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A Radical Conjugate Addition Approach to the Total Synthesis of Celogentin C

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A RADICAL CONJUGATE ADDITION APPROACH TO THE TOTAL SYNTHESIS OF CELOGENTIN C

by

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GRADUATE COMMITTEE APPROVAL

of a thesis submitted by

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ABSTRACT

A RADICAL CONJUGATE ADDITION APPROACH TO THE TOTAL SYNTHESIS OF CELOGENTIN C

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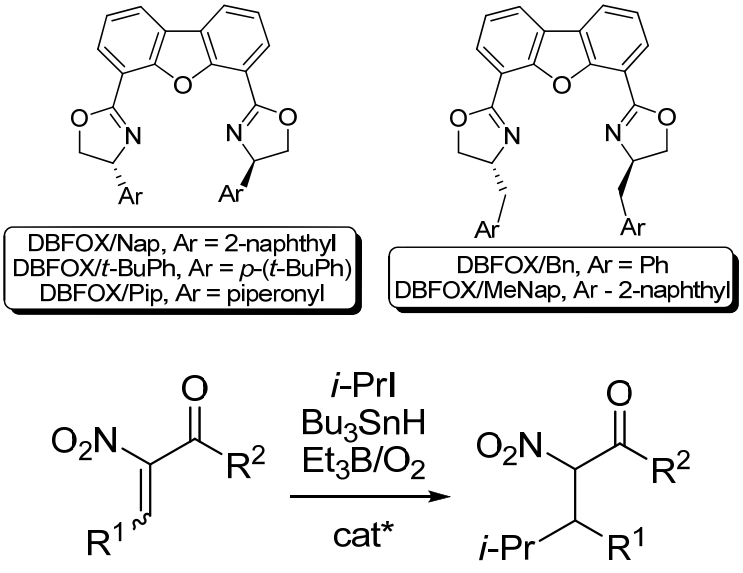
Department of Chemistry and Biochemistry

Master of Science



The synthesis of five chiral DBFOX (dibenzofuran-oxazoline) ligands with either aryl or benzyl substituents will be presented. The requisite amino alcohols were obtained with high enantioselectivity either commercially (DBFOX/Bn), via Sharpless asymmetric aminohydroxylation (DBFOX/Nap, DBFOX/*t*-BuPh, DBFOX/Pip), or via phase-transfer catalyzed asymmetric alkylation (DBFOX/MeNap). These ligands, complexed with

$Mg(NTf_2)_2$, were used as Lewis acid promoters of enantioselective radical conjugate additions to α/β-unsaturated nitro-amides/esters. A summary of these results is presented and discussed.

These findings led us to believe that our initial binding model between metal, ligand, and substrate was flawed. Thus, we figured that if we started with a functionality known to bind to both nitro groups and carbonyls, and then introduced a chiral element for control, we may be able to improve the β-carbon enantioselectivity. We have tried to accomplish this via hydrogen-bonding ligands (ureas and thioureas). Initial studies on achiral versions of this concept are discussed.

ACKNOWLEDGEMENTS

First note must definitely go to Dr. Castle, without whom I would never have finished this work. His constant pressure to move forward and patience with me allowed me to focus on completing this project. I wish to thank my associates in the Castle lab for encouragement and problem-solving.

I also wish to thank Dr. Liwen He, who pioneered the work with DBFOX/Ph, and was able to teach me a great deal of laboratory technique before he moved on. While I never really mastered tin chemistry, the skills he passed on to me definitely helped push the reactions forward. Also, Dr. Biplab Banerjee and Jay Kang deserve thanks for working on the reactions and making intermediates for the ligands.

Finally, I wish to thank my family, especially my mother, Donna L. Shambaugh, who was always there to provide encouragement whenever a setback or failed reaction occurred. I dedicate this thesis to her, as she always joked that it was her name that should have been on my scholastic projects.

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CHAPTER 1. INTRODUCTION

1.1 Celogentin C

Celogentin C (**1**, Figure 1), isolated by Kobayashi and co-workers from the seeds of *Celosia argentea*, is known to inhibit polymerization of microtubule protein (IC_{50} = 0.8 μM), and is the most potent natural product within the Moroidin family (Figure 2).[1] This renders Celogentin C a promising anti-mitotic and anti-tumor agent. Structurally, Celogentin C is a bicyclic octapeptide with two fused rings, possessing two unusual linkages, the first being the C-N bond between tryptophan and histidine residues to form the right-hand ring.

The second interesting feature of **1** is the C-C leucine-tryptophan linkage in the left-hand ring. This linkage forms a functionality known as a β-substituted amino acid. Since a conventional peptide coupling reaction would be unsuitable for this bond formation, a strategy for forming the core left-hand ring structure with an alkene, then installing the isopropyl group via a radical conjugate addition with high enantioselectivity, has been designed. To date, no total synthesis of this natural product has been published, though a model synthesis of the right-hand ring was published by the Castle group in 2006.[2] Two other researchers in the field, Moody[3] and Hutton,[4] have also worked toward and published results in the pursuit of this attractive synthetic target.

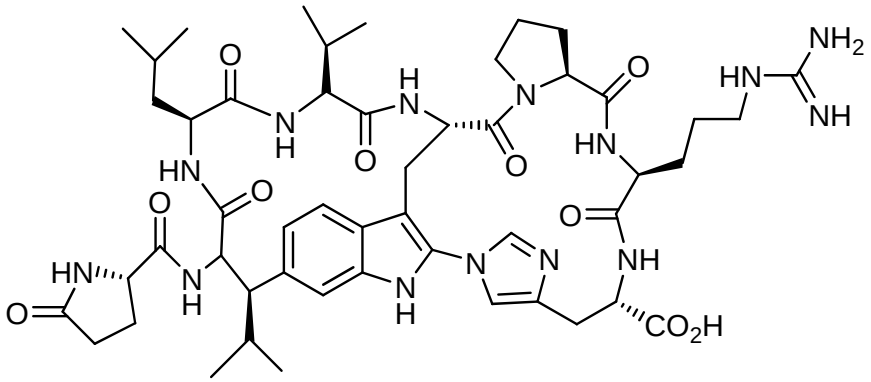
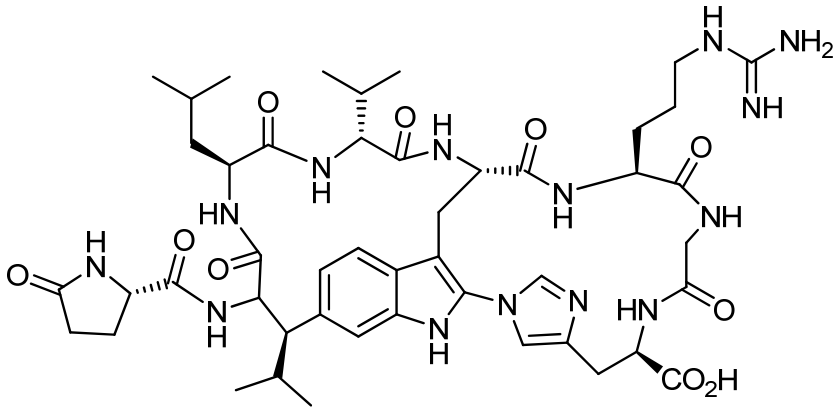
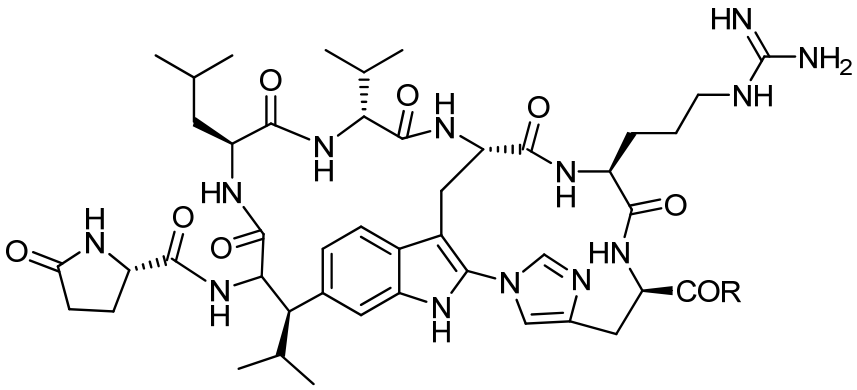


Figure 1. Celogentin C (**1**)



Moroidin

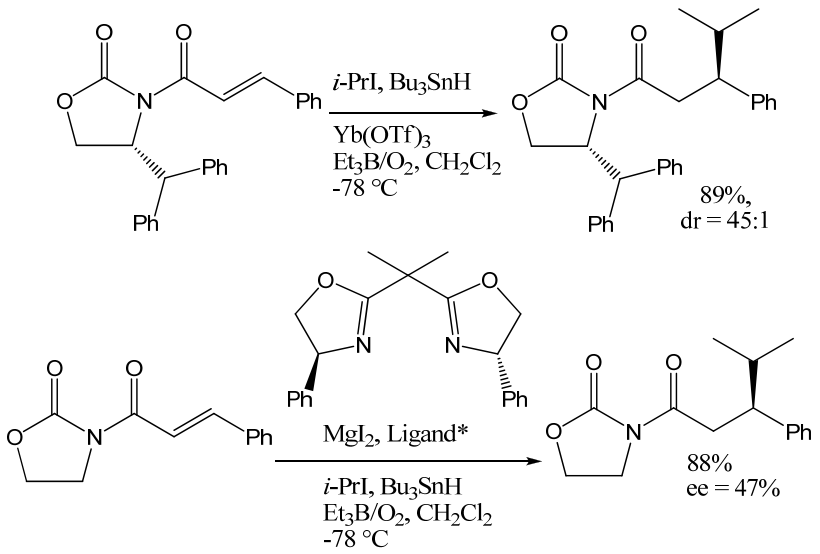


Celogentin A, R = OH
Celogentin B, R = His

Figure 2. Moroidin and Other Celogentins

1.2 Radical Conjugate Addition

The field of radical chemistry has blossomed within the past ten years, leading to a great deal of research. Traditionally, radicals have been thought of as mostly neutral, non-polar species. However, this paradigm has shifted, and recent work in radical donors and acceptors has been widespread, leading to a type of radical reaction known as a radical conjugate addition (RCA). The RCA is the use of a nucleophilic radical, often alkyl, which adds to an electron-deficient radical acceptor, such as an α, β-unsaturated carbonyl compound. In 2001, Zhang published a review on intramolecular RCA reactions,[5] and Castle published another review in 2005.[6] The scope and utility of RCA reactions is wide, with macrocyclizations,[7] alkyl additions,[8] and radical cascade[9] mechanisms, with reagents such as SmI_2[10] or R_3SnH.[11] Sibi was particularly noteworthy as a pioneer in Lewis-acid- promotion of intermolecular RCA reactions, especially using chiral auxiliaries and chiral Lewis acid complexes to promote stereoselectivity via oxazolidinones[12] and bis-oxazolines[13] (Scheme 1). His research also led to milder conditions for many products of other major reactions, such as aldol-type products.[14]



Scheme 1. Sibi's Early Work with Enantioselective RCA Reactions

In 2005, the Castle group published work that detailed how the DBFOX/Ph ligand, developed by Kanemasa and Curran (**2**, Figure 4)[15] was effective at facilitating the enantioselective synthesis of β-substituted α-amino acids via a Lewis acid-promoted RCA (Scheme 1).[16] This substructure is a commonly-occurring motif in many natural products, including **1**.[17] Such structures are also attractive synthetic targets as constrained analogues of natural α-amino acids.[18] While other methods exist for constructing these analogues,[19] the radical conjugate addition is attractive due to the mild conditions that do not interfere with acidic protons, such as peptide amide hydrogens.[20] Thus, one could generate a library of β-substituted α-amino acids from complex peptidic structures containing a radical acceptor, such as an electron-deficient alkene, by varying the nature of the radical.

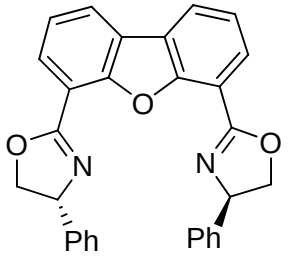
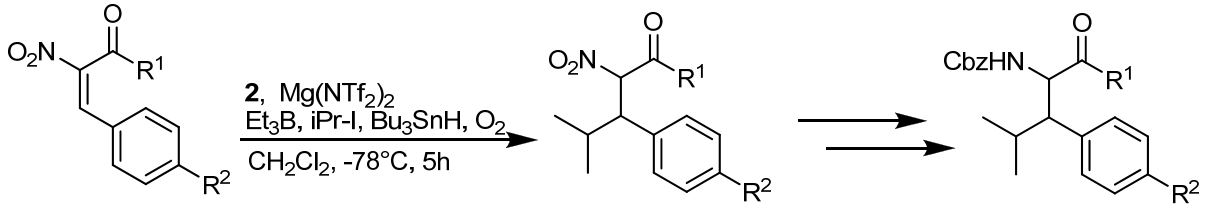


Figure 3. DBFOX/Ph (**2**)



R^1 = NHBn or OMe, R^2 = H, OMe, or F
50–88% ee, *syn/anti* = 1.4-2.6:1

Scheme 2. Mg/DBFOX-promoted Enantioselective Radical Conjugate Additions

1.3 Initial Results

After using a Knoevenagel condensation to prepare the requisite α-nitro, α,β-unsaturated esters, a wide range of Lewis acids were tested in the RCA. Mg and Zn gave the most promising initial results, but the most important factor of this stage was the observation of a slow addition in the absence of any Lewis acid promoter, as long as a large excess of alkyl iodide was used (20 eq). This crucial observation allowed a calculation of relative rates of acceleration for various conditions.

In order to determine if a stereoselective RCA would be possible, the Castle group experimented with Bu_3SnD. The α-hydrogen in the product which is installed via hydrogen atom abstraction is quite acidic, due to conjugation with the carbonyl and the presence of the nitro group. Thus, the RCA would be ill-suited to applications in organic synthesis, if epimerization of the newly-formed stereocenter could not be prevented. By substituting Bu_3SnD for Bu_3SnH, previous group members were able to observe D-H exchange in the products when H_2O was used in the workup of amide substrates, or when SiO_2 chromatography was employed in purification. Hydrogenation of the NO_2 group in the crude products, followed by *N*-Cbz protection, allowed purification of amide and ester products with α-D labels, indicating that the stereocenter was not epimerizing. This finding set the possibility for using chiral Lewis acid complexes to control the H atom abstraction, and potentially the addition, in a stereoselective RCA.

Work on determining the best chiral Lewis acid complex was next. Previous group members tried using variations of Curran's DBFOX/Ph ligand with various R groups α to the phenyl group (Figure 4). Dimethyl- or dibutyl-DBFOX ligands proved to

be less effective than the parent ligand (**2**), presumably because the added bulk interfered in the complexation with both Lewis acid and substrate.

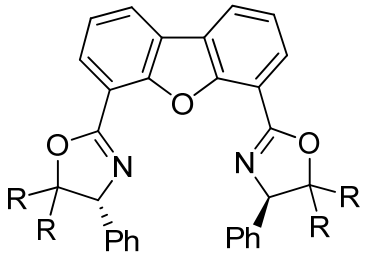
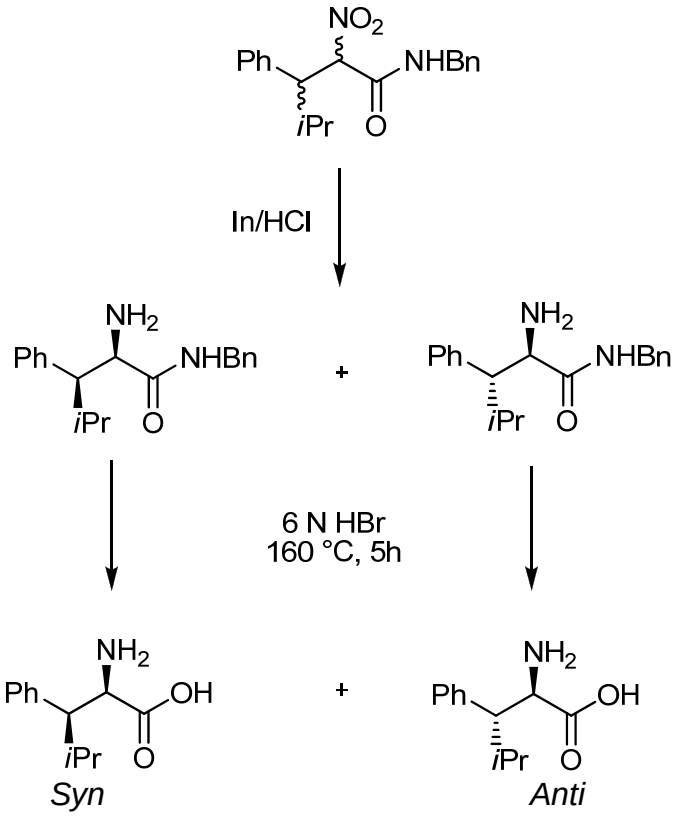


Figure 4. DBFOX/Ph-like Ligands (R = H, Me, *n*-Bu)

In order to accurately assess the selectivity of their methodology, the Castle group had to determine the absolute stereochemistry of their addition products. This was accomplished by reduction of the nitro group to an amine, then hydrolysis of the benzyl amide to an acid, to form known amino acids (Scheme 3).



Scheme 3. Absolute Configuration Determination

Comparison of resulting products' NMR and optical rotation data allowed them to quantify the amount of *syn* product and *anti* product (named as shown in Scheme 3) obtained from the RCA. From this data, they were able to determine the selectivity at the α-carbon and the β-carbon of the nitroalkene, which they dubbed "α ee" and "β ee." The results of their research were that they could obtain a high α ee (up to 83%), but the β ee was low (up to 25%).

1.4 Empirical Substrate-Lewis Acid Binding Model

The main disadvantage to the DBFOX/Ph-promoted radical conjugate additions is the lack of stereoselectivity at the β-carbon. This leads to a poor diastereomeric ratio, even though the enantiomeric excess of each diastereomer is good. Based on these findings, the Castle group suggested a binding model of the metal/ligand/substrate that explained the differences in selectivity between the two carbon stereocenters (Figure 5). The octahedral magnesium complex possessed a literature precedent,[21] and also helped to explain why the hydrogen abstraction by the α-carbonyl radical is more selective than the alkyl radical addition to the β-carbon. This model postulates that the aryl group (phenyl in this case) is used to shield one face of the alkene. Thus, by increasing the size of the aryl group, we could increase the effective shielding at the β-carbon, thereby increasing the diastereomeric ratios.

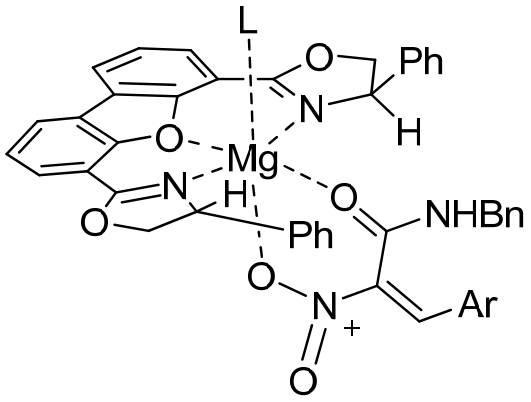


Figure 5. Substrate-Lewis Acid Binding Model

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CHAPTER 2. LIGAND PREPARATION

2.1 Amino Alcohol Preparation

The simplest way in which to increase the bulk of the aryl group attached to the DBFOX backbone structure was to vary the amino alcohol used and then follow the synthesis of **2** by Curran and Kanemasa.[1] With five modified DBFOX ligands in mind, we set out to synthesize the five amino alcohol precursors (Figure 1). For the first three ligands (**3**-**5**), we envisioned a simple two-step synthesis to install the functional groups and stereocenter.

