博士論文

希土類/Na 異種 2 核金属触媒による β-アミノ 3 級アルコールの迅速不斉合成と医薬品合成への応用

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Abbreviations

Ac	acetyl	h	hour(s)
API	active pharmaceutical ingredient	HOBt	1-hydroxybenzotriazole
aq.	aqueous	HPLC	high pressure liquid chromatography
Bn	benzyl	*i*	iso-
Boc	tertiary-butoxycarbonyl	m	meter(s), milli
Bu	butyl	Me	methyl
°C	degree celsius	mol	mole(s)
CD	circular dichroism	MTBE	*tert*-butyl methyl ether
CPME	cyclopentyl methyl ether	MWNT	multiwalled carbon nanotube
dba	dibenzylideneacetone	*n*	normal-
de	diastereomeric excess	Ph	phenyl
DIEA	*N,N*-diisopropylethylamine	^{i}Pr	iso-propyl
DMA	*N,N*-dimethylacetamide	*R*	rectus
DME	dimethoxyethane	*S*	sinister
DMF	*N,N*-dimethylformamide	RE	rare earth
Dr	diastereomeric retio	*t*	tertiary-
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide	Tf	trifluoromethanesulfonyl
		THF	tetrahydrofuran
ee	enantiomeric excess	THP	tetrahydropyran
eq.	equivalent	TIPS	triisopropylsilyl
Et	ethyl	TON	turnover number
g	gram(s)	μ	micro

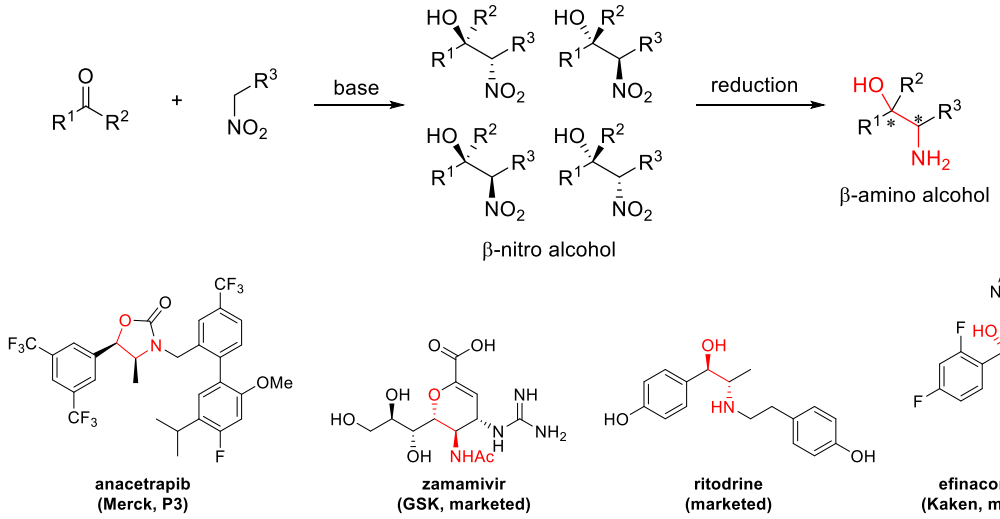
第 1 章

序論

1－1　触媒的不斉ニトロアルドール反応

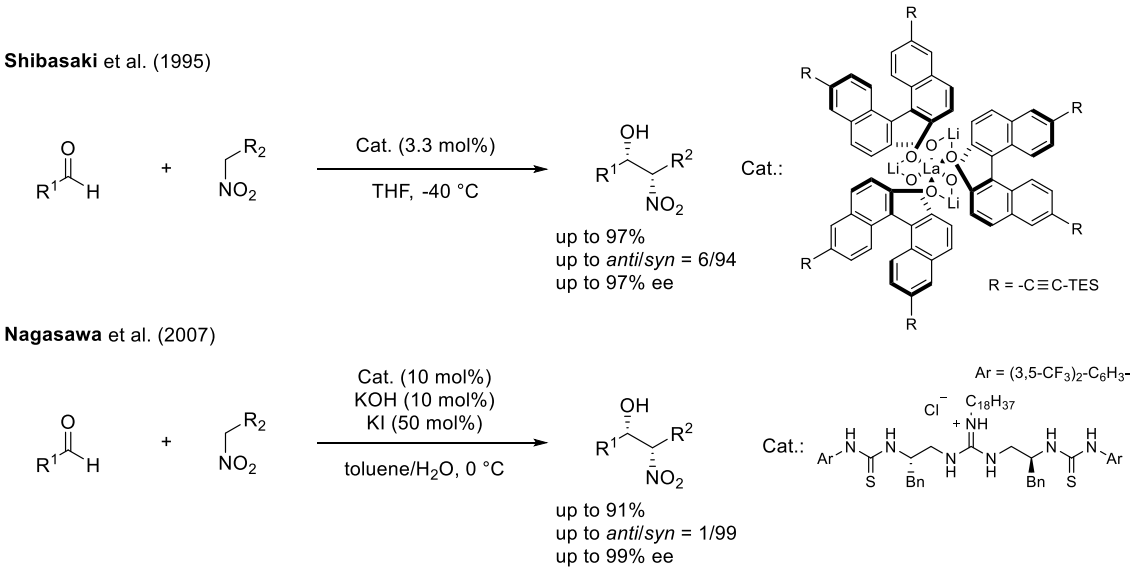
1828 年の Wöhler による尿素の合成[1]は、有機化合物は生命の作用でのみ作られるという生気論を打ち砕き、人類は有機化合物を人工的に合成する力を獲得した。20 世紀に入ると多種多様な有機化学反応が開発され、有機合成化学者は天然物に限らず、自ら設計した分子を自らの手で供給可能となり、医薬品や機能性材料の分野が飛躍的な発展を遂げた。医薬品や機能性材料、天然物といった複雑な有機分子を合成する上で重要なのは、分子の骨格を入手容易な原料から如何にして効率的に構築するかという点である。これを達成する上で C-C 結合形成反応は必要不可欠な技術であり、最も代表的な C-C 結合形成反応として、1872 年に Wurtz、Borodin によって発見されたアルドール反応[2]が挙げられる。アルドール反応はα水素をもつカルボニル化合物から発生させたエノラートをもう一つのカルボニル化合物へ求核付加させ、β-ヒドロキシカルボニル化合物を得る反応である。続いて 1895 年には Henry らにより、アルドール反応の発展形であるニトロアルドール反応が発見された[3,4]。ニトロアルドール反応は、ニトロ化合物から発生させたニトロナートを求核剤として用い、連続不斉炭素を有するβ-ニトロアルコールを得る反応である。生成物は還元反応によって、多くの医薬品や天然物に含まれるβ-アミノアルコールへ容易に誘導可能なため、ニトロアルドール反応は有機合成化学的に価値が高い。しかしながら、本反応は原理上、*syn* 体、*anti* 体並びにそれらの鏡像異性体の計 4 種の立体異性体を生成物として与える。従って、望む立体異性体のみを選択的に得る反応の開発は強く求められていた。

Scheme 1. Overview of nitroaldol reaction

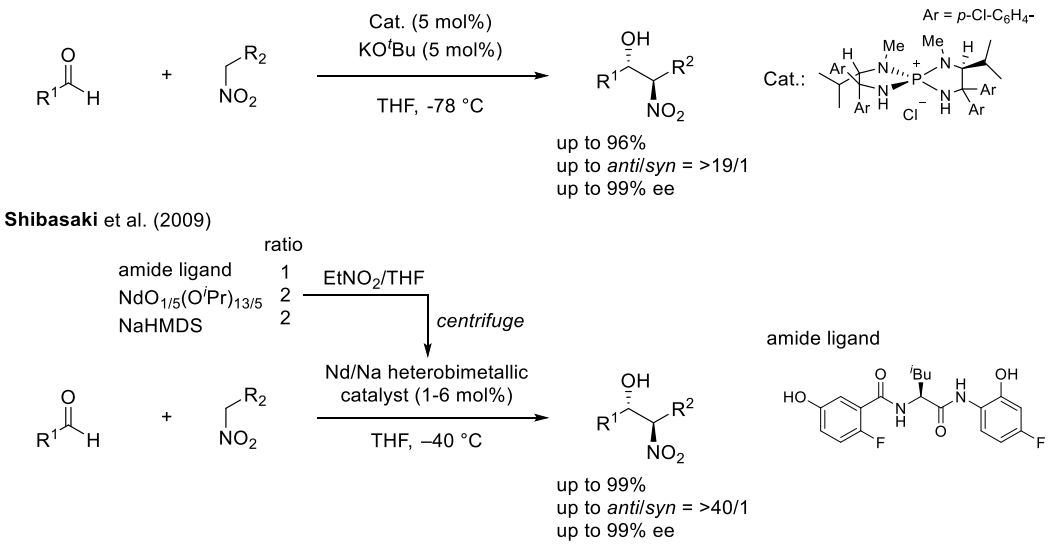


柴崎研究室では上記の選択性の課題を克服するために触媒的不斉ニトロアルドール反応の開発を精力的に推進し、1992 年にエナンチオ選択的反応[5]、1995 年にはランタン－アルカリ金属複合型触媒(LLB 触媒)を用いた *syn* 選択的触媒的不斉ニトロアルドール反応[6]の開発に世界に先駆けて成功した。本反応は多点認識型の LLB 触媒が基質間のプロトン移動を高い不斉収率で促進することから、廃棄物の副生が一切無い原子効率に優れた反応であった。本研究を皮切りに、世界中で触媒的不斉ニトロアルドール反応が活発に研究されたが、その多くは制御が容易な 6 員環遷移状態を経由する *syn* 選択的な反応であった[a,7]。*anti* 選択的な反応[8]は、2007 年に大井らがテトラアミノホスホニウム塩を触媒とした反応を世界で初めて報告[8a]し、続いて柴崎らが Nd/Na 異種 2 核金属触媒を用いる反応を報告した[9]。本反応は $NdO_{1/5}(O^iPr)_{13/5}$、NaHMDS とジアミド型配位子の単純混合により調製される不均一系触媒を用いる点が特徴であり、アルデヒドの *anti* 選択的触媒的不斉ニトロアルドール反応を広範な基質適用範囲下、高収率、高立体選択性で促進することを明らかにした[a]。

Scheme 2. Selected examples of *syn*-selective catalytic asymmetric nitroaldol reactions



Scheme 3. Selected examples of *anti*-selective catalytic asymmetric nitroaldol reactions



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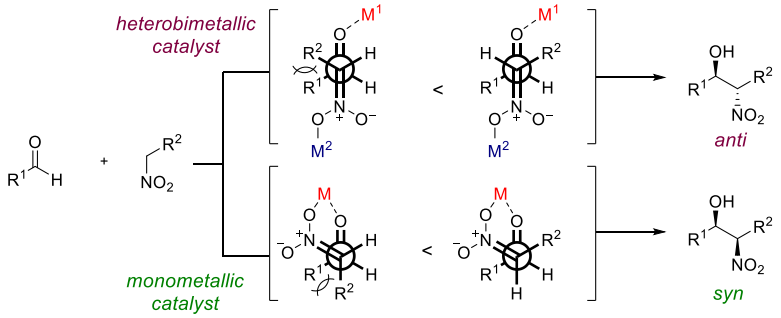
[a] Nd/Na 異種 2 核金属触媒の *anti* 選択性は Nd と Na がカルボニル基とニトロナートの酸素原子に別々に配位し、アンチパラレルな遷移状態を経て反応が進行することにより説明される。これは一般的な単核金属触媒が 6 員環遷移状態を経て *syn* 体を与えるのと対照的である。

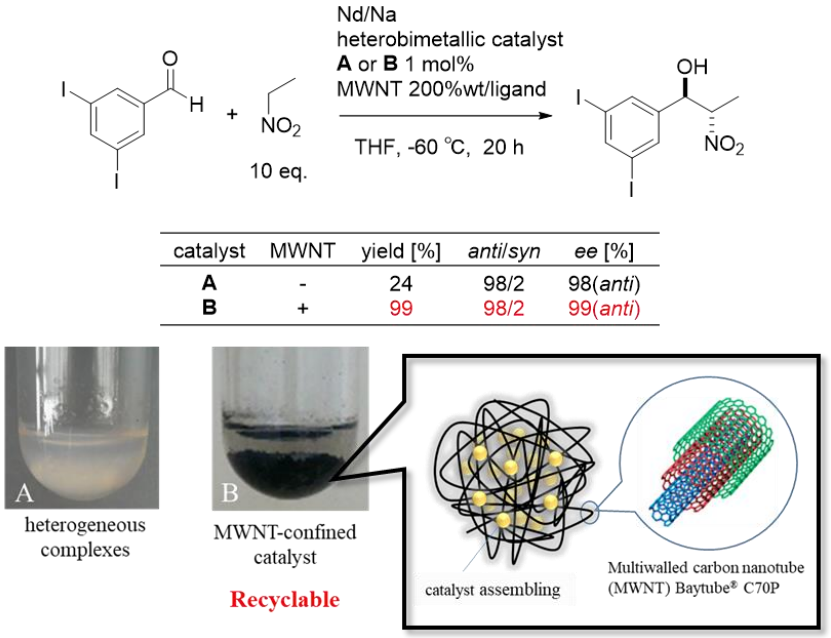


２－２　Nd/Na 異種２核金属触媒

前項で述べた Nd/Na 異種２核金属錯体を用いた *anti* 選択的触媒的不斉ニトロアルドール反応を実用的な反応とする上で三つの課題が残されていた。一つ目は本触媒が不均一系触媒でありながら再利用が出来ない点、二つ目は触媒調製に用いる試薬が高価かつ空気中で不安定なため調製が難しい点、三つ目は基質適用範囲がアルデヒドに限定され、合成できるのがβ-アミノ２級アルコールに限られていた点である。

2013 年に柴崎研究室の小川らは Nd/Na 異種２核金属触媒の多層カーボンナノチューブ(mulltiwalled carbon nanotube、以下 MWNT)への担持により、高立体選択性は維持したまま、触媒活性が向上することを見出した。反応に用いた MWNT は繊維状のナノチューブが複雑に絡み合った特徴的な中空構造を持ち、触媒が MWNT 内の 100 nm 以下の間隙で自己組織化することで、従来よりも微細化した触媒クラスターが生成する。その結果、触媒の表面積が増大し、触媒活性の大幅な向上に成功した。さらに MWNT 固定化触媒は反応後に容易に回収可能であり、触媒自体の安定性も向上していたため再利用が可能になった [10]。

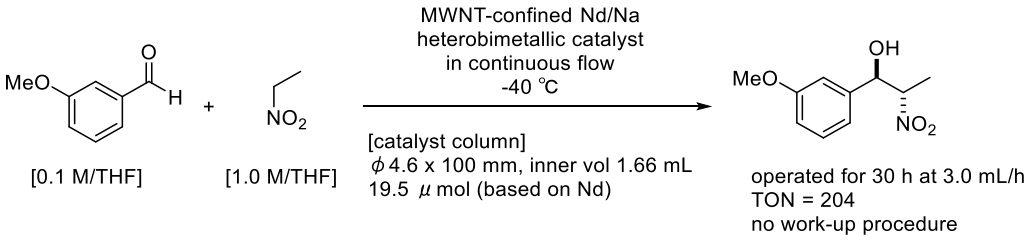
Scheme 4. MWNT confined catalyst for *anti*-selective catalytic asymmetric nitroaldol reaction

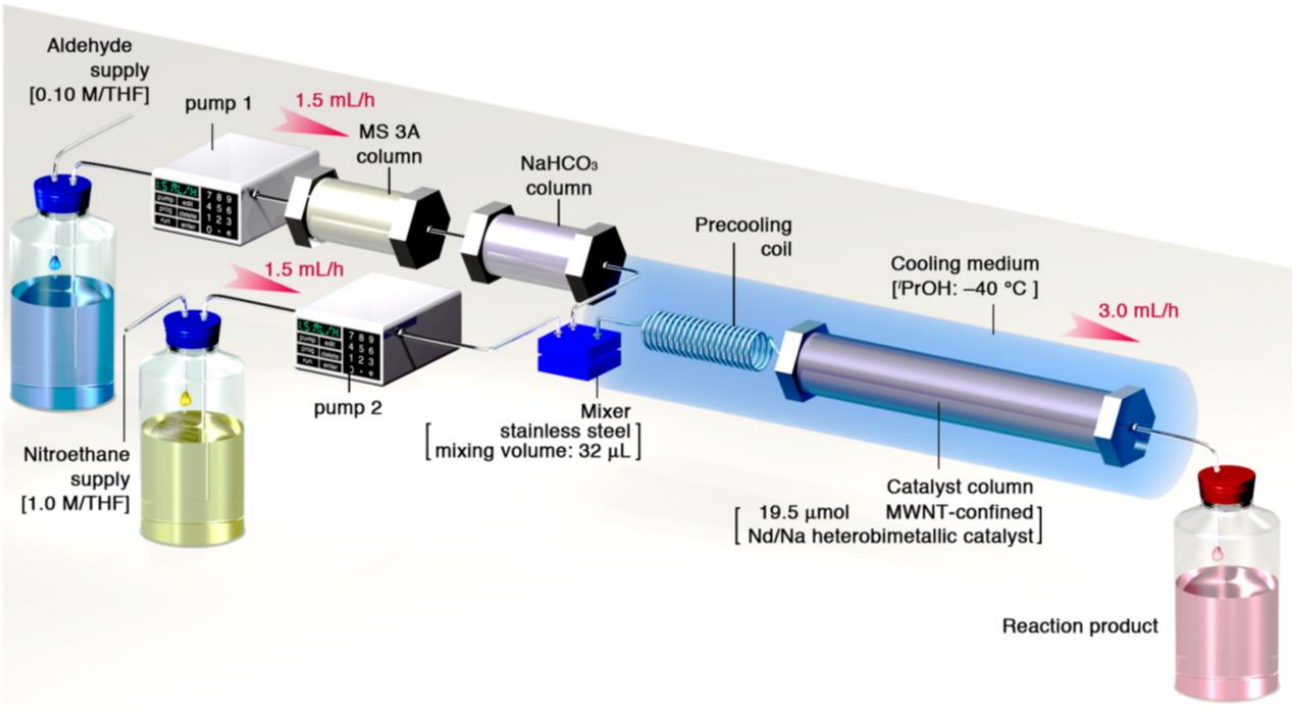


catalyst	MWNT	yield [%]	*anti*/*syn*	*ee* [%]
A	-	24	98/2	98(*anti*)
B	+	99	98/2	99(*anti*)

2014 年には柴崎研究室の橋本らが MWNT 固定化触媒を用いた連続フロー反応に成功した。連続フロー反応は MWNT 固定化触媒を封入した触媒カラムにアルデヒドとニトロアルカンの溶液を通液することで連続的に進行し、バッチ式反応と同等の収率、選択性でβ-ニトロアルコールが得られることを明らかにした。反応後は濃縮のみで目的物を取得可能であり、抽出やろ過などの煩雑な操作を必要としない。さらに冷却が必要な部位は触媒カラムのみで、従来のバッチ式の反応と比較して、冷却体積を大幅に削減できることから、省エネルギーで環境調和型の反応となった [11]。

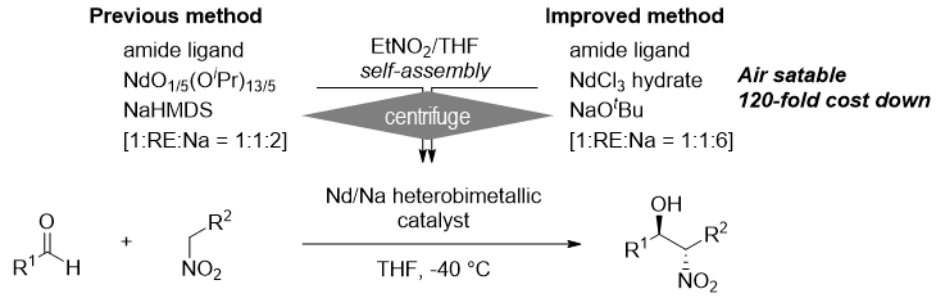
Scheme 5. *anti*-Selective catalytic asymmetric nitroaldol reaction in continuous flow platform





2016 年には柴崎研究室の野々山らが従来の $NdO_{1/5}(O^iPr)_{13/5}$ と NaHMDS に代わり、安価で空気中で安定な $NdCl_3{\cdot}6H_2O$ と NaO^tBu から Nd/Na 異種 2 核金属触媒を調製可能なことを明らかにした。本手法により、触媒調製に必要なコストが 120 分の 1 になった。また触媒調製にグローブボックスなどの特別な設備が不要となり、よりユーザーフレンドリーで汎用性の高い手法となった [12]。

Scheme 6. Bench-stable and inexpensive preparation method of Nd/Na heterobimetallic catalyst



以上の成果により、Nd/Na 異種 2 核金属触媒を用いた *anti* 選択的触媒的不斉ニトロアルドール反応は低コストで実用的な反応へと進化を遂げ、先に述べた課題を克服しつつある。しかしながら、依然として基質適用範囲はアルデヒドに限定され、2 級アルコールしか合成できない問題を抱えていた。

２－３　本論文の概要

前項までに柴﨑研究室で開発された Nd/Na 異種 2 核金属錯体が不斉ニトロアルドール反応を触媒し、*anti* 付加体を高収率、高立体選択性で与えることを述べた。しかしながら、従来の報告では本反応の基質適用範囲はアルデヒドに限られ、合成できるのは 2 級アルコールに限定されていた。本論文では、本反応の基質適用範囲をケトンへと広げ、β-アミノ 3 級アルコールの合成を行った結果と反応における特異な溶媒効果、更には医薬品合成や連続フロー合成へ応用した結果について述べる [13]。

第 1 章「序論」では、触媒的不斉ニトロアルドール反応の歴史と柴﨑研究室による Nd/Na 異種 2 核金属触媒を用いた *anti* 選択的触媒的不斉ニトロアルドール反応の実用化に向けたこれまでの開発の流れと課題について述べ、本研究の意義を明らかとした。

第 2 章「α-ケトエステルの *anti* 選択的触媒的不斉ニトロアルドール反応」では、Nd/Na 異種 2 核金属触媒を用いて、α-ケトエステルの *anti* 選択的触媒的不斉ニトロアルドール反応を検討した。反応検討中に 2-Me-THF が特異な溶媒効果を持つことを見出した。2-Me-THF がキラルな分子であることに着目し、光学活性な溶媒が本不斉反応に与える影響について精査した。さらに医薬品の不斉合成や連続フロー反応を通じて本反応の有用性を実証した。

第 3 章「溶媒依存性エナンチオ選択的不斉ニトロアルドール反応」では、α-ケトエステルの不斉ニトロアルドール反応において、L-アラニン由来のジアミド型配位子から調製した Nd/Na 異種 2 核金属触媒が THF と MTBE 中で正負が逆のエナンチオ選択性を与える興味深い現象を見出し、触媒を構成するジアミド型配位子の側鎖のサイズや反応溶媒がエナンチオ選択性に与える影響を精査した。

第 4 章「トリフルオロメチルケトンの *anti* 選択的触媒的不斉ニトロアルドール反応」では Nd/Na ならびに Pr/Na 異種 2 核金属触媒を用いて、電子求引性のトリフルオロメチル基で活性化されたトリフルオロメチルケトンの *anti* 選択的触媒的不斉ニトロアルドール反応を検討した。さらにトリフルオロメチル基含有 ephedrine 誘導体の合成を通じて本反応の有用性を実証した。

