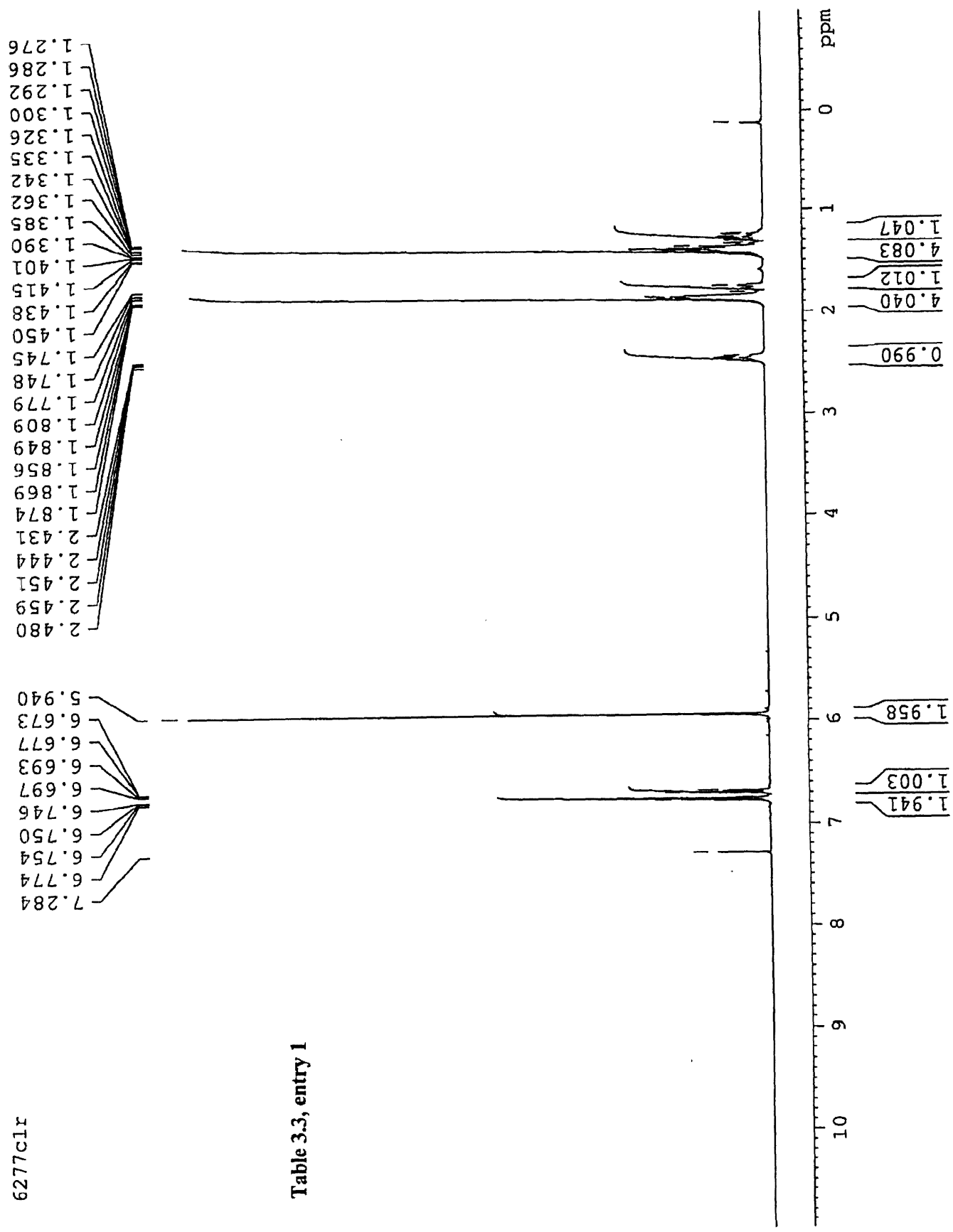