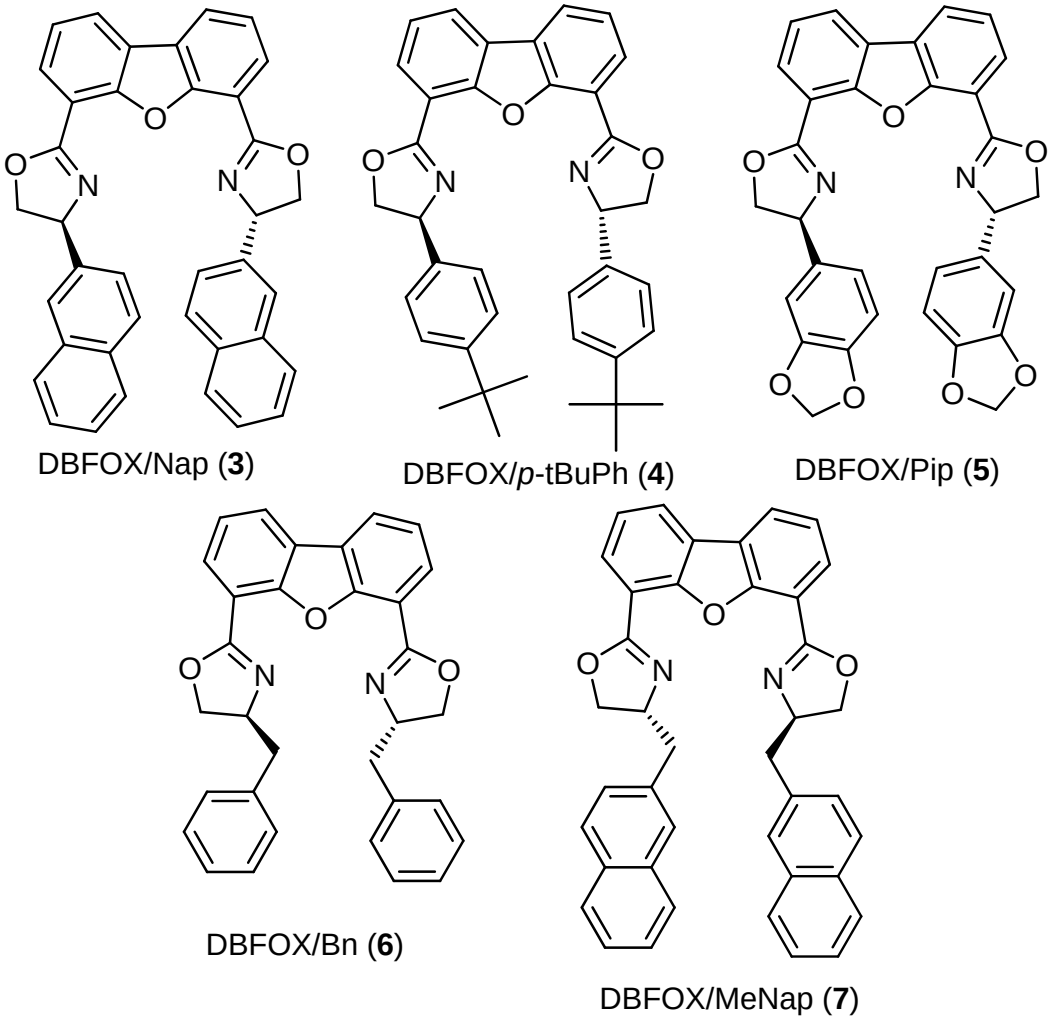
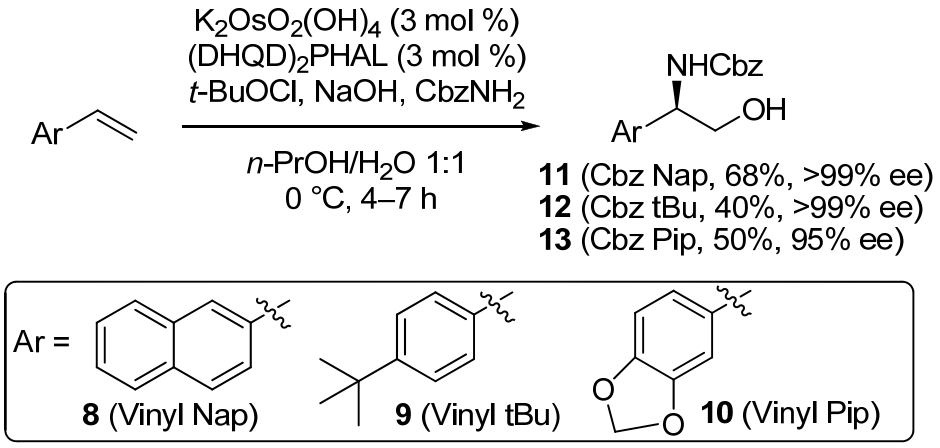


Figure 1. Proposed DBFOX Ligands

Naphthyl Cbz amino alcohol (Cbz Nap, **11)** was synthesized in two steps from 2-vinyl naphthalene (**8**) via Sharpless asymmetric aminohydroxylation (SAA)[1] as previously reported in moderate yields and excellent enantioselectivity (Scheme 1).[2] The *p*-tBuPh Cbz amino alcohol (Cbz tBu, **12**) was synthesized in the same manner, with slightly lower yields, but excellent selectivity (>99% ee). The benzodioxole Cbz amino alcohol (Cbz Pip, **13**) was obtained in the same way with moderate yield, but again, excellent selectivity (95% ee).



Scheme 1. SAA Reaction

One source of the low yields in the SAA reaction is the formation of the regioisomeric amino alcohol. By keeping the reaction at 0 ºC, this byproduct is minimized, affording a 3:1 ratio or better favoring the desired product. The exact amount of regioisomer formed in each case was not quantified, but was roughly calculable from crude ^{1}H NMR by the differences in methylene hydrogen chemical shifts.

With the SAA products in hand, the Cbz protecting group was removed via hydrogenolysis with 10% Pd/C, 1 atm of H_2, and NH_4OAc to increase the palladium turnover, presumably by dissociating the Pd/amine complex. Due to the nature of the

hydrogenation as a heterogeneous mixture, the rate was variable, but the reaction was usually done within 24 hours. A 20% loading of Pd/C did not seem to accelerate the reaction, but adding more than three equivalents of NH_4OAc resulted in sluggish reactivity. Using a higher pressure of H_2 proved to be counterproductive and removed the benzylic amine entirely. The crude product, with conversion verified by TLC and NMR, was taken directly on to the next stage of synthesis.

The fourth amino alcohol was commercially available at >99% ee as *D*-phenylalaninol (**14**, Figure 2). The fifth amino alcohol was neither commercially available nor did it have an available vinyl precursor. Methylenenaphthyl amino alcohol (**16**)[3] was synthesized in three steps from 2-(bromomethyl)naphthalene (**15**) via a chiral phase-transfer-catalyzed alkylation (Scheme 2).[4] The resulting iminoester (95% ee) was first hydrolyzed in dilute acid, then reduced with $LiBH_4$ to give the *S*-amino alcohol, whereas all the others were *R*-amino alcohols. This choice of stereochemistry was made based on availability of cinchonidine-derived phase-transfer catalyst. Initial reductions were carried out using LAH in refluxing THF overnight, but yields were typically low (50–70%). Fortunately, Dr. Biplab Banerjee, a co-worker in the Castle lab, was able to develop the borohydride conditions shown in Scheme 2 to improve the yield of this step.

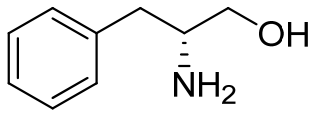
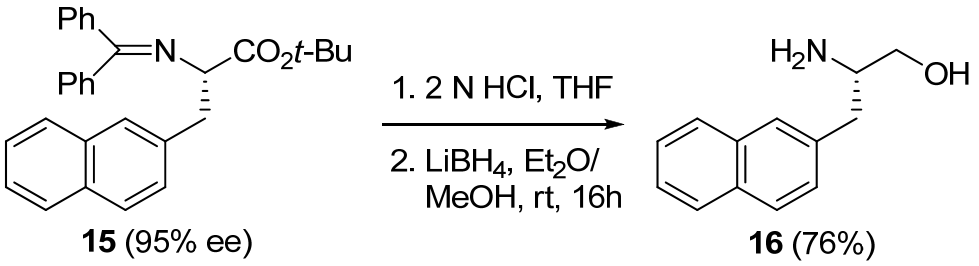


Figure 2. *D*-phenylalaninol (**14**)



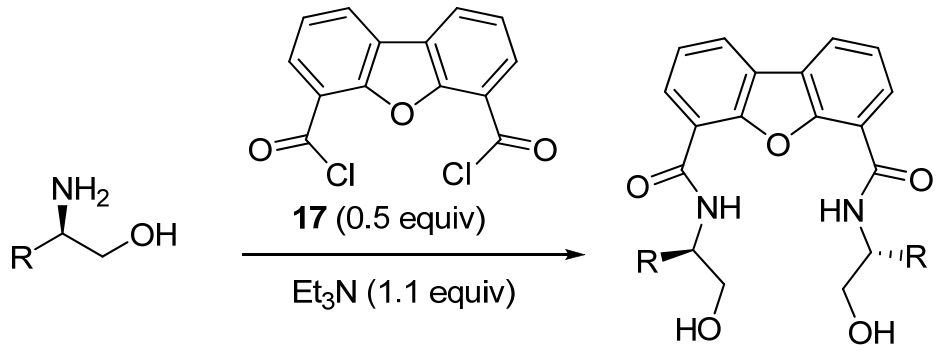
Scheme 2. Synthesis of MeNap Amino Alcohol

2.2 Bisoxazoline Formation

With all five amino alcohols in hand, we proceeded to follow the synthesis laid out by Curran and Kanemasa for **2**.[5] From commercially available dibenzofuran, a directed ortho-metallation, followed by installing a carboxylate at those two positions, gave the diacid. Conversion to the diacid chloride proceeded smoothly to provide the precursor (**17**) for the DBFOX ligand formation.

The amidation of **17** with amino alcohols **18** and **21** proceeded smoothly within a day at room temperature, analogous to the procedure outlined for DBFOX/Ph. Amidations with amino alcohols **19**, **20**, and **22** were sluggish and often low-yielding. This was remedied by elevating the temperature up to 90 ºC and allowing for longer reaction times. Presumably, the added bulk of the amino alcohols led to the decreased reactivity relative to phenylglycinol, though this does not help to explain the relative rates of Nap and MeNap. Furthermore, there were multiple cases of mono-amidated intermediate being isolated (as R-COCl or R-CO_2H), indicating that the second amidation was much more sluggish than the first.

Table 1. DBFOX/R Amidations



R	Solvent	Temp (ºC)	Time (hrs)	Prd	Yield (%)
Nap (**18**)	$CHCl_3$	35	24	**23**	91
tBu (**19**)	DMF	90	68	**24**	72
Pip (**20**)	DMF	90	67	**25**	88
Bn (**21**)	THF	45	107	**26**	79
MeNap (**22**)	DMF	120	86	**27**	67

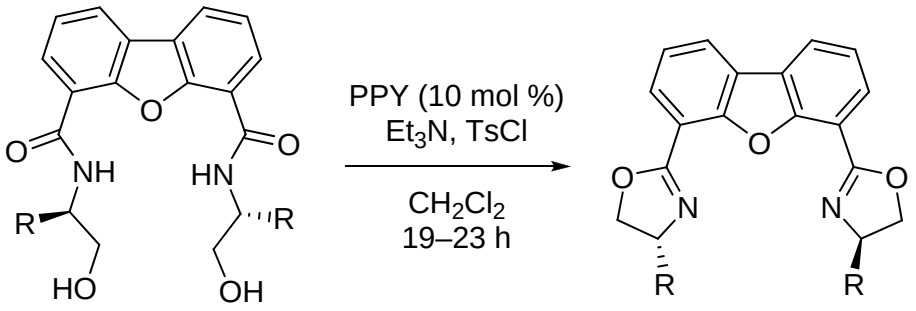
We speculated that one possibility as to the relative reactivity of the tBu and Pip amino alcohols compared to phenylglycinol could be attributed to the residual ammonium acetate used in the hydrogenolysis of the Cbz protecting group prior to the amidation. NH_4OAc is only mildly soluble in $CDCl_3$, and NMR's obtained of crude amino alcohols show roaming ammonium peaks, which is no surprise. However, what is surprising are occasional shifts of 0.1–0.2 ppm of the acetate peak were observed in some samples. This suggests that an acetate salt could have been slowing the nucleophilic attack of the nitrogen lone pair to the benzodioxole acid chloride. Further experimentation would be needed to verify or disprove this hypothesis.

The final step from the Curran-Kanemasa synthesis of **2** is a cyclodehydration mediated by diethylaminosulfur trifluoride (DAST).[5] Applied to the new amides, DAST cyclodehydrations were unreliable and often low-yielding. The original procedure reported that the purity of the diamide precursor was essential to the success of the DAST procedure. Due to the scale of many of the ligand preparations, recrystallization was impractical and often failed. The majority of the amides were purified by column chromatography (SiO_2), which likely left trace impurities responsible for the capricious yields.

A second procedure was reported by Evans and Woerpel in which they cyclodehydrated similar alkyl amino amides via tosyl chloride, Et_3N, and dimethylamino pyridine (DMAP).[6] This procedure allowed activation of the sulfoxide with DMAP, driving the tosylate formation to induce the nucleophilic attack of the amide oxygen in cyclization. While this procedure proved to be more reliable and robust than the DAST-mediated procedure, reactions were more sluggish (2-3 days) and lower-yielding. Increasing the amount of DMAP to stoichiometric amounts remedied this issue, but quickly became impractical, due to the difficulty of monitoring the reaction by TLC and NMR from DMAP overlapping product signals.

Fortunately for us, an article was discovered around the same time that dealt with highly-activated DMAP analogues, particularly 4-pyrrolidinopyridine (PPY).[6] A catalytic amount (10 or 20 mol %) of PPY mediated the cyclodehydration of amides **23-27** within 24 hours with good yields (Table 2).

Table 2. DBFOX/R Cyclodehydrations



R	Time (hrs)	Prd	Yield (%)
Nap (**23**)	19	**3**	88
tBu (**24**)	19	**4**	58
Pip (**25**)	20	**5**	64
Bn (**26**)	19	**6**	83
MeNap (**27**)	23	**7**	82

2.3 References

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CHAPTER 3. RADICAL CONJUGATE ADDITIONS WITH NEW DBFOX LIGANDS

3.1 Ligand Evaluation on Model Substrate

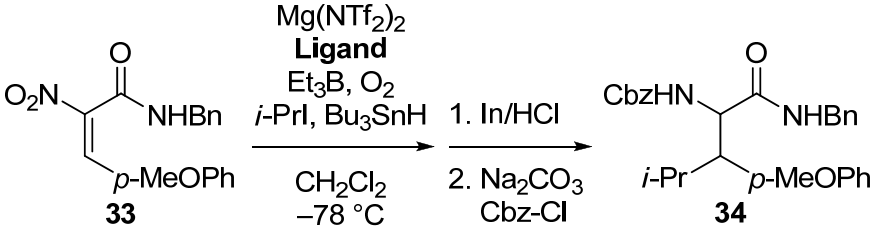
With five new DBFOX ligands in hand, the next step of the project was to test each of these ligands in place of DBFOX/Ph (**2**) on the model substrate. All other conditions were kept constant. Since achieving high selectivity in both the addition and H-atom abstraction steps were key, the full three-step sequence to inhibit epimerization at the α-carbon was performed (Scheme 1). Only one change was made to the procedure as constituted in the 2005 paper:[1] the ligand and Lewis acid were stirred overnight in order to ensure complexation. Early trials resulted in a large percentage of products characterized by the reduction of the double bond, rather than the radical addition. We theorized that one possible cause of this increase in byproducts was a lack of association between the new ligands, which are bulkier than **2**, and $Mg(NTf_2)_2$. Thus, without the electron-rich DBFOX ligands to lower the Lewis acidity of the Mg, conjugate reduction by Bu_3SnH was favored, a hypothesis supported by observations from the initial work,[1] where stronger Lewis acids promoted the conjugate reduction at a slow rate.

Upon increasing the initial complexation time, the percentage of reduction product was minimized and yields of addition product were increased. The kinetic extent of complexation was first monitored by NMR, but it soon became apparent that an easier visual cue could be used: Initial solubility of $Mg(NTf_2)_2$ in CH_2Cl_2 was minor, resulting in a cloudy suspension. Upon complexation with the ligand, it dissolved and the solution cleared.

It was our initial hypothesis that these bulkier DBFOX ligands would increase the diastereoselectivity of the addition step over the results reported with **2**. Initial trials with

DBFOX/Nap (**3**) and DBFOX/*p*-tBuPh (**4**) confirmed this hypothesis (Table 1). DBFOX/Bn (**6**) and DBFOX/MeNap (**7**) also showed increased selectivity at the β-carbon stereocenter. Surprisingly, DBFOX/Pip (**5**) showed worse selectivity than **2**, leading to a possible theory that the heteroatoms in the dioxole ring participated in some way to our detriment. Also surprising was the significantly lower yields obtained when **7** was used. Since the improvements over **2** were minimal (and less than those observed with **3**), this was never optimized. Perhaps the lower yields are due to an even slower rate of ligand-Mg complexation, and could potentially be remedied by a longer initial stirring before substrate addition.

Table 1. Ligand Evaluation in Radical Conjugate Addition



Ligand	% Yield	*syn/anti*	% ee (*syn, anti*)[a]	α ee, β ee (%)
2[b]	76	1.4:1	88, 76	83, 20
3	65	1.8:1	96, 97	96, 30
4	57	1.6:1	84, 79	28, 28
5	75	1.2:1	76, 79	78, 12
6	80	1.5:1	82, 80	81, 25
7	44	1.6:1	92, 90[c]	91, 25

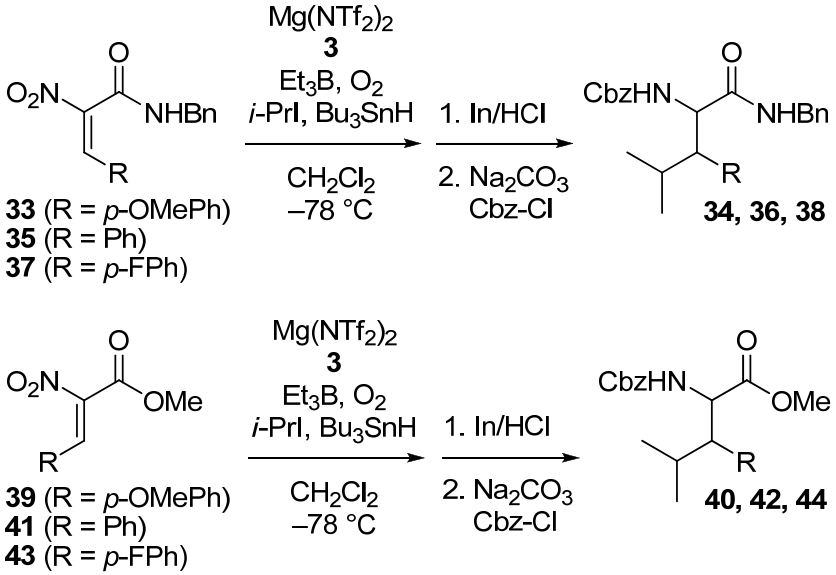
[a] Determined by chiral HPLC (see Ch. 5 for details). [b] Data from Ref. 1. [c] Major enantiomers were opposite those obtained from reactions with **3–6**.

3.2 Substrate Scope of DBFOX/Nap-Mediated Additions

With the improvements observed at both stereocenters using **3**, we set out to investigate if these trends held with the other amide and ester radical acceptors used in the initial studies with **2** (Table 2). Amide substrates **35** and **37** underwent the Mg/**3**-promoted radical conjugate addition with improved enantio- and diastereoselectivity. The best results were still from **33**, which contained the more electron-rich *p*-methoxyphenyl alkene β-substituent. However, when esters **39, 41,** and **43** were employed, lower yields and lower selectivities were observed for all three substrates.

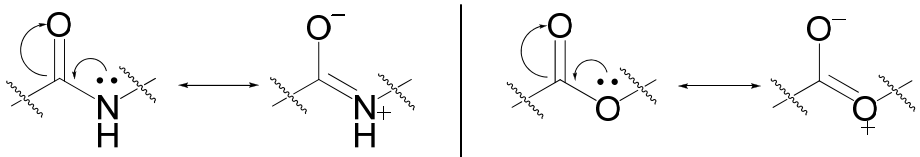
One possible explanation for this flip-flop in the trend could be the carbonyl-Lewis acid complex interaction. Amides have a stronger tendacy to bind to Lewis acids[2] because of the resonance between the nitrogen lone pair and carbonyl oxygen, which results in a greater negative charge on the more electronegative oxygen (Figure 1). Esters do not share this level of resonance, since the oxygen is less prone to lone pair donation. This difference alone does not serve as an adequate explanation for the significant changes observed in the radical conjugate additions between the amide and ester substrates, as well as the trend differences in data resulting from the switch from DBFOX/Ph to DBFOX/Nap.

Table 2. Reaction Scope of DBFOX/Nap (**3**)



Substrate	Ligand	% Yield	*syn/anti*	% ee (*syn, anti*)[a]
33	**2**[b]	76	1.4:1	88, 76
33	**3**	65	1.8:1	96, 97
35	**2**[b]	66	1.4:1	64, 62
35	**3**	60	1.7:1	73, 71
37	**2**[b]	59	1.6:1	72, 50
37	**3**	63	2.0:1	80, 61
39	**2**[b]	75	2.6:1	21, 28
39	**3**	38	2.2:1	11, 15
41	**2**[b]	60	1.7:1	9, 17
41	**3**	28	1.3:1	2, 5
43	**2**[b]	66	1.7:1	6, 12
45	**3**	17	1.4:1	3, 3

[a] Determined by chiral HPLC (See Ch. 5 for details). [b] Data from Ref. 1



Right Structure Contributes More to Actual Structure of Amide

Left Structure Contributes More to Actual Structure of Ester

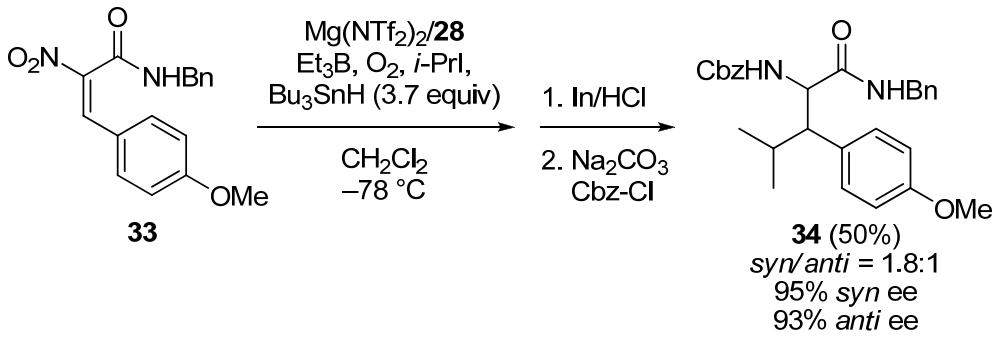
Figure 1. Difference Between Amide and Ester Carbonyls

3.3 Methodology Considerations

Faced with these findings, we began to wonder if our empirical binding model might be inaccurate, because the carbonyl difference had such a major effect on the reaction, which suggests a primarily monodentate substrate-auxiliary interaction instead of the postulated bidentate interaction. Although nitro-Lewis acid complexation has been reported previously,[3] the data, which show a minimal improvement in the stereoselectivity at the β-carbon of the amide substrates, combined with a sharp decline of selectivity with the ester substrates, argue against this model.

The reactions summarized in Tables 1 and 2 were all conducted with a substantial quantity of Bu_3SnH (three additions, 2.5 equivalents each) to ensure complete conversion. The goal of this project was to enhance the scope, value, and practicality of this methodology, so we explored the same reaction of the DBFOX/Nap–$Mg(NTf_2)_2$–directed addition of isopropyl radical to **33** with one-half the amount of tin per loading (Scheme 2). While yields were slightly lower, the dr and ee values remained comparable. No other values were changed. Further optimization and experimentation could restore the reaction to its previous levels of yield or higher in the future. These findings are fortuitous, as the only troublesome reagent in the radical

conjugate addition sequence is the tin. However, its impact can be minimized by employing a procedure published by Harrowven,[4] in which a 10% w/w mixture of ground KF in silica gel was used in the purification to remove a significant level of tin byproduct impurity from the Cbz-protected amino amides and esters.