第 5 章「結論」では本論文を総括した。

References

1. Wöhler, F. *Ann. der Phy. und Chem.* **1828**, *88*, 253.
2. (a) Wurtz, C. A. *Bull. Soc. Chim. Fr.* **1872**, *17*, 436. (b) Wurtz, C. A. *J. prakt . Chem.* **1972**, *5*, 457.
3. Henry, L. C. R. *Hebd. Seances Acad. Sci.* **1895**, *120*, 1265.
4. For reviews of asymmetric nitroaldol reaction, see: (a) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315. (b) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561. (c) Blay, G.; Hernández-Olmos, V.; Pedro, J. *Synlett* **2011**, 1195.
5. Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418.
6. Sasai, H.; Tokunaga, T.; Watanabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388.
7. For selected examples of *syn*-selective catalytic asymmetric nitroaldol reactions, see: (a) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Eur. J. Org. Chem.* **2006**, 2894. (b) Arai, T.; Watanabe, M.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 3595. (c) Sohtome, Y.; Takemura, N.; Takada, K.; Takagi, R.; Iguchi, T.; Nagasawa, K. *Chem. - Asian J.* **2007**, *2*, 1150. (d) Arai, T.; Takashita, R.; Endo, Y.; Watanabe, M.; Yanagisawa, A. *J. Org. Chem.* **2008**, *73*, 4903. (e) Kim, H. Y.; Oh, K. *Org. Lett.* **2009**, *11*, 5682. (f) Jin, W.; Li, X.; Wan, B. *J. Org. Chem.* **2011**, *76*, 484. (g) White, J. D.; Shaw, S. *Org. Lett.* **2012**, *14*, 6270. (h) Qin, D. D.; Yu, W.; Zhou, J. D.; Zhang, Y. C.; Ruan, Y. P.; Zhou, Z. H.; Chen, H. B. *Chem. - Eur. J.* **2013,** *19*, 16541. (i) Kaldun, J.; Prause, F.; Scharnagel, D.; Freitag, F.; Breuning, M. *ChemCatChem* **2016**, *8*, 1846.
8. For selected examples of *anti*-selective catalytic asymmetric nitroaldol reactions, see: (a) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392. (b) Handa, S.; Nagawa, K.; Sohtome, Y.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3230. (c) Sohtome, Y.; Kato, Y.; Handa, S.; Aoyama, N.; Nagawa, K.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2008**, *10*, 2231. (d) Uraguchi, D.; Nakamura, S.; Ooi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7562. (e) Lang, K.; Park, J.; Hong, S. *Angew. Chem., Int. Ed*. **2012**, *51*, 1620. (f) Xu, K.; Lai, G.; Zha, Z.; Pan, S.; Chen, H.; Wang, Z. *Chem. - Eur. J.* **2012**, *18*, 12357. (g) Li, Y.; Deng, P.; Zeng, Y.; Xiong, Y.; Zhou, H. *Org. Lett.* **2016**, *18*, 1578. (h) Blay, G.; Domingo, L. R.; Hernández-Olmos, V.; Pedro, J. R. *Chem. - Eur. J.* **2008**, *14*, 4725. (i) Ube, H.; Terada, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3895. (j) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. *Org. Lett.* **2010**, *12*, 3058. (k) Noole, A.; Lippur, K.; Metsala, A.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2010**, *75*, 1313. (l) Qiong ji, Y.; Qi, G.; Judeh, Z. M. A. *Eur. J. Org. Chem.* **2011**, 4892. (m) Boobalan, R.; Lee, G.-H.; Chen, C. *Adv. Synth. Catal.* **2012**, *354*, 2511. (n) Yao, L.; Wei, Y.; Wang, P.; He, W.; Zhang, S. *Tetrahedron* **2012**, *68*, 9119. (o) Arai, T.; Joko, A.; Sato, K. *Synlett* **2015**, *26*, 209.
9. (a) Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2008**, 49, 272. (b) Nitabaru, T.; Nojiri, A.; Kobayashi, M.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 13860. (c) Nitabaru, T.; Kumagai, N.; Shibasaki, M. *Molecules* **2010**, *15*, 1280.
10. (a) Ogawa, T.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 6196. (b) Sureshkumar, D.; Hashimoto, K.; Kumagai, N.; Shibasaki, M. *J. Org. Chem.* **2013**, *78*, 11494.
11. Hashimoto, K.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2014**, *16*, 3496.
12. (a) Nonoyama, A.; Hashimoto, K.; Saito, A.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2016**, *57*, 1815. (b) Nonoyama, A.; Kumagai, N.; Shibasaki, M. *Tetrahedron* **2017**, *73*, 1517.
13. For reviews of the construction of tetrasubstituted stereogenic centers, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Christoffers, J.; Baro, A. Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis; Wiley-VCH: Weinheim, Germany, 2005. (c) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (d) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873. (e) Shibasaki, M.; Kanai, M. *Chem. Rev.* **2008**, *108*, 2853. (f) Kumagai, N.; Shibasaki, M. *Bull. Chem. Soc. Jpn.* **2015**, *88*, 503.

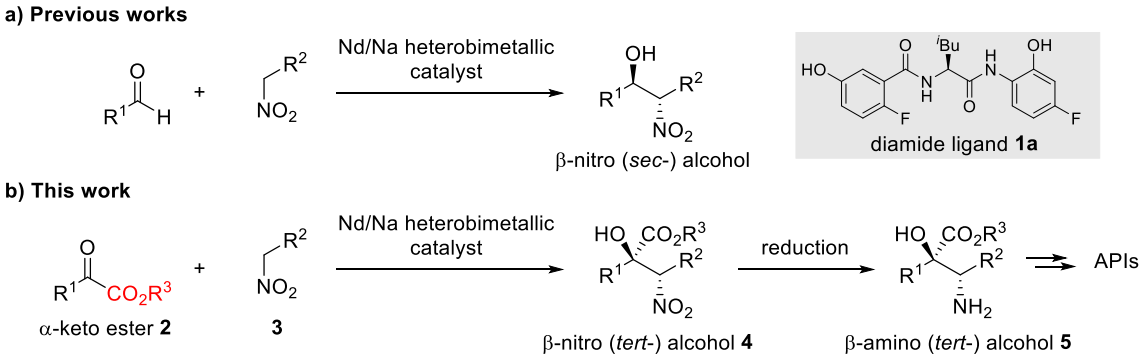
第 2 章

α-ケトエステルの *anti* 選択的触媒的不斉ニトロアルドール反応

２－１　はじめに

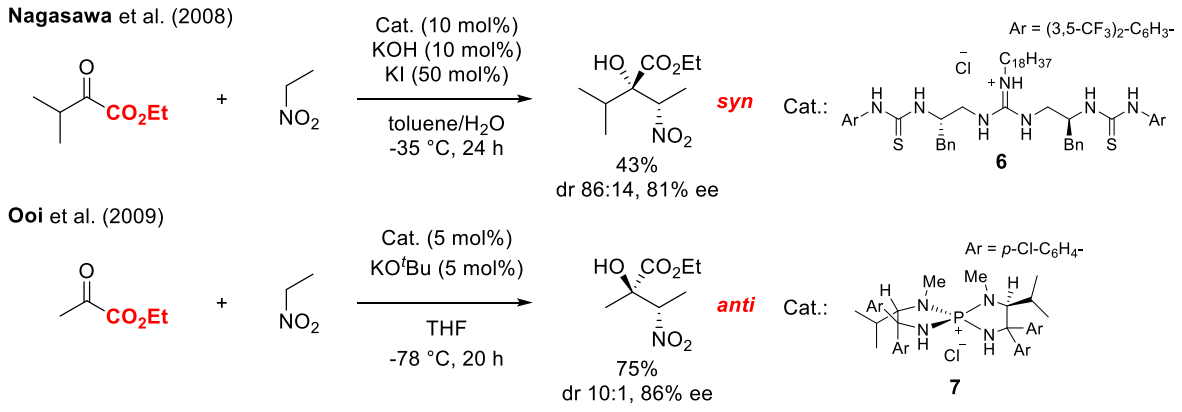
序論において、柴崎研究室で開発されたジアミド型配位子 **1a** をリガンドとする Nd/Na 異種 2 核金属錯体が不斉ニトロアルドール反応を触媒し、*anti* 付加体が高収率、高立体選択性で得られることを述べた。しかしながら、従来の報告では本触媒の適用範囲はアルデヒドに限られ、本反応で合成できるのは 2 級アルコールに限定されていた。本章では、本反応の基質適用範囲をケトンへと広げ、3 級アルコールの合成を試みた。具体的には、電子求引性のエステル基で活性化されたケトンである α-ケトエステルを基質とした反応を検討した。本反応によって得られる α-ニトロ 3 級アルコールはニトロ基の還元反応により、医薬品等に散見される β-アミノ 3 級アルコールへ容易に誘導可能であり、本反応の開発により、不斉水素化反応では合成が難しい光学活性 β-アミノ 3 級アルコールを短工程で合成する手段を提供できると考えた(Scheme 1)。

Scheme 1. Nitroaldol reaction of Nd/Na heterobimetallic catalyst



これまで、α-ケトエステルとニトロメタンのエナンチオ選択的なニトロアルドール反応は多数報告されていた [1]。一方、求核剤としてニトロエタンを用いたエナンチオおよびジアステレオ選択的なニトロアルドール反応の報告は 2 例にとどまっていた(Scheme 2)。長澤らはグアニジウム塩 **6** を触媒とした *syn* 選択的な反応を報告している [2]。また、大井らはホスホニウム塩 **7** を触媒とした *anti* 選択的な反応を報告している [3]。しかしながらどちらの反応も、収率や選択性は中程度であり、基質適用範囲はアルキルケトンに限られていた。これらの課題を克服するべく、Nd/Na 異種 2 核金属触媒を α-ケトエステルの不斉ニトロアルドール反応へ適用し、β-ニトロ 3 級アルコールを汎用的に合成できる方法の確立を目指した。

Scheme 2. Past examples for enantio- and diastereo-selective nitroaldol reaction of α-keto esters

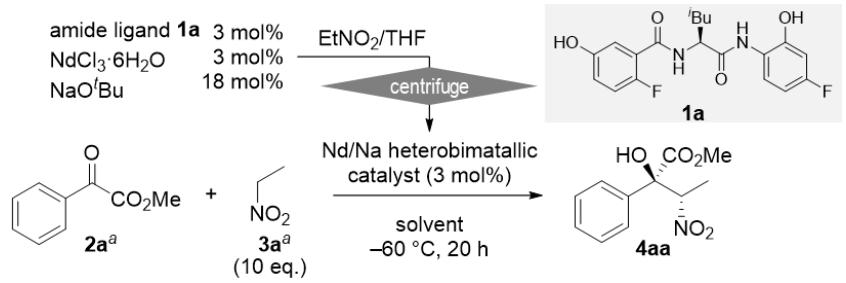


２－２　反応溶媒の検討

α-ケトエステルの *anti* 選択的触媒的不斉ニトロアルドール反応の反応溶媒の最適化を行った(Table 1)。ジアミド型配位子 **1a**、$NdCl_3 \cdot 6H_2O$、NaO^tBu から調製した Nd/Na 異種 2 核金属触媒を用い、α-ケトエステル 2a とニトロエタン **3a** の反応を検討した。まず、過去のアルデヒドの反応の報告で最適溶媒であった THF 中で反応を行ったところ、高収率、高立体選択性で *anti* 付加体 **4aa** を与えた(99% yield, 95% ee, *anti*/*syn* = >98/2) (entry 1)。各種エーテル系溶媒を検討した結果、THF よりもやや嵩高い 2-Me-THF 中でほぼ完璧な収率と立体選択性で反応が進行することを見出した(99% yield, 99% ee, *anti*/*syn* = >98/2) (entry 7)。一方、より嵩高い 2,5-Me_2-THF やエーテル系以外の溶媒を用いた場合には収率、立体選択性が大きく低下した(entry 8-12)。

以上の結果より、THF、2-Me-THF が本反応の最適溶媒であることを明らかにした。

Table 1. Solvent screening



entry	solvent[b]	yield[c] (%)	*anti*/*syn*[c]	% ee[d] (*anti*)	entry	solvent[b]	yield[c] (%)	*anti*/*syn*[c]	% ee[d] (*anti*)
1	THF	99	> 98/2	95	7	2-Me-THF	99	> 98/2	99
2	Et_2O	99	97/3	65	8	2,5-Me_2-THF	99	98/2	85
3	DME	48	90/10	61	9	toluene	64	98/2	88
4	CPME	99	95/5	77	10	EtOAc	34	96/4	87
5	MTBE	99	98/2	85	11	MeCN	0	-	-
6	4-Me-THP	87	90/10	35	12	CH_2Cl_2	76	86/14	0

[a] **2a**: 0.12 mmol, **3a**: 1.2 mmol. [b] CPME: cyclopentyl methyl ether, MTBE: *tert* -butyl methyl ether, 4-Me-THP: 4-methyltetrahydropyran, 2,5-Me_2-THF: 2,5-dimethyltetrahydrofuran (mixture of isomers). [c] Determined by ^{1}H NMR analysis. [d] Determined by chiral HPLC analysis.

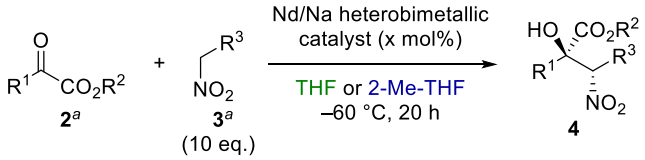
２－３　基質一般性の検討

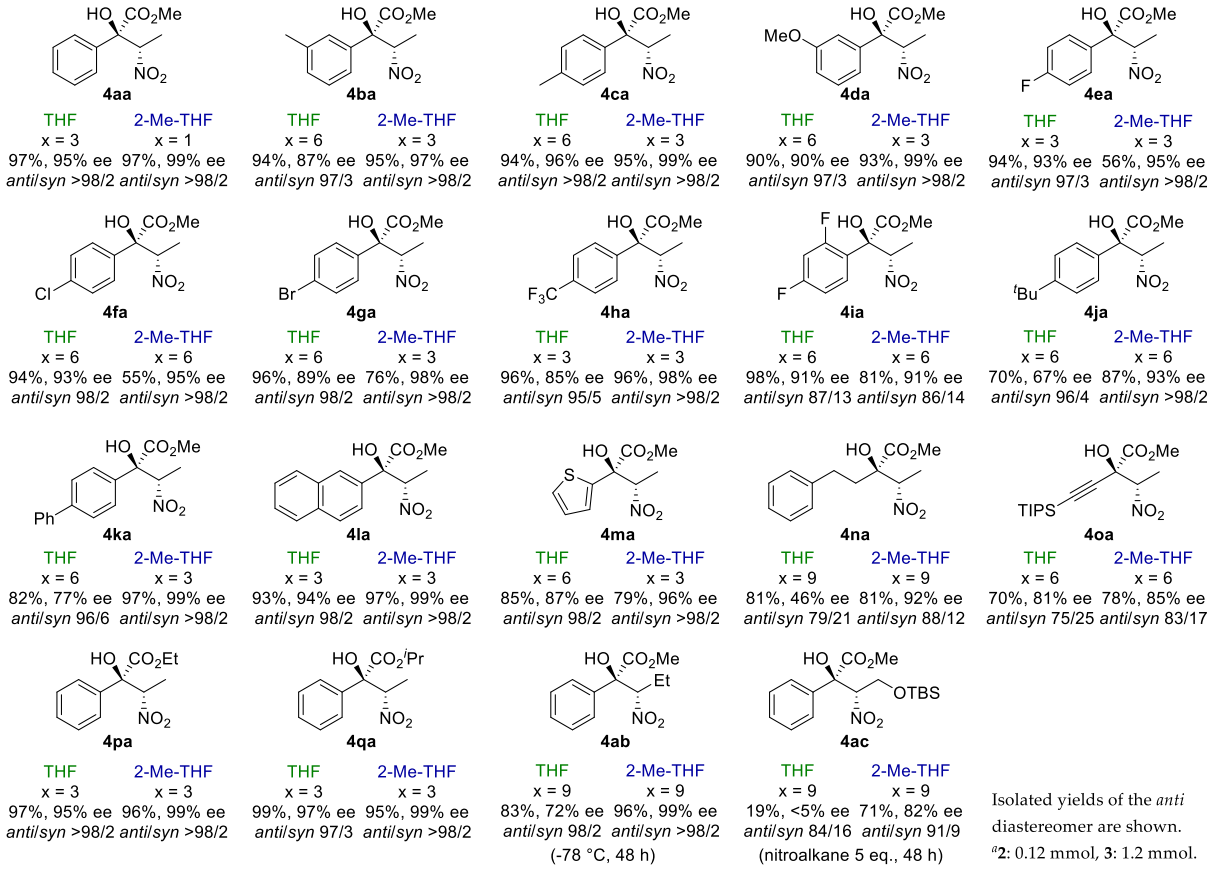
α-ケトエステルの *anti* 選択的触媒的不斉ニトロアルドール反応の基質一般性を調べた。前項で良好な結果を与えた THF と 2-Me-THF 中で反応を行った結果を Scheme 3 に示す。まず無置換のフェニルケトンを基質とした用いた場合、反応は良好に進行し、高収率、高立体選択性で **4aa** が得られた(THF: 97% yield, 95% ee, *anti*/*syn* = >98/2, 2-Me-THF: 97% yield, 99% ee, *anti*/*syn* = >98/2)。この際、2-Me-THF 中において、触媒量を 1 mol%まで低減しても良好な収率、選択性を維持した。電子供与性の Me 基、OMe 基が置換したフェニルケトンや電子求引性のハロゲン、トリフルオロメチル基が置換したフェニルケトンにおいても高収率、高立体選択性で反応が進行した。嵩高い ^{t}Bu 基や Ph 基がパラ位に置換したフェニルケトンでは、THF 中で立体選択性が中程度であったものの(**4ja**: 67% ee, **4ka**: 77% ee)、2-Me-THF 中で高い立体選択性で目的物を与えた(**4ja**: 93% ee, **4ka**: 99% ee)。複素環式ケトン、アルキルケトンやアルキニルケトンは反応性が低く、最大 9 mol%の触媒量が必要

であったが、2-Me-THF 中で良好な結果を与えた。α-ケトエステルのエステル部位がエチルエステル、イソプロピルエステルの場合もメチルエステルと遜色ない結果を与えた。さらに、求核剤としてニトロプロパンやニトロエタノールの保護体を用いた場合にも 2-Me-THF 中で反応は良好に進行し、対応する付加体 **3ab**, **3ac** が高い立体選択性で得られた。

以上、本反応は幅広い基質一般性で進行し、対応する β-ニトロアルコールを高収率、高立体選択性で与えた。

Scheme 3. Reaction scope





2－4　溶媒効果に関する検討

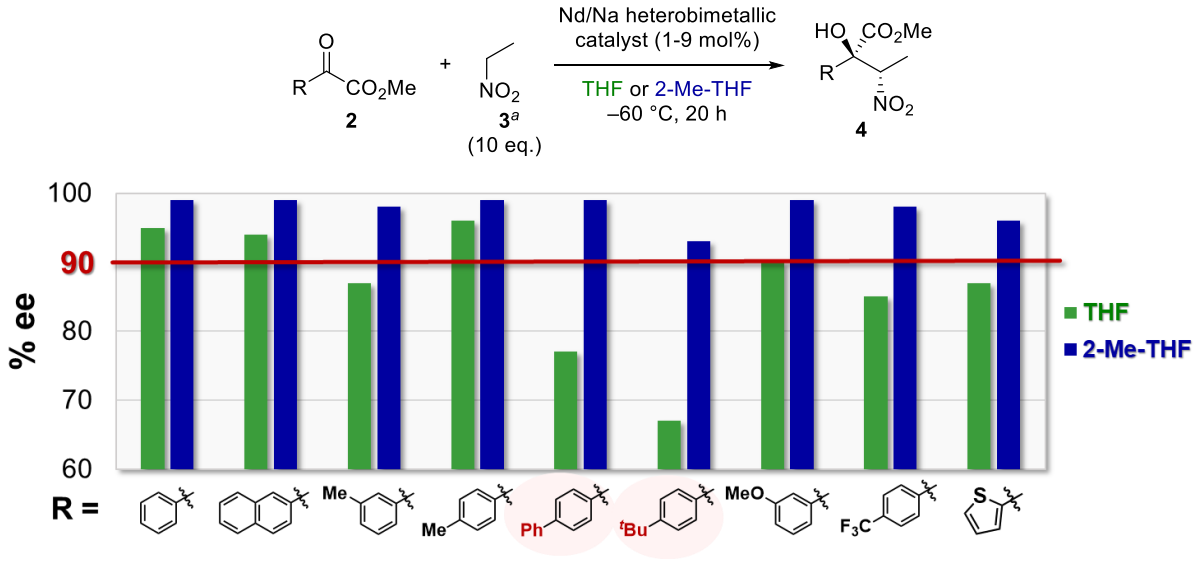
前項の基質一般性の検討における THF と 2-Me-THF の結果を比較すると、ほぼすべての基質において 2-Me-THF 中での収率、立体選択性が THF 中での値を上回った(Figure 1)。特に **2a** と **3b** の反応は 2-Me-THF 中で THF 中よりも 6.1 倍ほど早く進行した(P18, Figure 3)。立体選択性の面においても、嵩高い ^{t}Bu 基や Ph 基が置換したフェニルケトンでは、THF 中では中程度(**4ja**: 67% ee, **4ka**: 77% ee)に留まった一方で、2-Me-THF 中で高立体選択性(**4ja**: 93% ee, **4ka**: 99% ee)で付加体を与え、反応結果に顕著な差が表れた。THF と 2-Me-THF

は物理的、化学的性質が類似した溶媒[4]であるにも関わらず結果に差が表れた理由として、次のような作業仮説を立案した。

1) 配位性溶媒である THF や 2-Me-THF は 2nd リガンドとして触媒に取り込まれている。
2) キラル触媒は 2-Me-THF の不斉を認識し、一方の鏡像異性体と優先的に相互作用している。
3) その結果、触媒周辺の不斉環境が増幅され、反応の面選択性が向上している。

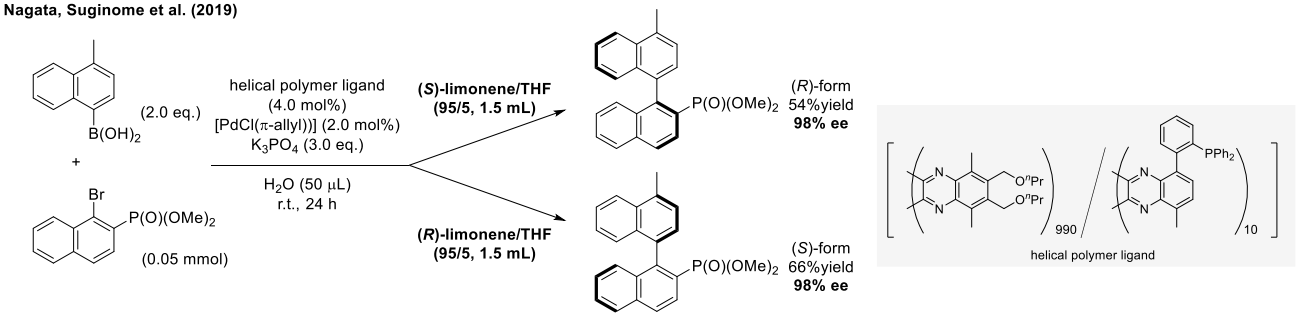
以上の作業仮説を検証するために、光学活性な 2-Me-THF を合成し、*R* 体、*S* 体溶媒中でそれぞれ反応を行い、立体選択性と反応性を比較した[a]。

Figure 1. Comparison of the enantioselectivity of THF and 2-Me-THF



[a] 1975 年に Seebach により光学活性な溶媒中で不斉反応を行う概念が提唱されて[5]以降、光学活性なイオン性溶媒中の不斉反応に関する研究が活発に進められている[6]。一方、2-Me-THF のような中性の光学活性溶媒中で不斉反応を行った例は少なく[7]、溶媒の不斉が反応の立体選択性に大きな影響を与えた例は下記の 1 例に限られる。