Table 3.3, entry 1

6264b

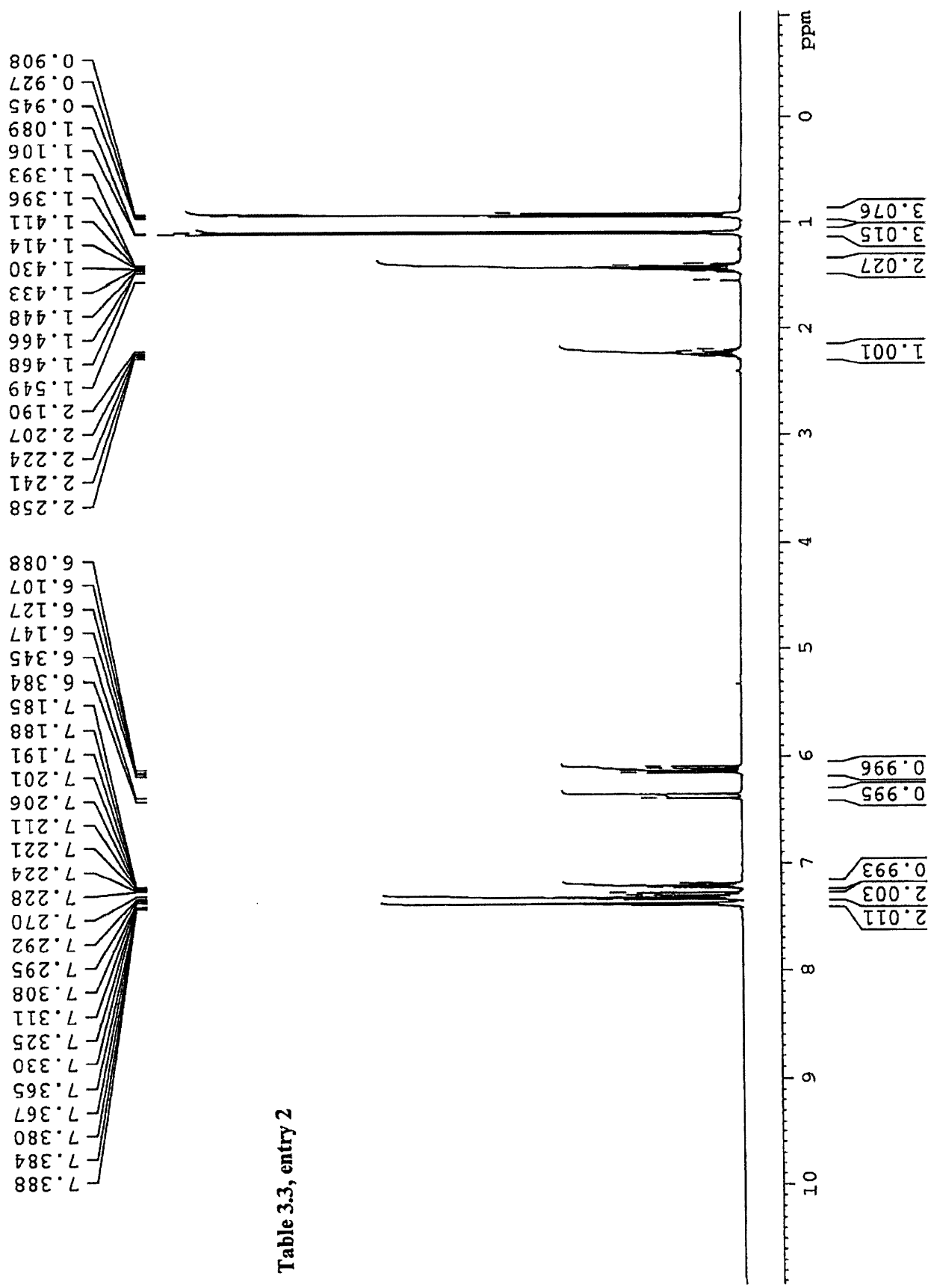