Scheme 1. Radical Conjugate Addition with Reduced Tin Loadings

3.4 References

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CHAPTER 4. INITIAL EXAMINATION OF HYDROGEN-BONDING CATALYSTS

4.1 Ureas and Thioureas

Evidence was obtained through experimentation that suggested our hypothesized binding model was inaccurate. Thus, we began to explore the possibility of other systems that are known to interact with both nitro groups and carbonyls, such as hydrogen bond donors Hydrogen bonding reagents have been extensively used in chemistry, and have received special attention in recent literature as part of a complex chemical scaffold to bring two reacting elements together.[1] We wanted to use these same principles to hydrogen bond to both Lewis basic groups, inducing a conformational change that would twist the carbonyl out of the plane from the rest of the nitroalkene (Figure 1). Removal of this conjugation may cause the amino portion of the amide to preferentially shield one face of the alkene from radical attack. One reason this might occur is that the dipole alignment in the natural planar conformer between the nitro group and carbonyl group destabilizes the compound. By hydrogen bonding to a rigid backbone, a twist can be imposed to bring these two dipoles out of plane with each other, relieving that electronic interference. Of course, it is difficult to predict which functional group will twist.

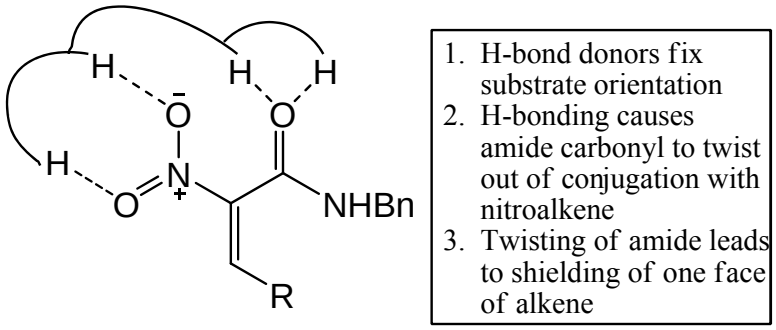

Figure 1. Proposed Catalyst-Substrate Binding

Rigid hydrogen bond donors would be the best option for the proposed binding shown in Figure 1. A fixed backbone combined with a chiral element away from the binding site would be able to transfer that chirality via sterics to the proposed "twisted" binding model. We decided to survey a series of ureas and thioureas, as these functional groups have exhibited hydrogen bonding to nitro groups.[2-4] Takenaka recently discovered an aminopyridinium ion that also complexes well with nitroalkenes.[5] A set of seven donors were proposed as simple, achiral ligands to test the extent to which hydrogen bonding will catalyze the radical conjugate addition (Figure 2). We hoped that the thioureas would act as the better catalyst, since thioureas are more Lewis acidic than ureas. However, we are aware that the thiocarbonyl may interfere with the radical chemistry.

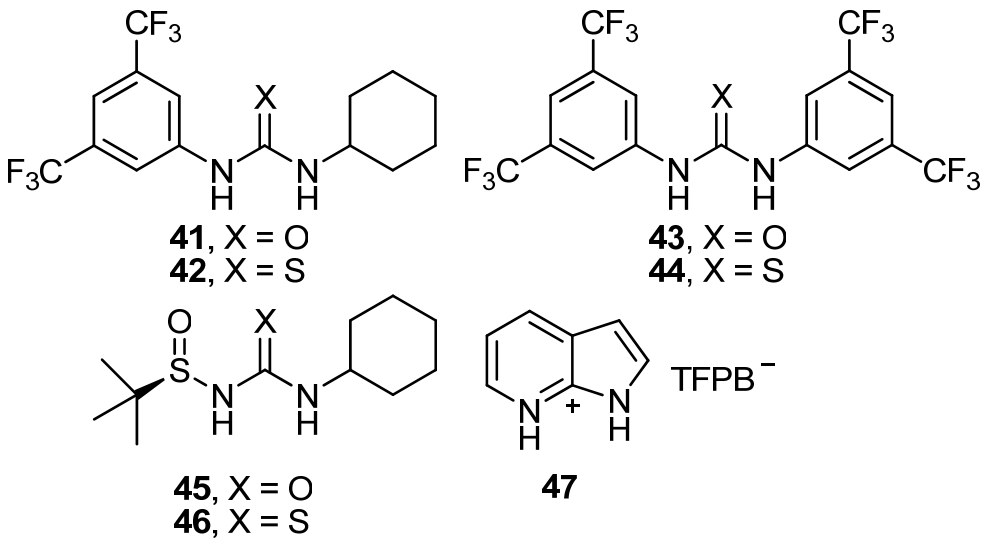

Figure 2. Hydrogen Bond Donors

4.2 Radical Conjugate Additions with Achiral Hydrogen Bond Donors

Compounds **41**–**47** were synthesized and we performed the radical conjugate addition as outlined previously, substituting the DBFOX/Mg complex with the various

hydrogen bond donors. Since **41**–**47** are achiral, we performed only the radical conjugate addition, unlike the previous studies where precautions were taken to prevent epimerization by reducing the nitroalkene product to an amine, then protecting with CbzCl before purifying.

Initial results on the screening process were difficult to unravel, as tin removal became a major problem. Nonetheless, we were able to see the peaks corresponding to the substrate starting material and the addition product on both MS and ^{1}H NMR. Using ligand **45**, we saw an approximate two to one ratio of product to starting material, with no evidence of reduction byproducts. Masses for these fractions are unreliable still, due to the tin contamination and multiple purification attempts.

4.3 Conclusions

The syntheses of five new DBFOX ligands were accomplished, and these ligands were then tested in a radical conjugate addition reaction. DBFOX/Nap exhibited minor increases in enantio- and diastereoselectivity over DBFOX/Ph with α/β-unsaturated-α-nitroamide substrates, but the corresponding nitroesters exhibited decreased yields and selectivities. This data caused us to revisit our empirical binding model, which had postulated an octahedral magnesium complex with a bidentate complexation to the substrate. With the major differences between substrate reactivity, we had to consider that the carbonyl–Lewis acid coordination was major compared to the nitro–Lewis acid complexation, which may or may not exist. We then began model studies utilizing hydrogen-bond donors, which are known to bind to both nitro groups and carbonyls. The results of these studies are still in progress.

4.4 References

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CHAPTER 5. EXPERIMENTAL AND SPECTROSCOPIC DATA

5.1 General Methods

Tetrahydrofuran, *N*,*N*-dimethylformamide, triethylamine, methylene chloride, and methanol were dried by passage through a Glass Contour solvent drying system containing cylinders of activated alumina.[1] Flash chromatography was carried out using 60–230 mesh silica gel. ^{1}H NMR spectra were obtained on a Varian 500 MHz spectrometer, with chloroform (7.27 ppm) or tetramethylsilane (0.00 ppm) as an internal reference. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), br s (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). ^{13}C NMR spectra were obtained on a Varian spectrometer operating at 125 MHz, with chloroform (77.23 ppm) as internal reference. Infrared spectra were obtained on a Nicolet Avatar 360 FT-IR Spectrometer. Optical rotations were obtained using a Perkin-Elmer 241 Polarimeter. Mass spectral data were obtained using ESI techniques from the Brigham Young University mass spectrometry facility.

5.2 Experimental Details

(*R*)-Benzyl 2-hydroxy-1-(naphthalene-2-yl)ethylcarbamate (11). To a stirred solution of benzyl carbamate (1.47 g, 9.74 mmol) in 1-propanol (13 mL) was added freshly prepared sodium hydroxide solution (414 mg in 13 mL H_2O), with a 3 mL aliquot set aside. Freshly prepared sodium hypochlorite (1.20 g, 11.0 mmol) was then added, followed by $(DHQD)_2PHAL$ (40 mg, 0.05 mmol). The mixture was stirred until homogeneous, then immersed in a 0 °C ice bath. After 10 minutes, 2-vinylnaphthalene

(502.3 mg, 3.26 mmol, **8**) was added. The aliquot of NaOH solution was used to dissolve the $K_2OsO_2(OH)_4$ (25.4 mg, 0.07 mmol). This was then added to the bulk solution. The solution was stirred at 0°C for 4.5 hours, at which time the stirring ceased and the flask was cooled to -25°C to precipitate product. The product was collected by filtration, washed with cold 1:1 nPrOH-H_2O, and dried overnight on the benchtop to afford product (288.3 mg, 0.90 mmol, 68%) as a white solid. *If product did not precipitate*, the solution was quenched with satd. aq. sodium sulfite, then stirred at 0°C for 15 mins. The aqueous layer was separated and extracted with 3 x 15 mL of EtOAc. The combined organic layers were washed with water (10 mL), brine (10 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. Flash chromatography (SiO_2, 2 x 20 cm, 30-50% EtOAc/hexane gradient elution) provided product, occasionally contaminated with regioisomer. Spectral data for **11** were identical to those previously reported.[2]

(*R*)-Benzyl 1-(4-*tert*-butylphenyl)-2-hydroxyethylcarbamate (12). Prepared from *p-tert*-butylstyrene (**9**, 150 μL, 135 mg, 0.83 mmol) according to the procedure given for the preparation of **11**. Compound **12** (109.5 mg, 0.33 mmol, 40%) was obtained as a white solid: $[\alpha]^{25}_D$ –3.6 (*c* 0.50, EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.27 (m, 9H), 5.20–5.12 (m, 1H), 5.13 (s 2H), 4.86–4.80 (m, 1H), 3.62–3.54 (m, 1H), 3.37–3.31 (m, 1H), 2.52 (s, 1H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.3, 151.3, 138.7, 136.6, 128.8 (2C), 128.44 (2C), 128.40, 125.9 (2C), 125.8 (2C), 73.7, 67.2, 48.6, 34.8, 31.6 (3C); IR (film) ν_{max} 3377, 3260, 3062, 2924, 2855, 1696, 1282, 1157, 1084, 989 cm^{-1}; HRMS (ESI) *m/z* 328.19092 (MH^+, $C_{20}H_{25}NO_2H$ requires 328.19072). **12** was obtained in >99% ee, as analyzed by HPLC (Chiralcel OD-H, 65:35 hexane:*i*-PrOH, 0.70 mL/min; t_R = 7.9 min, 9.4 min (major)).

(*R*)-Benzyl 1-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxyethylcarbamate (13). Prepared from 5-vinylbenzo[*d*][1,3]dioxole[3] (**10**, 96 mg, 0.65 mmol) according to the procedure given for the preparation of **11**. Compound **13** (102 mg, 0.32 mmol, 50%) was obtained as an off-white solid: $[\alpha]^{25}_{D}$ –10.9 (*c* 1.0, EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.27 (m, 5H), 6.80–6.76 (m, 3H), 5.95 (s 2H), 5.44 (d, *J* = 3.5 Hz, 1H), 5.13 (d, *J* = 12.0 Hz, 1H), 5.08 (d, *J* = 12.0 Hz, 1H), 4.80–4.71 (m, 1H), 3.91–3.75 (s, 2H), 2.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.5, 148.3, 147.5, 136.4, 133.2, 128.8 (2C), 128.5 (3C), 120.1, 108.8, 107.3, 101.4, 67.3, 66.8, 57.1; IR (film) ν_{max} 3395, 3310, 3090, 3050, 2950, 2895, 2780, 1697, 1504, 1440, 1370, 1320, 1244, 1038, 940 cm^{-1}; HRMS (ESI) *m/z* 338.09908 (MNa^+, $C_{17}H_{17}NO_5Na$ requires 338.09989). **13** was obtained in 95% ee, as analyzed by HPLC (Chiralcel OD-H, 80:20 hexane:*i*-PrOH, 0.80 mL/min; t_R = 10.0 min (major), 15.5 min).

Hydrogenolysis of the Cbz group: To a solution of **11** (16.2 mg, 0.050 mmol) in MeOH (2 mL) was added solid ammonium acetate (12 mg, 0.15 mmol). After stirring for a minute, 10% Pd/C (2.3 mg, 20% w/w to substrate) was added. The vial was evacuated, then a positive pressure of H_2 was applied. This was repeated twice more to ensure the absence of air in the reaction container. The positive pressure of H_2 was kept on the system for 23 hours, at which time the flask was evacuated and opened and the solution was run through a plug of Celite to remove the Pd/C. The solution was washed with 5 mL water to remove NH_4OAc. Reaction completion was verified by NMR and TLC.

(*S*)-*tert*-Butyl 2-(diphenylmethyleneamino)-3-(naphthalene-2-yl)propanoate (15): A solution of *N*-(diphenylmethylene)glycine *tert*-butyl ester (50.0 mg, 0.17 mmol) and *N*-(2',3',4'-trifluoro)benzylhydrocinchonidinium bromide[4] (9.5 mg, 0.017 mmol) in

$PhCH_3$–$CHCl_3$ (7:3, 750 μL) was treated with 2-(bromomethyl)naphthalene (96.6 mg, 0.423 mmol). The solution was then cooled to –20 °C, treated with 50% aqueous KOH (250 μL), and stirred at –20 °C for 12 h. The resultant mixture was diluted with Et_2O (20 mL), washed with H_2O (3 × 5 mL), dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 × 25 cm, 10% EtOAc–hexanes elution) afforded **15** (62.0 mg, 0.14 mmol, 84%) as a yellow oil. Spectral data for this compound were identical to those previously reported.[5] **15** was obtained in 95% ee, as analyzed by HPLC (Chiralcel OD-H, 99.8:0.2 hexane:*i*-PrOH, 1.0 mL/min; t_R = 9.5 min (major), 15.6 min).

(*S*)-2-Amino-3-(naphthalene-2-yl)propan-1-ol (16). A solution of **15** (150 mg, 0.34 mmol) in THF (2.0 mL) was treated with HCl (2 N, 500 μL) and stirred at rt for 4 h. The resultant mixture was treated with sat aq $NaHCO_3$ (1.5 mL) and extracted with EtOAc (3 × 3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 1.0 × 18 cm, 100% EtOAc elution) afforded the free amine (77.0 mg, 0.28 mmol, 83%).

A solution of this amine (40 mg, 0.15 mmol) in anhydrous Et_2O (2.0 mL) was treated with anhydrous CH_3OH (8.8 μL, 7.0 mg, 0.22 mmol) followed by $LiBH_4$ (4.8 mg, 0.22 mmol). The resultant mixture was stirred at rt under Ar for 16 h, then treated with H_2O (0.5 mL) and CH_3OH (0.3 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo to afford **16** (26.9 mg, 0.13 mmol, 91%) as an off-white solid. Spectral data for this compound were identical to those previously reported.[6]

***N*^{4},*N*^{6}-bis((*R*)-2-Hydroxy-1-(napthalen-2-yl)ethyl)dibenzo[*b,d*]furan-4,6-dicarboxamide (18)**: A flask with magnetic stirbar was charged with diacid chloride **17**

(74.7 mg, 0.25 mmol) and anhydrous solvent ($CHCl_3$, pre-treated with basic alumina, 2 mL). This was placed into a 0°C ice bath under argon and stirred for 5 minutes. A solution of deprotected naphthyl amino alcohol (90 mg, 0.48 mmol), Et_3N (0.08 mL, 0.51 mmol), and $CHCl_3$ (1 mL) was added dropwise to the dibenzofuran. The flask was then heated in an oil bath to 35 °C for 24 hours. Solid ammonium chloride (50 mg) was added to quench the reaction, and this was stirred at room temperature for 30 mins. Then, the solution was filtered. The solid was stirred in THF for an additional 30 mins, and then filtered again. The combined organic extracts were concentrated in vacuo. Flash chromatography (SiO_2, 1.5 x 20 cm, 50%/80%/100% EtOAc-hexanes gradient elution) afforded **18** (133.9 mg, 0.23 mmol, 91%) as a yellow oil: $[\alpha]^{25}_D$ +131 (*c* 0.1, 95% EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.14 (d, *J* = 7.5 Hz, 2H), 8.04 (d, *J* = 7.5 Hz, 2H), 8.01 (d, *J* = 6.5 Hz, 2H), 7.87 (s, 2H), 7.80–7.72 (m, 8H), 7.53–7.47 (m, 4H), 7.44–7.39 (m, 2H), 5.45 (dd, *J* = 10.0, 6.5 Hz, 2H), 4.10–4.04 (m, 2H), 4.02–3.97 (m, 2H), 3.34 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.5 (2C), 153.4 (2C), 136.5 (2C), 133.3 (2C), 132.9 (2C), 128.6 (2C), 127.9 (2C), 127.6 (2C), 127.5 (2C), 126.2 (2C), 125.9 (2C), 125.6 (2C), 124.8 (2C), 124.3 (2C), 124.2 (2C), 123.6 (2C), 118.9 (2C), 66.0 (2C), 56.6 (2C); IR (film) ν_{max} 3325, 2920, 2349, 1731, 1695, 1682, 1658, 1641, 1592, 1547, 1539, 1531, 1462, 1060, 954, 806, 737, 617, 559 cm^{-1}; HRMS (ESI) *m/z* 595.22258 (MH^+, $C_{38}H_{30}N_2O_5H$ requires 595.22275).

***N*^{4},*N*^{6}-bis((*R*)-1-(4-*tert*-Butylphenyl)-2-hydroxyethyl)dibenzo[*b*,*d*]furan-4,6-dicarboxamide (19).** Compound **19** was prepared from deprotected *p*-*tert*-butyl phenyl amino alcohol (200 mg, 1.03 mmol) and **17** (160 mg, 0.54 mmol) according to the procedure given for the preparation of **18**, with the exceptions that DMF (6 mL total) was

used as the reaction solvent and the reaction was stirred at 90 °C for 68 h. Compound **19** (240 mg, 0.39 mmol, 72%) was obtained as a light yellow solid: $[\alpha]^{25}_{D}$ +0.8 (*c* 0.25, EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz, mixture of rotamers) δ 8.30 and 8.21 (2d, *J* = 7.5 and 7.5 Hz, 2H), 8.09 and 8.02 (2d, *J* = 8.0 and 8.0 Hz, 2H), 7.98–7.94 and 7.86–7.82 (2m, 2H), 7.52 and 7.48 (2t, *J* = 7.5 and 7.5 Hz, 2H), 7.40–7.36 (m, 8H), 5.09 (d, *J* = 9.5 Hz, 2H), 4.31–4.21 (m, 2H), 4.07 and 4.01 and 3.71 (3 br s, 2H), 3.51 (t, *J* = 11.5 Hz, 2H), 1.34 (s, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz, mixture of rotamers) δ 164.2 and 164.0 (2C), 152.6 and 152.4 (2C), 151.0 (2C), 138.7 and 138.6 (2C), 129.6 and 129.3 (2C), 125.7 (4C), 125.5 (4C), 124.2 and 124.1 (2C), 124.0 (2C), 123.9 and 123.8 (2C), 118.5 (2C), 73.1 and 72.9 (2C), 47.6 and 47.5 (2C), 34.6 (2C), 31.3 (6C); IR (film) ν_{max} 3418, 2961, 2868, 1644, 1543, 1426, 1407, 1298, 1270, 1181, 1157, 1108, 1084, 910 cm^{-1}; HRMS (ESI) *m/z* 607.31665 (MH^+, $C_{38}H_{42}N_2O_5H$ requires 607.31341).

***N*^{4},*N*^{6}-bis((*R*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-2-hydroxyethyl)dibenzo[*b*,*d*]furan-4,6-dicarboxamide (20).** Compound **20** was prepared from deprotected piperonal amino alcohol (9.0 mg, 0.050 mmol) and **17** (7.9 mg, 0.027 mmol) according to the procedure given for the synthesis of **18**, with the exceptions that DMF (3 mL total) was used as the reaction solvent and the reaction was stirred at 90 °C for 67 h. Compound **20** (13.9 mg, 0.024 mmol, 88%) was obtained as white solid: $[\alpha]^{25}_{D}$ +7.6 (*c* 0.25, EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.11 (d, *J* = 7.5 Hz, 2H), 7.99 (d, *J* = 7.5 Hz, 2H), 7.85 (d, *J* = 6.5 Hz, 2H), 7.49–7.45 (m, 2H), 6.93–6.90 (m, 4H), 6.79 (dd, *J* = 7.5, 2.0 Hz, 2H), 5.92 (s, 4H), 5.21 (d, *J* = 3.5 Hz, 2H), 4.04–3.98 (m, 2H), 3.96–3.89 (m, 2H), 3.33 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.4 (2C), 153.4 (2C) 148.0 (2C), 147.1 (2C), 133.1 (2C), 127.4 (2C), 124.4 (2C), 124.3 (2C), 123.7 (2C), 120.1 (2C), 118.8 (2C), 108.5 (2C),

107.3 (2C), 101.1 (2C), 66.2 (2C), 56.2 (2C); IR (film) ν_{max} 3274, 2920, 2868, 1638, 1542, 1503, 1488, 1440, 1233, 1191, 1040, 932 cm^{-1}; HRMS (ESI) *m/z* 583.17130 (MH^+, $C_{32}H_{26}N_2O_9H$ requires 583.17111).

***N*^{4},*N*^{6}-bis((*R*)-1-Hydroxy-3-phenylpropan-2-yl)dibenzo[*b*,*d*]furan-4,6-dicarboxamide (21).** Compound **21** was prepared from **14** (19.1 mg, 0.12 mmol) and **17** (18.5 mg, 0.063 mmol) according to the procedure given for the synthesis of **18**, with the exceptions that THF (2 mL total) was used as the reaction solvent and the reaction was stirred at 45 °C for 107 h. Compound **21** (26.1 mg, 0.050 mmol, 79%) was obtained as a white solid: $[\alpha]^{25}_D$ +75 (*c* 0.50, EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.05 (d, *J* = 7.5 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.38–7.29 (m, 8H), 7.24 (t, *J* = 7.5 Hz, 2H), 4.49–4.39 (m, 2H), 3.90 (d, *J* = 10.0 Hz, 2H), 3.79 (d, *J* = 12.0 Hz, 2H), 3.45 (s, 2H), 3.16 (dd, *J* = 13.5, 6.0 Hz, 2H), 3.05 (dd, *J* = 13.5, 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.6 (2C), 153.4 (2C), 138.2 (2C), 129.7 (4C), 128.9 (4C), 127.7 (2C), 126.9 (2C), 124.6 (2C), 124.4 (2C), 123.9 (2C), 119.2 (2C), 63.3 (2C), 53.8 (2C), 37.2 (2C); IR (film) ν_{max} 3390, 2924, 2853, 1657, 1629, 1617, 1538, 1457, 1261, 1194, 1086, 1035 cm^{-1}; HRMS (ESI) *m/z* 523.22020 (MH^+, $C_{32}H_{30}N_2O_5H$ requires 523.22275).