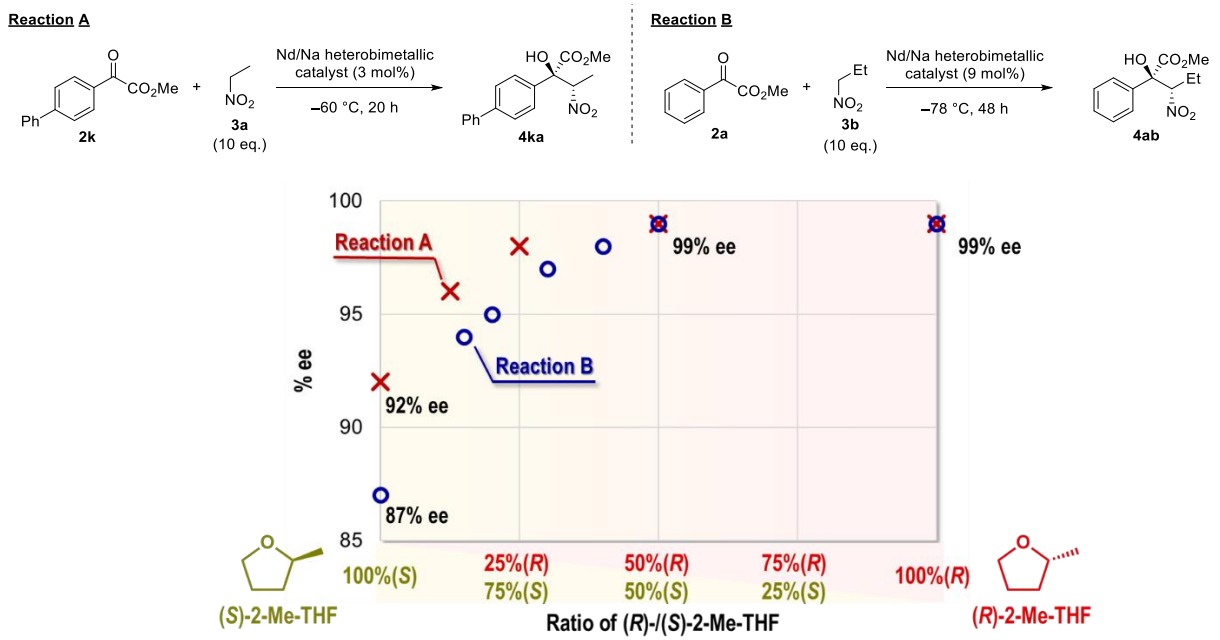
長田、杉野目らはキノキサリンが連なったらせん状高分子を配位子としたアキラルな Pd 触媒を用いた不斉鈴木カップリングを報告している[7c]。本反応の立体選択性は溶媒として用いるリモネンの不斉により誘起され、*S*体溶媒を用いた場合には *R*体が、*R*体溶媒を用いた場合には *S*体がそれぞれ高い立体選択性で得られる。



２－４－１　光学活性 2-Me-THF を用いた反応

反応 A(**2k+3a**)、反応 B(**2a+3b**)を様々なエナンチオ比に調製した 2-Me-THF 中で行い、エナンチオ選択性を比較した[b](Figure 2)。その結果、どちらの反応も *R* 体溶媒中で *S* 体溶媒よりも高い立体選択性を与えた。この結果は、キラル触媒が 2-Me-THF の不斉を認識し、*R* 体溶媒と触媒の相互作用が反応の立体選択性を向上させることを示している。また、*R* 体溶媒の比が増加するに従い立体選択性が向上するものの、*R* 体溶媒の比が 50%(=ラセミ体溶媒)で 99% ee で値が飽和することから、*R* 体溶媒が *S* 体溶媒よりも触媒に対して、強い親和性を持っていることが示された。

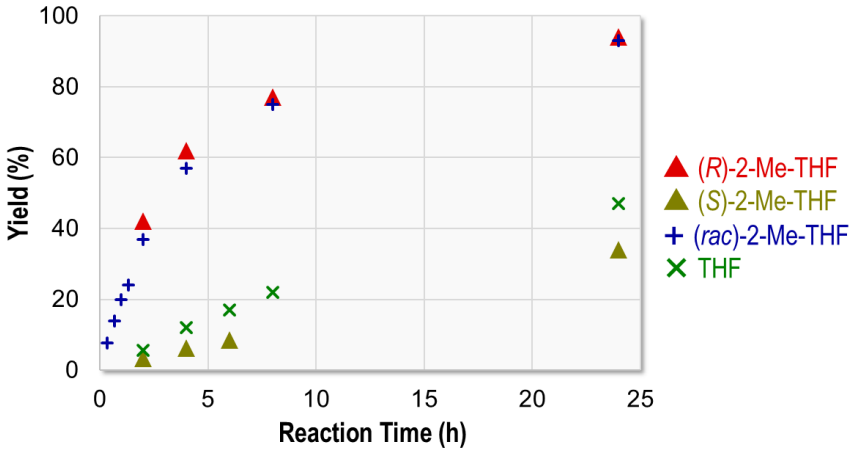
Figure 2. Enantioselectivity of reactions in chiral 2-Me-THF



[b] 反応 A、反応 B は THF 中と 2-Me-THF 中での選択性の差が大きく、溶媒効果の差が出やすいと予想した。

続いて、反応速度の面から溶媒効果について検証した。上記の反応 B の収率の計時変化を各種溶媒中で調べたところ、反応速度は(*R*)-2-MeTHF > *rac*-2-Me-THF > THF > (*S*)-2-Me-THF の順となった(Figure 3)。すなわち、*R* 体溶媒中で *S* 体溶媒中よりも反応が早く進行し、*R* 体溶媒は反応を加速することが明らかになった。またラセミ体溶媒と *R* 体溶媒中の速度に大きな差が見られなかったことから、先の検討結果と同様に *R* 体の溶媒が優先的に触媒と相互作用することが確認された。

Figure 3. Reaction profile of reaction B (**2a** + **3b**) in different reaction media

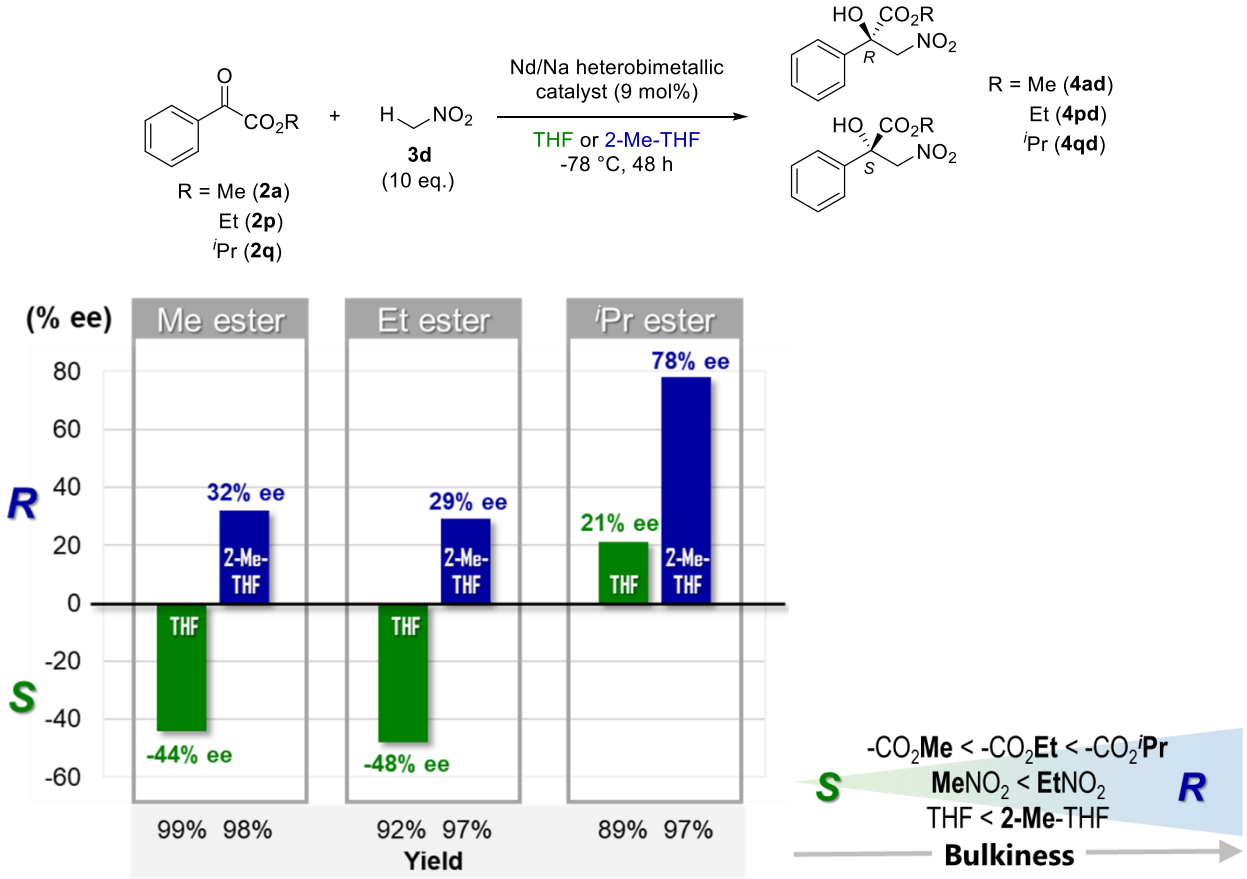


以上、選択性と反応速度の両面から本反応の溶媒効果について検証し、2-Me-THF の触媒への配位が反応に良好な影響を与えることを示した。この特異な溶媒効果は、異種 2 核金属触媒を構成する Nd 原子が高い配位数を取ることが可能であり、また高い酸素親和性を持つことに由来していると考えている [8]。

２－４－２　ニトロメタンを求核剤とした溶媒依存性エナンチオ選択的反応

本反応の特異な溶媒効果は、ニトロメタンを求核剤とした反応でも確認された。ニトロメタンと α-ケトエステル(R = Me, Et, ^{i}Pr)の反応は 2-Me-THF 中ではすべての場合で 2*R* 体を主生成物として与えた一方、THF 中では Me エステルおよび Et エステルの反応で逆のエナンチオマーである 2*S* 体を主生成物として与えた(Figure 4)。本現象は 1) THF や 2-Me-THF が触媒へ配位し、触媒周辺の不斉環境に影響を与えていること、2) コンパクトな THF が配位した触媒クラスターは、コンパクトな基質同士を反応させる際に通常とは逆のエナンチオ選択性を与える高次構造を取ることを示している。溶媒に依存したエナンチオ選択性の逆転現象は L-アラニンから調製したコンパクトな配位子を用いた反応においても確認された。この結果については 3 章で詳しく述べる。

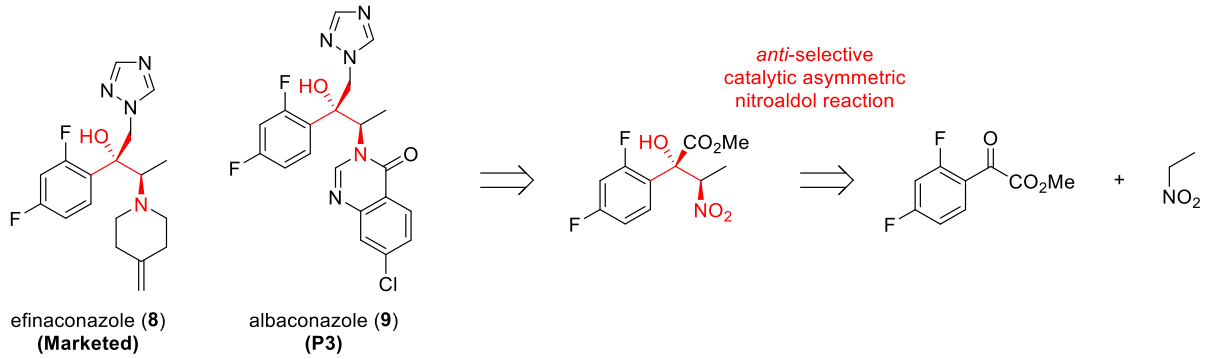
Figure 4. Divergent enantioselectivity in the nitroaldol reaction of nitromethane



２－５　医薬品合成への応用

α-ケトエステルの *anti* 選択的触媒的不斉ニトロアルドール反応を利用した医薬品の合成について述べる。efinaconazole (**8**)並びに albaconazole (**9**)は真菌の細胞膜構成成分であるエルゴステロールの生合成を阻害することからトリアゾール系抗真菌剤として知られている[9]。**8** は Jublia®や Clenafin®として既に上市済みの医薬品であるが、工業的には合成の終盤でラセミ体を光学分割する非効率的な方法により製造されている[10]。今回私は、*anti* 選択的触媒的不斉ニトロアルドール反応を **8** および **9** の合成に適用し、光学活性 β-アミノ 3 級アルコール部位を立体選択的に一挙に構築することで、効率的な合成法を提供できると考えた(Scheme 4)。

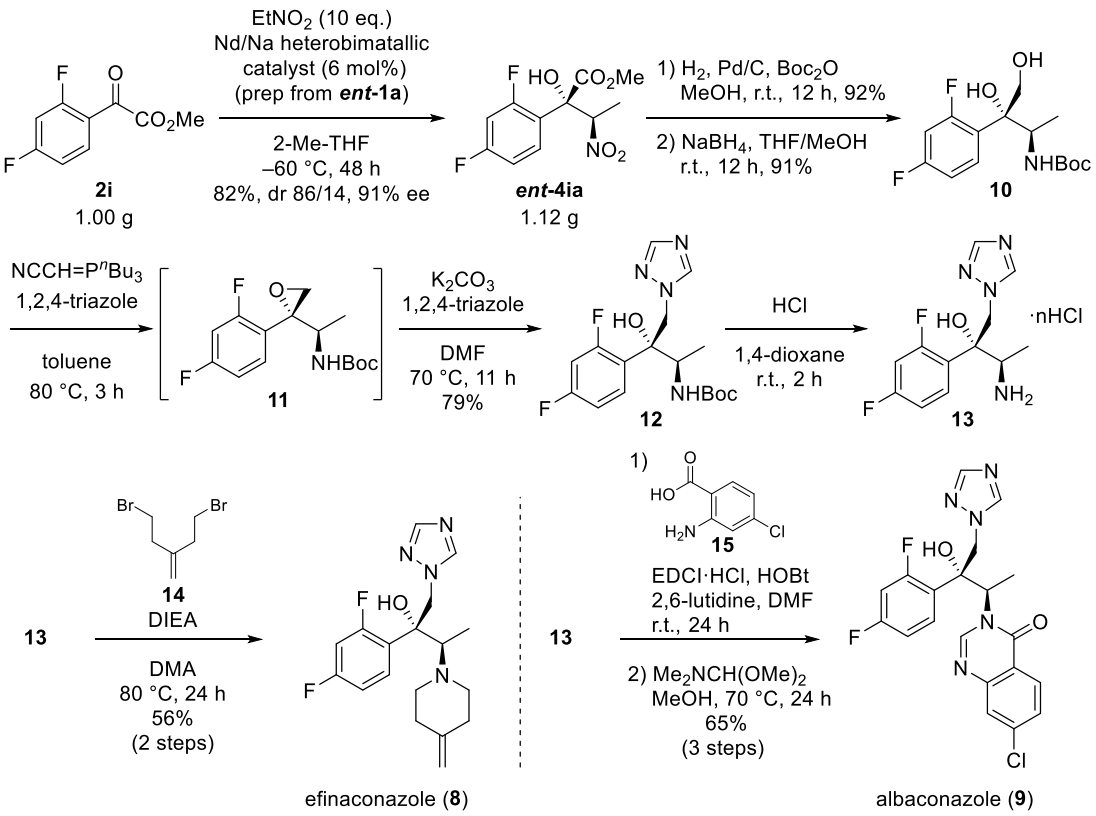
Scheme 4. Retrosynthetic analysis of efinaconazole and albaconazole



最初に本合成の鍵反応となる α-ケトエステル **2i** とニトロエタンの *anti* 選択的触媒的不斉ニトロアルドール反応を行ったところ、グラムスケールでも反応は良好に進行し、収率 82%、91% ee の立体選択性で ***ent*-4ia** が得られ、連続不斉中心を持つ **8** ならびに **9** の主骨格を一挙に構築した。なお、今回は医薬品と同一の立体化学を持つ化合物を合成するために ***ent*-1a** を配位子として用いた。次にニトロ基を接触水素化した後に Boc 基による保護、エステル基を還元し、ジオール **10** を得た。続いて、**10** に対し、角田試薬[11]による光延反応条件下、1,2,4-トリアゾールの導入を試みたところ、エポキシ **11** を経由し、β-アミノアルコール **12** が得られた[c]。続いて酸性条件下、Boc 基を脱保護し、共通中間体 **13** を得た。続いて、共通中間体 **13** とジブロミド **14** を塩基性条件下反応させ、ピペリジン環構築を試みたところ中程度の収率で efinaconazole (**8**)が得られた[12]。また、共通中間体 **13** と 2-アミノ-4-クロロ安息香酸 **15**、DMF のジメチルアセタールを順次縮合し、キナゾロン環を構築し、albaconazole (**9**)を合成した[13](Scheme 5)。

以上、医薬品の不斉合成により、*anti* 選択的触媒的不斉ニトロアルドール反応の実用性を示した。

Scheme 5. Stereoselective synthesis of efinaconazole and albaconazole



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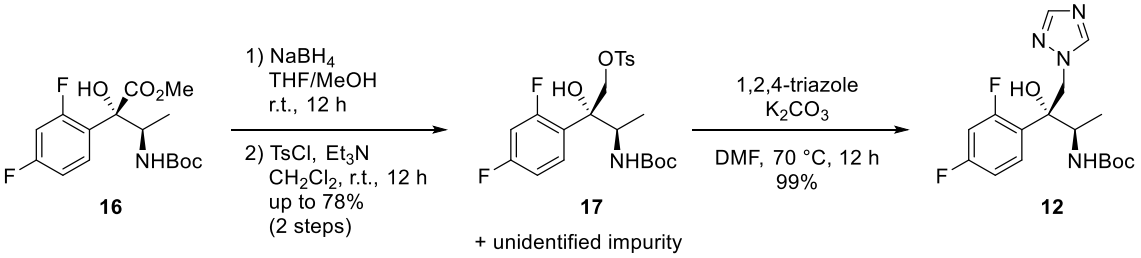
[c]β-アミノアルコール **12** への変換はトシル体 **17** を経由する方法でも実施可能であった。本変換反応は高価な角田試薬を使用しない点で優れているが、トシル化反応時に構造未知の不純物が生成し、再現性に乏しい点が課題となっている。



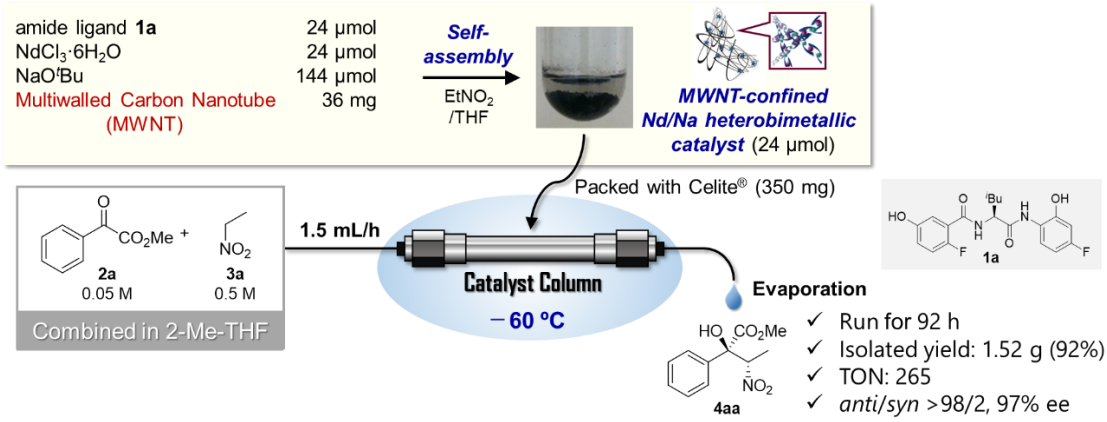
２－８　MWNT 担持型固定化触媒による連続フロー反応

連続フロー反応は一般的に従来のバッチ式反応と比較して、安全で再現性が高く、スケールアップが容易なことから、近年産業界で注目が高まっている[14]。フロー系で触媒反応を行う上では、固体触媒を詰めた触媒カラムに反応溶液を通液させる方法が反応後の後処理が簡便であり、最も効率的とされているが、不均一系の不斉触媒の開発は発展途上の分野であるため、本手法にて不斉反応に成功した例は少ない[15,16]。

今回私は、本触媒が不均一触媒であることに着目し、本反応を連続フロー反応へ展開した。まず多層カーボンナノチューブ(multiwalled carbon nanotube、以下 MWNT)固定型の Nd/Na 異種 2 核金属触媒を調製した。序論で述べたように、触媒を MWNT へ固定化すると触媒活性や耐久性、カラムに詰めた際の通液性が向上し、連続フロー反応に適した触媒となることが柴崎研究室から既に報告されている。MWNT 固定型触媒は触媒調製時に他の試薬と一緒に MWNT を混合するだけで簡便に調製可能である。本触媒をセライトと一緒にステンレス製カラムに詰め、触媒カラムを作成した。続いて、触媒カラムに所定の濃度に調製した **2a** と **3a** の 2-Me-THF 溶液を通液したところ、反応は良好に進行し、92 時間の連続運転で 1.52 g の **4aa** が得られた(92% yield、TON: 265)。立体選択性は 97% ee でバッチ式反応と遜色ない結果を与えた。

連続フロー反応後の後処理は濃縮のみであり、抽出やろ過といった触媒と目的物を分離する操作は不要であった。また冷却が必要な部位は触媒カラムのみであり、バッチ式反応と比較して冷却体積を大幅に低減可能であることから、本法は工業化に適した環境調和型のプロセスであると考えられる。

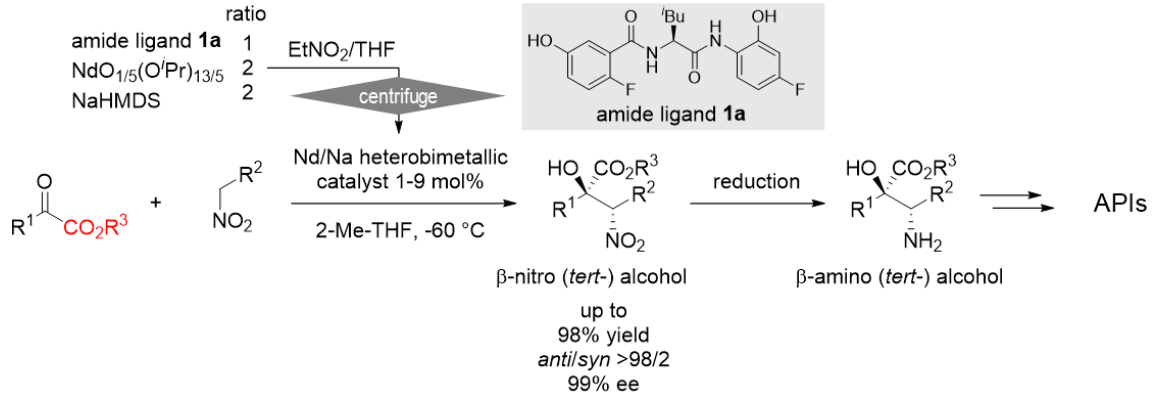
Scheme 6. Reaction in a Continuous-flow platform



２－９　　まとめ

本章では、Nd/Na 異種 2 核金属触媒を用いた *α*-ケトエステルの *anti* 選択的触媒的不斉ニトロアルドール反応について述べた。本反応は広範の基質に適用可能であり、2-Me-THF 中で特異的に良好な収率、選択性を与えた。本溶媒効果について検証するために、光学活性な 2-Me-THF 中で反応を行った結果、Nd/Na 異種 2 核金属触媒が 2-Me-THF が持つ不斉を認識し、(*R*)-2-Me-THF が触媒へ配位することで高収率、高立体選択性が達成されることを明らかとした。さらに本反応を利用した efinaconazole と albaconazole の立体選択的な合成と MWNT 固定型の触媒を用いた連続フロー反応への適用を通じて、本反応の有用性と実用性を実証した [17]。