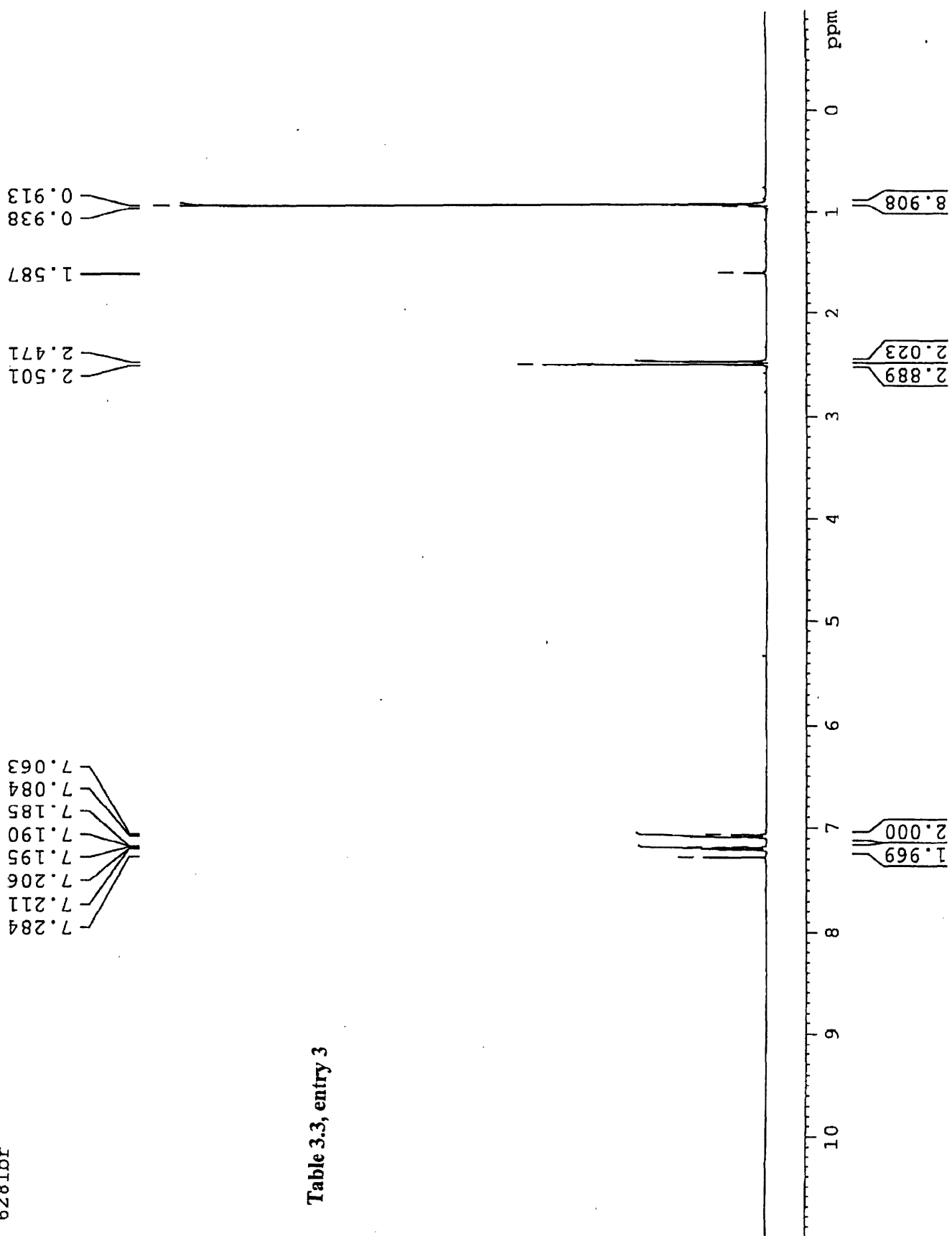