***N*^{4},*N*^{6}-bis((*S*)-1-Hydroxy-3-(naphthalen-2-yl)propan-2-yl)dibenzo[*b*,*d*]furan-4,6-dicarboxamide (22).** Compound **22** was prepared from **16** (34.0 mg, 0.17 mmol) and **17** (23.4 mg, 0.080 mmol) according to the procedure given for the synthesis of **18**, with the exceptions that DMF (5 mL total) was used as the reaction solvent and the reaction was stirred at 120 °C for 86 h. Compound **22** (33.2 mg, 0.053 mmol, 67%) was obtained as a yellow oil: $[\alpha]^{25}_D$ –19 (*c* 0.17, EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.10

(d, *J* = 7.5 Hz, 2H), 7.96 (d, *J* = 7.5 Hz, 2H), 7.84–7.78 (m, 6H), 7.78–7.74 (m, 2H), 7.61 (d, *J* = 7.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.48–7.42 (m, 6H), 4.57–4.49 (m, 2H), 3.94 (dd, *J* = 11.5, 3.0 Hz, 2H), 3.84 (dd, *J* = 11.5, 4.0 Hz, 2H), 3.35 (dd, *J* = 13.5, 6.0 Hz, 2H), 3.23 (dd, *J* = 13.0, 8.5 Hz, 2H), 2.97 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.3 (2C), 153.3 (2C), 135.6 (2C), 133.7 (2C), 132.3 (2C), 128.3 (2C), 128.0 (2C), 127.8 (2C), 127.7 (2C), 127.6 (2C), 127.5 (2C), 126.1 (2C), 125.5 (2C), 124.4 (2C), 124.2 (2C), 123.7 (2C), 119.0 (2C), 62.9 (2C), 53.6 (2C), 37.1 (2C); IR (film) ν_{max} 3392, 2923, 2869, 1651, 1536, 1399, 1375, 1325, 1245, 1200, 1195, 1080, 1025, 1015, 1003, 925 cm^{-1}; HRMS (ESI) *m/z* 623.25377 (MH^+, $C_{40}H_{34}N_2O_5H$ requires 623.25405).

4,6-bis((*R*)-4-(Naphthalen-2-yl)-4,5-dihydrooxazol-2-yl)dibenzo[*b*,*d*]furan (23). A solution of **18** (59.2 mg, 0.10 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was treated with Et_3N (40 μL, 29.1 mg, 0.29 mmol) and 4-pyrrolidinopyridine (4.8 mg, 0.032 mmol). The mixture was stirred at 0 °C for 10 min, then treated dropwise with a solution of TsCl (45.9 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (1.5 mL). The resultant mixture was vigorously stirred at rt for 19 h, then treated with sat aq NH_4Cl (7 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (SiO_2, 1.5 x 19 cm, 20–100% EtOAc in hexanes gradient elution) afforded **23** (49.1 mg, 0.088 mmol, 88%) as an off-white solid: $[\alpha]^{25}_D$ -28 (*c* 0.13, 95% EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.24 (d, *J* = 8.0 Hz, 2H), 8.17 (d, *J* = 7.5 Hz, 2H), 7.87 (s, 2H), 7.80 (d, *J* = 8.0 Hz, 4H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.53–7.48 (m, 4H), 7.44–7.36 (m, 4H), 5.68 (t, *J* = 9.0 Hz, 2H), 4.96 (t, *J* = 9.0 Hz, 2H), 4.40 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.5 (2C), 154.4 (2C), 145.3 (2C), 139.8 (2C), 133.4 (2C), 132.8 (2C), 128.8 (2C), 128.6 (2C), 127.9 (2C), 127.7 (2C),

126.2 (2C), 125.8 (2C), 125.5 (2C), 124.9 (2C), 124.8 (2C), 123.9 (2C), 123.1 (2C), 74.8 (2C), 70.1 (2C); IR (film) ν_{max} 2928, 1650, 1494, 1427, 1185, 1124, 984, 747, 700 cm^{-1}; HRMS (ESI) *m/z* 559.20263 (MH^+, $C_{38}H_{26}N_2O_3H$ requires 559.20162).

4,6-bis((*R*)-4-(4-*tert*-Butylphenyl)-4,5-dihydrooxazol-2-yl)dibenzo[*b*,*d*]furan (24). Compound **24** was prepared from **19** (2.9 mg, 0.0048 mmol) according to the procedure given for the synthesis of **23**. Compound **24** (1.6 mg, 0.0028 mmol, 58%) was obtained as an off-white solid: $[\alpha]^{25}_D$ +36 (*c* 0.05, 95% EtOH); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.15 (t, *J* = 7.5 Hz, 4H), 7.50–7.32 (m, 10H), 5.70 (dt, *J* = 18.0, 9.0 Hz, 2H), 4.66–4.58 (m, 2H), 4.25–4.15 (m, 2H), 1.32 (s, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.0 (2C), 154.4 (2C), 151.2 (2C), 137.9 (2C), 128.5 (2C), 125.9 (4C), 125.6 (4C), 124.8 (2C), 123.6 (2C), 123.0 (2C), 113.5 (2C), 80.6 (2C), 63.4 (2C), 34.6 (2C), 31.3 (6C); IR (film) ν_{max} 2959, 1651, 1427, 1185, 1120, 1059 cm^{-1}; HRMS (ESI) *m/z* 571.29856 (MH^+, $C_{38}H_{38}N_2O_3H$ requires 571.29552).

4,6-bis((*R*)-4-(Benzo[*d*][1,3]dioxol-5-yl)-4,5-dihydrooxazol-2-yl)dibenzo[*b*,*d*] furan (25). Compound **25** was prepared from **20** (19.1 mg, 0.0328 mmol) according to the procedure given for the synthesis of **23**. Compound **25** (11.9 mg, 0.0210 mmol, 64%) was obtained as a beige solid: $[\alpha]^{25}_D$ –2.5 (*c* 0.12, EtOH); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.16 (d, *J* = 7.5 Hz, 2H), 8.13 (d, *J* = 8.0 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 6.98 (s, 2H), 6.87 (d, *J* = 7.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 5.92 (d, *J* = 6.0 Hz, 4H), 5.46 (t, *J* = 9.5 Hz, 2H), 4.91 (t, *J* = 9.0 Hz, 2H), 4.35 (t, *J* = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.2 (2C), 154.3 (2C), 147.9 (2C), 146.9 (2C), 136.5 (2C), 128.7 (2C), 124.8 (2C), 123.8 (2C), 123.0 (2C), 120.0 (2C), 113.2 (2C), 108.3 (2C), 107.4 (2C), 101.0 (2C),

74.8 (2C), 69.6 (2C); IR (film) ν_{max} 2924, 1654, 1489, 1428, 1248, 1188, 1039, 935, 749 cm^{-1}; HRMS (ESI) *m/z* 547.14990, (MH^+, $C_{32}H_{22}N_2O_7H$ requires 547.14998).

4,6-bis((*R*)-4-Benzyl-4,5-dihydrooxazol-2-yl)dibenzo[*b,d*] furan (26). Compound **26** was prepared from **21** (66.4 mg, 0.13 mmol) according to the procedure given for the synthesis of **23**, with the exception that 0.20 equiv of 4-pyrrolidinopyridine were employed. Compound **26** (50.0 mg, 0.11 mmol, 83%) was obtained as a beige solid: $[\alpha]^{25}_D$ –43 (*c* 0.26, EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (t, *J* = 7.5 Hz, 4H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.35–7.29 (m, 8H), 7.26–7.21 (m, 2H), 4.78–4.70 (m, 2H), 4.52 (t, *J* = 8.5 Hz, 2H), 4.25 (t, *J* = 8.0 Hz, 2H), 3.39 (dd, *J* = 14.0, 4.5 Hz, 2H), 2.87 (dd, *J* = 13.5, 4.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.7 (2C), 154.2 (2C), 138.1 (2C), 129.3 (4C), 128.7 (4C), 128.6 (2C), 126.5 (2C), 124.8 (2C), 123.7 (2C), 123.0 (2C), 113.3 (2C), 72.0 (2C), 67.9 (2C), 41.7 (2C); IR (film) ν_{max} 2923, 1651, 1494, 1427, 1185, 1125, 984 cm^{-1}; HRMS (ESI) *m/z* 487.20193 (MH^+, $C_{32}H_{26}N_2O_3H$ requires 487.20162).

4,6-bis((*S*)-4-(Naphthalen-2-ylmethyl)-4,5-dihydrooxazol-2-yl)dibenzo[*b,d*] furan (27). Compound **27** was prepared from **22** (36.8 mg, 0.059 mmol) according to the procedure given for the synthesis of **23**, with the exception that 0.20 equiv of 4-pyrrolidinopyridine were employed. Compound **27** (28.3 mg, 0.048 mmol, 82%) was obtained as a beige solid: $[\alpha]^{25}_D$ +72 (*c* 0.17, 95% EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12–8.10 (m, 4H), 7.78–7.74 (m, 6H), 7.72 (s, 2H), 7.47–7.41 (m, 8H), 4.86–4.80 (m, 2H), 4.48 (t, *J* = 9.0 Hz, 2H), 4.26 (t, *J* = 8.5 Hz, 2H), 3.51 (dd, *J* = 14.0, 5.0 Hz, 2H), 3.03 (dd, *J* = 14.0, 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.7 (2C), 154.2 (2C), 135.5 (2C), 133.5 (2C), 132.3 (2C), 128.7 (2C), 128.2 (2C), 127.8 (2C), 127.7 (2C), 127.6 (2C), 127.5 (2C), 126.1 (2C), 125.5 (2C), 124.8 (2C), 123.7 (2C), 123.1 (2C),

113.3 (2C), 71.9 (2C), 67.8 (2C), 41.8 (2C); IR (film) ν_{max} 3052, 2925, 2853, 1652, 1507, 1427, 1185, 1124, 984 cm^{-1}; HRMS (ESI) *m/z* 587.23438 (MH^+, $C_{40}H_{30}N_2O_3H$ requires 587.23292).

5.3 References

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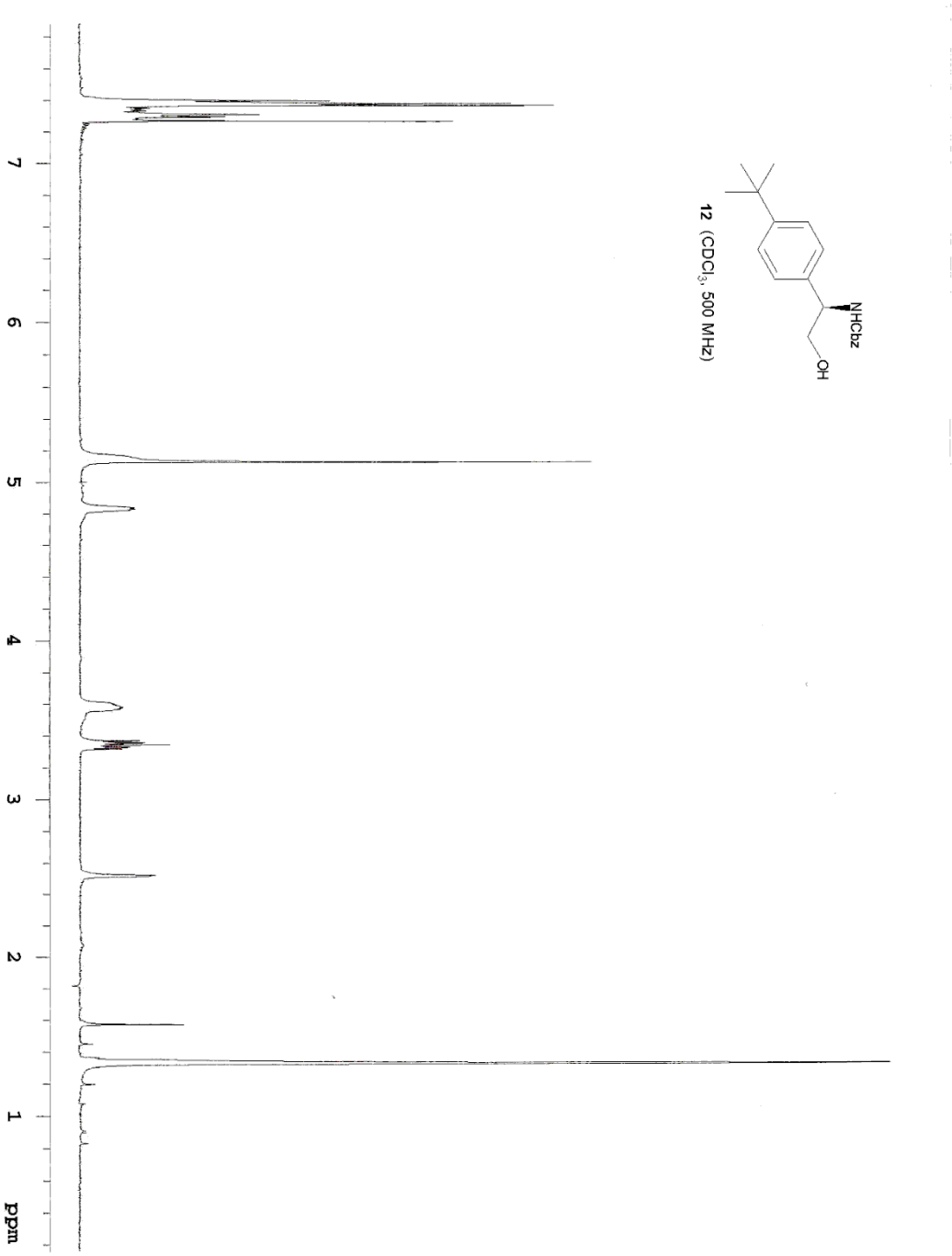
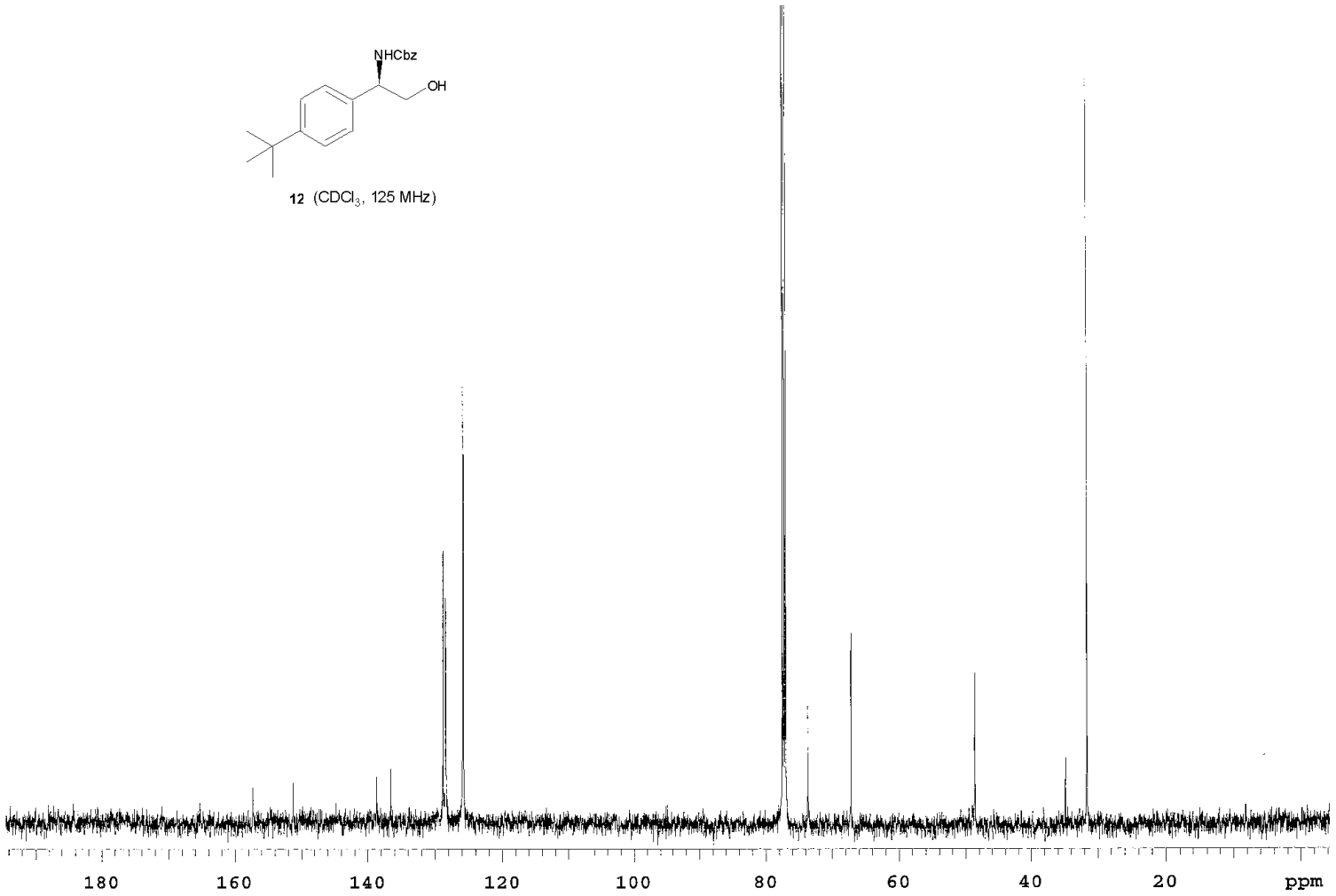
5.4 Selected NMR Spectra and HPLC Traces