Scheme 7. Summary of chapter 2



References

1. (a) Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222. (b) Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875. (c) Lu, S.-F.; Du, D.-M.; Zhang, S.-W.; Xu, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3433. (d) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167. (e) Du, D.-M.; Lu, S.-F.; Fang, T.; Xu, J. *J. Org. Chem.* **2005**, *70*, 3712. (f) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732. (g) Qin, B.; Xiao, X.; Liu, X.; Huang, J.; Wen, Y.; Feng, X. J. J. Org. Chem. **2007**, 72, 9323. (h) Blay, G.; Hernandez-Olmos, V.; Pedro, J. R. *Org. Biomol. Chem.* **2008**, *6*, 468. (i) Bulut, A.; Aslan, A.; Dogan, Ö. *J. Org. Chem.* **2008**, *73*, 7373. (j) Cochi, A.; Métro, T.-X.; Pardo, D. G.; Cossy, J. *Org. Lett.* **2010**, *12*, 3693. (k) Xu, H.; Wolf, C. *Synlett* **2010**, 2765. (l) Blay, G.; Hernandez-Olmos, V.; Pedro, J. R. *Chem. - Eur. J.* **2011**, *17*, 3768. (m) Yao, Q. J.; Khong, D. T.; Gao, Q.; Judeh, Z. M. A. *Synthesis* **2014**, *46*, 1793. (n) Grosseheilmann, J.; Bandomir, J.; Kragl, U. *Chem. - Eur. J.* **2015**, *21*, 18957. (o) Li, Y.; Huang, Y.; Gui, Y.; Sun, J.; Li, J.; Zha, Z.; Wang, Z. *Org. Lett.* **2017**, *19*, 6416. (p) He, F.; Chen, G.; Yang, J.; Liang, G.; Deng, P.; Xiong, Y.; Zhou, H. *RSC Adv.* **2018**, *8*, 9414. (q) Yamada, T.; Kuwata, M.; Takakura, R.; Monguchi, Y.; Sajiki, H.; Sawama, Y. *Adv. Synth. Catal.* **2018**, *360*, 637.
2. Takada, K.; Takemura, N.; Cho, K.; Sohtome, Y.; Nagasawa, K. *Tetrahedron Lett.* **2008**, *49*, 1623.
3. Uraguchi, D.; Ito, T.; Nakamura, S.; Sakaki, S.; Ooi, T. *Chem. Lett.* **2009**, *38*, 1052.
4. Quirk, R. P.; Kester, D. E. J. Organomet. Chem. **1977**, 127, 111. (b) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1995**, *117*, 9863. (c) Aycock, D. F. *Org. Process Res. Dev.* **2007**, *11*, 156.
5. Seebach, D.; Oei, H. A. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 634.
6. (a) Pégot, B.; Vo-Thanh, G.; Gori, D.; Loupy, A. *Tetrahedron Lett.* **2004**, *45*, 6425. (b) Baudequin, C.; Brégeon, D.; Levillain, J.; Guillen, F.; Plaquevent, J.-C.; Gaumont, A.-C. *Tetrahedron: Asymmetry* **2005**, *16*, 3921. (c) Ding, J.; Desikan, V.; Han, X.; Xiao, T. L.; Ding, R.; Jenks, W. S.; Armstrong, D. W. *Org. Lett.* **2005**, *7*, 335. (d) Wang, Z.; Wang, Q.; Zhang, Y.; Bao, W. *Tetrahedron Lett.* **2005**, *46*, 4657. (e) Gausepohl, R.; Buskens, P.; Kleinen, J.; Bruckmann, A.; Lehmann, C. W.; Klankermayer, J.; Leitner, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 3689. (f) Chen, D.; Schmitkamp, M.; Francio, G.; Klankermayer, J.; Leitner, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7339.
7. (a) Laarhoven, W. H.; Cuppen, T. J. H. M. *J. Chem. Soc., Chem. Commun.* **1977**, 47a. (b) Choi, Y. H.; Kwak, J.; Jeong, N. *Tetrahedron Lett.* **2009**, *50*, 6068. (c) Nagata, Y.; Takeda, R.; Suginome, M. *ACS Cent. Sci.* **2019**, *5*, 1235.
8. Cotton, S. A. *Lanthanide and Actinide Chemistry*; Wiley: Hoboken, NJ, 2006.
9. Peyton, L. R.; Gallagher, S.; Hashemzadeh, M. *Drugs of Today* **2015**, *51*, 705.
10. (a) Xu, X. Preparation of efinaconazole. CN Patent 104327047, 2014. (b) Bao, J.; Huang, Y.; Ding, W.; Jiang, Y.; Zhang, X. Synthetic method of efinaconazole and intermediate thereof. CN Patent 104292214 A, 2014.
11. (a) Tsunoda, T.; Ozaki, F.; Ito, S. *Tetrahedron Lett.* **1994**, *35*, 5081. (b) Tsunoda, T.; Nagaku, M.; Nagino, C.; Kawamura, Y.; Ozaki, F.; Hioki, H.; Ito, S. *Tetrahedron Lett.* **1995**, *36*, 2531. (c) Tsunoda, T.; Ozaki, F.; Shirakata, N.; Tamaoka, Y.; Yamamoto, H.; Ito, S. *Tetrahedron Lett.* **1996**, *37*, 2463.
12. For previous examples of synthsis of efinaconazole, see: (a) Ogura, H.; Kobayashi, H.; Nagai, K.; Nishida, T.; Naito, T.; Tatsumi, Y.; Yokoo, M.; Arika, T. *Chem. Pharm. Bull.* **1999**, *47*, 1417. (b) Tatsumi, Y.; Yokoo, M.; Arika, T.; Yamaguchi, H. *Antimicrob. Agents Chemother.* **2001**, *45*, 1493. (c) Tatsumi, Y.; Nagashima, M.; Shibanushi, T.; Iwata, A.; Kangawa, Y.; Inui, F.; Siu, W. J. J.; Pillai, R.; Nishiyama, Y. *Antimicrob. Agents Chemother.* **2013**, *57*, 2405. (d) Tamura, K.; Kumagai, N.; Shibasaki, M. *J. Org. Chem.* **2014**, *79*, 3272.
13. For previous examples of synthsis of albaconazole, see: Bartroli, J.; Turmo, E.; Algueró, M.; Boncompte, E.; Vericat, M. L.; Conte, L.; Ramis, J.; Merlos, M.; Garćıa-Rafanell, J.; Forn, J. *J. Med. Chem.* **1998**, *41*, 1869.
14. For reviews of flow reactions, see: (a) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675. (b) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011**, *47*, 4583. (c) Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, *354*, 17. (d) Baxendale, I. R. *J. Chem. Technol. Biotechnol.* **2013**, *88*, 519. (e) Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**, *42*, 8849. (f) Tsubogo, T.; Ishiwata, T.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 6590. (g) Zhao, D.; Ding, K. *ACS Catal.* **2013**, *3*, 928. (h) Atodiresei, I.; Vila, C.; Rueping, M. *ACS Catal.* **2015**, *5*, 1972. (i) Munirathinam, R.; Huskens, J.; Verboom, W. *Adv. Synth. Catal.* **2015**, *357*, 1093. (j)

Britton, J.; Raston, C. L. *Chem. Soc. Rev.* **2017**, *46*, 1250. (k) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev.* **2017**, *117*, 11796.
15. For reviews of asymmetric flow catalysis, see: (a) Mak, X. Y.; Laurino, P.; Seeberger, P. H. Beilstein *J. Org. Chem.* **2009**, *5*, 19. (b) Ishitani, H.; Saito, Y.; Kobayashi, S. *Top. Organomet. Chem.* **2016**, *57*, 213.
16. For leading examples of the utility of flow catalysis for streamlined synthesis of therapeutics, see: (a) Tsubogo, T.; Oyamada, H.; Kobayashi, S. *Nature* **2015**, *520*, 329. (b) Ziegler, R. E.; Desai, B. K.; Jee, J. A.; Gupton, B. F.; Roper, T. D.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2018**, *57*, 7181.
17. Karasawa, T.; Oriez, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2018**, *140*, 12290.

Experimental Section for chapter 2 entitled

anti-Selective Catalytic Asymmetric Nitroaldol Reaction of α-Keto Esters

Table of Contents:

A. General Methods

A-1. Reactions and purifications

Unless otherwise noted, all reactions were carried out in an oven-dried glassware fitted with a 3-way glass stopcock under an argon atmosphere with magnetically stirred chips. All work-up and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Thin layer chromatography (TLC) was performed on Merck TLC plates (0.25 mm) pre-coated with silica gel 60 F254 and visualized by UV quenching and staining with $KMnO_4$ or ninhydrine. Flash column chromatography was performed on a Biotage Isolera Spektra One with a Redisep column.

A-2. Characterizations

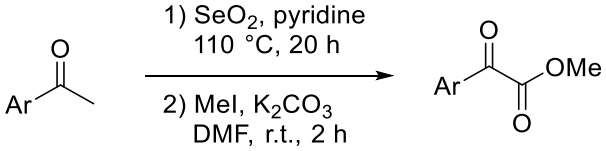
Infrared (IR) spectra were recorded on a HORIBA FT210 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL ECS-400. Chemical shifts (δ) are given in ppm relative to residual solvent peaks.[1] Data for ^{1}H NMR are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet), q (quartet), m (multiplet), br (broad). For ^{19}F NMR, chemical shifts were reported in the scale relative to $PhCF_3$ (δ –62.7680 ppm in $CDCl_3$) as an external reference. High performance liquid chromatography (HPLC) analysis was performed on Jasco analytical instruments with single pump and UV detector. Optical rotation was measured using a 1 mL cell with a 10 cm path length on a JASCO polarimeter P-1030. High-resolution mass spectra were measured on a Thermo Fisher Scientific LTQ Orbitrap XL.

A-3. Solvents and reagents

THF, Et_2O, DME, CPME, toluene, CH_2Cl_2 and DMF were purified by passing through a solvent purification system (Glass Contour). 2-Me-THF was purchased from Aldrich (anhydrous and inhibitor-free). Nitroethane (**3a**), nitropropane (**3b**) and nitromethane (**3d**) were purchased from TCI Co. Ltd. and nitroethane was used after distillation. Amide-based ligand **1a** and ***ent*-1a** were prepared by the reported procedure.[2] $NdCl_3 \bullet 6H_2O$ was purchased from Wako Pure Chemical Co. Ltd. and used after grinding with a mortar. 2.0 M NaO^tBu/THF was purchased from Aldrich. All other starting materials were used as supplied by commercial venders or prepared by the method described corresponding reference.

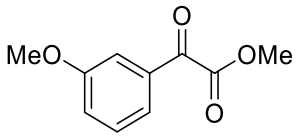
B. Preparation of α-keto esters

Methyl benzoylformate (**2a**), ethyl benzoylformate (**2p**) were purchased from TCI Co. Ltd. α-Keto ester **2n**[3] and **2q**[4] were prepared according to the known procedure. α-Keto esters **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, **2j**, **2k**, **2l** and **2m** were prepared by general procedure A. α-Keto esters **2b**,[3] **2c**,[3] **2e**,[5] **3f**,[5] **3g**,[5] **3h**,[3] **3l**[3] and **3m**[3] are known compounds.



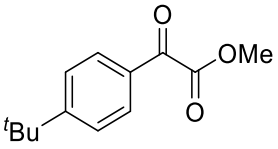
General procedure A: To a solution of functionalized acetophenone in pyridine (1.0 M) was added selenium dioxide (2.0 eq.) at room temperature and the mixture was stirred at 110 °C for 20 h. After filtration of the reaction mixture, the residue was washed with CH_2Cl_2 and the filtrate was concentrated in *vacuo*. The resulting residue was used for the next reaction without further purification. To a solution of above residue in DMF (0.6 M) was added K_2CO_3 (3.0 eq.) and MeI (3.0 eq.) at 0 °C and the mixture was stirred at room temperature for 2 h. After quenching with 1 N HCl aq., the resulting mixture was extracted with Et_2O. The combined organic layers were washed with sat. $NaHCO_3$ aq., 10% $Na_2S_2O_3$ aq. and brine, then dried over Na_2SO_4. After concentration in *vacuo*, the resulting residue was purified by silica gel chromatography (EtOAc/*n*-hexane) to give the corresponding α-keto methyl ester.

Methyl 2-(3-methoxyphenyl)-2-oxoacetate (2d):



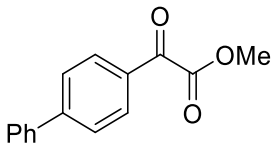
Prepared by the general procedure A from 3′-methoxy acetophenone (1.00 g, 6.7 mmol, 1.0 eq.) and isolated as a colorless oil (1.20 g, 6.2 mmol, 93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (ddt, *J* = 1.0, 1.5, 8.0 Hz, 1H), 7.53 (dd, *J* = 1.5, 2.7 Hz, 1H), 7.41 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.21 (ddt, J = 1.0, 2.7, 8.0 Hz, 1H), 3.98 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.3, 164.4, 160.3, 134.0, 130.3, 123.6, 122.3, 113.6, 58.9, 53.1; IR (thin film) *ν* 1741, 1686, 1598, 1582, 1488, 1432, 1253, 1198, 1156, 1019 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_{10}O_4Na$ *m*/*z* 217.0482 [M+Na]$^+$, found 217.0473

Methyl 2-(4-(*tert*-butyl)phenyl)-2-oxoacetate (2j):



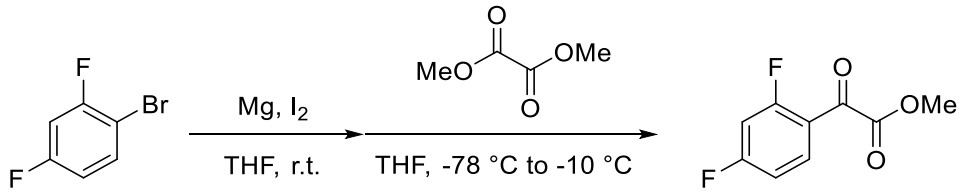
Prepared by the general procedure A from 4′-*tert*-butyl acetophenone (1.50 g, 8.5 mmol, 1.0 eq.) and isolated as a colorless oil (1.75 g, 7.9 mmol, 93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H), 3.97 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 164.6, 159.5, 130.4, 130.3, 126.3, 53.0, 35.7, 31.3; IR (thin film) *ν* 2964, 1741, 1684, 1604, 1216, 1175, 1109, 1002, 853, 718 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{16}O_3Na$ *m*/*z* 243.1003 [M+Na]$^+$, found 243.0993

Methyl 2-([1,1'-biphenyl]-4-yl)-2-oxoacetate (2k):



Prepared by the general procedure A from 4′-phenyl acetophenone (1.50 g, 7.6 mmol, 1.0 eq.) and isolated as a white solid (1.49 g, 6.2 mmol, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (m, 2H), 7.74 (m, 2H), 7.64 (m, 2H), 7.51-7.43 (m, 3H), 4.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.9, 164.4, 148.0, 139.8, 131.5, 131.1, 129.4, 129.0, 127.8, 127.7, 53.2; IR (thin film) *ν* 1736, 1685, 1602, 1213, 1173, 1025, 1003, 855, 744, 695 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{12}O_3Na$ *m*/*z* 263.0690 [M+Na]$^+$, found 263.0677

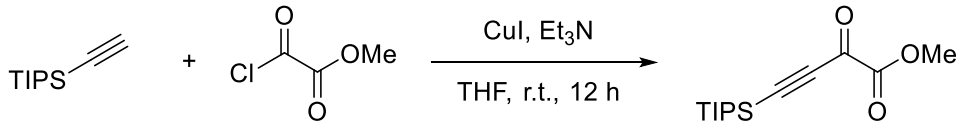
Methyl 2-(2,4-difluorophenyl)-2-oxoacetate (2i):



2i

To a flame-dried round bottom flask were added magnesium turnings (1.30 g, 53.4 mmol, 1.35 eq.), one small piece of crystal of iodine and THF (16 mL) at room temperature. 1-Bromo-2,4-difluorobenzene (5.8 mL, 51.8 mmol, 1.3 eq.) in THF (24 mL) was added dropwise for 1 h at room temperature and the resulting mixture was stirred for 15 min. The resulting mixture was added slowly to a solution of dimethyl oxalate (4.70 g, 39.8 mmol, 1.0 eq.) in THF (24 mL) at -78 °C. The mixture was stirred at -78°C for 3 h then the temperature was slowly increased to -10 °C. After stirring for 1 h, 1 N HCl aq. was added slowly and the resulting mixture was extracted 4 times with EtOAc . The combined organic layers were washed with brine, and dried over Na_2SO_4. After concentration in *vacuo*, the resulting residue was purified by silica gel chromatography (EtOAc/*n*-hexane) to give methyl 2-(2,4-difluorophenyl)-2-oxoacetate (**2i**, 6.40 g, 32.0 mmol, 80%) as a pale yellow solid.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (m, 1H), 7.04 (m, 1H), 6.91 (m, 1H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 167.9 (dd, *J* = 12.4, 259.6 Hz), 164.8, 164.3 (dd, *J* = 13.1, 258.8 Hz), 133.6 (dd, *J* = 2.9, 10.9 Hz), 119.1 (dd, J = 3.7, 10.9 Hz), 113.6 (dd, *J* = 3.6, 21.9), 105.7 (dd, *J* = 24.8, 24.8 Hz), 53.8; ^{19}F NMR (376 MHz, $CDCl_3$) -97.1, -106.8; IR (thin film) *ν* 1749, 1692, 1611, 1273, 1231, 1204, 1181, 1099, 1008 cm^{-1}; HRMS (ESI) calcd. for $C_9H_6F_2O_3Na$ *m*/*z* 223.0188 [M+Na]$^+$, found 223.0180

Methyl 2-oxo-4-(triisopropylsilyl)but-3-ynoate (2o):



2o

To a solution of ethynyltriisopropylsilane (2.22 mL, 10 mmol) in THF (25 mL) were added CuI (190 mg, 1.0 mmol, 0.1 eq.) and Et_3N (2.77 mL, 0.020 mol, 2.0 eq.) at room temperature, and methyl 2-chloro-2-oxoacetate (1.11 mL, 12 mmol, 1.2 eq.) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 12 h. After quench with 1 N HCl aq. (25 mL), the resulting mixture was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with sat. $NaHCO_3$ aq. (25 mL) and brine (25 mL), and dried over Na_2SO_4. After concentration in *vacuo*, the resulting residue was purified by silica gel chromatography (EtOAc/*n*-hexane) to give methyl 2-oxo-4-(triisopropylsilyl)but-3-ynoate (**2o**, 1.97 g, 7.4 mmol, 74%) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 1.15 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 159.6, 105.9, 102.7, 53.9, 18.8, 11.3; IR (thin film) *ν* 2947, 2868, 2147, 1763, 1747, 1685, 1268, 1101 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{24}O_3SiNa$ *m*/*z* 291.1398 [M+Na]$^+$, found 291.1392

C. Preparation of catalyst for anti-selective catalytic asymmetric nitroaldol reaction

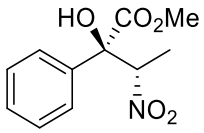
A flame-dried test tube (20 mL) was charged with $NdCl_3 \bullet 6H_2O$ (8.6 mg, 0.024 mmol) and amide based ligand **1a** (0.024 mmol), and dried under vacuum at room temperature at least for 5 min. Ar was backfilled (evacuation/backfill was repeated 5 times) to the test tube, then THF (600 μL) was added at room temperature. After stirring the resulting slightly cloudy suspension at 60 °C for 30 min, 2.0 M NaO^{t}Bu/THF (72 μL, 0.144 mmol) was added slowly at the same temperature. After stirring the resulting mixture at 60 °C for 1 h (white precipitate appeared), the mixture was cooled to room temperature and nitroethane (172 μL, 2.4 mmol) was added. Self-assembly of Nd/Na catalyst initiated in a few minutes and the resulting mixture was stirred at room temperature for 12 h to give a thick white suspension. The whole suspension was transferred to an Eppendorf tube with THF washing (0.5 mL x 2). The tube was centrifuged at ca. 10,000 rpm for 30 sec. The supernatant

was decanted and THF (1.6 mL) was added. The tube was agitated using a vortex mixer for 30 sec and centrifuged again, then the supernatant was decanted (washing process). This washing process was repeated again. The resulting precipitate was agitated with reaction solvent (1.6 mL) and a part of resulting suspension (0.015 mmol/1000 μL) was used for *anti*-selective catalytic asymmetric nitroaldol reaction. (Note: THF and nitroethane were essential for formation of the heterogeneous catalyst. Self-assembly did not proceed well with a solvent other than THF nor a nitroalkane other than nitroethane.)

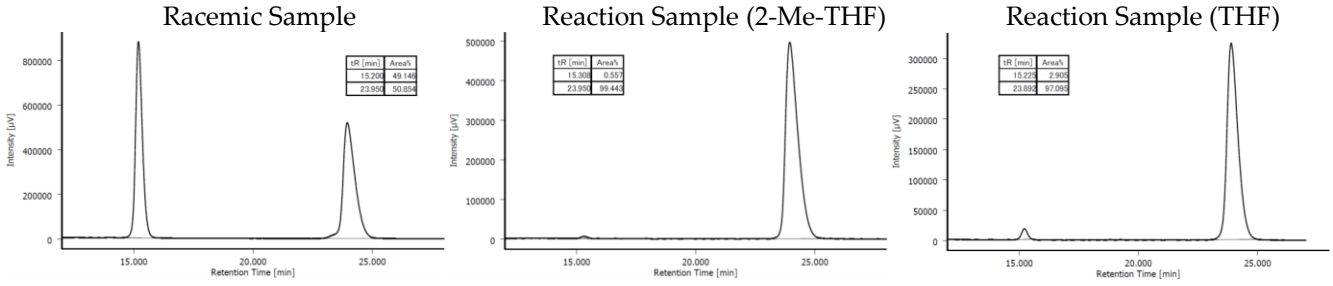
D. Representive procedure for anti-selective catalytic asymmetric nitroaldol reaction

A flame-dried 20 mL test tube was charged with 2-Me-THF (1120 μL) and catalyst suspension prepared in above section (80 μL, 0.0012 mmol, 1 mol%) (total 1200 μL). After adding nitroethane (86 μL, 1.2 mmol, 10 eq.) at room temperature, the mixture was cooled to –60 °C and then 0.82 M methyl benzoylformate (**2a**)/2-Me-THF (146 μL, 0.12 mmol) was added dropwise for 1 min. After stirring the reaction mixture at the same temperature for 20 h, 0.2 M AcOH/THF (500 μL) was added slowly and warmed to room temperature. H_2O (1 mL) was added and the resulting mixture was extracted with EtOAc (2 mL). The organic layer was dried over Na_2SO_4. After removal of volatiles under reduced pressure, the resulting residue was analyzed by ^1H NMR to determine diastereomeric ratio of product (*anti*/*syn* = >98/2). The crude product was purified by silica gel column chromatography (EtOAc/*n*-hexane) to give **4aa** as a white solid and a single diastereomer (27.7 mg, 11.5 mmol, 97%). Enantiomeric excess was determined by chiral HPLC analysis (99% ee).