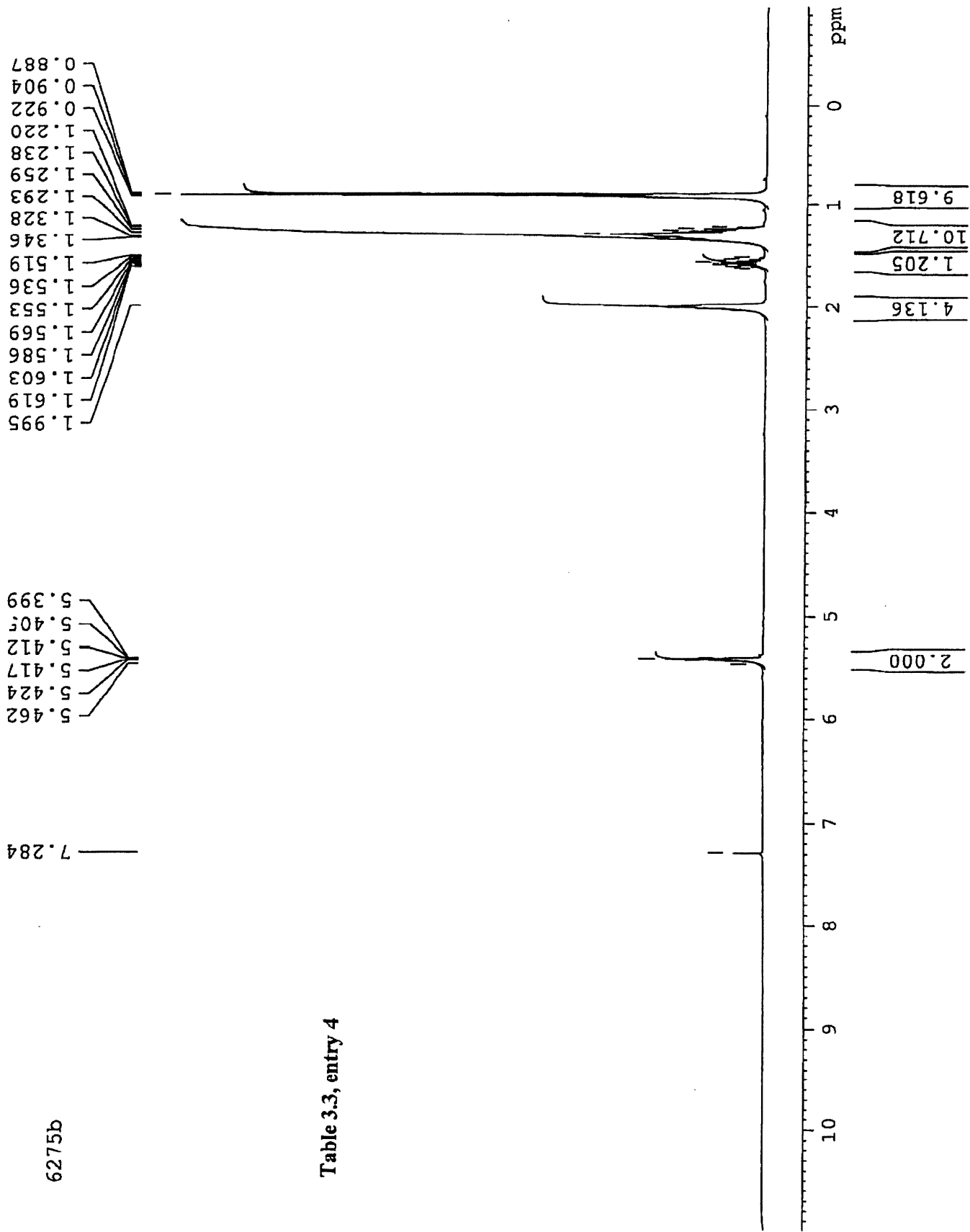