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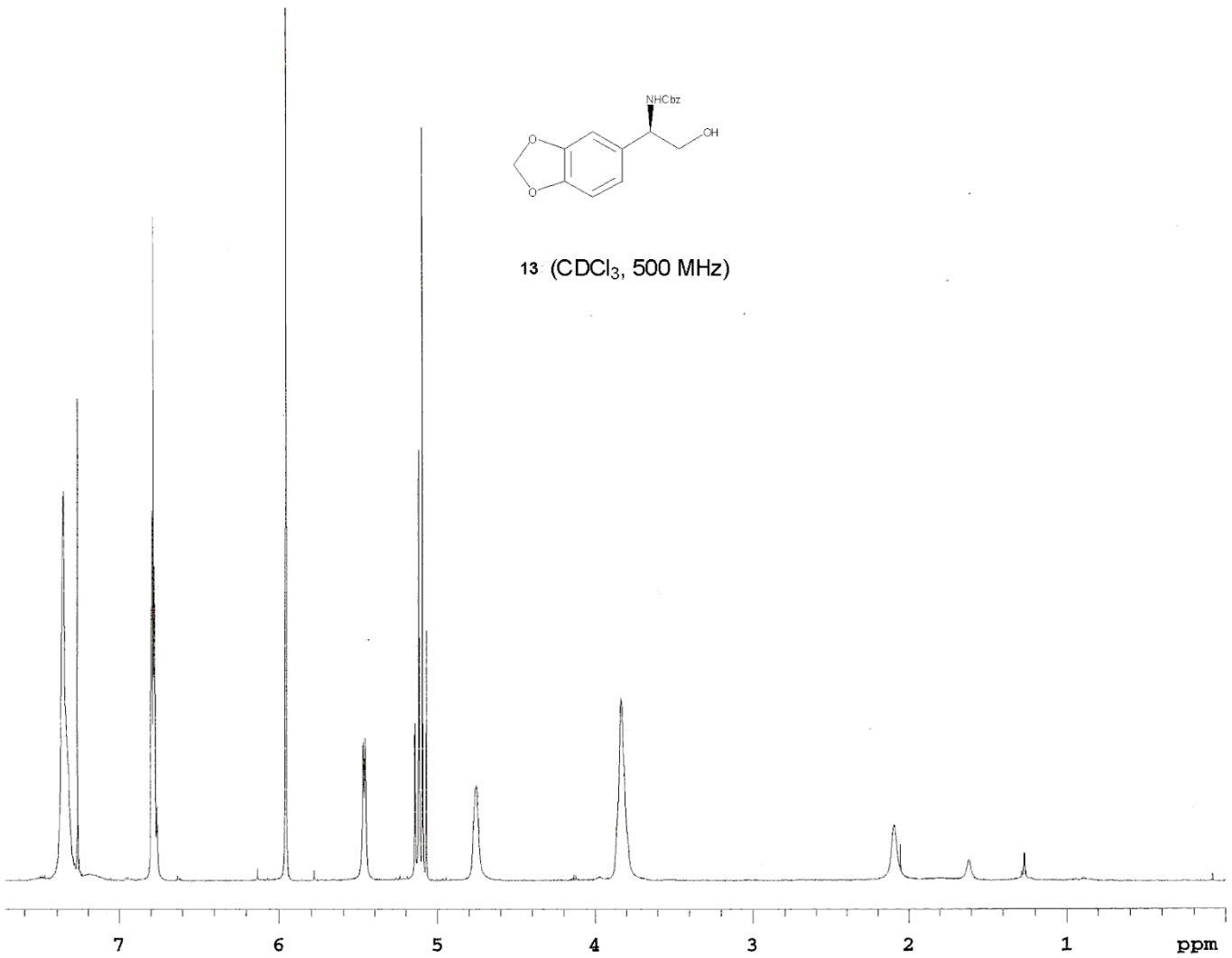
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4
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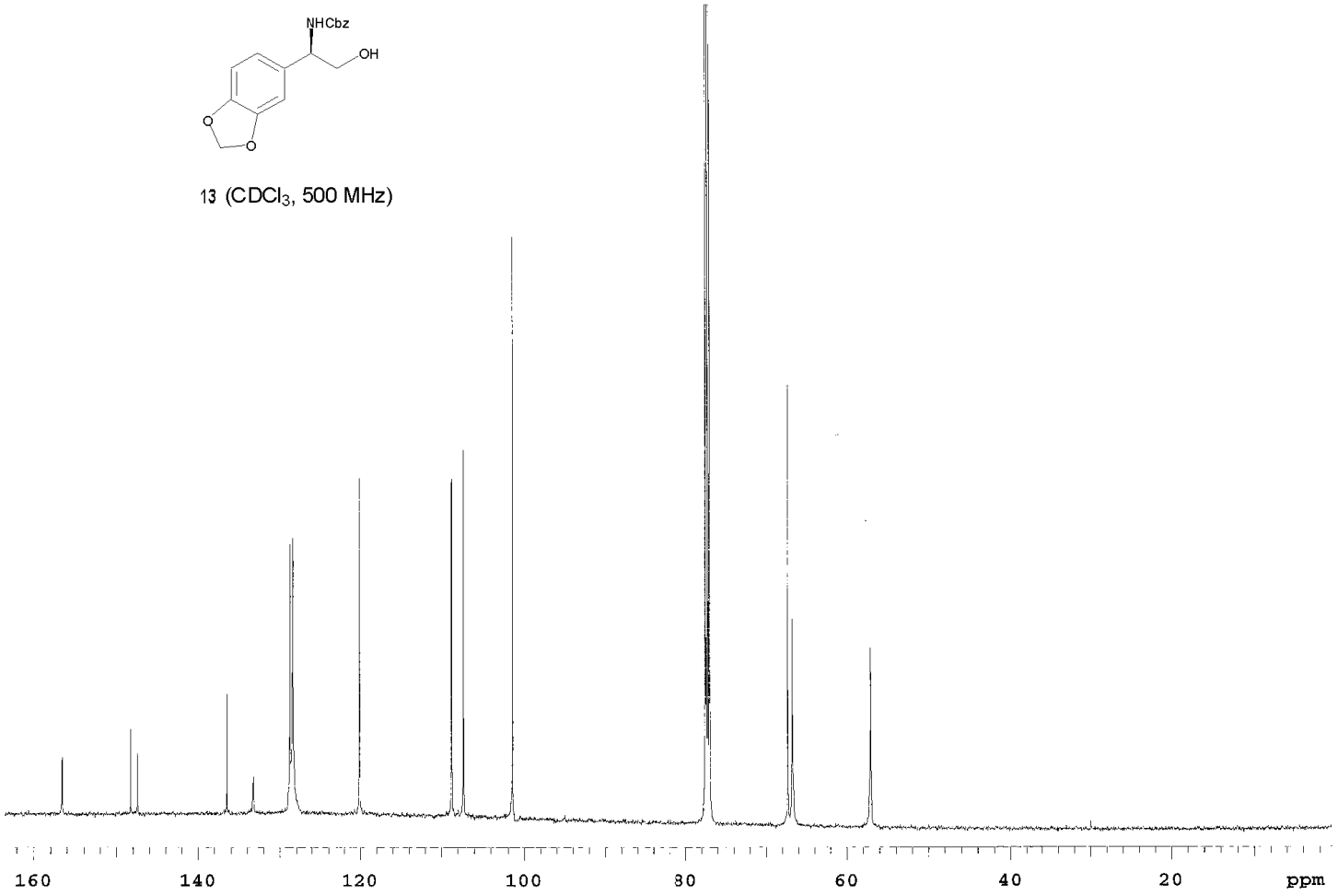
1
ppm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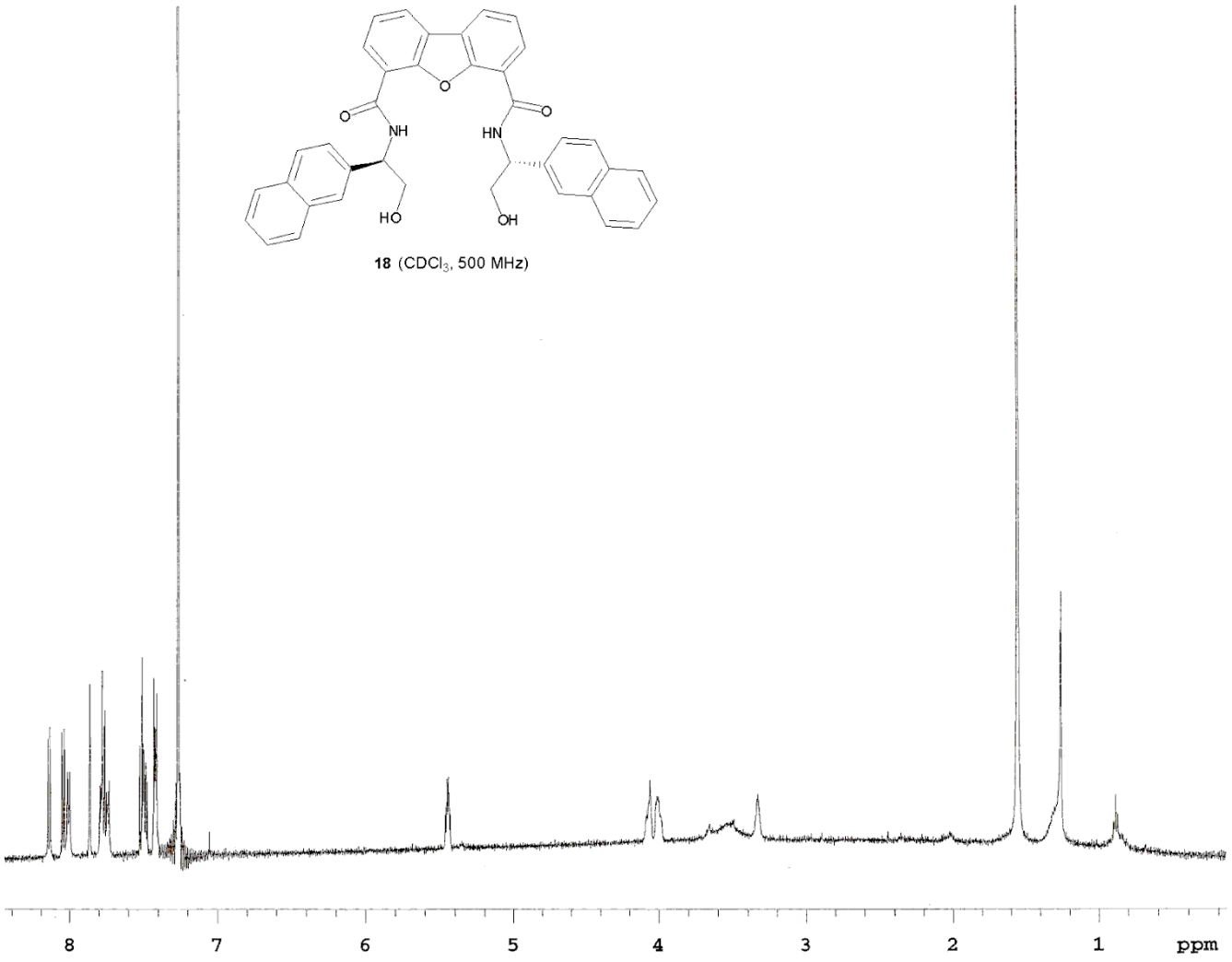
60
40
20
ppm



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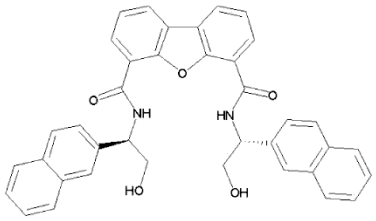

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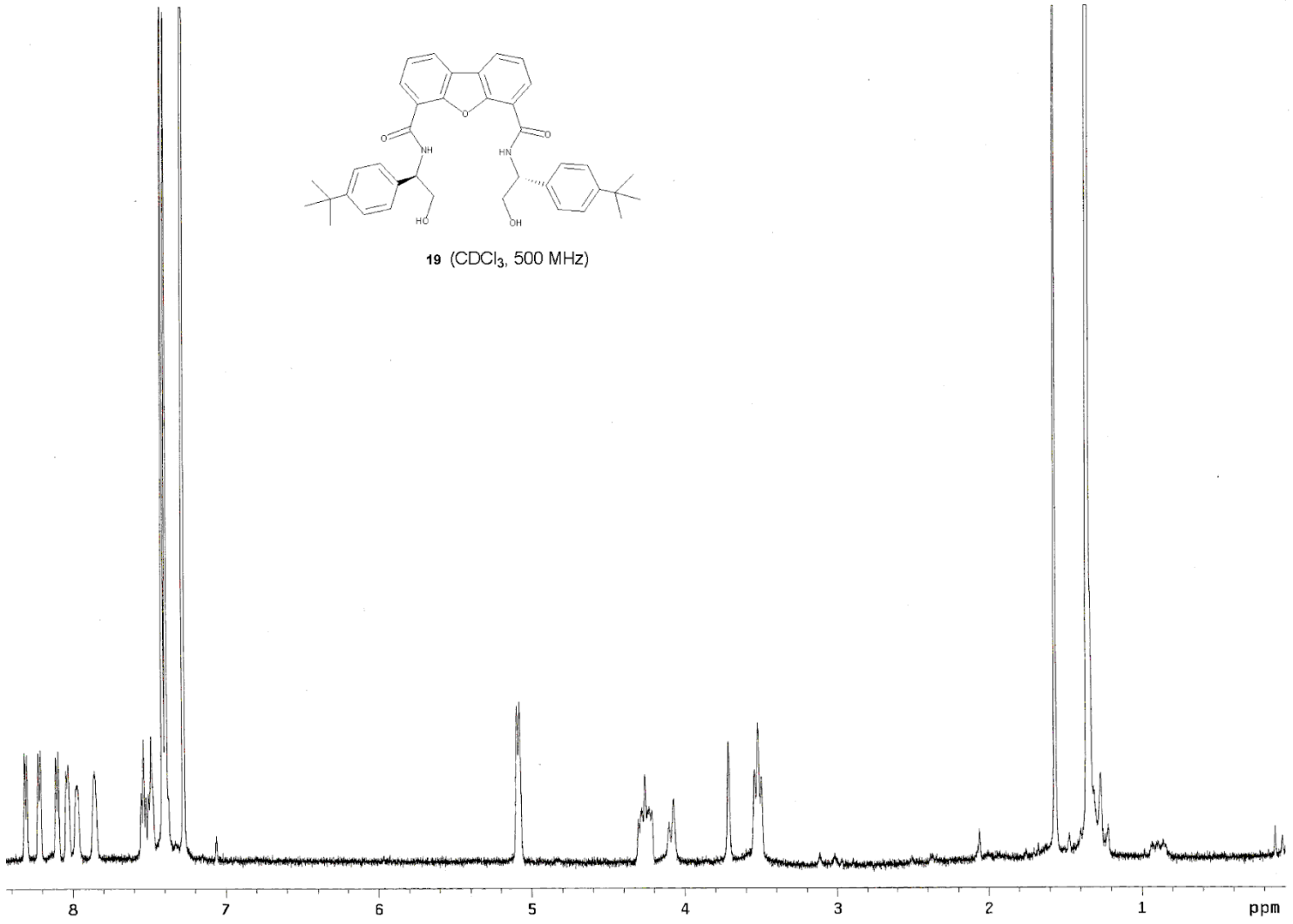

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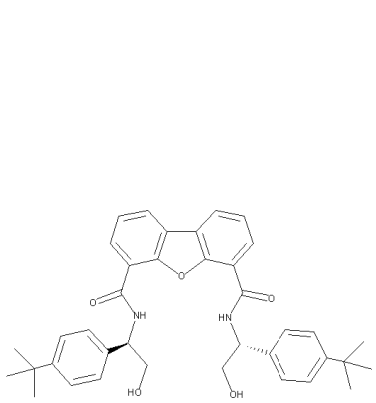

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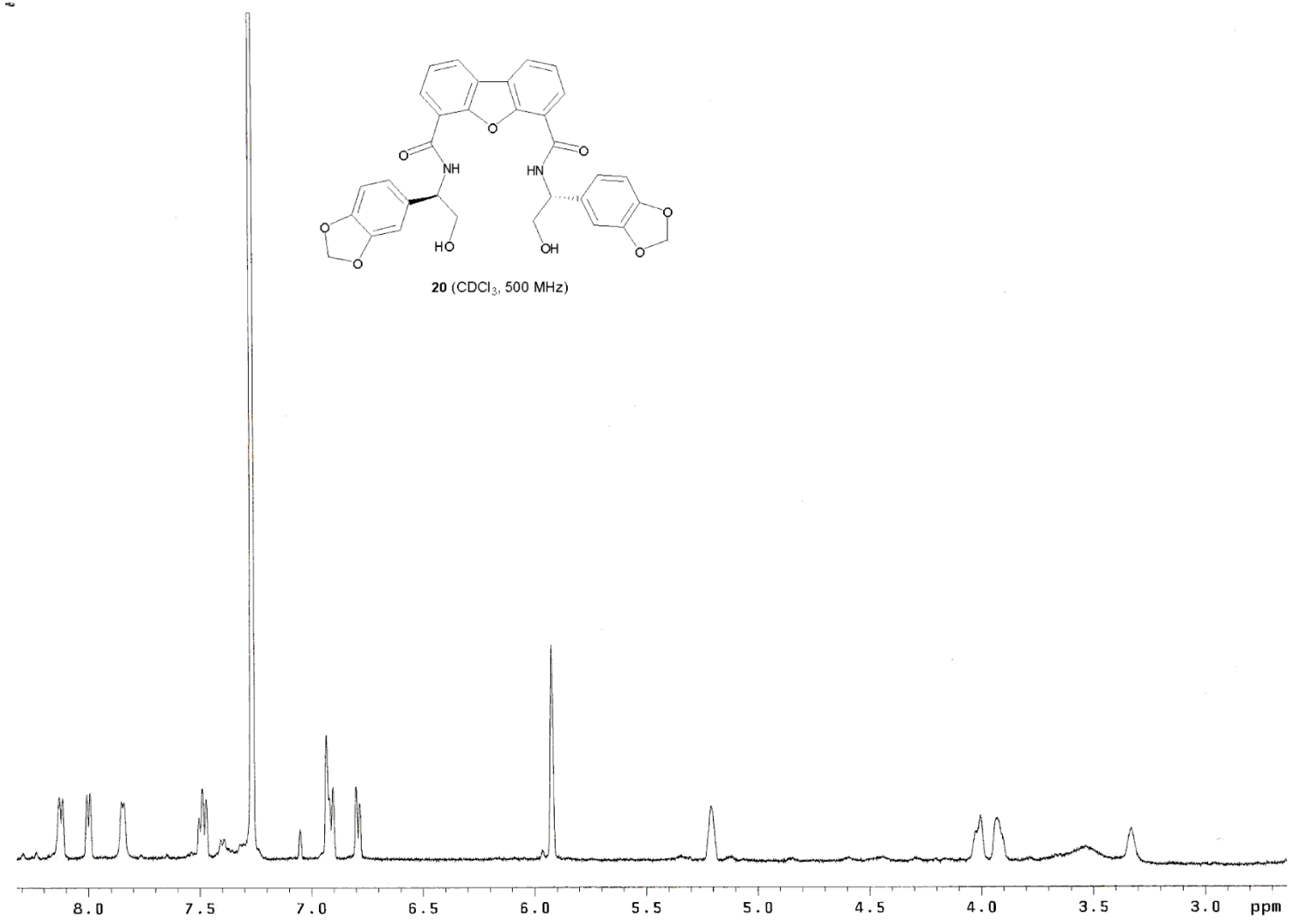
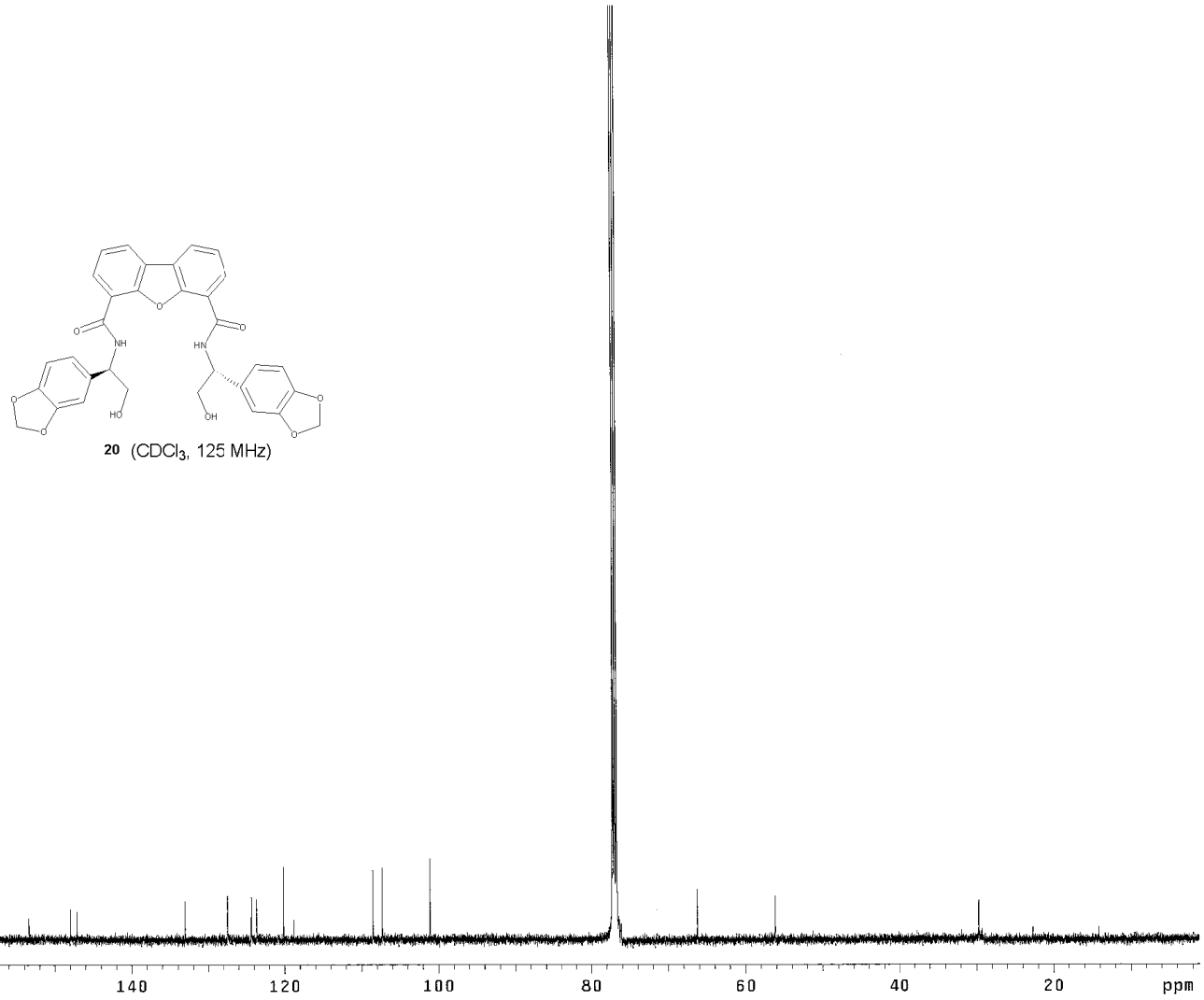
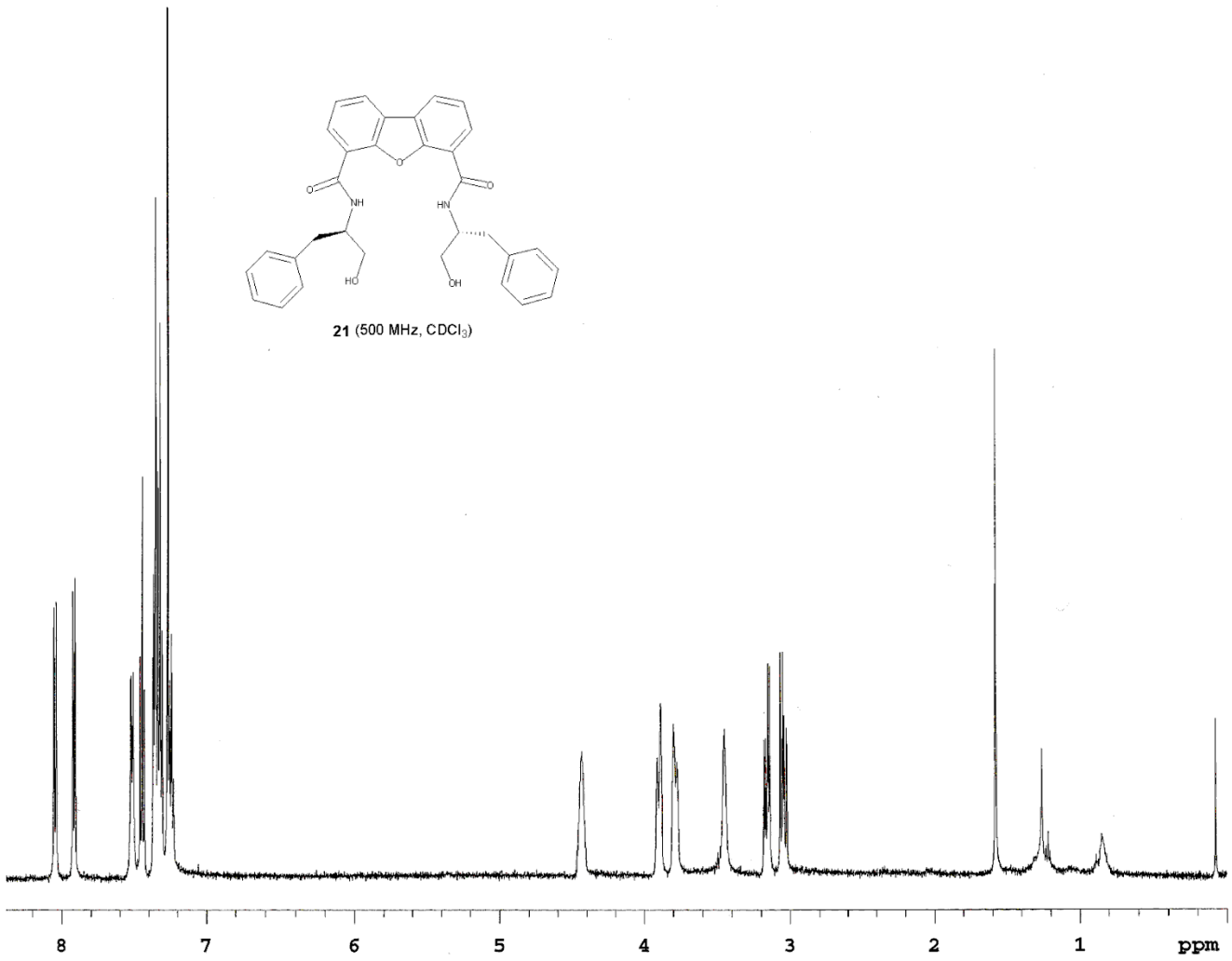