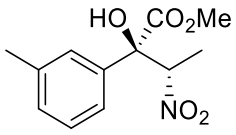
Methyl (2*R*,3*S*)-2-hydroxy-3-nitro-2-phenylbutanoate (4aa):



White solid; 27.7 mg (97%, reaction in 2-Me-THF), 27.8 mg (97%, reaction in THF); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.63 (m, 2H), 7.43-7.34 (m, 3H), 5.35 (q, *J* = 6.8 Hz, 1H), 4.10 (s, 1H), 3.86 (s, 3H), 1.38 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 136.6, 128.9, 128.9, 125.5, 87.2, 78.7, 54.0, 13.1; IR (thin film) *ν* 3499, 1733, 1555, 1449, 1389, 1360, 1260, 1176, 1157, 703 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{13}NO_5Na$ *m*/*z* 261.0686 $[M+Na]^+$, found 262.0687; $[\alpha]_D^{25}$ -44.3 (*c* 1.32, $CHCl_3$, 99% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 24.0 min (major), 15.3 min (minor):

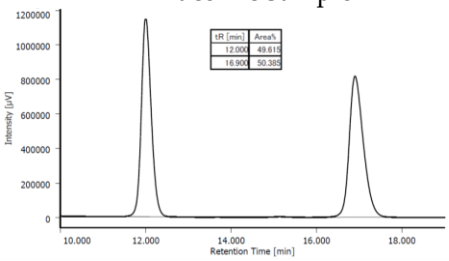


Methyl (2*R*,3*S*)-2-hydroxy-3-nitro-2-(*m*-tolyl)butanoate (4ba):

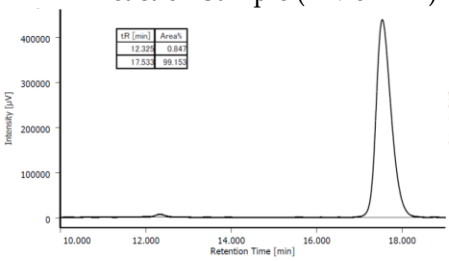


White solid; 28.9 mg (95%, reaction in 2-Me-THF), 28.7 mg (94%, reaction in THF); ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.28 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 5.34 (q, *J* = 7.1 Hz, 1H), 4.08 (s, 1H), 3.85 (s, 3H), 2.38 (s, 3H), 1.39 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 139.0, 136.8, 129.9, 129.1, 126.4, 122.9, 87.5, 79.0, 54.2, 22.0, 13.5; IR (thin film) *ν* 3491, 2955, 1738, 1552, 1439, 1387, 1360, 1263, 1236, 1160, 698 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{15}NO_5Na$ *m*/*z* 276.0842 $[M+Na]^+$, found 276.0844; $[\alpha]_D^{25}$ -47.2 (*c* 1.39, $CHCl_3$, 98% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 17.5 min (major), 12.3 min (minor):

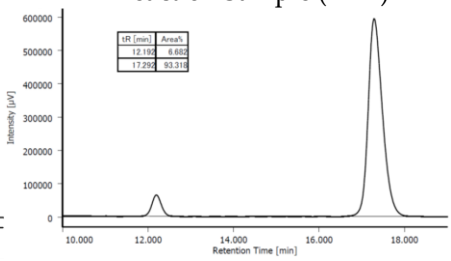
Racemic Sample



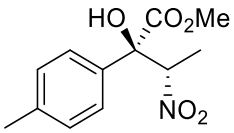
Reaction Sample (2-Me-THF)



Reaction Sample (THF)

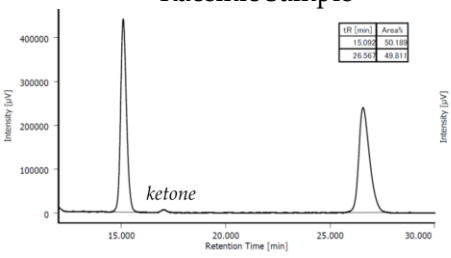


Methyl (2*R*,3*S*)-2-hydroxy-3-nitro-2-(*p*-tolyl)butanoate (4ca):

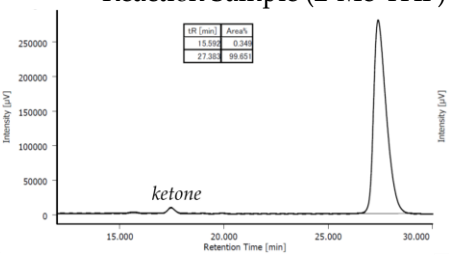


White solid; 28.8 mg (95%, reaction in 2-Me-THF), 28.6 mg (94%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 5.33 (q, *J* = 7.1 Hz, 1H), 4.07 (s, 1H), 3.84 (s, 3H), 2.35 (s, 3H), 1.38 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 139.1, 133.9, 129.9, 125.7, 87.5, 79.0, 54.2, 21.4, 13.4; IR (thin film) *ν* 3491, 2955, 1739, 1553, 1510, 1448, 1388, 1360, 1261, 1157 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{15}NO_5Na$ *m*/*z* 276.0842 $[M+Na]^+$, found 276.0843, found 276.0844; $[\alpha]_D^{25}$ -41.8 (*c* 1.29, $CHCl_3$, 99% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 27.4 min (major), 15.6 min (minor):

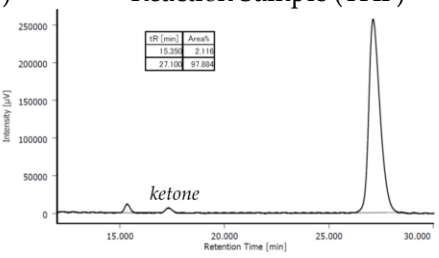
Racemic Sample



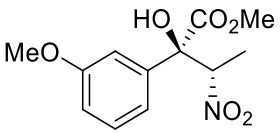
Reaction Sample (2-Me-THF)



Reaction Sample (THF)

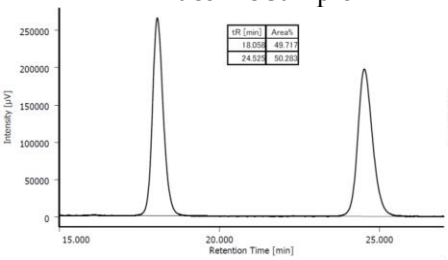


Methyl (2*R*,3*S*)-2-hydroxy-2-(3-methoxyphenyl)-3-nitrobutanoate (4da):

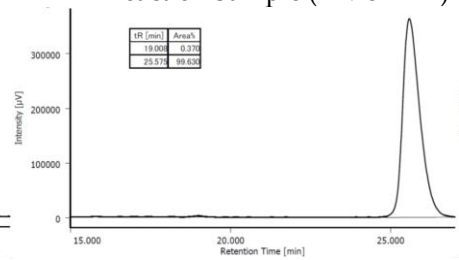


White solid; 30.0 mg (93%, reaction in 2-Me-THF), 29.1 mg (90%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.22 (dd, *J* = 2.2, 2.2 Hz, 1H), 7.18 (ddd, *J* = 0.7, 2.2, 8.0 Hz, 1H), 6.89 (ddd, *J* = 0.7, 2.2, 8.0 Hz, 1H), 5.33 (q, *J* = 6.8 Hz, 1H), 4.10 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 1.38 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 160.0, 138.2, 129.9, 117.7, 114.1, 111.6, 87.1, 78.6, 55.4, 54.0, 13.1; IR (thin film) *ν* 3486, 2955, 1739, 1600, 1552, 1436, 1265, 1159, 1048, 695 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{15}NO_6Na$ *m*/*z* 292.0792 $[M+Na]^+$, found 292.0796; $[\alpha]_D^{25}$ -49.1 (*c* 1.54, $CHCl_3$, 99% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 25.6 min (major), 19.0 min (minor):

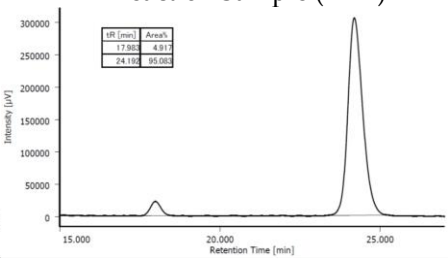
Racemic Sample



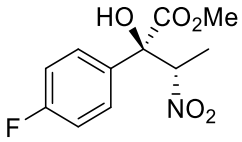
Reaction Sample (2-Me-THF)



Reaction Sample (THF)

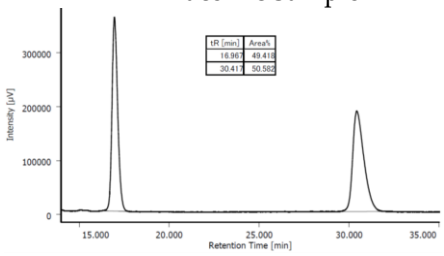


Methyl (2*R*,3*S*)-2-(4-fluorophenyl)-2-hydroxy-3-nitrobutanoate (4ea):

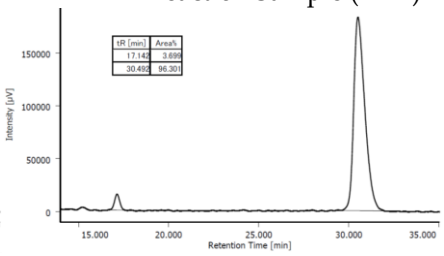


White solid; 29.1 mg (94%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.61 (m, 2H), 7.11-7.07 (m, 2H), 5.31 (q, *J* = 7.1 Hz, 1H), 4.12 (s, 1H), 3.86 (s, 3H), 1.37 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 163.3 (d, *J* = 247.2 Hz), 132.6 (d, *J* = 2.9 Hz), 127.9 (d, *J* = 8.0 Hz), 116.2 (d, J = 21.9 Hz), 87.4, 78.7, 54.4, 13.3; ^{19}F NMR (376 MHz, $CDCl_3$) -112.9; IR (thin film) *ν* 3488, 1739, 1604, 1554, 1508, 1262, 1230, 1162, 840, 820 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}NFO_5Na$ *m*/*z* 280.0592 [M+Na]$^+$, found 280.0593; $[\alpha]_D^{25}$ -35.0 (*c* 1.87, $CHCl_3$, 93% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 17.5 min (major), 31.8 min (minor):

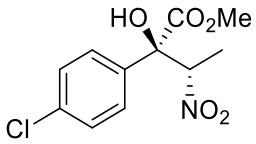
Racemic Sample



Reaction Sample (THF)

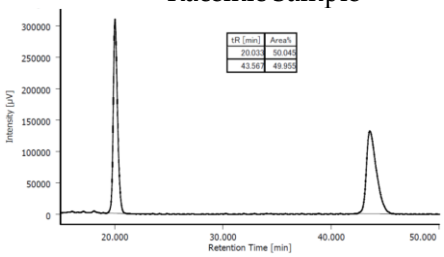


Methyl (2*R*,3*S*)-2-(4-chlorophenyl)-2-hydroxy-3-nitrobutanoate (4fa):

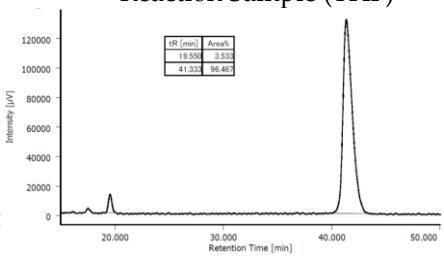


White solid; 31.0 mg (94%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (ddd, *J* = 2.7, 2.7, 8.8 Hz, 2H), 7.38 (ddd, *J* = 2.7, 2.7, 8.8 Hz, 2H), 5.30 (q, *J* = 7.1 Hz, 1H), 4.12 (s, 1H), 3.86 (s, 3H), 1.38 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 135.5, 135.4, 129.4, 127.4, 87.3, 78.7, 54.5, 13.3; IR (thin film) *ν* 3485, 1739, 1554, 1486, 1439, 1388, 1360, 1260, 1155, 1011 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}ClNO_5Na$ *m*/*z* 296.0296 [M+Na]$^+$, found 296.0297; $[\alpha]_D^{25}$ -27.8 (*c* 1.49, $CHCl_3$, 95% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 19.8 min (major), 42.4 min (minor):

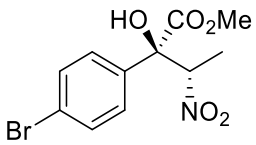
Racemic Sample



Reaction Sample (THF)

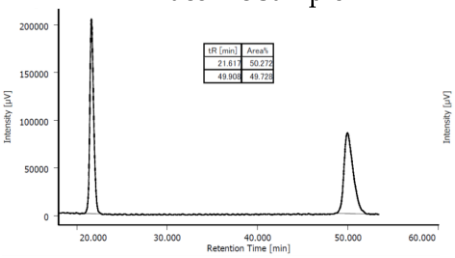


Methyl (2*R*,3*S*)-2-(4-bromophenyl)-2-hydroxy-3-nitrobutanoate (4ga):

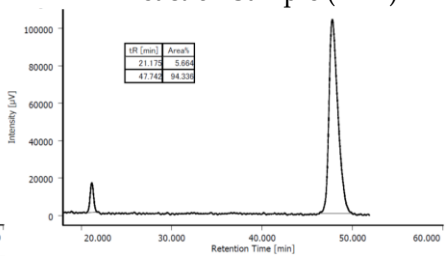


White solid; 36.5 mg (96%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.50 (m, 4H), 5.30 (q, *J* = 7.1 Hz, 1H), 4.11 (s, 1H), 3.86 (s, 3H), 1.38 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 135.7, 132.1, 127.4, 123.3, 86.9, 78.5, 54.2, 13.0; IR (thin film) *ν* 3486, 1739, 1555, 1487, 1439, 1388, 1360, 1260, 1155, 1011 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}BrNO_5Na$ *m*/*z* 339.9791 [M+Na]$^+$, found 339.9792; $[\alpha]_D^{25}$ -27.4 (*c* 1.41, $CHCl_3$, 98% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 21.4 min (major), 48.5 min (minor):

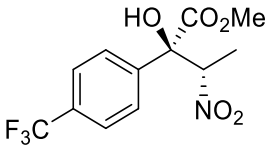
Racemic Sample



Reaction Sample (THF)

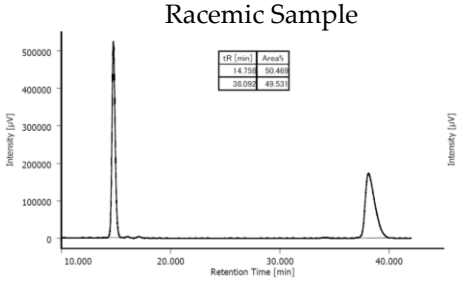


Methyl (2*R*,3*S*)-2-hydroxy-3-nitro-2-(4-(trifluoromethyl)phenyl)butanoate (4ha):

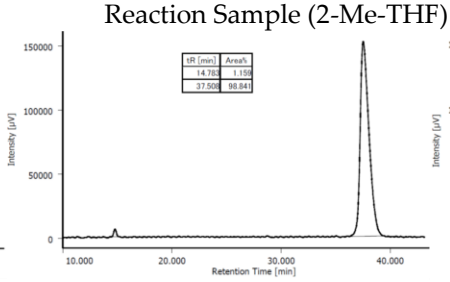


White solid; 35.4 mg (96%, reaction in 2-Me-THF), 35.5 mg (96%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 5.36 (q, *J* = 6.8 Hz, 1H), 4.18 (s, 1H), 3.88 (s, 3H), 1.38 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 140.9, 131.6 (q, *J* = 31.8 Hz), 126.5, 126.2 (q, *J* = 3.6 Hz), 124.1 (q, *J* = 270.5 Hz), 87.2, 78.9, 54.6, 13.4; ^{19}F NMR (376 MHz, $CDCl_3$) -62.8; IR (thin film) *ν* 3490, 1742, 1556, 1328, 1264, 1167, 1128, 1113, 1070, 845 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{12}F_3NO_5Na$ *m*/*z* 330.0517 $[M+Na]^+$, found 330.0562; $[\alpha]_D^{25}$ -36.0 (*c* 1.52, $CHCl_3$, 98% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 37.5 min (major), 14.8 min (minor):

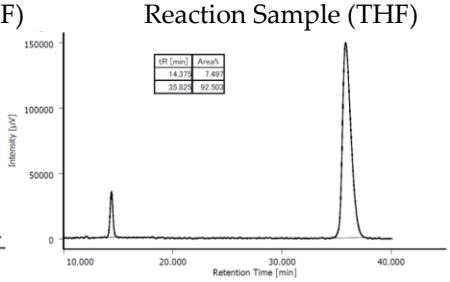
Racemic Sample



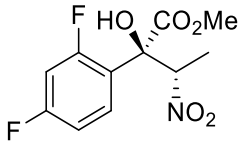
Reaction Sample (2-Me-THF)



Reaction Sample (THF)

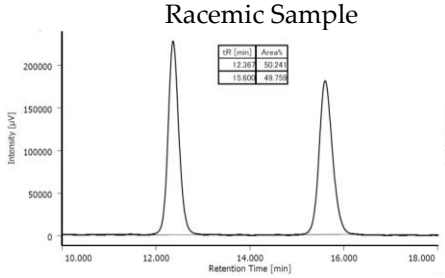


Methyl (2*R*,3*S*)-2-(2,4-difluorophenyl)-2-hydroxy-3-nitrobutanoate (4ia):

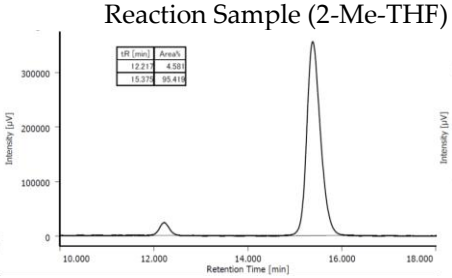


Colorless oil; 26.1 mg (79%, reaction in 2-Me-THF), 29.4 mg (89%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.73 (m, 1H), 6.98-6.92 (m, 1H), 6.87-6.81 (m, 1H), 5.72 (q, *J* = 7.1 Hz, 1H), 4.47 (s, 1H), 3.86 (s, 3H), 1.46 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 163.9 (dd, *J* = 11.7, 250.1 Hz), 159.4 (dd, *J* = 11.7, 249.4 Hz), 130.4 (dd, *J* = 5.1, 9.5 Hz), 120.7 (dd, *J* = 4.4, 13.1 Hz), 112.4 (dd, *J* = 3.7, 21.2 Hz), 105.2 (dd, *J* = 26.3, 27.7 Hz), 84.9 (d, *J* = 8.8 Hz), 77.6, 54.6, 13.4; ^{19}F NMR (376 MHz, $CDCl_3$) -105.5, -108.4; IR (thin film) *ν* 3470, 1742, 1614, 1556, 1499, 1281, 1261, 1159, 1139, 975 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{11}F_2NO_5Na$ *m*/*z* 298.0498 $[M+Na]^+$, found 298.0496; $[\alpha]_D^{25}$ -17.2 (*c* 1.46, $CHCl_3$, 91% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 15.4 min (major), 12.2 min (minor):

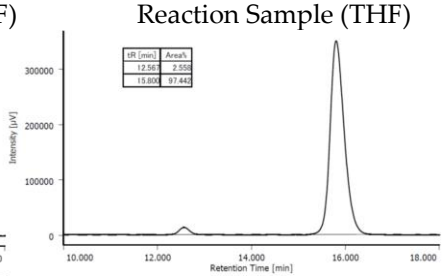
Racemic Sample



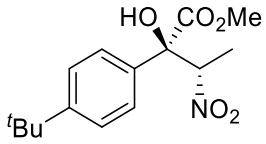
Reaction Sample (2-Me-THF)



Reaction Sample (THF)

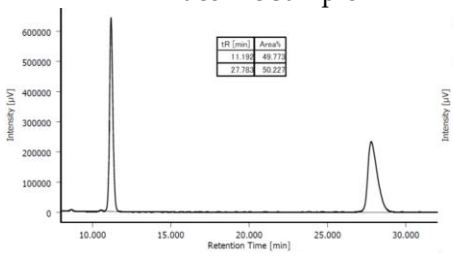


Methyl (2*R*,3*S*)-2-(4-(*tert*-butyl)phenyl)-2-hydroxy-3-nitrobutanoate (4ja):

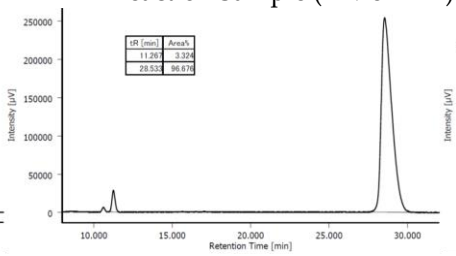


White solid; 30.8 mg (87%, reaction in 2-Me-THF), 24.8mg (70%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (ddd, *J* = 2.2, 2.2, 6.8 Hz, 2H), 7.40 (ddd, *J* = 2.2, 2.2, 6.8 Hz, 2H), 5.34 (q, *J* = 7.1 Hz, 1H), 4.06 (s, 1H), 3.85 (s, 3H), 1.39 (d, *J* = 7.1 Hz, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 152.3, 133.8, 126.1, 125.5, 87.6, 79.0, 54.2, 34.9, 31.6, 13.5; IR (thin film) *ν* 3491, 2961, 1738, 1553, 1387, 1362, 1262, 1158 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{21}N_5Na$ *m*/*z* 318.1323 [M+Na]$^+$, found 318.1315; $[\alpha]_D^{25}$ -29.7 (*c* 1.41, $CHCl_3$, 93% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 28.5 min (major), 11.3 min (minor):

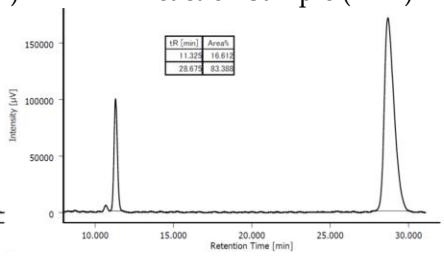
Racemic Sample



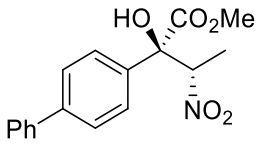
Reaction Sample (2-Me-THF)



Reaction Sample (THF)

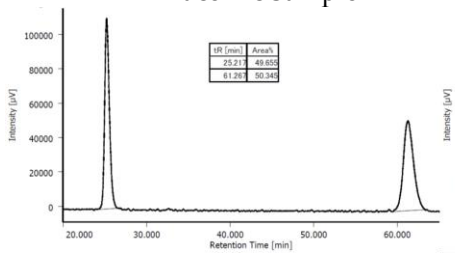


Methyl (2*R*,3*S*)-2-([1,1'-biphenyl]-4-yl)-2-hydroxy-3-nitrobutanoate (4ka):

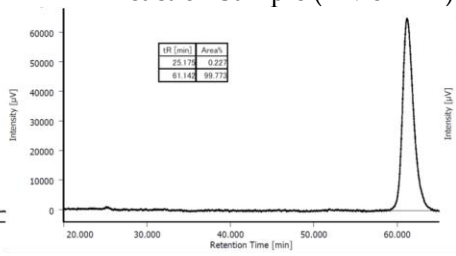


White solid; 36.7 mg (97%, reaction in 2-Me-THF), 31.0 mg (82%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.69 (m, 2H), 7.64-7.58 (m, 4H), 7.47-7.44 (m, 2H), 7.39-7.36 (m, 1H), 5.39 (q, *J* = 7.1 Hz, 1H), 4.14 (s, 1H), 3.88 (s, 3H), 1.44 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 142.1, 140.4, 135.8, 129.2, 128.1, 127.9, 127.4, 126.3, 87.5, 79.0, 54.3, 13.5; IR (thin film) *ν* 3540, 1731, 1538, 1308, 1261, 1069, 1003, 904, 742, 688 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{13}N_7O_3Na$ *m*/*z* 338.0983 [M+Na]$^+$, found 338.0996; $[\alpha]_D^{25}$ -28.3 (*c* 1.63, $CHCl_3$, 99% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 61.1 min (major), 25.2 min (minor):

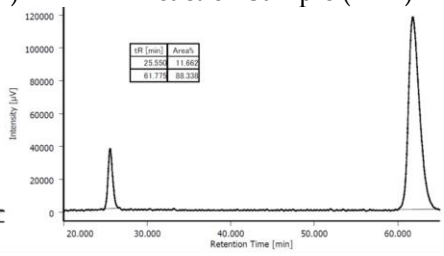
Racemic Sample



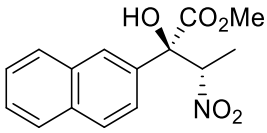
Reaction Sample (2-Me-THF)



Reaction Sample (THF)

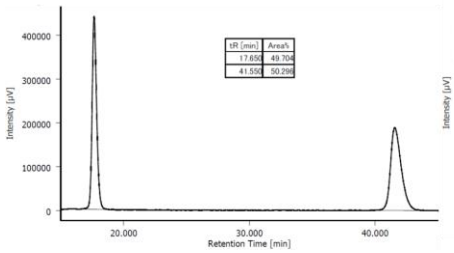


Methyl (2*R*,3*S*)-2-hydroxy-2-(naphthalen-2-yl)-3-nitrobutanoate (4la):