Table 3.3, entry 2

6281br

Table 3.3, entry 3





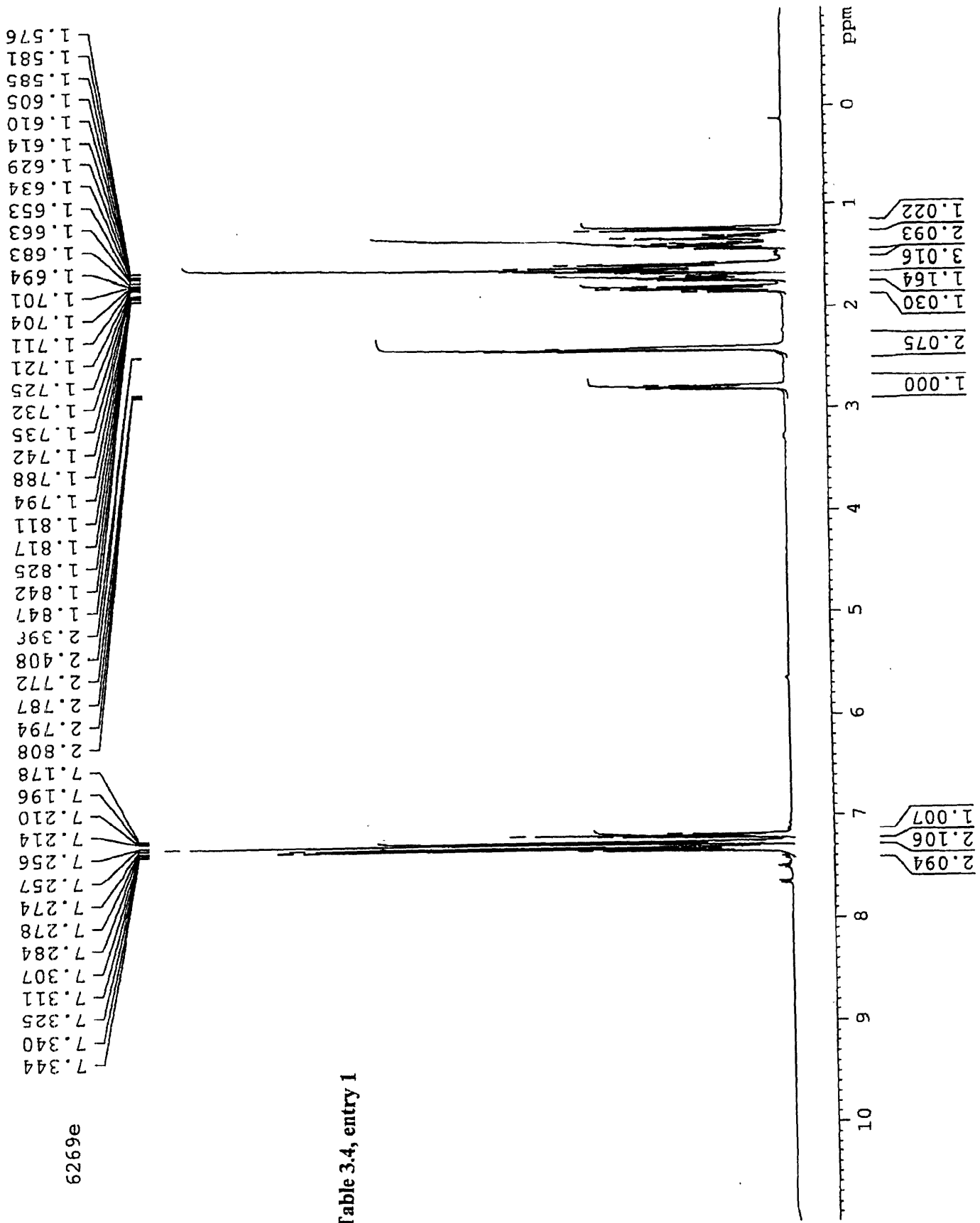
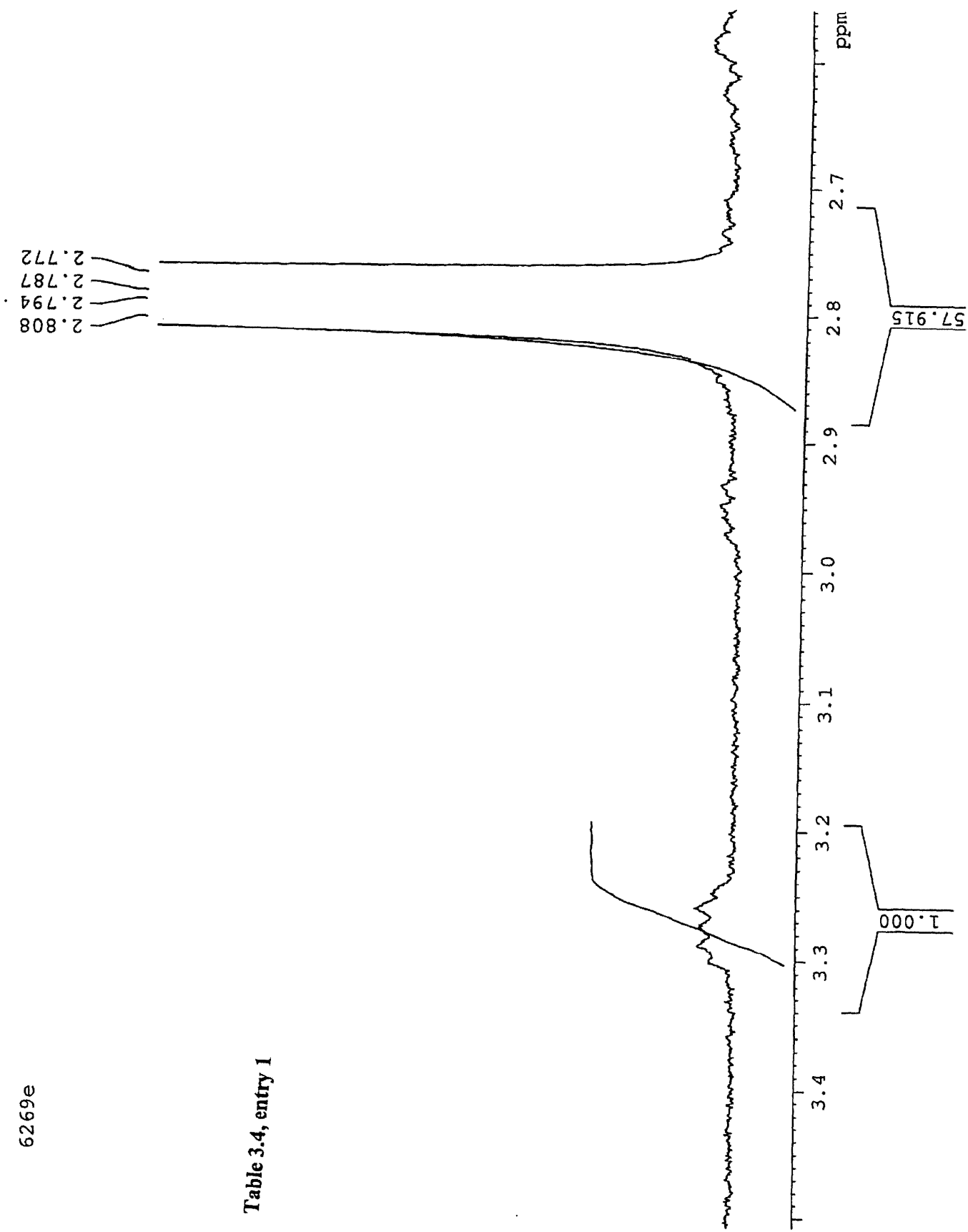