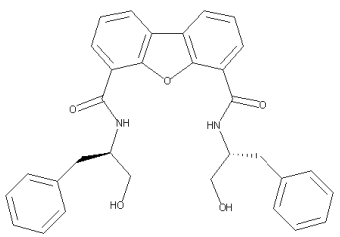
20 ($CDCl_3$, 500 MHz)



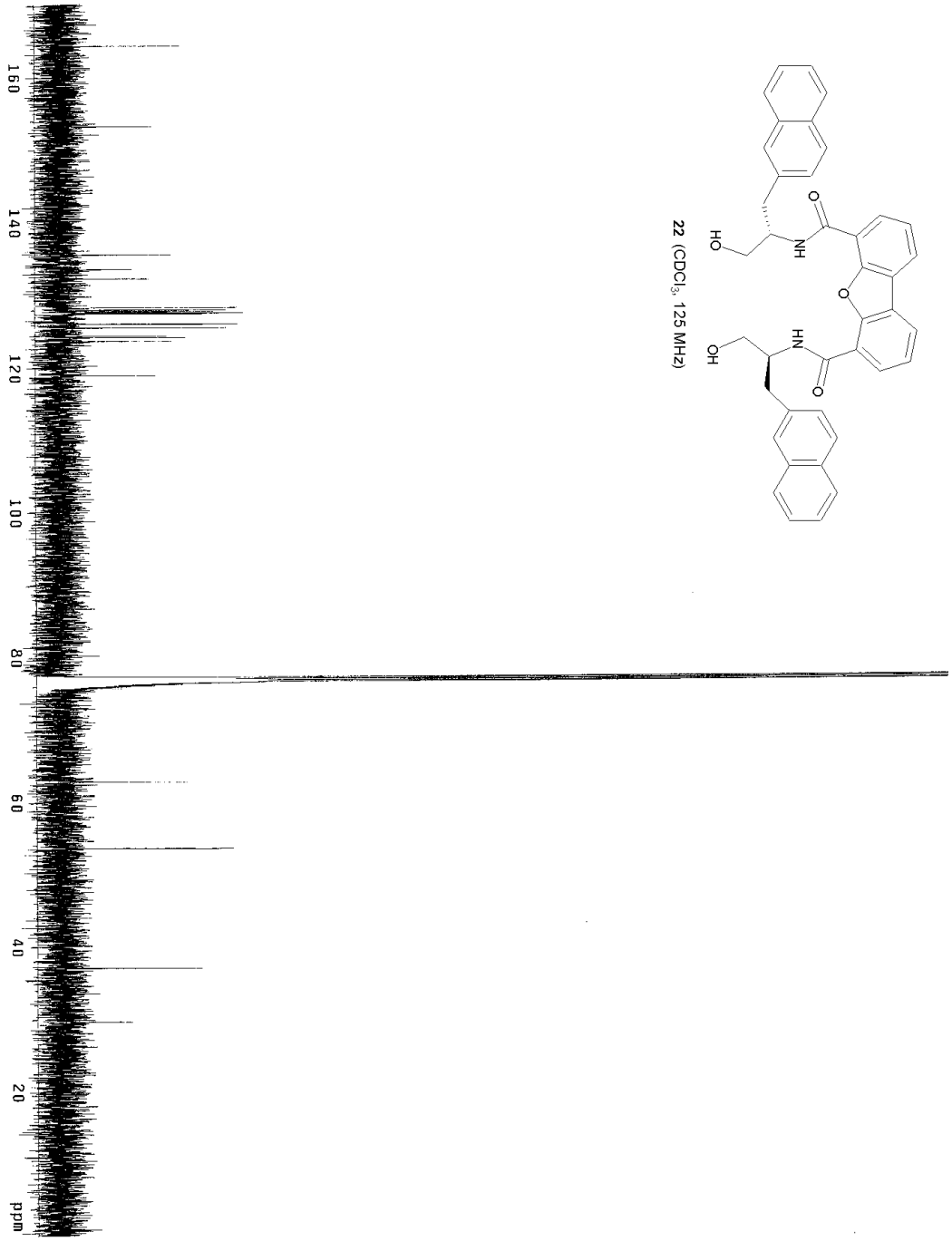
20 ($CDCl_3$, 125 MHz)



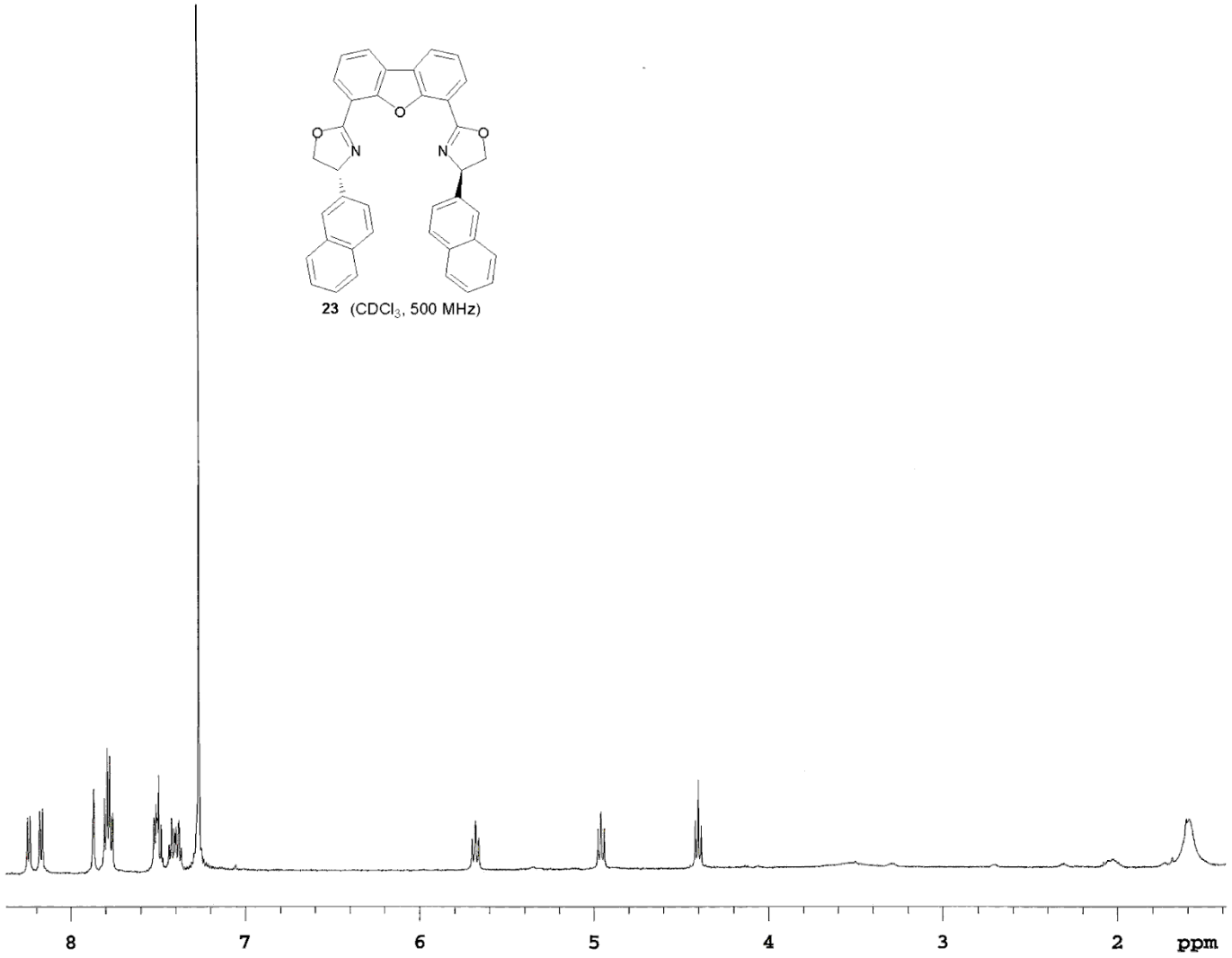
21 (500 MHz, $CDCl_3$)



21 ($CDCl_3$, 125 MHz)



22 ($CDCl_3$, 125 MHz)

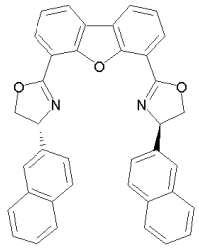


23 ($CDCl_3$, 500 MHz)

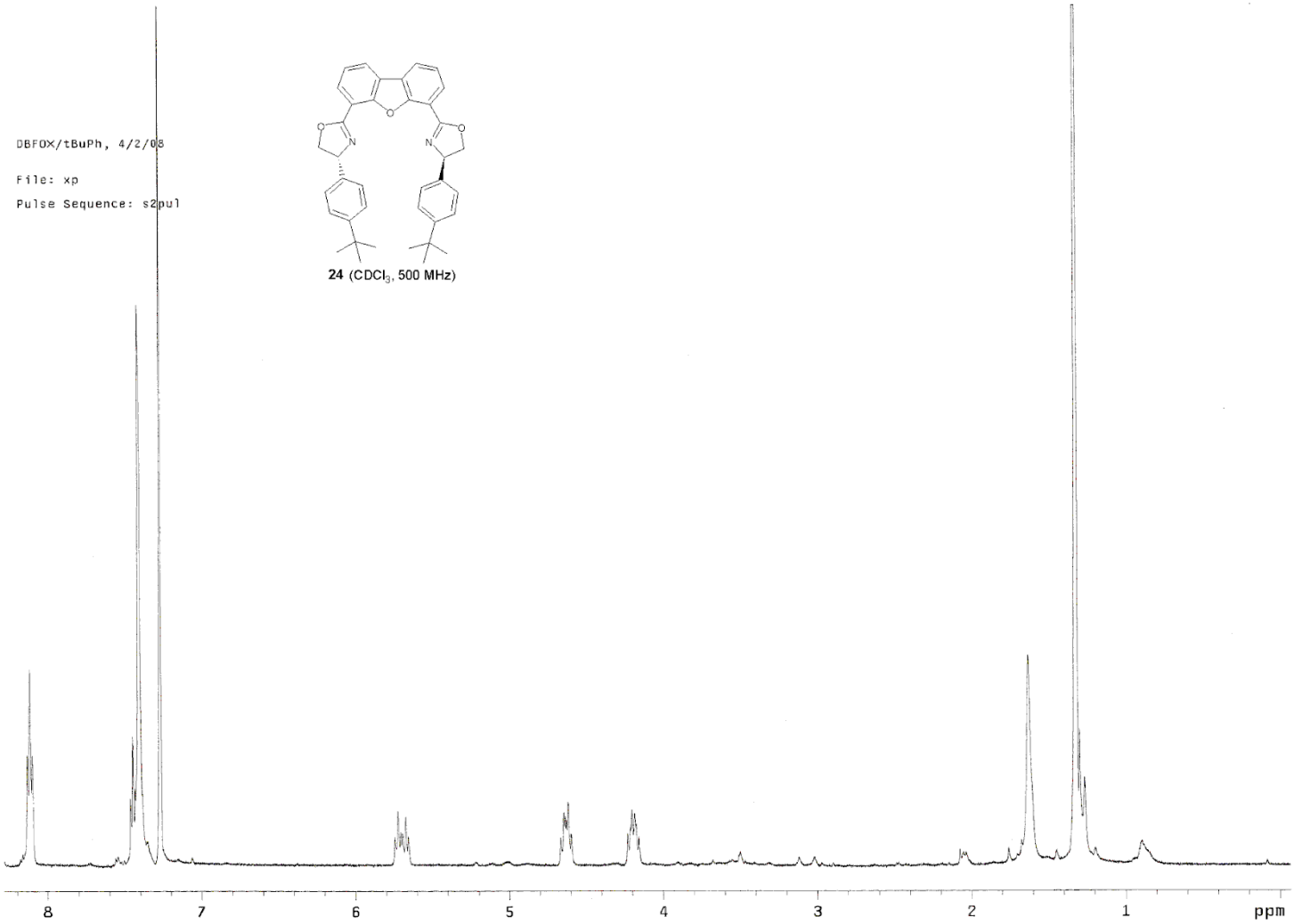
DBFOX/Naph

File: xp

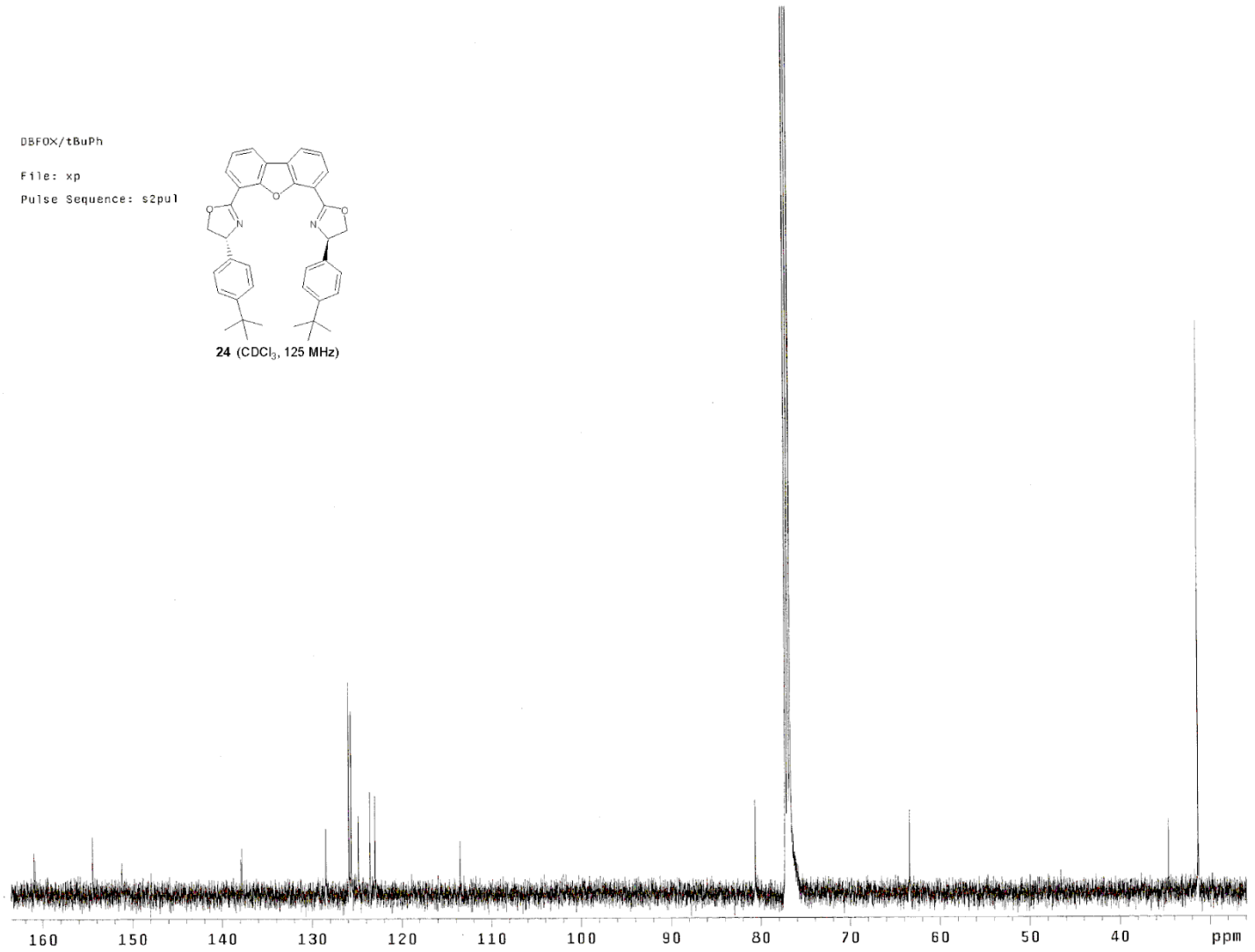
Pulse Sequence: s2pul

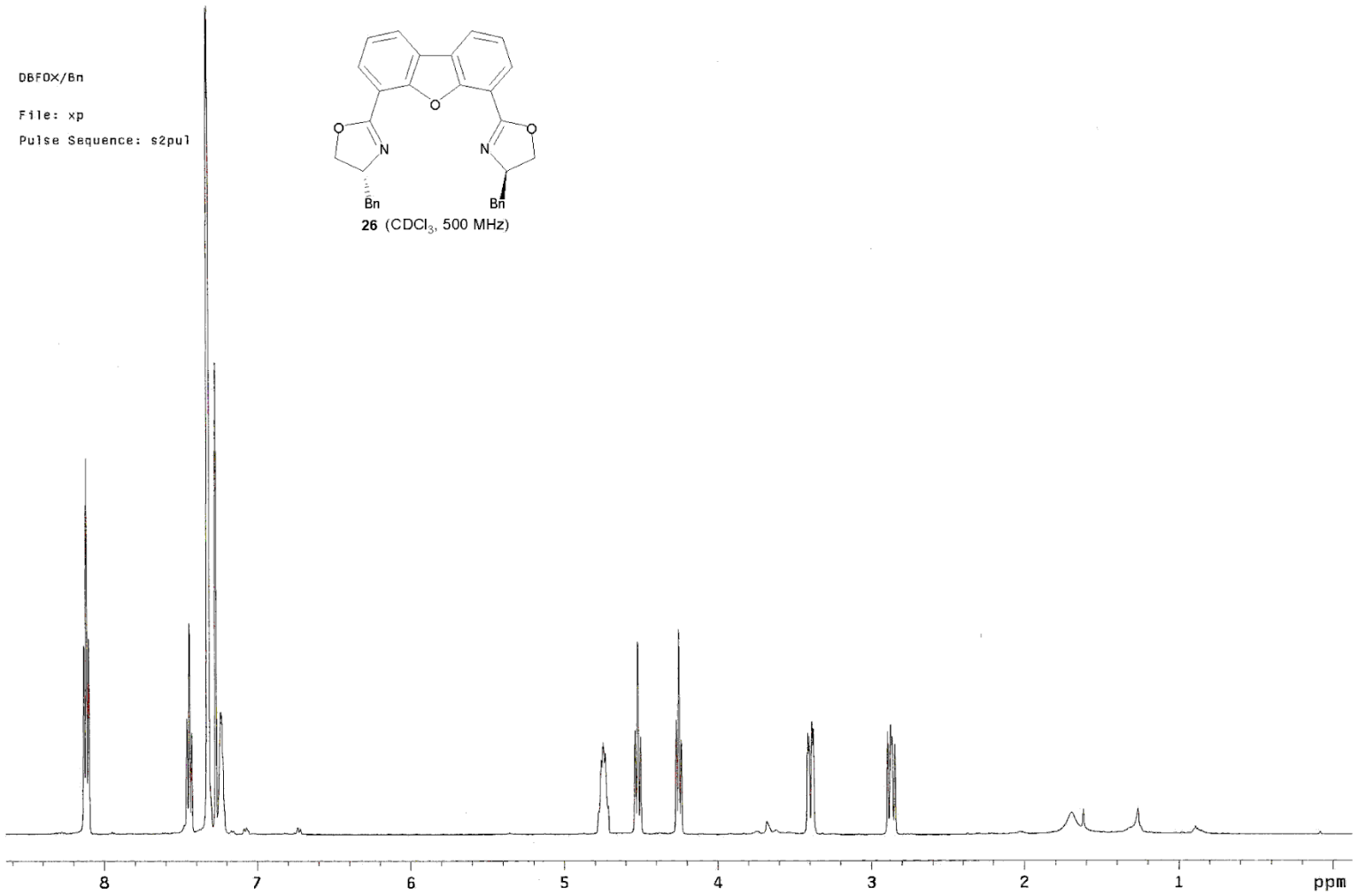


23 ($CDCl_3$, 125 MHz)



24 ($CDCl_3$, 500 MHz)


DBFOX/tBuPh
File: xp
Pulse Sequence: s2pul
24 (CDCl3, 125 MHz)
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

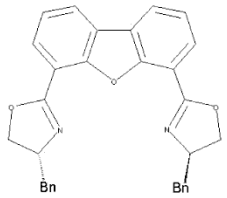


26 ($CDCl_3$, 500 MHz)

DBFOX/Bn

File: xp

Pulse Sequence: s2pul

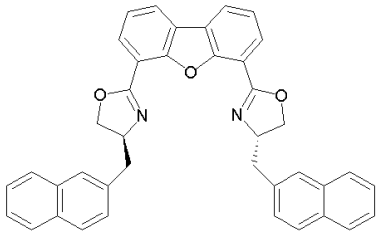


26 ($CDCl_3$, 500 MHz)