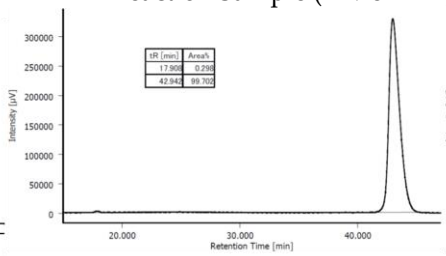


White solid; 33.7 mg (97%, reaction in 2-Me-THF), 32.4 mg (93%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 1.7 Hz, 1H), 7.90-7.84 (m, 3H), 7.67 (dd, *J* = 2.0, 8.6 Hz, 1H), 7.55-7.51 (m, 2H), 5.49 (q, *J* = 7.1 Hz, 1H), 4.24 (s, 1H), 3.87 (s, 3H), 1.41 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 134.4, 133.8, 133.7, 129.4, 129.2, 128.2, 127.6, 127.4, 126.1, 123.2, 87.7, 79.6, 54.7, 13.8; IR (thin film) *ν* 3535, 1740, 1550, 1362, 1264, 1242, 1206, 1163, 822, 753 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{15}NO_5Na$ *m*/*z* 312.0842 [M+Na]$^+$, found 312.0844; $[\alpha]_D^{25}$ -81.5 (*c* 1.35, $CHCl_3$, 99% ee); HPLC analysis: CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 42.9 min (major), 17.9 min (minor):

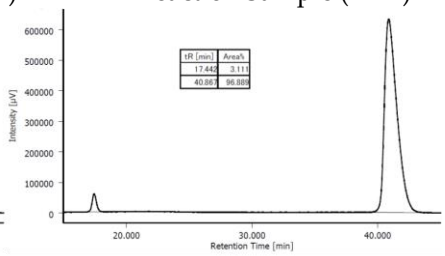
Racemic Sample



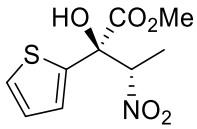
Reaction Sample (2-Me-THF)



Reaction Sample (THF)

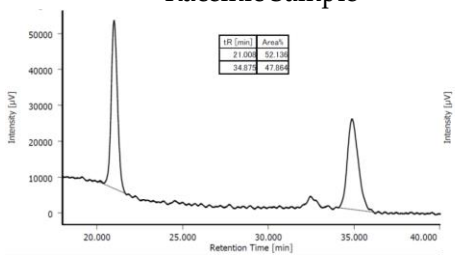


Methyl (2*R*,3*S*)-2-hydroxy-3-nitro-2-(thiophen-2-yl)butanoate (4ma):

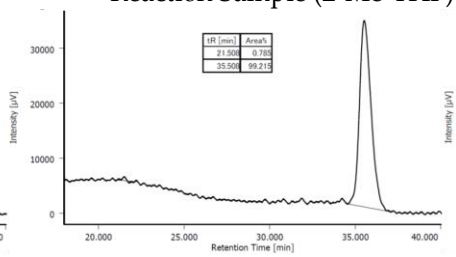


Colorless oil; 23.2 mg (79%, reaction in 2-Me-THF), 25.0 mg (85%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 1.2, 5.0 Hz, 1H), 7.15 (dd, *J* = 1.2, 3.7 Hz, 1H), 7.02 (dd, *J* = 3.7, 5.0 Hz, 1H), 5.25 (q, *J* = 6.8 Hz, 1H), 4.28 (s, 1H), 3.91 (s, 3H), 1.49 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 141.4, 128.0, 127.0, 125.6, 87.4, 78.2, 54.5, 13.3; IR (thin film) *ν* 3481, 1741, 1553, 1360, 1265, 1232, 1148, 712 cm^{-1}; HRMS (ESI) calcd. for $C_9H_{11}NO_5SNa$ *m*/*z* 268.0261 $[M+Na]^+$, found 268.0251; $[\alpha]_D^{25}$ -30.0 (*c* 1.21, $CHCl_3$, 98% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 35.5 min (major), 21.5 min (minor):

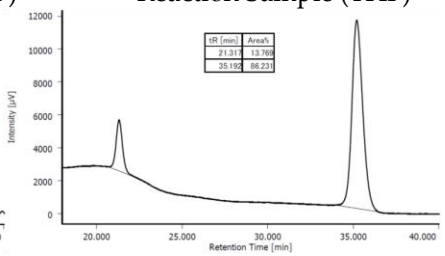
Racemic Sample



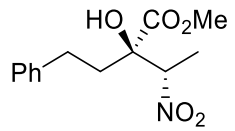
Reaction Sample (2-Me-THF)



Reaction Sample (THF)

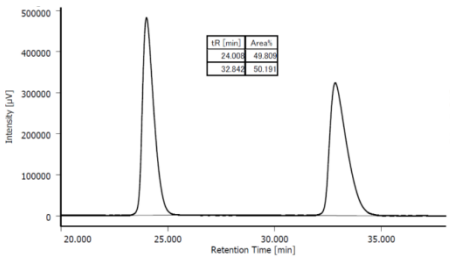


Methyl (2*R*,3*S*)-2-hydroxy-3-nitro-2-phenethylbutanoate (4na):

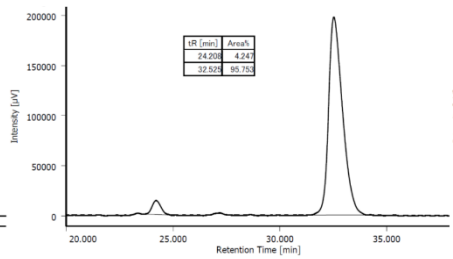


Colorless oil; 26.0 g (81%, reaction in 2-Me-THF), 25.9 mg (81%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.23-7.18 (m, 1H), 7.17-7,14 m, 2H), 4.90 (q, *J* = 7.1 Hz, 1H), 3.85 (s, 3H), 3.62 (s, 1H), 2.86-2.79 (m, 1H), 2.38-2.30 (m, 1H), 1.98-1.94 (m, 2H), 1.64 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 140.7, 128.9, 128.7, 126.7, 87.5, 78.2, 53.9, 38.2, 30.0, 13.1; IR (thin film) *ν* 3496, 1740, 1552, 1256, 1199, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{16}NO_5$ *m*/*z* 266.1034 [M-H]-, found 266.1031; $[\alpha]_D^{25}$ 7.1 (*c* 1.34, $CHCl_3$, 92% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 32.5 min (major), 24.2 min (minor):

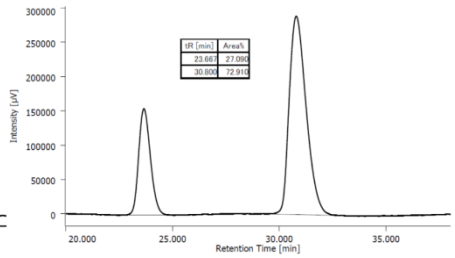
Racemic Sample



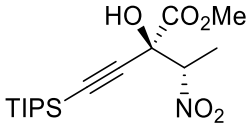
Reaction Sample (2-Me-THF)



Reac



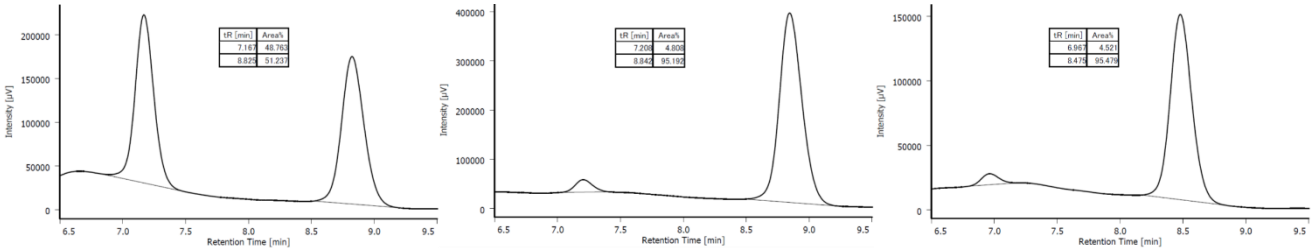
Methyl (*R*)-2-hydroxy-2-((*S*)-1-nitroethyl)-4-(triisopropylsilyl)but-3-ynoate (4oa):



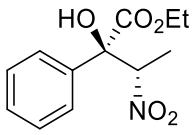
Colorless oil; 32.2 mg (78%, reaction in 2-Me-THF), 29.2 mg (70%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (q, *J* = 7.1 Hz, 1H), 3.92 (s, 3H), 3.84 (s, 1H), 1.85 (d, *J* = 7.1 Hz, 3H), 1.07-1.04 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 101.4, 91.1, 85.9, 72.5, 54.7, 18.8, 13.6, 11.3; IR (thin film) *ν* 3490, 2946, 2867, 1751, 1559, 1387, 1261, 1148,

882, 679 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{28}NO_5Si$ *m/z* 342.1742 [M-H]$^-$, found 342.1746; $[\alpha]_D^{25}$ 5.3 (*c* 1.38, $CHCl_3$, 91% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 8.8 min (major), 7.2 min (minor):

Racemic Sample | Reaction Sample (2-Me-THF) | Reaction Sample(THF)

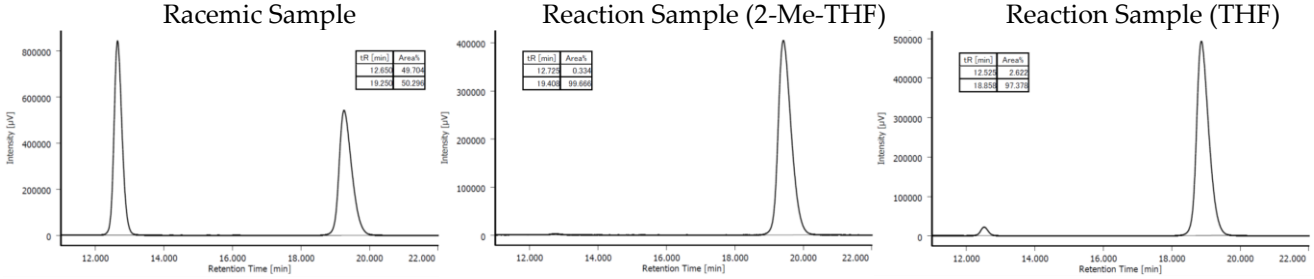


Ethyl (2*R*,3*S*)-2-hydroxy-3-nitro-2-phenylbutanoate (4pa):

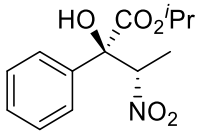


Colorless oil; 29.2 mg (96%, reaction in 2-Me-THF), 29.5 mg (97%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.64 (m, 2H), 7.42-7.33 (m, 3H), 5.35 (q, *J* = 7.1 Hz, 1H), 4.35-4.27 (m, 2H), 4.10 (s, 1H), 1.38 (d, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 137.1, 129.1, 129.1, 125.9, 87.5, 78.8, 63.7, 14.2, 13.5; IR (thin film) *ν* 3487, 1735, 1554, 1449, 1388, 1360, 1254, 1154, 1030, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{15}NO_5Na$ *m/z* 276.0842 [M+Na]$^+$, found 276.084; $[\alpha]_D^{25}$ -34.7 (*c* 1.56, $CHCl_3$, 99% ee); HPLC analysis: CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 19.4 min (major), 12.7 min (minor):

Racemic Sample | Reaction Sample (2-Me-THF) | Reaction Sample (THF)

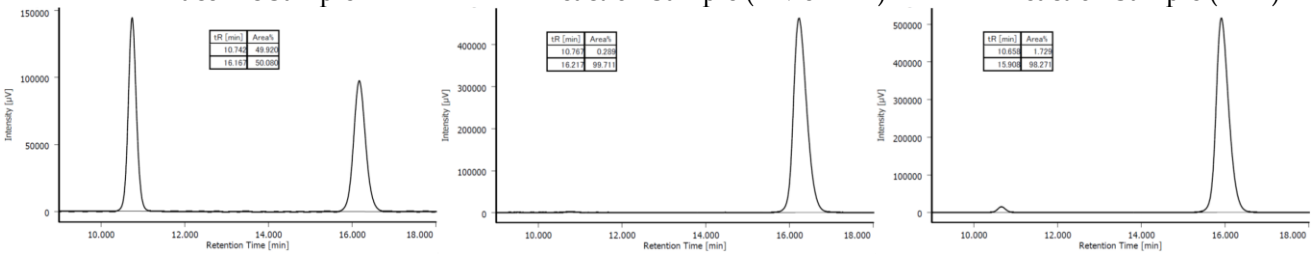


Isopropyl (2*R*,3*S*)-2-hydroxy-3-nitro-2-phenylbutanoate (4qa):

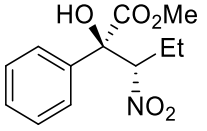


White solid; 30.4 mg (95%, reaction in 2-Me-THF), 31.9 mg (99%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.64 (m, 2H), 7.42-7.33 (m, 3H), 5.33 (q, *J* = 6.8 Hz, 1H), 5.12 (qq, *J* = 6.1, 6.1 Hz, 1H), 4.10 (s, 1H), 1.38 (d, *J* = 6.8 Hz, 3H), 1.31 (d = 6.1 Hz, 3H), 1.26 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 137.3, 129.1, 129.0, 125.9, 87.4, 78.7, 72.0, 21.8, 21.7, 13.5; IR (thin film) *ν* 3518, 2985, 1732, 1546, 1445, 1359, 1269, 1175, 705, 607 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{17}NO_5Na$ *m/z* 290.0999 [M+Na]$^+$, found 290.0998; $[\alpha]_D^{25}$ -24.1 (*c* 1.22, $CHCl_3$, 99% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 16.2 min (major), 10.7 min (minor):

Racemic Sample | Reaction Sample (2-Me-THF) | Reaction Sample (THF)

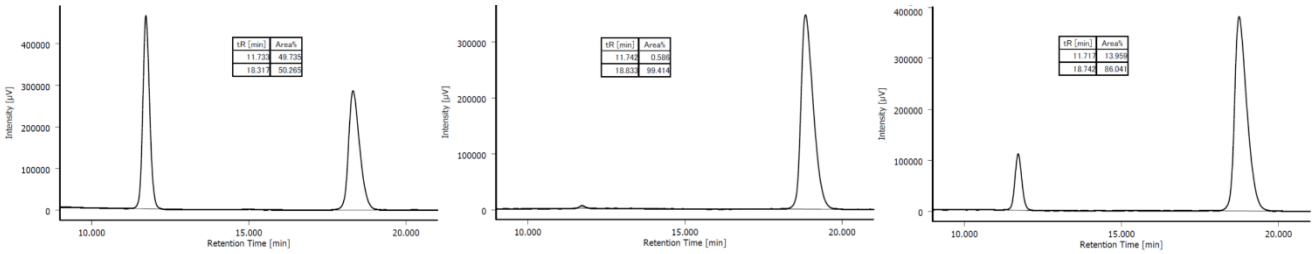


Methyl (2*R*,3*S*)-2-hydroxy-3-nitro-2-phenylpentanoate (4ab):

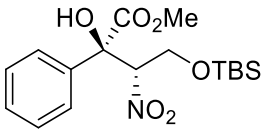


White solid; 29.1 mg (96%, reaction in 2-Me-THF), 25.3 mg (83%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.64 (m, 2H), 7.43-7.34 (m, 3H), 5.16 (dd, *J* = 3.2, 10.3 Hz, 1H), 4.21 (s, 1H), 3.81 (s, 3H), 2.04 (ddq, *J* = 3.2, 7.6, 10.3 Hz, 1H), 1.56 (ddq, *J* = 3.2, 4.4, 7.6 Hz, 1H), 0.90 (dd, *J* = 7.6, 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 136.7, 129.3, 129.2, 125.8, 94.3, 79.6, 54.2, 21.6, 11.3; IR (thin film) *ν* 3503, 2956, 1737, 1552, 1368, 1260, 1172, 1147, 743, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{15}NO_5Na$ *m*/*z* 276.0853 $[M+Na]^+$, found 276.0844; $[\alpha]_D^{25}$ -34.2 (*c* 1.33, $CHCl_3$, 99% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 18.8 min (major), 11.7 min (minor):

Racemic Sample | Reaction Sample (2-Me-THF) | Reaction Sample (THF)

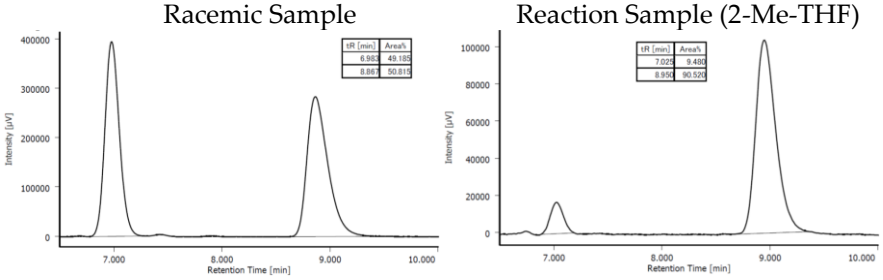


Methyl (2*R*,3*S*)-4-((tert-butyldimethylsilyl)oxy)-2-hydroxy-3-nitro-2-phenylbutanoate (4ac):

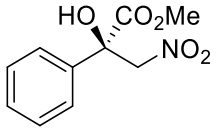


Colorless oil; 31.5 mg (71%, reaction in 2-Me-THF), 8.4 mg (19%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.65 (m, 2H), 7.44-7.36 (m, 3H), 5.37 (dd, *J* = 2.9, 7.5 Hz, 1H), 4.44 (s, 1H), 4.10 (dd, *J* = 7.5, 11.7 Hz, 1H), 3.82 (s, 3H), 3.79 (dd, *J* = 2.9, 11.7 Hz, 1H), 0.79 (s, 9H), -0.07 (s, 3H), -0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 136.7, 129.4, 129.3, 125.8, 93.2, 79.0, 61.0, 54.3, 25.9, 18.4, -5.5; IR (thin film) *ν* 3490, 2955, 2931, 2858, 1740, 1558, 1360, 1258, 1122, 836 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{26}NO_6Si$ *m*/*z* 368.1535 $[M-H]^-$, found 368.1536; $[\alpha]_D^{25}$ -25.4 (*c* 1.58, $CHCl_3$, 81% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 9.0 min (major), 7.0 min (minor):

Racemic Sample | Reaction Sample (2-Me-THF)

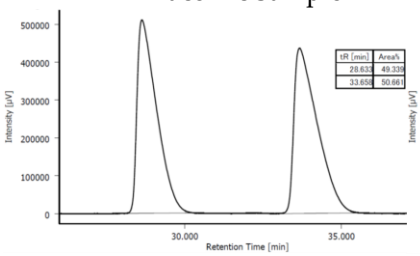


Methyl (*R*)-2-hydroxy-3-nitro-2-phenylpropanoate (4ad):

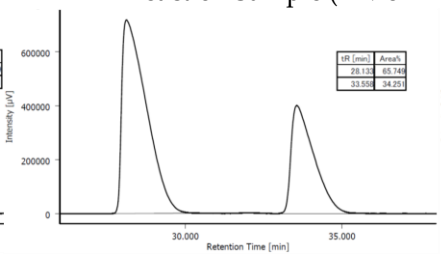


Colorless oil; 25.7 mg (95%, reaction in 2-Me-THF), 26.8 mg (99%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.59 (m, 2H), 7.41-7.39 (m, 3H), 5.26 (dd, *J* = 1.0, 14.2 Hz, 1H), 4.69 (d, *J* = 14.2 Hz, 1H), 4.21 (d, *J* = 1.0 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 136.9, 129.9, 129.6, 125.9, 81.5, 76.8, 54.8; IR (thin film) *ν* 3490, 1739, 1559, 1377, 1270, 1229, 1139, 697 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_{10}NO_5$ *m*/*z* 224.0564 $[M-H]^-$, found 224.0565; $[\alpha]_D^{25}$ 10.3 (*c* 1.63, $CHCl_3$, -44% ee: Reaction sample (THF), (*S*) isomer major)); HPLC analysis: Daicel CHIRALPAK IE, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 28.1 min ((*R*) isomer), 33.6 min ((*S*) isomer):

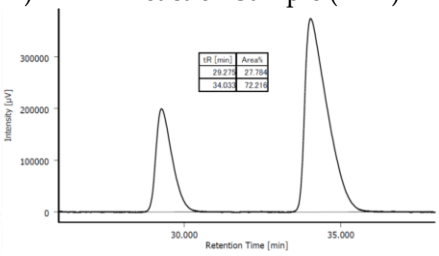
Racemic Sample



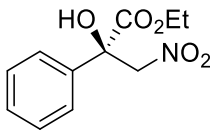
Reaction Sample (2-Me-THF)



Reaction Sample (THF)

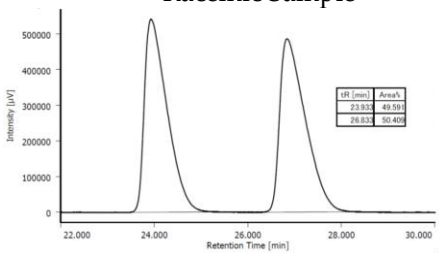


Ethyl (*R*)-2-hydroxy-3-nitro-2-phenylpropanoate (4pd):

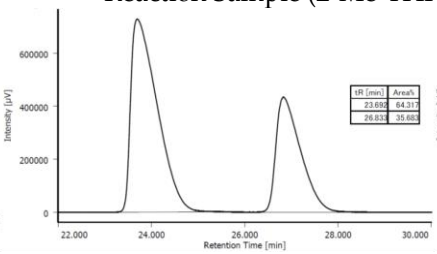


White solid; 27.8 mg (97%, reaction in 2-Me-THF), 26.4 mg (92%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.60 (m, 2H), 7.43-7.37 (m, 3H), 5.26 (dd, *J* = 1.0, 14.2 Hz, 1H), 4.68 (d, *J* = 14.2 Hz, 1H), 4.42-4.32 (m, 2H), 4.22 (d, *J* = 1.0 Hz, 1H), 1.34 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 136.5, 129.2, 128.9, 125.3, 80.8, 76.0, 63.6, 14.0; IR (thin film) *ν* 3490, 1739, 1559, 1377, 1270, 1229, 1139, 697 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{13}NO_5Na$ *m*/*z* 262.0686 [M+Na]$^+$, found 262.0688; $[\alpha]_D^{25}$ 5.5 (*c* 0.28, $CHCl_3$, -48% ee, Reaction Sample (THF), (*S*) isomer major); HPLC analysis: Daicel CHIRALPAK IE, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 23.7 min ((*R*) isomer), 26.8 min ((*S*) isomer):

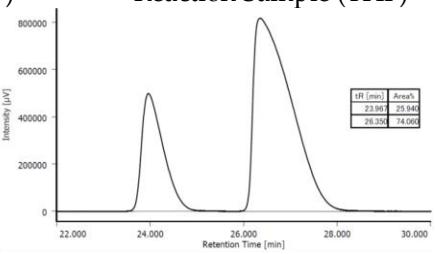
Racemic Sample



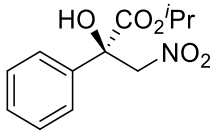
Reaction Sample (2-Me-THF)



Reaction Sample (THF)

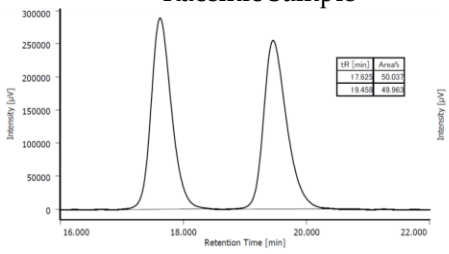


Isopropyl (*R*)-2-hydroxy-3-nitro-2-phenylpropanoate (5qd):

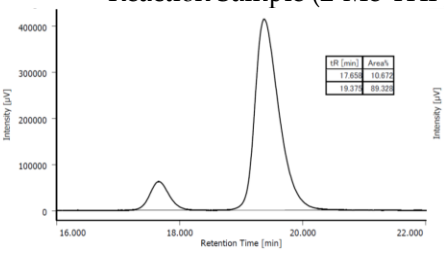


White solid; 29.4 mg (97%, reaction in 2-Me-THF), 27.0 mg (89%, reaction in THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H), 7.30, 7.24 (m, 3H), 5.11 (dd, *J* = 1.0, 14.2 Hz, 1H), 5.07 (tt, *J* = 6.4, 6.4 Hz, 1H), 4.54 (d, *J* = 14.2 Hz, 1H), 4.10 (d, *J* = 1.0 Hz, 1H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 137.0, 129.4, 129.2, 81.1, 76.2, 72.3, 21.8, 21.8; IR (thin film) *ν* 3487, 2986, 1730, 1555, 1380, 1278, 1247, 1146 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{15}NO_5Na$ *m*/*z* 276.0842 [M+Na]$^+$, found 276.0843; $[\alpha]_D^{25}$ -5.6 (*c* 1.58, $CHCl_3$, 78% ee, Reaction Sample (2-Me-THF), (*R*) isomer major); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 17.7 min ((*S*) isomer), 19.4 min ((*R*) isomer):

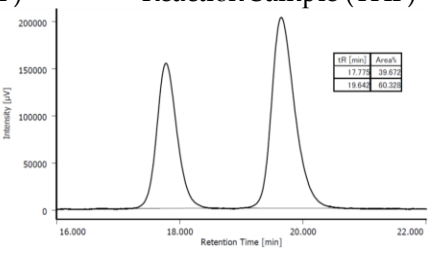
Racemic Sample



Reaction Sample (2-Me-THF)

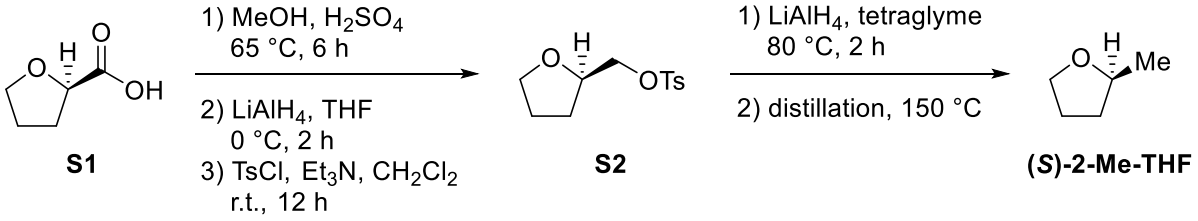


Reaction Sample (THF)



E. Preparation of optically active 2-Me-THF

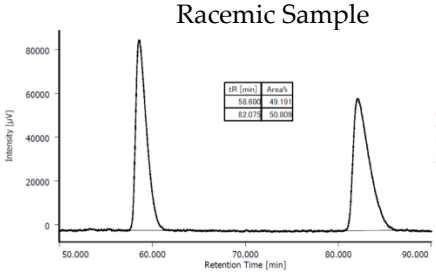
(*S*)-2-Me-THF was prepared by the following procedure and (*R*)-2-Me-THF was prepared by the same procedure from *ent*-**S1** ((*S*)-tetrahydrofuran-2-carboxylic acid, purchased from TCI Co. Ltd.).