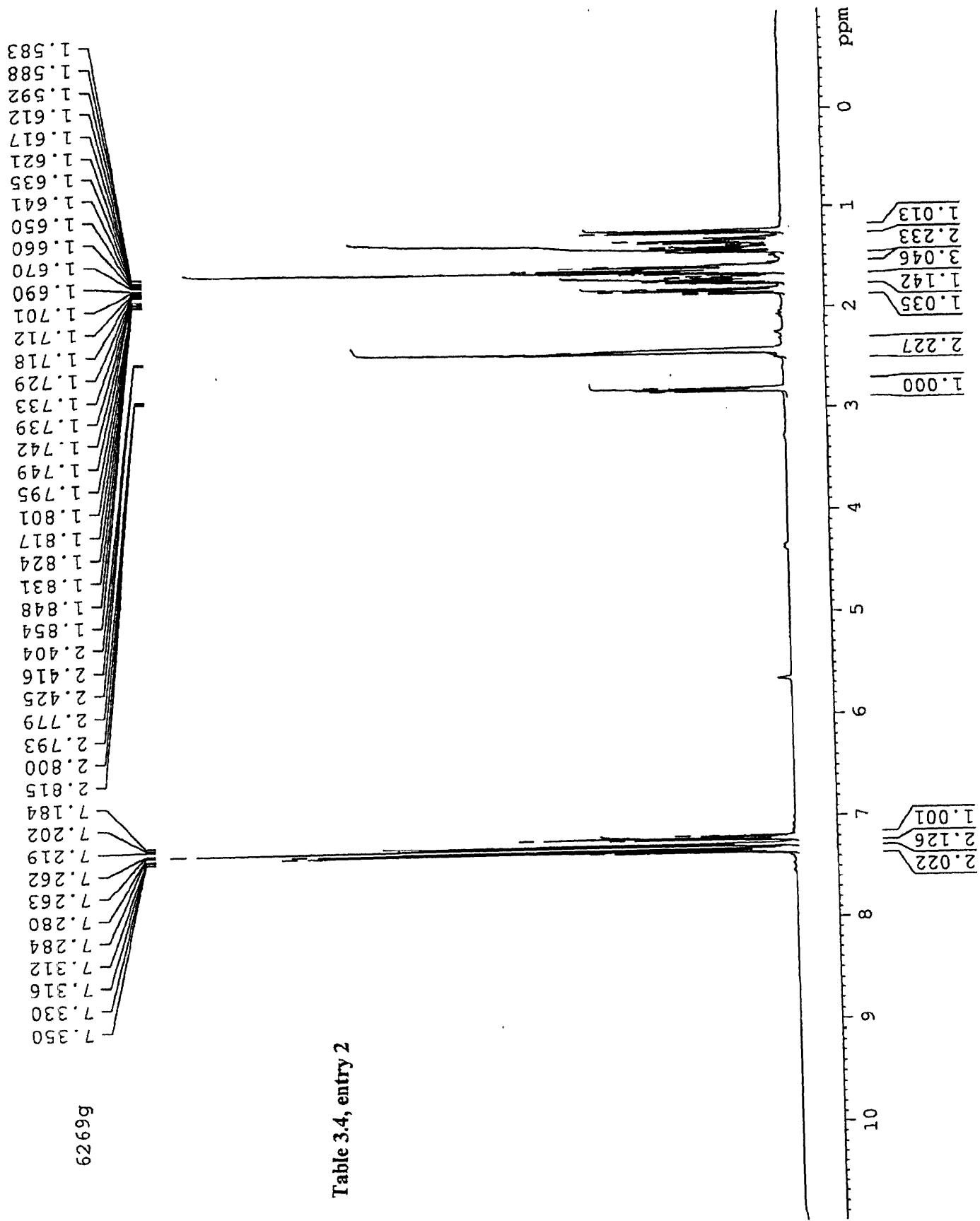
Table 3.4, entry 1

6269e

6269e

Table 3.4, entry 1





6269g

Table 3.4, entry 2

62.6c

Table 3.4, entry 2