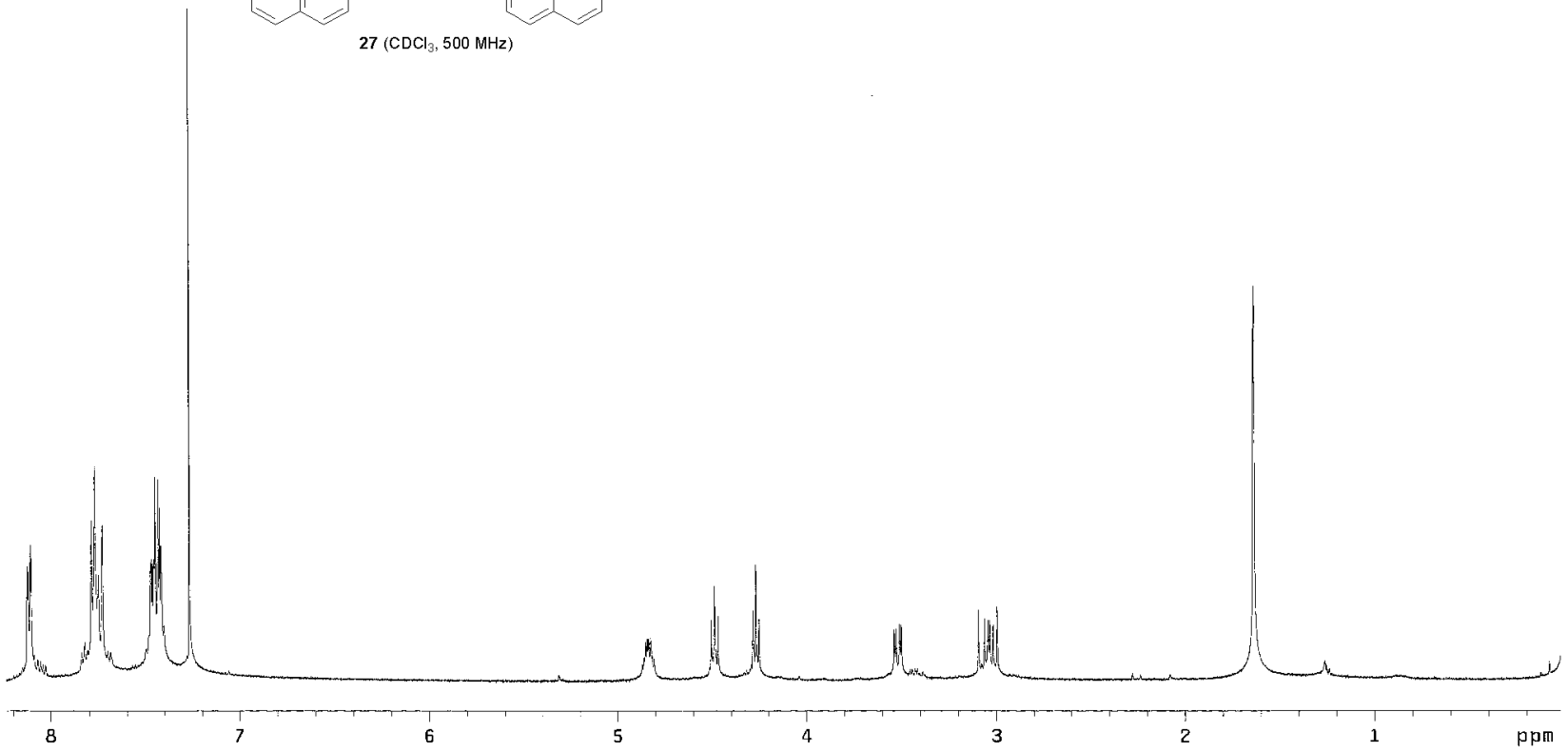
DBFOX/MeNaph

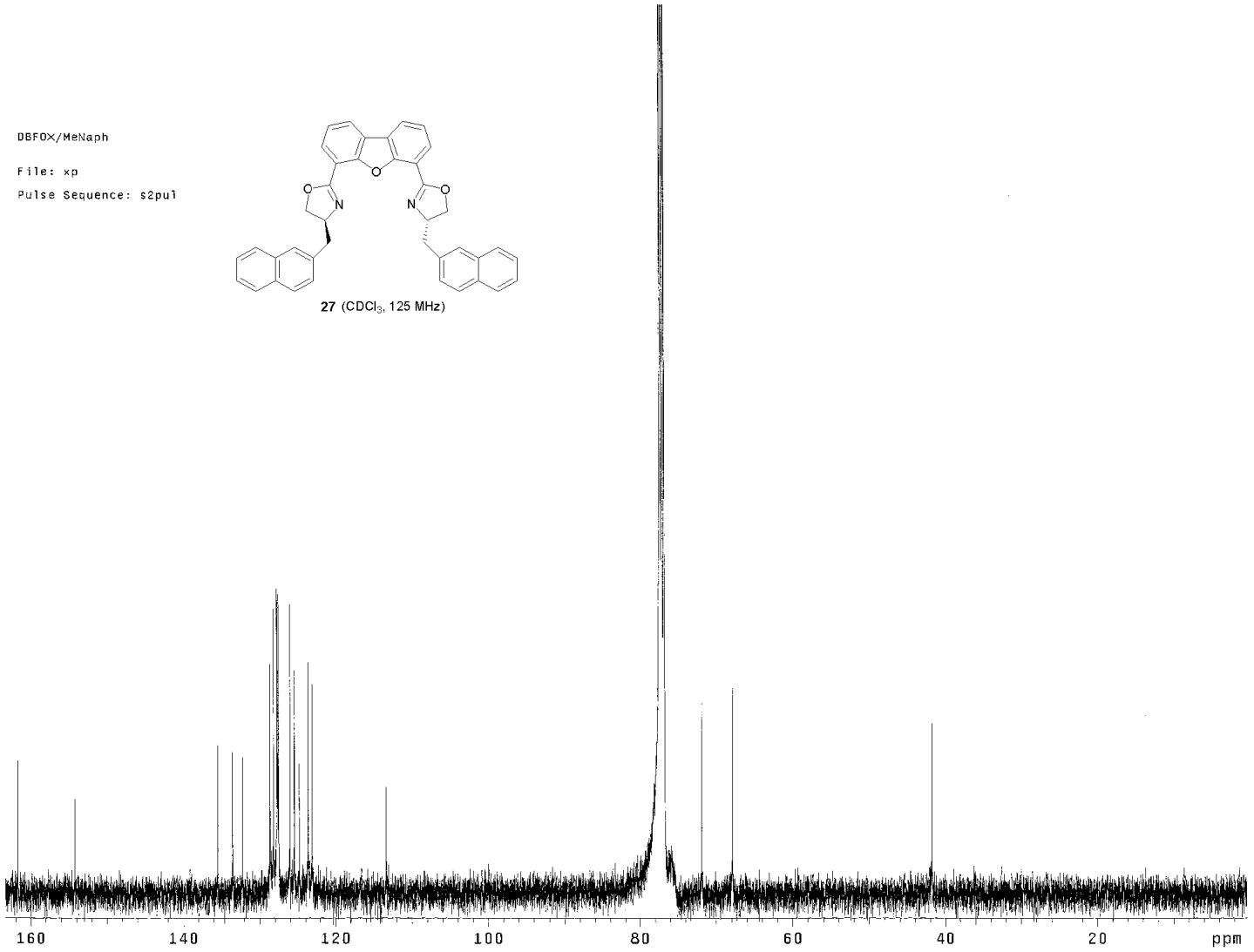
File: xp

Pulse Sequence: s2pul



27 ($CDCl_3$, 500 MHz)



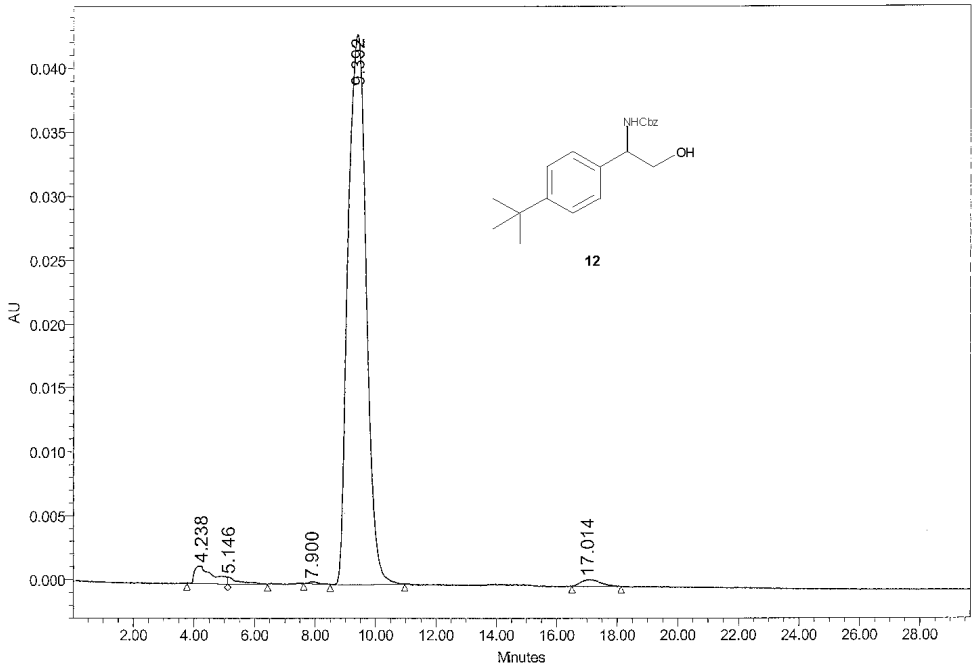


27 ($CDCl_3$, 125 MHz)

Reported by User: System Project Name: Chiral

SAMPLE INFORMATION

Sample Name:	SGC-SAA5-6/13	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	6/13/2006 5:31:35 PM
Vial:	1	Acq. Method Set:	Chiral AA
Injection #:	4	Date Processed:	6/13/2006 6:02:21 PM
Injection Volume:	25.00 ul	Processing Method:	Chiral
Run Time:	40.0 Minutes	Channel Name:	Extract 254.0
Sample Set Name:		Proc. Chnl. Descr.:	PDA 254.0 nm



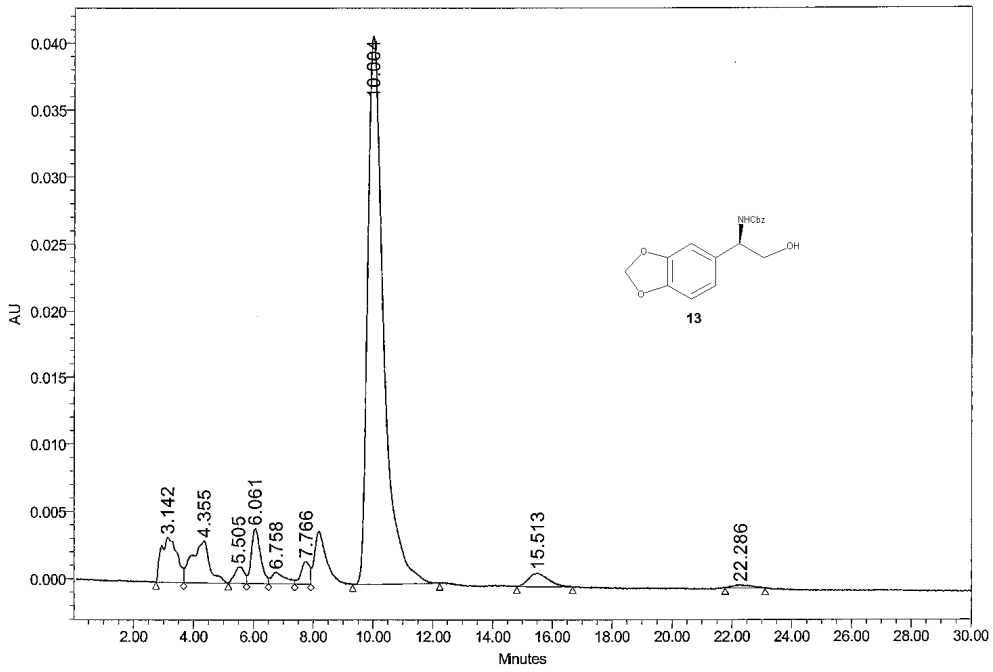
	RT	Area	% Area	Inj Vol (ul)
1	4.238	58362	3.05	25.00
2	5.146	14292	0.75	25.00
3	7.900	4114	0.22	25.00
4	9.392	1809836	94.72	25.00
5	17.014	24024	1.26	25.00

Report Method: Chiral Printed 12:22:09 PM 3/19/2008 Page: 1 of 1

Reported by User: System Project Name: Chiral

SAMPLE INFORMATION

Sample Name:	SGC-Pip2-7/14	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	7/14/2006 2:18:16 PM
Vial:	1	Acq. Method Set:	Chiral AA
Injection #:	2	Date Processed:	7/14/2006 3:38:25 PM
Injection Volume:	20.00 ul	Processing Method:	Chiral
Run Time:	30.0 Minutes	Channel Name:	Extract 254.0
Sample Set Name:		Proc. Chnl. Descr.:	PDA 254.0 nm



	RT	Area	% Area
1	3.142	124090	6.21
2	4.355	128329	6.42
3	5.505	27892	1.40
4	6.061	86627	4.33
5	6.758	27752	1.39
6	7.766	33116	1.66

	RT	Area	% Area
7	10.004	1512768	75.69
8	15.513	47429	2.37
9	22.286	10720	0.54

Report Method: Chiral Printed 2:25:39 PM 3/25/2008 Page: 1 of 1

Empower software

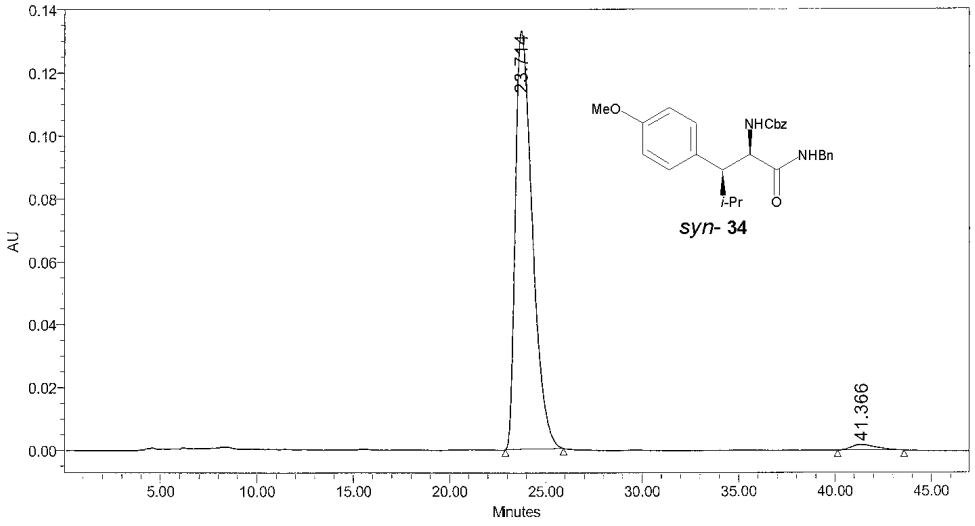
Default Individual Report

Reported by User: System

Project Name: Chiral

SAMPLE INFORMATION

Sample Name:	SGC-RCA-Naph-1b	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	4/24/2007 8:10:10 PM
Vial:	1	Acq. Method Set:	Chiral Aldol
Injection #:	4	Date Processed:	4/24/2007 9:04:03 PM
Injection Volume:	20.00 ul	Processing Method:	Chiral Aldol
Run Time:	50.0 Minutes	Channel Name:	Wvln Ch2
Sample Set Name:		Proc. Chnl. Descr.:	PDA 254.0 nm



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Peak Results

	Name	RT	Area	Height	%Area
1		23.714	8196996	132826	98.16
2		41.366	153877	1748	1.84

Empower software

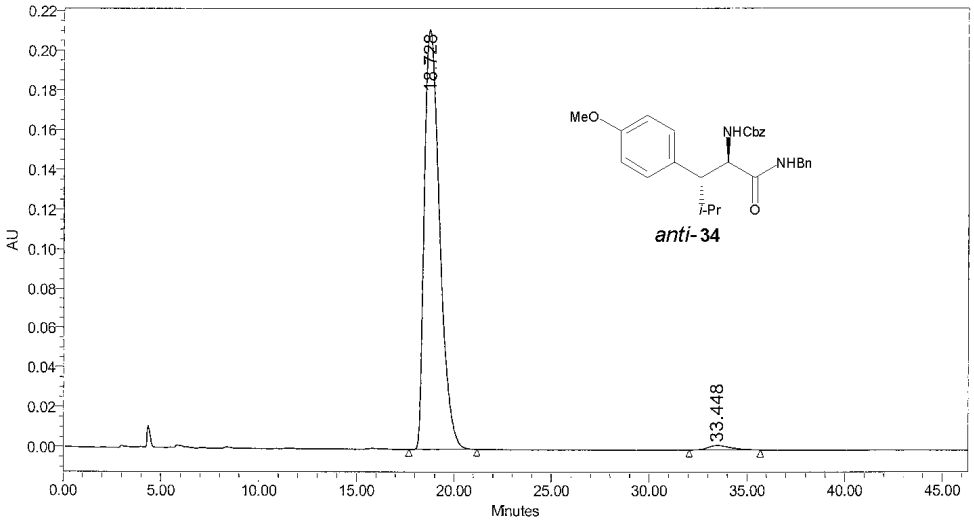
Default Individual Report

Reported by User: System

Project Name: Chiral

SAMPLE INFORMATION

Sample Name:	SGC-RCA-Naph-2	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	4/26/2007 9:28:34 AM
Vial:	1	Acq. Method Set:	Chiral Aldol
Injection #:	1	Date Processed:	4/26/2007 10:17:17 AM
Injection Volume:	20.00 ul	Processing Method:	Chiral Aldol
Run Time:	50.0 Minutes	Channel Name:	Wvln Ch2
Sample Set Name:		Proc. Chnl. Descr.:	PDA 254.0 nm



Peak Results

	Name	RT	Area	Height	% Area
1		18.728	11548383	211744	98.37
2		33.448	190790	2316	1.63

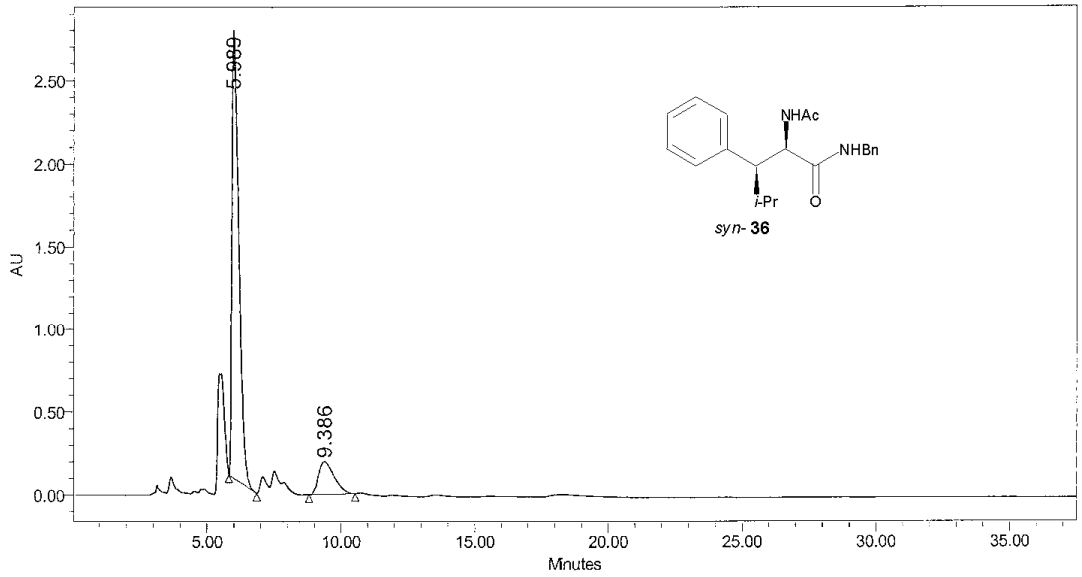
Default Individual Report

Reported by User: System

Project Name: Chiral

SAMPLE INFORMATION

Sample Name:	SGC-RCA-Rerun8	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	4/21/2008 12:52:32 PM
Vial:	1	Acq. Method Set:	Chiral Aldol
Injection #:	2	Date Processed:	4/22/2008 10:46:12 AM
Injection Volume:	20.00 ul	Processing Method:	Chiral Aldol
Run Time:	40.0 Minutes	Channel Name:	Wvln Ch1
Sample Set Name:		Proc. Chnl. Descr.:	PDA 235.0 nm



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Peak Results

	RT	Area	Height	% Area
1	5.989	48399762	2710493	85.77
2	9.386	8028889	197351	14.23

Empower software

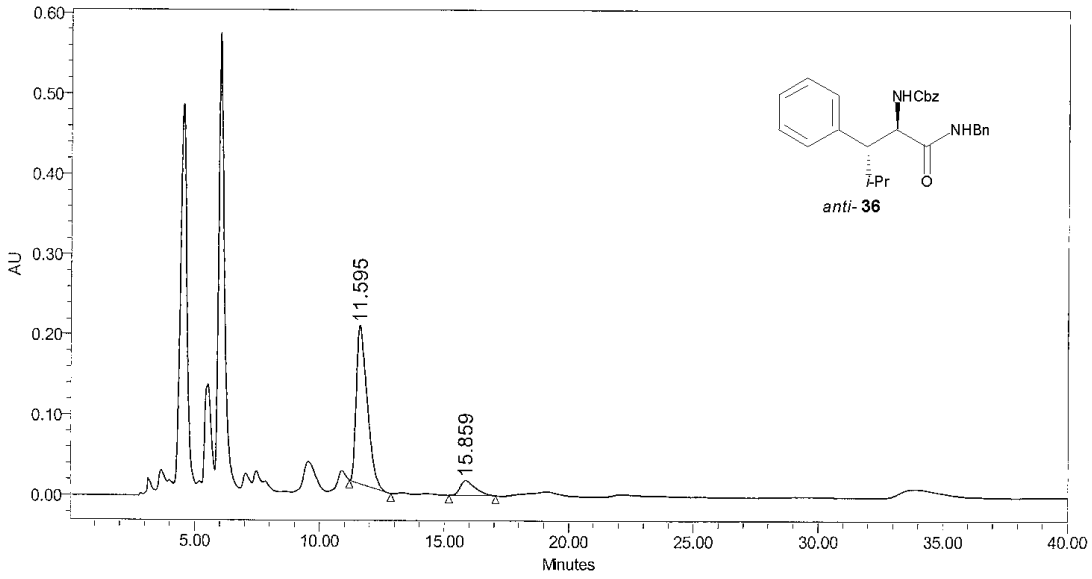
Default Individual Report

Reported by User: System

Project Name: Chiral

SAMPLE INFORMATION

Sample Name:	SGC-RCA-Rerun14	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	4/29/2008 2:23:58 PM
Vial:	1	Acq. Method Set:	Chiral Aldol
Injection #:	2	Date Processed:	4/29/2008 5:34:34 PM
Injection Volume:	20.00 ul	Processing Method:	Chiral Aldol
Run Time:	40.0 Minutes	Channel Name:	Wvln Ch1
Sample Set Name:		Proc. Chnl. Descr.:	PDA 235.0 nm