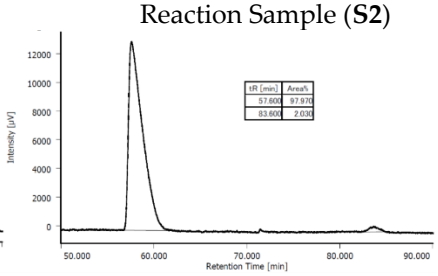
(*R*)-(Tetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (S2):

To a solution of (*R*)-tetrahydrofuran-2-carboxylic acid (**S1**, 25.0 g, 0.215 mol, purchased from TCI Co. Ltd.) in MeOH (250 mL) was added H_2SO_4 (2 mL) at room temperature and the resulting mixture was stirred at 65 °C for 6 h. After concentration in *vacuo* (40 °C, 100 hPa), H_2O was added to the residue. The resulting mixture was extracted with Et_2O (100 mL x 5) and the combined organic layers were dried over Na_2SO_4. After condensation in *vacuo* (40 °C, 100 hPa), the resulting residue was used for the next reaction without further purification. To a suspension of $LiAlH_4$ (16.3 g, 0.430 mol, 2.0 eq.) in THF (300 mL) was added a solution of the above residue in THF (100 mL) dropwise at 0 °C for 1 h, and the resulting mixture was stirred at room temperature for 1 h. After cooling mixture to 0 °C, H_2O (20 mL), 15% NaOH aq. (20 mL) and H_2O (60 mL) were added dropwise in sequence, and the resulting mixture was stirred at room temperature for 1 h. After filtration though Celite pad, the residue was washed with EtOAc (200 mL x 4). The combined filtrates were concentrated in *vacuo* (40 °C, 100 hPa) and sat. NH_4Cl aq. (100 mL) was added to the residue. The resulting mixture was extracted with EtOAc (200 mL x 5), and the combined organic layers were dried over Na_2SO_4. After concentration in *vacuo* (40 °C, 100 hPa), the resulting residue was used for the next reaction without further purification. To a solution of the above residue in CH_2Cl_2 (150 mL) were added TsCl (41.1 g, 0.215 mol, 1.0 eq.) and Et_3N (32.8 mL, 0.237 mol, 1.1 eq.) at 0 °C, and the resulting mixture was stirred at room temperature for 12 h. After filtration to remove Et_3N•HCl, the amine salt was washed with CH_2Cl_2 (100 mL), and 1 N HCl aq. (100 mL) was added to the filtrate. The resulting mixture was extracted with CH_2Cl_2 (100 mL) and the organic layer was washed with sat. $NaHCO_3$ aq. (100 mL) and brine (100 mL), and dried over Na_2SO_4. After concentration in *vacuo*, the resulting residue was purified by silica gel chromatography (EtOAc/*n*-hexane) to give (*R*)-(tetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (**S2**, 36.7 g, 0.143 mol, 67%) as colorless oil. Enantiomeric excess was determined by chiral HPLC analysis (96% ee).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 4.11-3.96 (m, 3H), 3.81-3.70 (m, 2H), 2.44-1.83 (m, 3H), 1.85-1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 133.4, 130.2, 128.3, 76.3, 71.8, 69.0, 28.2, 25.9, 22.0; IR (thin film) *ν* 2953, 2874, 1358, 1189, 1175, 1095, 965, 815, 663, 554 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{16}O_4SNa$ *m*/*z* 279.0662 [M+Na]$^+$, found 279.0660; $[\alpha]_D^{25}$ -17.2 (*c* 1.05, $CHCl_3$, 96% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 254 nm, flow rate = 1.0 mL/min, t_R = 58.6 min (**S2**), 82.1 min (*ent*-**S2**):

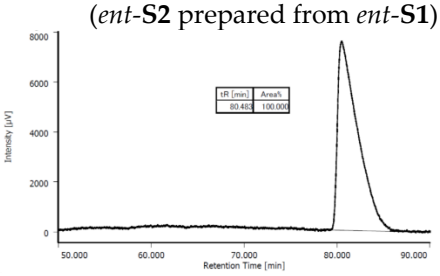
Racemic Sample



Reaction Sample (**S2**)



Reaction Sample (*ent*-**S2** prepared from *ent*-**S1**)



(*S*)-2-Me-THF:

To a suspension of $LiAlH_4$ (8.15 g, 0.215 mol, 1.5 eq.) in tetraglyme (200 mL) was added a solution of (*R*)-(tetrahydrofuran-2-yl)methyl 4-methylbenzenesulfonate (**S2**, 36.7 g, 0.131 mol) in tetraglyme (50 mL) dropwise

at 80 °C for 1.5 h. After stirring the resulting mixture at 80 °C for 2 h, distillation apparatus (condenser, thermometer and collection flask) was attached to the reaction flask. The collection flask was cooled to -78 °C and the reaction mixture was warmed to 150 °C. Atmospheric distillation was continued until refluxing ceased, delivering pure (*S*)-2-Me-THF (2.21 g, 0.0257 mol, 18%) to the collection flask as colorless oil. Synthesized chiral solvent was treated with MS3Å (100 mg, pellet type) to reduce water content (<50 ppm, KF) before the catalytic reaction.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69-3.86 (m, 2H), 3.73-3.68 (m, 1H), 2.02-1.84 (m, 3H), 1.45-1.39 (m, 1H), 1.23 (d, *J* = 3.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 75.6, 68.1, 33.4, 26.2, 21.3; $[\alpha]_D^{25}$ 21.4 (*c* 1.00, $CHCl_3$) (lit. [6] $[\alpha]_D^{25}$ 19.4 (*c* 1.43, $CHCl_3$))

F. Preparation of MWNT-confined catalyst and its application of the continuous flow reaction

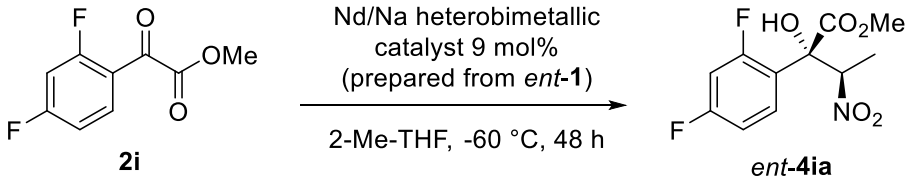
A flame-dried test tube (20 mL) was charged with $NdCl_3 \bullet 6H_2O$ (8.6 mg, 0.024 mmol) and amide based ligand **1a** (9.1 mg, 0.024 mmol), and dried under vacuum at room temperature at least for 5 min. Ar was backfilled (evacuation/backfill was repeated 5 times) to the test tube, and THF (600 μL) was added at room temperature. After stirring the resulting slightly cloudy suspension at 60 °C for 30 min, 2.0 M NaO^{t}Bu/THF (72 μL, 0.144 mmol) was added slowly at the same temperature. After stirring the resulting mixture at 60 °C for 1 h (white precipitate appeared), the mixture was cooled to room temperature, and MWNT (Baytube® C70P, 36 mg, 400wt% to ligand **1a**) and nitroethane (172 μL, 2.4 mmol) were added to initiate self-assembly of catalyst in the fibrous matrix of MWNT. After stirring at room temperature for 12 h, dried Celite (350 mg [pretreatment: Celite (50 g) was suspended in THF (250 mL) then filtered, which was subsequently washed by THF (250 mL). The washed Celite was dried under vacuum (ca. 0.6 kPa) at room temperature]) and THF (2 mL) were added to the MWNT-catalyst suspension. The resulting mottled black/white suspension was transferred to YMC stainless-steel empty column (φ 4.6 x 100 mm) fitted with an end-capping bearing and 2 μm stainless-steel frit at the bottom under mostly Ar atmosphere (operated under the Ar flow with an inverted funnel). The elution of THF was accelerated by suction from the bottom side using a syringe. All the solid material was transferred by rinsing with minimum amount of THF (ca. 1 mL), then the top of the column was sealed with an end capping bearing and 2 μm stainless-steel frit. The catalyst column and a syringe pump (Harvard PHP-ULTRA 4400) were concatenated with stainless-steel tubing (inner diameter 1/16 inch) as shown in scheme 3. THF was passed through column at 12 mL/h at room temperature for 2 h to wash the MWNT-confined catalyst, and subsequently, 2-Me-THF solution of nitroethane (0.5 M) was passed through column at 3.0 mL/h at room temperature for 1 h to activate the MWNT-confined catalyst. The catalyst column was immersed into a cryogenic reactor operated at -60 °C. The combined substrate solution (methyl benzoylformate (0.05 M) and nitroetane (0.5 M) in 2-Me-THF) was passed through column at 1.5 mL/h and the eluted sample for the first 2 h was not collected because of reaction equilibration. After that, the nitroaldol reaction was occasionally monitored (Table S1). Yield, diastereomeric ratio and enantiometric excess were determined using small aliquot of the eluted sample. After 92 h, the collected eluent was concentrated in *vacuo* and the resulting residue was analyzed by ^{1}H NMR to determine diastereomeric ratio of product (*anti*/*syn* = >98/2). The crude product was purified by silica gel column chromatography (EtOAc/*n*-hexane) to give **4aa** (1.52 g, 6.35 mmol, 92%, 97% ee) as a white solid and a single diastereomer. TON was calculated as 265.

Table S1. Profile of flow reaction

duration (h)	eluted in total (mL)	passed SM in total (mmol)	NMR yield (%)	*anti* /*syn*	ee (%)
0 - 2	3.0	0.15	91	>98/2	95
2 - 4	6.0	0.30	99	>98/2	97
4 - 6	9.0	0.45	99	>98/2	98
6 - 20	30.0	1.50	99	>98/2	98
20 - 22	33.0	1.65	99	>98/2	98
22 - 66	99.0	4.95	99	>98/2	98
66 - 68	102.0	5.10	99	>98/2	97
68 - 90	135.0	6.75	96	>98/2	97
90 - 92	138.0	6.90	91	>98/2	94

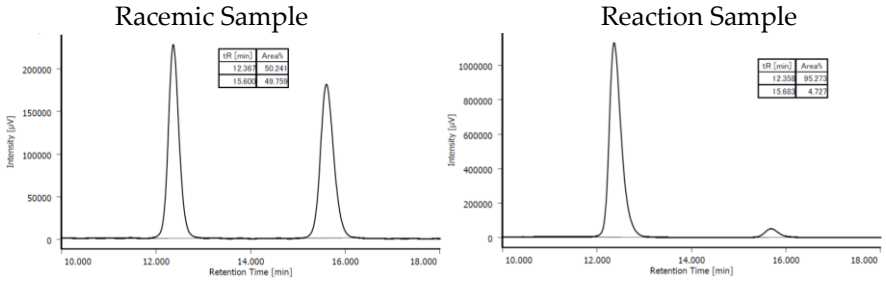
G. Stereoselective synthesis of efinaconazole and albaconazole

Methyl (2*S*,3*R*)-2-(2,4-difluorophenyl)-2-hydroxy-3-nitrobutanoate (*ent*-4ka):

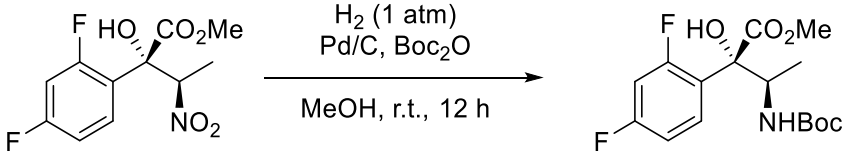


2i *ent*-**4ia**

A flame-dried round-bottom flask (30 mL) was charged with $NdCl_3 \bullet 6H_2O$ (108 mg, 0.300 mmol, 9 mol%) and amide-based ligand *ent*-**1a** (114 mg, 0.300 mmol, 9 mol%), and dried under vacuum at room temperature for 5 min. Ar was backfilled (evacuation/backfill was repeated 5 times) to the test tube, and THF (7.5 mL) was added using well-dried syringes and needles at room temperature. After stirring the resulting slightly cloudy suspension at 60 °C for 30 min, 2.0 M NaO^tBu/THF (900 μL, 1.80 mmol, 54 mol%) was added dropwise at the same temperature. After stirring the resulting mixture at 60 °C for 1 h (white precipitate appeared), the mixture was cooled to room temperature and nitroethane (2.14 mL, 30.0 mmol, 3.0 eq.) was added. Self-assembly of Nd/Na catalyst initiated in a few minutes and the resulting mixture was stirred at room temperature for 12 h to give a thick white suspension. The whole suspension was transferred to a conical tube (50 mL) with THF washing (6.25 mL x 2). The tube was centrifuged at ca. 4,000 rpm for 1 min. The supernatant was decanted and THF (20 mL) was added. The tube was agitated using a vortex mixer for 1 min and centrifuged again, then the supernatant was decanted (washing process). This washing process was repeated again. The resulting precipitate was agitated with 2-Me-THF (20 mL) and the resulting suspension was transferred to a flame-dried round-bottom flask (100 mL). After adding 2-Me-THF (30 mL) and nitroethane (3.57 mL, 50.0 mmol, 10 eq.), the mixture was cooled to –78 °C and then a solution of methyl 2-(2,4-difluorophenyl)-2-oxoacetate (**2i**, 1.00 g, 5.00 mmol, 1.0 eq.) in 2-Me-THF (5.1 mL) was added dropwise for 5 min. After stirring the reaction mixture at the same temperature for 48 h, 0.2 M AcOH/THF (6.25 mL) was added slowly and warmed to room temperature. H_2O (12.5 mL) was added and the resulting mixture was extracted with EtOAc (25 mL). The organic layer was dried over Na_2SO_4. After removal of volatiles under reduced pressure, the resulting residue was analyzed by ^1H NMR to determine diastereomeric ratio of product (*anti*/*syn* = 86/14). The crude product was purified by silica gel column chromatography (*n*-hexane/ EtOAc) to give methyl (2*S*,3*R*)-2-(2,4-difluorophenyl)-2-hydroxy-3-nitrobutanoate (*ent*-**4ia**, 1.12 g, 82%) as a white solid and a single diastereomer. Enantiomeric excess was determined by chiral HPLC analysis (91% ee).; HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 12.4 min (major), 15.9 min (minor):

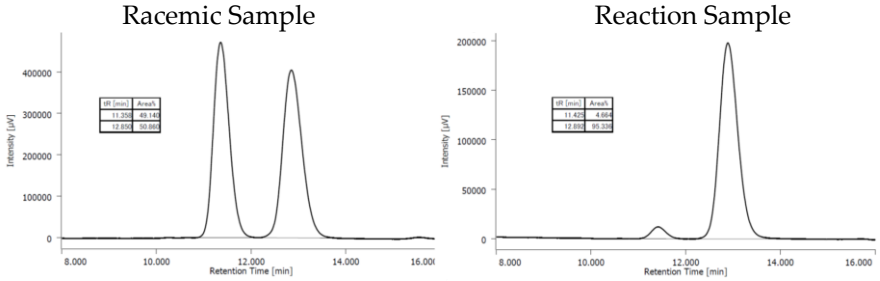


Methyl (2*S*,3*R*)-3-((*tert*-butoxycarbonyl)amino)-2-(2,4-difluorophenyl)-2-hydroxybutanoate (S3):

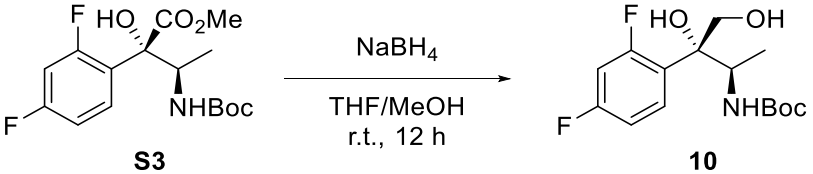


ent-**4ia** **S3**

To a solution of *ent*-**4ia** (43.5 mg, 0.158 mmol, 91% ee) in MeOH (1 mL) were added Pd/C (10 mg [10 wt%Pd, 55% wet]) and Boc_2O (138 mg, 0.632 mmol, 4.0 eq.), the resulting mixture was stirred at room temperature under H_2 atmosphere (1 atm, balloon) for 12 h. After purging with Ar, the mixture was filtered through a syringe filter and the filtrate was concentrated in *vacuo*. The resulting residue was purified by silica gel chromatography (EtOAc/*n*-hexane) to give methyl (2*S*,3*R*)-3-((*tert*-butoxycarbonyl)amino)-2-(2,4-difluorophenyl)-2-hydroxybutanoate (**S3**, 50.0 mg, 0.144 mmol, 92%) as a white solid. Enantiomeric excess was determined by chiral HPLC analysis (91% ee).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.60 (m, 1H), 6.89-6.85 (m, 1H), 6.83-6.78 (m, 1H), 4.94 (dt, *J* = 6.6, 9.3 Hz, 1H), 4.85 (d, J = 9.3 Hz, 1H), 4.25 (s, 1H), 3.76 (s, 3H), 1.48 (s, 9H), 1.04 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 163.3 (dd, *J* = 12.4, 248.6 Hz), 161.7 (dd, *J* = 11.7, 251.6 Hz), 155.3, 130.3 (dd, *J* = 5.1, 9.5 Hz), 122.4 (dd, *J* = 3.6, 12.4 Hz), 111.5 (dd, *J* = 2.9, 20.4 Hz), 105.1 (dd, *J* = 24.8, 27.7 Hz), 79.9, 79.2 (d, *J* = 4.4 Hz), 54.0, 50.4 (d, *J* = 8.0 Hz), 28.6, 16.1; ^{19}F NMR (376 MHz, $CDCl_3$) -105.3, -110.3; IR (thin film) ν 3450, 1723, 1614, 1501, 1367, 1262, 1245, 1165, 1136, 976 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{20}F_2NO_5$ *m*/*z* 344.1315 [M-H]$^-$, found 344.1312; $[\alpha]_D^{25}$ -24.3 (*c* 1.41, $CHCl_3$, 91% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 12.9 min (major), 11.4 min (minor):



***tert*-Butyl ((2*R*,3*S*)-3-(2,4-difluorophenyl)-3,4-dihydroxybutan-2-yl)carbamate (10):**

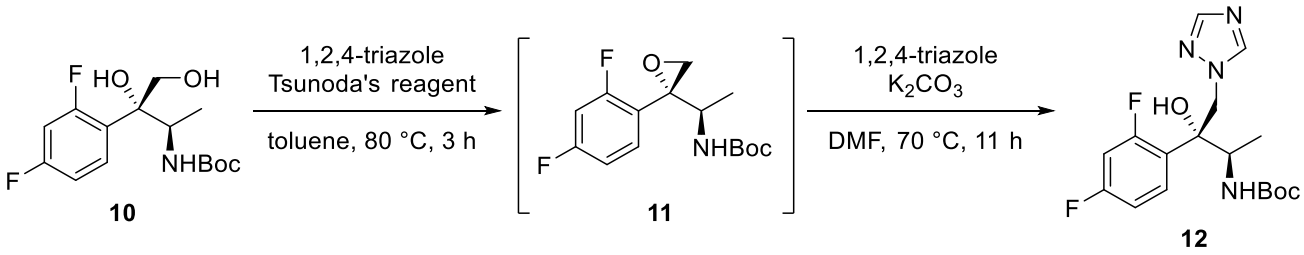


S3 **10**

To a solution of **S3** (100 mg, 0.290 mmol) in THF (5 mL) and MeOH (0.5 mL) was added $NaBH_4$ (32.9 mg, 0.869 mmol, 3.0 eq.) at 0 °C and the resulting mixture was stirred at room temperature for 12 h. After quenching with sat. NH_4Cl aq. (4 mL), the resulting mixture was extracted with EtOAc (8 mL x 4). The combined organic layers were dried over Na_2SO_4 and concentrated in *vacuo*. The resulting residue was purified by silica gel

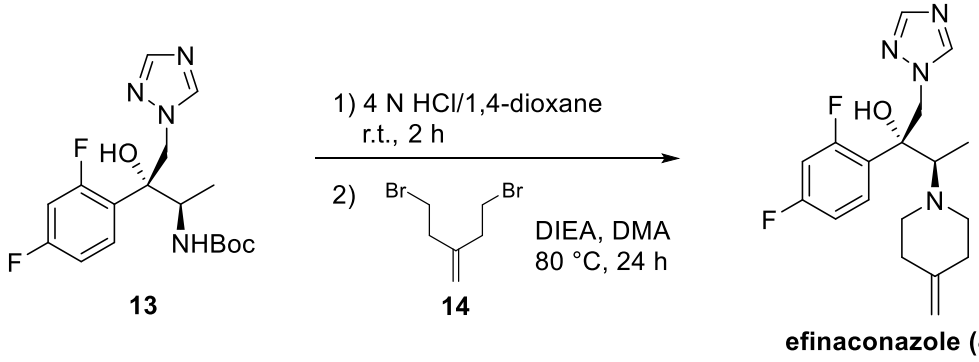
chromatography (EtOAc/*n*-hexane) to give *tert*-butyl ((2*R*,3*S*)-3-(2,4-difluorophenyl)-3,4-dihydroxybutan-2-yl)carbamate (**10**, 83.6 mg, 0.263 mmol, 91%) as a white solid.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.59 (m, 1H), 6.92-6.87 (m, 1H), 6.81-6.76 (m, 1H), 4.86 (d, *J* = 8.8 Hz, 1H), 4.29 (dt, *J* = 6.7, 8.8 Hz, 1H), 3.90 (m, 2H), 3.77 (brs, 1H), 2.31 (brs, 1H), 1.46 (s, 9H), 0.93 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (dd, *J* = 12.4, 247.9 Hz), 159.4 (dd, *J* = 11.7, 246.5 Hz), 156.8, 130.7 (dd, *J* = 6.6, 9.5 Hz), 125.3 (d, *J* = 13.1 Hz), 111.6 (dd, *J* = 3.7, 20.4 Hz), 104.6 (dd, *J* = 24.8, 27.7 Hz), 80.4, 78.8 (d, *J* = 5.1 Hz), 61.3, 50.2, 28.7, 16.7; ^{19}F NMR (376 MHz, $CDCl_3$) -107.8, -111.6; IR (thin film) *ν* 3440, 2980, 2937, 1690, 1616, 1499, 1166, 1061, 968, 850 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{21}F_2NO_4Na$ m/z 340.1331 [M+Na]$^+$, found 340.1334; $[\alpha]_D^{25}$ -0.3 (*c* 0.81, $CHCl_3$, 91% ee)