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Peak Results

	RT	Area	Height	% Area
1	11.595	5958845	196432	88.44
2	15.859	779068	18448	11.56

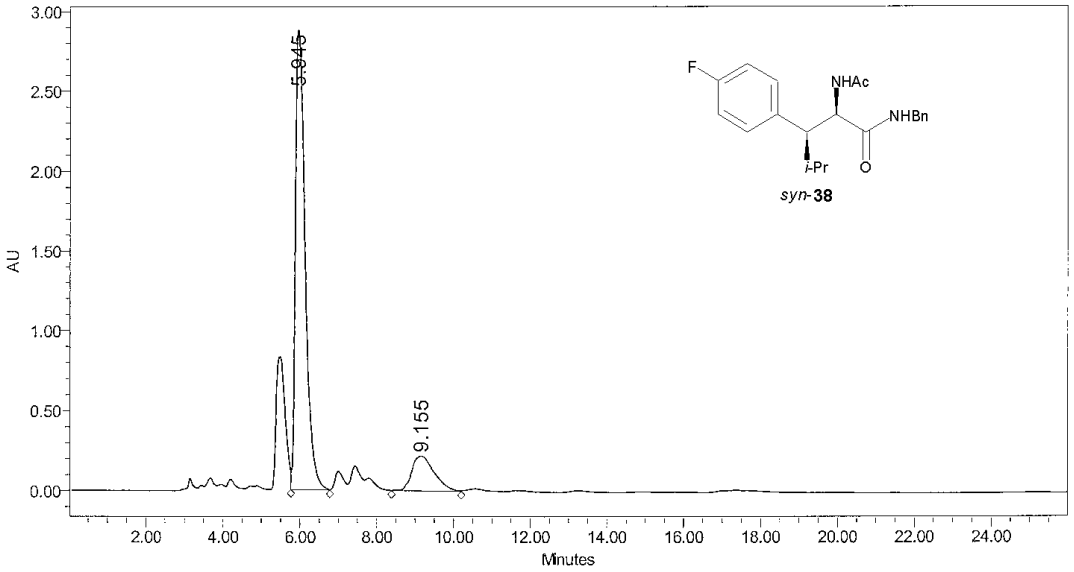
Empower software

Default Individual Report

Reported by User: System Project Name: Chiral

SAMPLE INFORMATION

Sample Name:	SGC-RCA-Rerun2	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	4/17/2008 6:03:16 PM
Vial:	1	Acq. Method Set:	Chiral Aldol
Injection #:	2	Date Processed:	4/19/2008 2:43:33 PM
Injection Volume:	20.00 ul	Processing Method:	Chiral Aldol
Run Time:	30.0 Minutes	Channel Name:	Wvln Ch1
Sample Set Name:		Proc. Chnl. Descr.:	PDA 235.0 nm



Peak Results

	RT	Area	Height	% Area
1	5.945	50520408	2883259	84.82
2	9.155	9039571	219435	15.18

Empower software

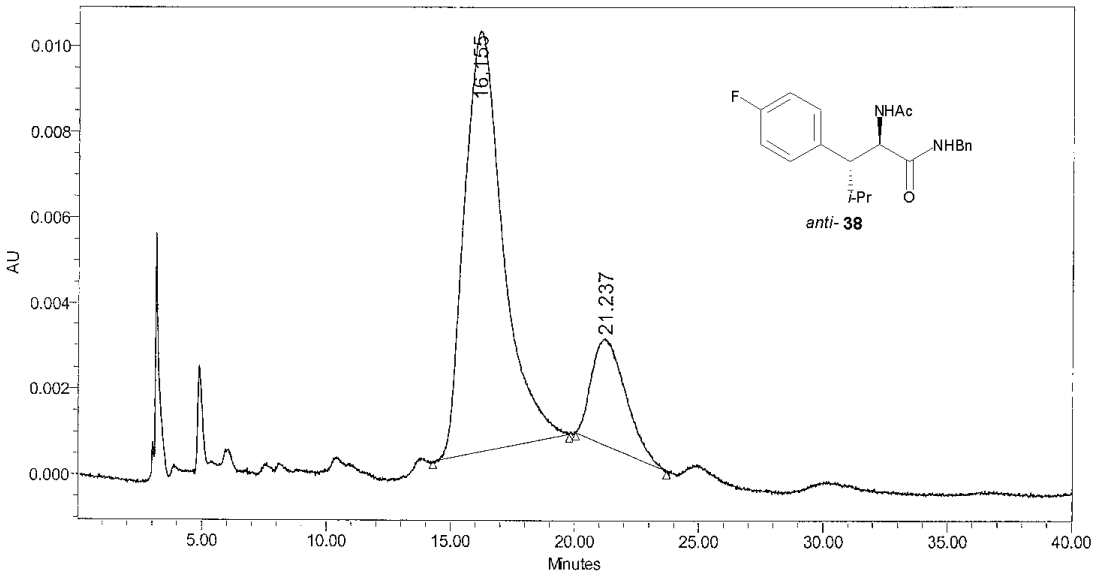
Default Individual Report

Reported by User: System

Project Name: Chiral

SAMPLE INFORMATION

Sample Name:	SGC-RCA-Rerun16b	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	5/6/2008 2:37:03 PM
Vial:	1	Acq. Method Set:	Chiral Aldol
Injection #:	4	Date Processed:	5/10/2008 3:17:41 PM
Injection Volume:	20.00 ul	Processing Method:	Chiral Aldol
Run Time:	40.0 Minutes	Channel Name:	Wvln Ch3
Sample Set Name:		Proc. Chnl. Descr.:	PDA 254.0 nm



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Peak Results

	RT	Area	Height	% Area
1	16.155	1059407	9815	81.73
2	21.237	236768	2469	18.27

EMPOWER software

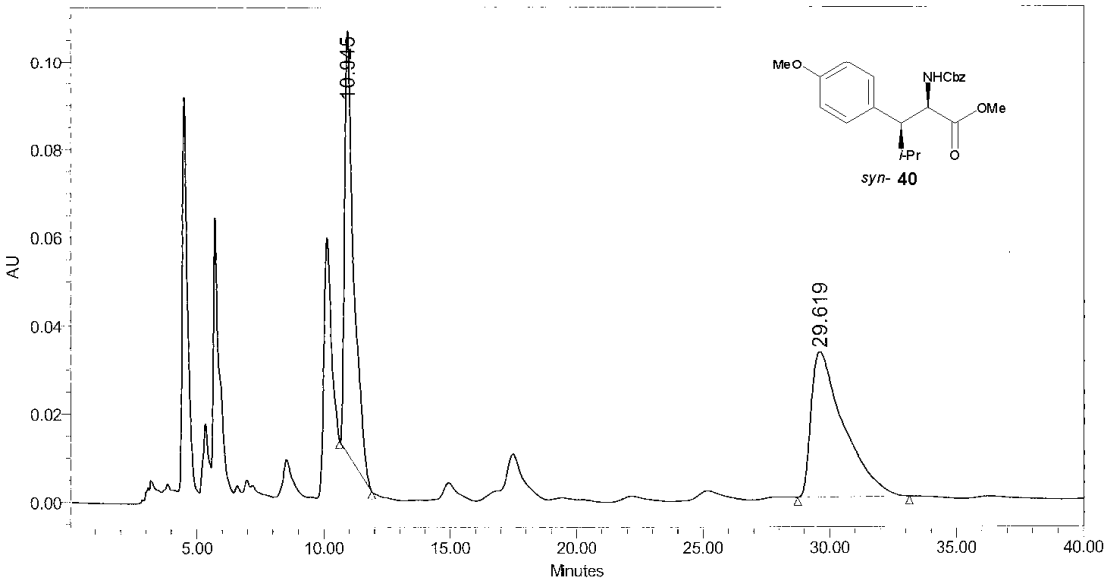
Default Individual Report

Reported by User: System

Project Name: Chiral

SAMPLE INFORMATION

Sample Name:	SGC-OMeOMe3	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	5/26/2008 5:18:07 PM
Vial:	1	Acq. Method Set:	Chiral Aldol
Injection #:	5	Date Processed:	5/27/2008 1:04:32 PM
Injection Volume:	20.00 ul	Processing Method:	Chiral Aldol
Run Time:	40.0 Minutes	Channel Name:	Wvln Ch4
Sample Set Name:		Proc. Chnl. Descr.:	PDA 235.0 nm



Peak Results

	RT	Area	Height	% Area
1	10.945	2383063	96093	44.79
2	29.619	2937827	32982	55.21

Empower software

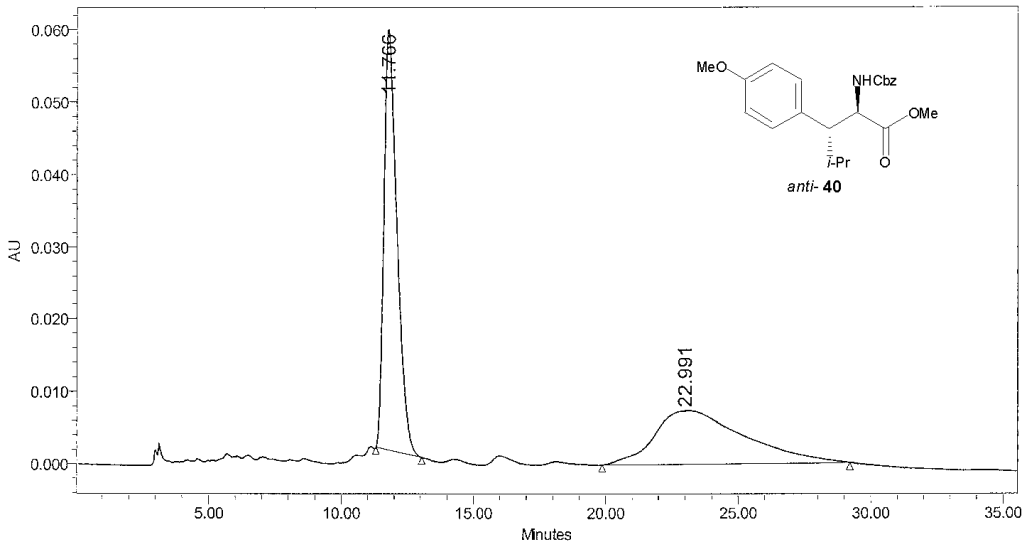
Default Individual Report

Reported by User: System

Project Name: Chiral

SAMPLE INFORMATION

Sample Name:	SGC-RCA-Rerun3b	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	4/25/2008 2:40:48 PM
Vial:	1	Acq. Method Set:	Chiral Aldol
Injection #:	2	Date Processed:	4/25/2008 8:50:56 PM
Injection Volume:	20.00 ul	Processing Method:	Chiral Aldol
Run Time:	40.0 Minutes	Channel Name:	Wvln Ch2
Sample Set Name:		Proc. Chnl. Descr.:	PDA 254.0 nm



Peak Results

	RT	Area	Height	% Area
1	11.766	2000995	58045	53.30
2	22.991	1752911	7437	46.70

Empower software

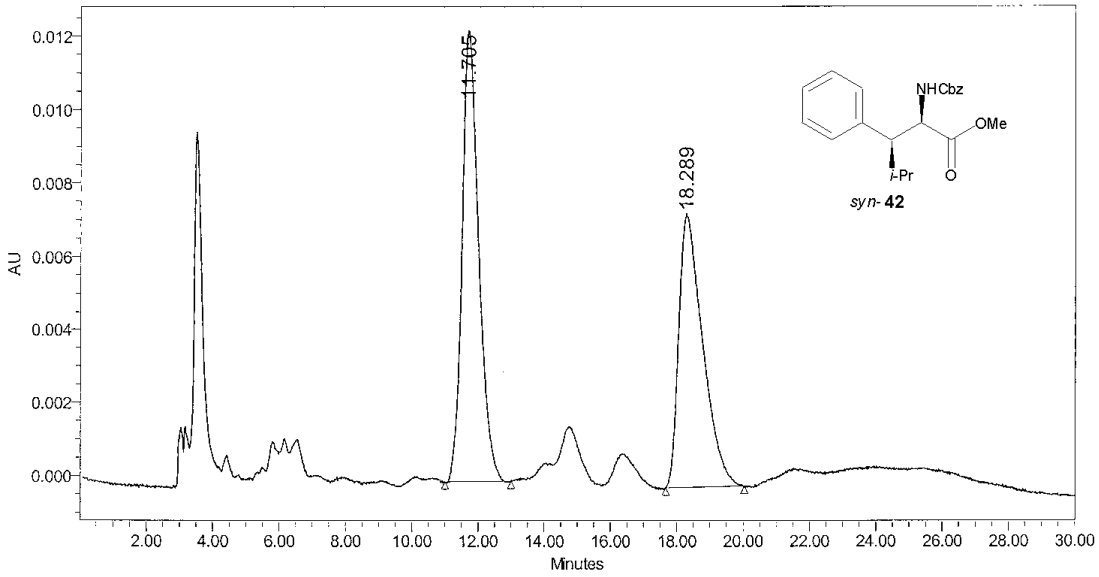
Default Individual Report

Reported by User: System

Project Name: Chiral

SAMPLE INFORMATION

Sample Name:	SGC-RCA-Rerun4	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	4/18/2008 4:54:53 PM
Vial:	1	Acq. Method Set:	Chiral Aldol
Injection #:	2	Date Processed:	4/19/2008 2:50:19 PM
Injection Volume:	20.00 ul	Processing Method:	Chiral Aldol
Run Time:	30.0 Minutes	Channel Name:	Wvln Ch1
Sample Set Name:		Proc. Chnl. Descr.:	PDA 235.0 nm



Peak Results

	RT	Area	Height	% Area
1	11.705	427213	12325	53.33
2	18.289	373931	7445	46.67

Empower software

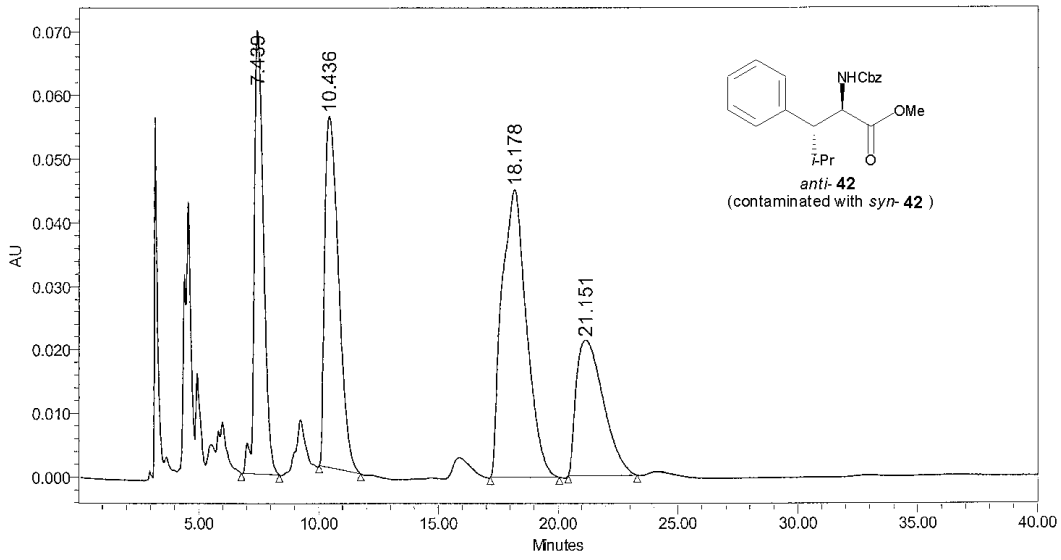
Default Individual Report

Reported by User: System

Project Name: Chiral

SAMPLE INFORMATION

Sample Name:	SGC-RCA-Rerun7	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	4/21/2008 11:40:26 AM
Vial:	1	Acq. Method Set:	Chiral Aldol
Injection #:	1	Date Processed:	4/22/2008 12:13:38 PM
Injection Volume:	20.00 ul	Processing Method:	Chiral Aldol
Run Time:	40.0 Minutes	Channel Name:	Wvln Ch4
Sample Set Name:		Proc. Chnl. Descr.:	PDA 254.0 nm



Peak Results

	RT	Area	Height	% Area
1	7.439	1846775	69713	20.61
2	10.436	2218681	55204	24.76
3	18.178	3224544	45287	35.99
4	21.151	1669943	21263	18.64

Empower software

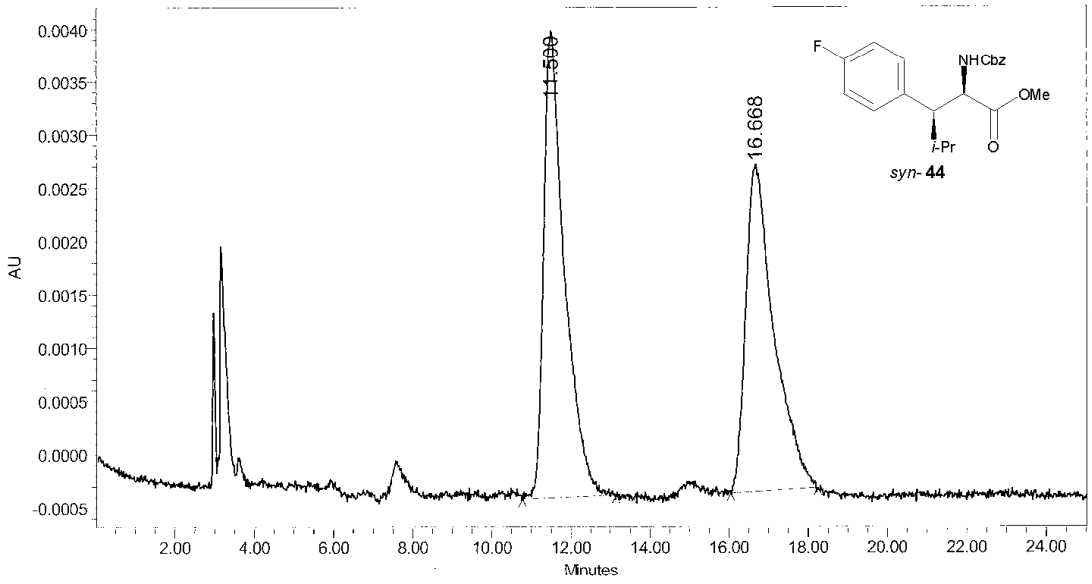
Default Individual Report

Reported by User: System

Project Name: Chiral

SAMPLE INFORMATION

Sample Name:	SGC-RCARerun25	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	5/20/2008 12:05:59 PM
Vial:	1	Acq. Method Set:	Chiral Aldol
Injection #:	2	Date Processed:	5/20/2008 12:45:06 PM
Injection Volume:	20.00 ul	Processing Method:	Chiral Aldol
Run Time:	25.0 Minutes	Channel Name:	Wvln Ch2
Sample Set Name:		Proc. Chnl. Descr.:	PDA 254.0 nm



Peak Results

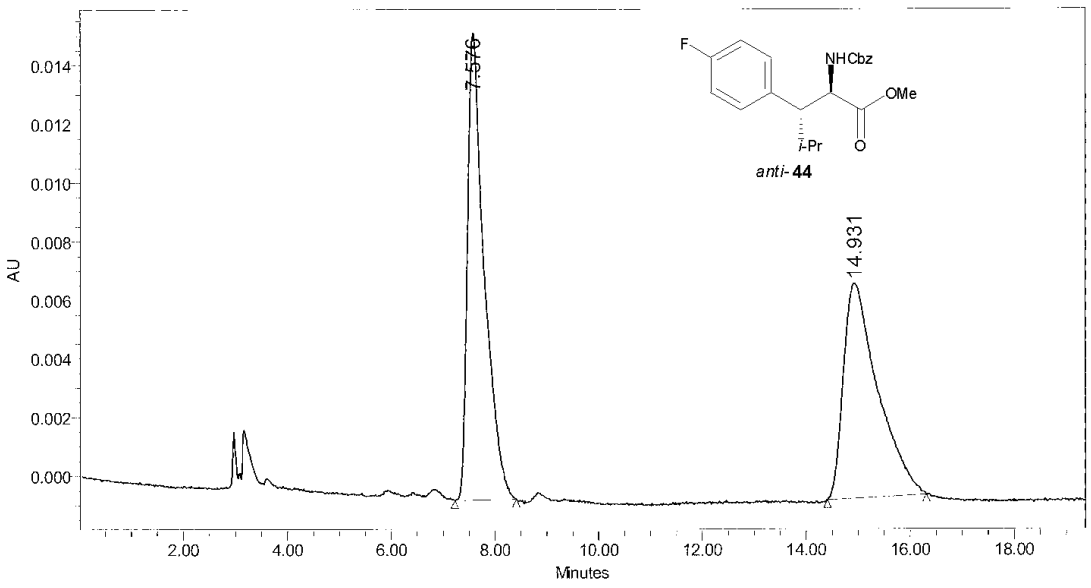
	RT	Area	Height	% Area
1	11.500	160877	4381	51.43
2	16.668	151954	3059	48.57

Reported by User: System

Project Name: Chiral

SAMPLE INFORMATION

Sample Name:	SGC-RCARerun24	Acquired By:	System
Sample Type:	Unknown	Date Acquired:	5/20/2008 11:06:02 AM
Vial:	1	Acq. Method Set:	Chiral Aldol
Injection #:	1	Date Processed:	5/20/2008 11:27:43 AM
Injection Volume:	20.00 ul	Processing Method:	Chiral Aldol
Run Time:	30.0 Minutes	Channel Name:	Wvln Ch2
Sample Set Name:		Proc. Chnl. Descr.:	PDA 254.0 nm



Peak Results

	RT	Area	Height	% Area
1	7.576	356554	15925	51.45
2	14.931	336474	7343	48.55