***tert*-Butyl ((2*R*,3*R*)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)butan-2-yl)carbamate (12):**



To a suspension of **10** (340 mg, 1.07 mmol, 1.0 eq.) and 1,2,4-triazole (74 mg, 1.07 mmol, 1.0 eq.) in toluene (6.7 mL) was added (cyanomethylene)tributylphosphorane (Tsunoda's reagent, 309 μL, 1.17 mmol, 1.1 eq.) at room temperature and the resulting mixture was stirred at 80 °C for 3 h. After concentration in *vacuo*, the resulting residue was used for the next reaction. To a solution of the above residue in DMF (5.3 mL) was added 1,2,4-triazole (88 mg, 1.27 mmol, 1.1 eq.) and K_2CO_3 (444 mg, 3.21 mmol, 3.0 eq.) at room temperature, and the resulting mixture was stirred at 70 °C for 11 h. After cooling the reaction mixture to room temperature, H_2O was added and the aqueous layer was extracted 3 times with EtOAc. The combined organic layers were washed 8 times with small amount of H_2O and one time with brine and dried over Na_2SO_4. After concentration in *vacuo*, the resulting residue was purified by silica gel chromatography (EtOAc/*n*-hexane) to give *tert*-butyl ((2*R*,3*R*)-3-(2,4-difluorophenyl)-3-hydroxy-4-(1*H*-1,2,4-triazol-1-yl)butan-2-yl)carbamate (**12**, 312 mg, 0.847 mmol, 79% for 2 steps) as a white solid.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.77 (s, 1H), 7.39-7.30 (m, 1H), 6.77-6.69 (m, 2H), 5.08 (d, *J* = 9.0 Hz, 1H), 5.07 (s, 1H), 4.99 (d, *J* = 14.4 Hz, 1H), 4.52 (d, *J* = 14.4 Hz, 1H), 4.38 (dt, *J* = 6.9, 9.0 Hz, 1H), 1.48 (s, 9H), 0.90 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (dd, *J* = 12.1, 248.6 Hz), 158.8 (dd, *J* = 11.7, 244.3 Hz), 156.4, 152.7, 144.7, 130.8 (dd, *J* = 6.6, 9.5 Hz), 124.2 (dd, *J* = 4.4, 13.9 Hz), 112.3 (dd, *J* = 2.9, 20.4 Hz), 104.8 (dd, *J* = 26.3, 27.7 Hz), 80.5, 79.4 (d, *J* = 5.1 Hz), 55.7 (d, *J* = 5.8 Hz), 51.1 (d, *J* = 36.5 Hz), 29.1, 16.8; ^{19}F NMR (376 MHz, $CDCl_3$) -108.9, -110.1; IR (thin film) *ν* 3344, 1709, 1618, 1500, 1367, 1273, 1167, 1140, 1065, 965 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{21}F_2N_4O_3$ m/z 367.1587 [M-H]$^-$, found 367.1585; $[\alpha]_D^{25}$ -79.7 (*c* 0.64, $CHCl_3$, 91% ee)

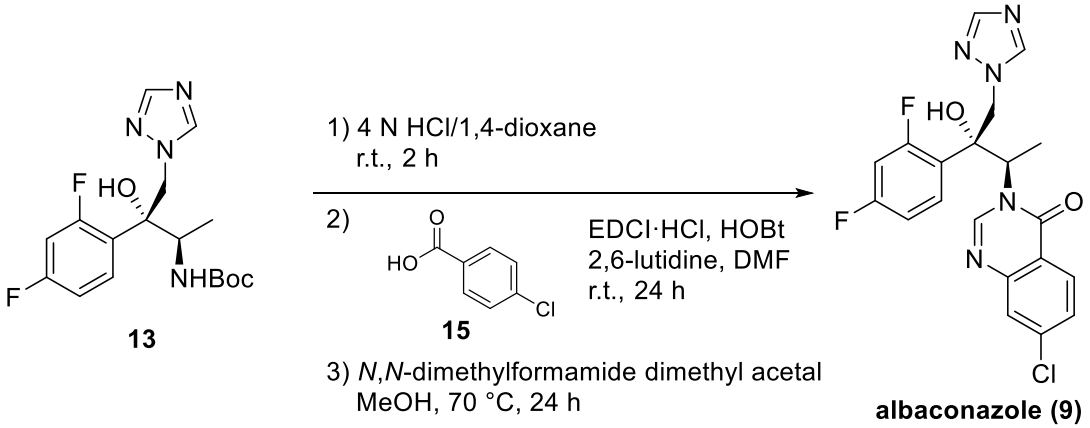
Efinaconazole (8):



13 (60 mg, 0.163 mmol, 1.0 eq.) was treated with 4 N HCl/1,4-dioxane (1.6 mL) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was concentrated in *vacuo*. The amorphous white solid was obtained and used for the next reaction without further purification. To a solution of the above solid in DMA

(650 μL) was added DIEA (94 μL, 0.541 mmol, 3.3 eq.) at room temperature. After 5 min of vigorous stirring, a solution of 3-methylene-1,5-dibromopentane (**14**, 43 mg, 0.180 mmol, 1.1 eq.) in DMA (650 μL) was added at room temperature. After stirring the reaction mixture at 80 °C for 24 h, H_2O was added at room temperature. The resulting mixture was extracted 4 times with EtOAc and the combined organic layers were washed 8 times with H_2O, and dried over Na_2SO_4. After concentration in *vacuo*, the resulting residue was purified by silica gel chromatography (EtOAc/*n*-hexane) to give efinaconazole (**8**, 32 mg, 0.091 mmol, 56% for 2 steps) as a white solid.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.77 (s, 1H), 7.53-7.47 (m, 1H), 6.80-6.70 (m, 1H), 5.44 (s, 1H), 4.87 (d, *J* = 14.7 Hz, 1H), 4.79 (d, *J* = 14.7 Hz, 1H), 4.63 (s, 2H), 2.90 (q, *J* = 7.1 Hz, 1H), 2.69 (br s, 2H), 2.34 (br s, 2H), 2.26-2.15 (m, 4H), 0.94 (dd, *J* = 2.4, 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1 (dd, *J* = 12.4, 247.9 Hz), 158.9 (dd, *J* = 11.7, 244.3 Hz), 151.7, 146.3, 144.8, 131.1 (dd, *J* = 5.8, 9.5 Hz), 125.0 (dd, *J* = 3.7, 13.1 Hz), 111.8 (dd, *J* = 2.9, 20.4 Hz), 108.5, 104.4 (dd, *J* = 25.5, 28.4 Hz), 78.0 (d, *J* = 5.8 Hz), 64.8, 56.2 (d, *J* = 8.0 Hz), 52.8 (br s), 35.5, 7.9 (d, *J* = 3.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) -106.0, -111.0; IR (thin film) *ν* 3421, 3073, 2978, 2938, 2899, 2810, 1615, 1498, 1418, 1273, 1241, 965 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{21}F_2N_4O$ *m/z* 347.1689 [M-H]$^-$, found 347.1690; $[\alpha]_D^{25}$ -81.5 (*c* 1.00, $CHCl_3$, 91% ee)

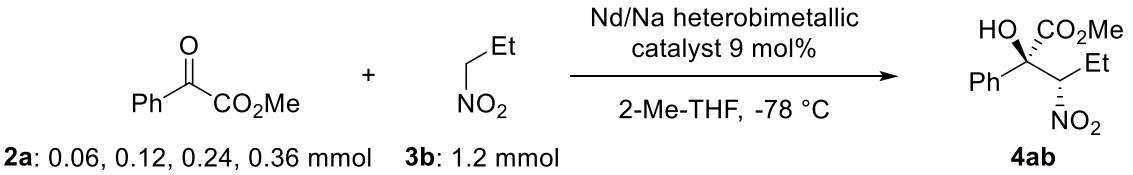
Albaconazole (9):



13 (30 mg, 0.081 mmol, 1.0 eq.) was treated with 4 N HCl/1,4-dioxane (1.6 mL) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was concentrated in *vacuo*. The amorphous white solid was obtained and used for the next reaction without further purification. To the solution of the above solid and 4-chloroanthranillic acid (**15**, 14 mg, 0.081 mmol, 1 eq.) were added EDCI•HCl (19.0 mg, 0.099 mmol, 1.2 eq.) and 2,6-lutidine (29 μL, 0.248 mmol, 3.0 eq.). After stirring at room temperature for 24 h, MeOH (270 μL) and *N*,*N*-dimethylformamide dimethyl acetal (43 μL, 0.320 mmol, 4.0 eq.) was added. The resulting mixture was heated to 70 °C and stirred for 24 h and H_2O was added at room temperature. The resulting mixture was extracted 2 times with EtOAc and the combined organic layers were washed 8 times with H_2O and 1 time with brine, and dried over Na_2SO_4. After concentration in *vacuo*, the resulting residue was purified by silica gel chromatography (EtOAc/*n*-hexane) to give albaconazole (**9**, 23 mg, 0.053 mmol, 65% for 3 steps) as a white solid.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.26 (d, *J* = 8.6 Hz, 1H), 7.76 (s, 1H), 7,75 (d, *J* = 2.0 Hz, 1H), 7.73 (s, 1H), 7.50-7.44 (m, 2H), 6.86-6.78 (m, 2H), 5.91 (dq, *J* = 1.5, 7.1 Hz, 1H), 5.33 (d, *J* = 1.5 Hz, 1H), 5.15 (d, *J* = 14.2 Hz, 1H), 4.01 (d, *J* = 14.2 Hz, 1H), 1.29 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (dd, *J* = 13.1, 250.8 Hz), 161.4, 158.4 (dd, *J* = 11.7, 245.0 Hz), 152.3, 148.5, 147.3, 144.4, 141.5, 130.8 (dd, *J* = 5.8, 9.5 Hz), 129.0, 128.5, 127.3, 123.0 (dd, *J* = 3.7, 13.1 Hz), 120.0, 112.3 (dd, *J* = 2.9, 20.4 Hz), 104.9 (dd, *J* = 25.5, 27.0 Hz), 78.6 (d, *J* = 5.1 Hz), 54.8 (d, *J* = 5.8 Hz), 51.8 (*J* = 3.7 Hz), 15.7; ^{19}F NMR (376 MHz, $CDCl_3$) -108.6, -108.8; IR (thin film) *ν* 3384, 1674, 1602, 1499, 1462, 1404, 1275, 1141, 966, 756 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{15}ClF_2N_5O_2$ *m/z* 430.0888 [M-H]$^-$, found 430.0898; $[\alpha]_D^{25}$ -7.9 (*c* 0.99, $CHCl_3$, 91% ee)

H. Initial Rate Kinetic Study

Initial rate kinetics with variable initial concentration of α-keto ester (**3a**)



2a: 0.06, 0.12, 0.24, 0.36 mmol **3b**: 1.2 mmol **4ab**

Experiments were done in a similar manner as described in section 2-3.
By assuming pseudo first-order consumption of **2a** to give **4ab**, ln v_{obs} is plotted versus ln [**2a**] (Figure S1), showing 0.91th order dependency in initial concentration of the catalyst components.

[**2a**]		v_{obs}
0.36 mmol	0.3 M	0.0374 M/h
0.24 mmol	0.2 M	0.0218 M/h
0.12 mmol	0.1 M	0.0173 M/h
0.06 mmol	0.05 M	0.0052 M/h

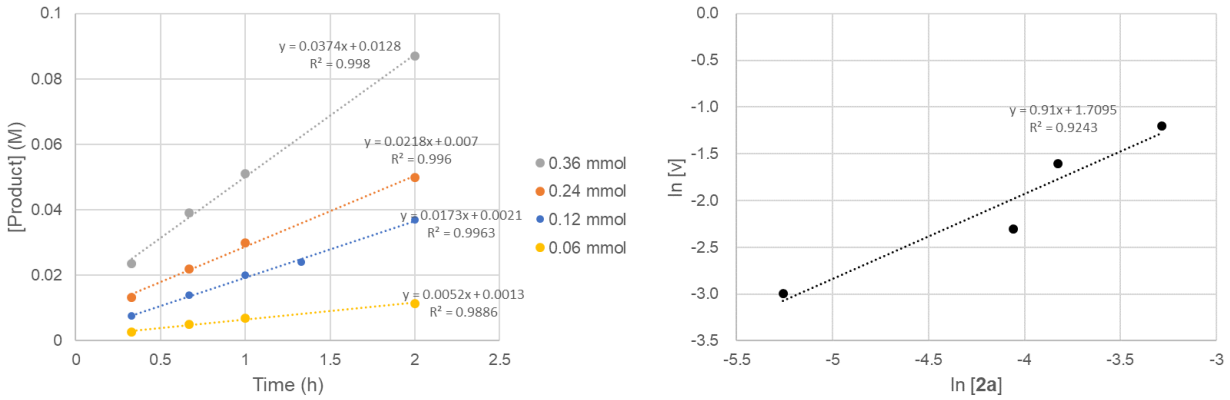


Figure S1. Initial rate kinetic study on the concentration of α-keto ester (2a).

I. Determination of Absolute Configuration

The absolute configuration of nitroaldol product **4a** was determined by X-ray crystallographic analysis. Single crystals of **4aa** were obtained from a solution of *n*-hexane. A suitable crystal was selected and the sample was measured on a Rigaku R-AXIS RAPID diffractometer using graphite monochromated Cu-Ka radiation. The data were collected at 93 K. Refined structure and crystallographic parameters are summarized in Figure S2 and Table S2. The ORTEP diagram was drawn by Mercury 3.8. CCDC 1856272 contains the supplementary crystallographic data for **4aa**.

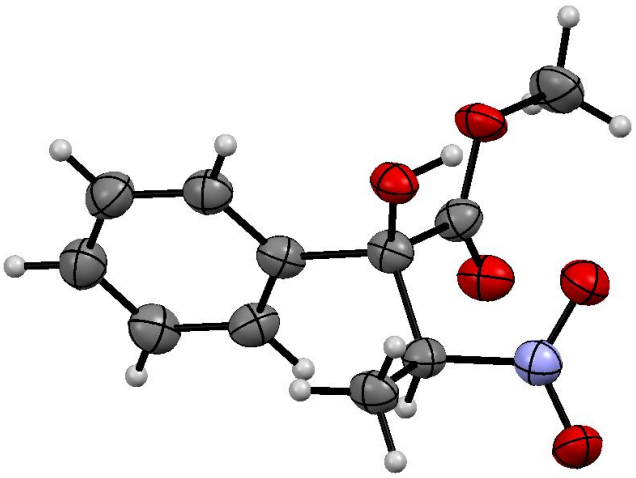


Figure S2. ORTEP diagram of **4aa**. Color code; grey: C, white: H, blue: N, red: O

Table S2. Selected crystal data of **4aa**

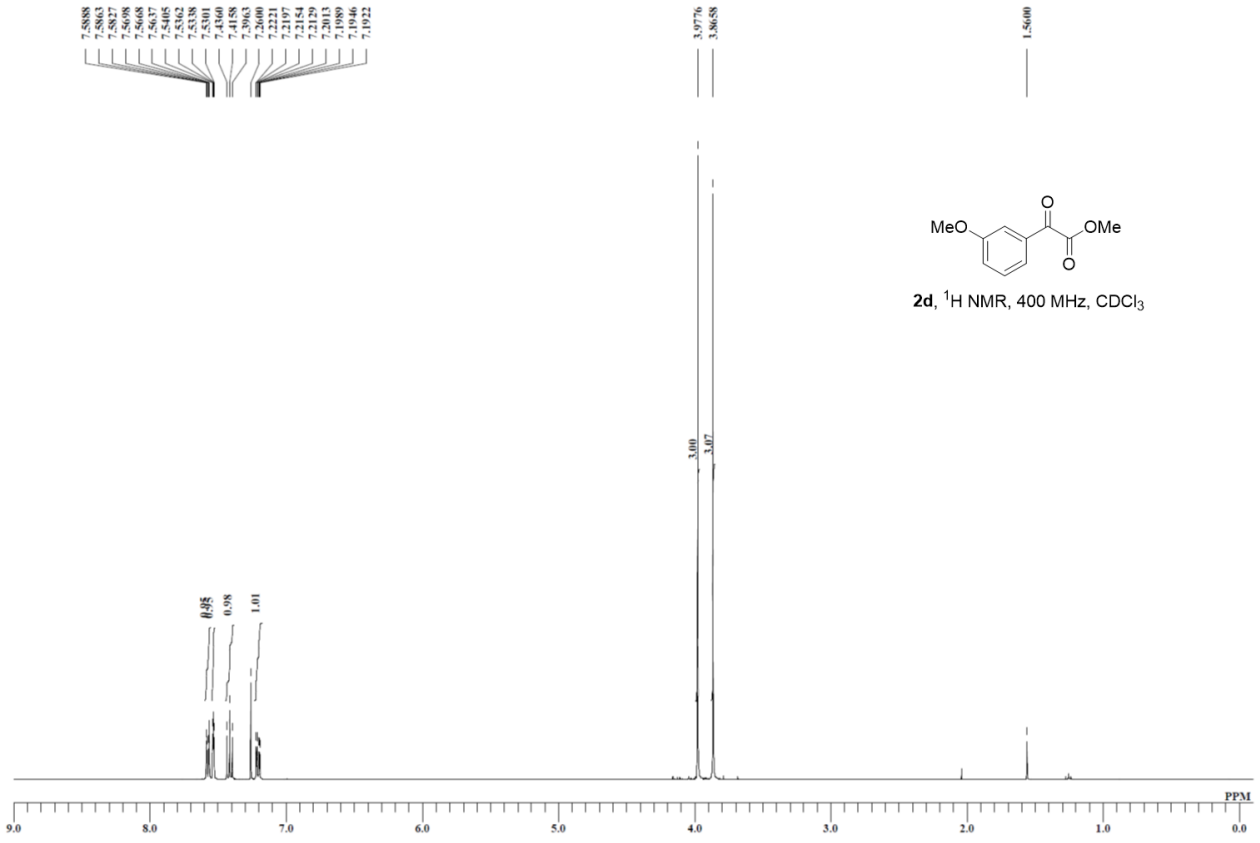
Empirical Formula	$C_{11}H_{13}NO_5$
Formula Weight	239.23
Crystal Color, Habit	colorless, platelet
Crystal Dimensions	0.200 x 0.050 x 0.010 mm
Crystal System	orthorhombic
Lattice Parameters	
a	5.5866(4) Å
b	7.8505(5) Å
c	26.064(2) Å
V	1143.07(15) Å^3
Space Group	$P2_12_12_1$ (#19)
Z value	4
D_{calc}	1.390 g/cm^3
R1	0.0594
Flack parameter[7]	–0.0(3)
F_{000}	504

The absolute configuration of nitroaldol product were **4pa**[8] and **4qa**[9] determined by comparison of its chiral HPLC retention time with literture data.

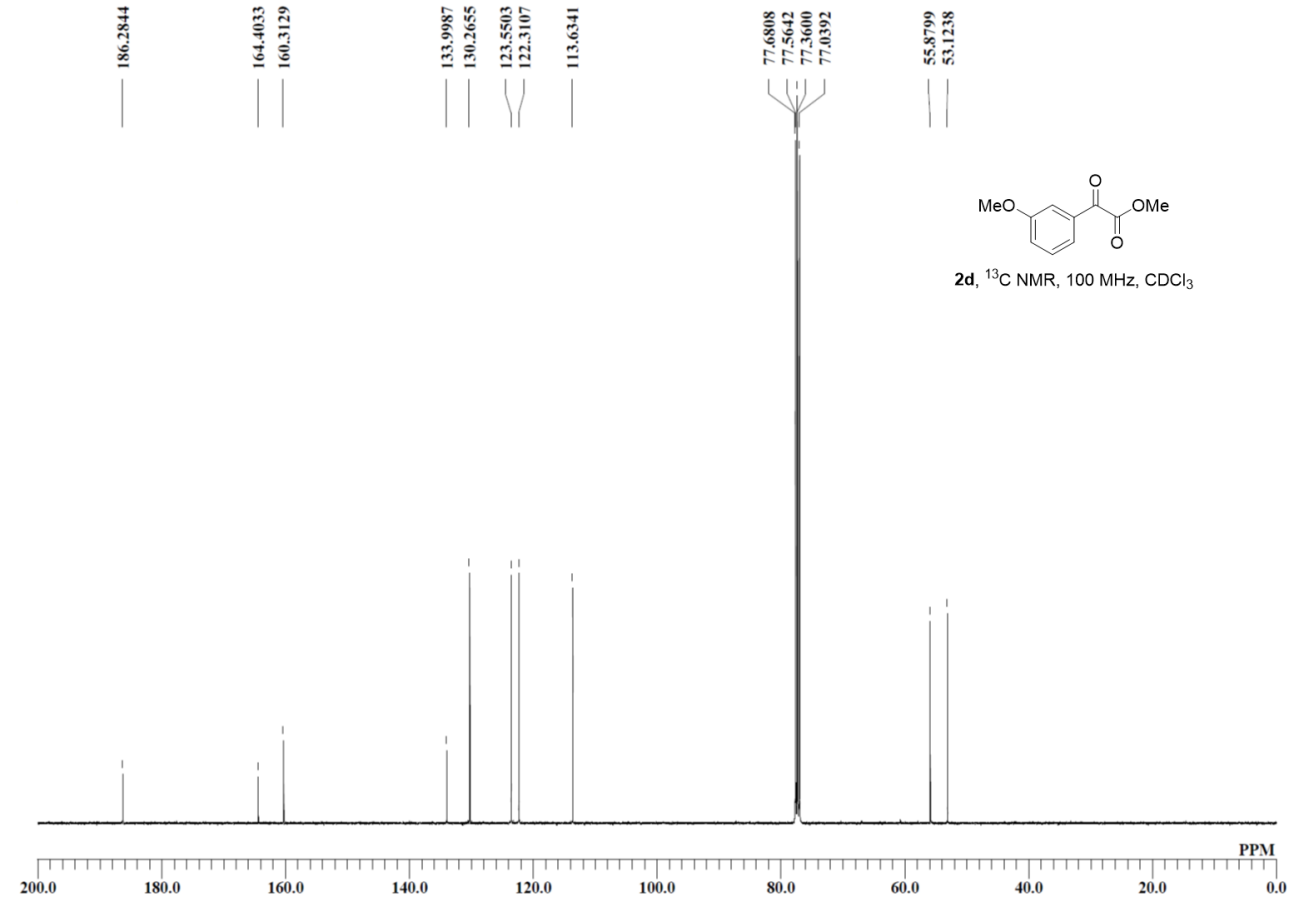
J. References for Experimental Section of Chapter 2

1 Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176.
2 Nitabaru, T.; Nojiri, A.; Kobayashi, M.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 13860.
3 Wu, H. L.; Wu, P. Y.; Shen, Y. Y.; Uang, B. J. *J. Org. Chem.* **2008**, *73*, 6445.
4 Kurono, N.; Uemura, M.; Ohkuma, T. *Eur. J. Org. Chem.* **2010**, *8*, 1455.
5 Zhuang, J.; Wang, C.; Xie, F.; Zhang, W. *Tetrahedron* **2009**, *65*, 9797.
6 Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474.
7 Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876.
8 Blay, G.; Olmos, V. H.; Pedro, J. R. *Chem. Eur. J.* **2011**, *17*, 3768.
9 Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732.

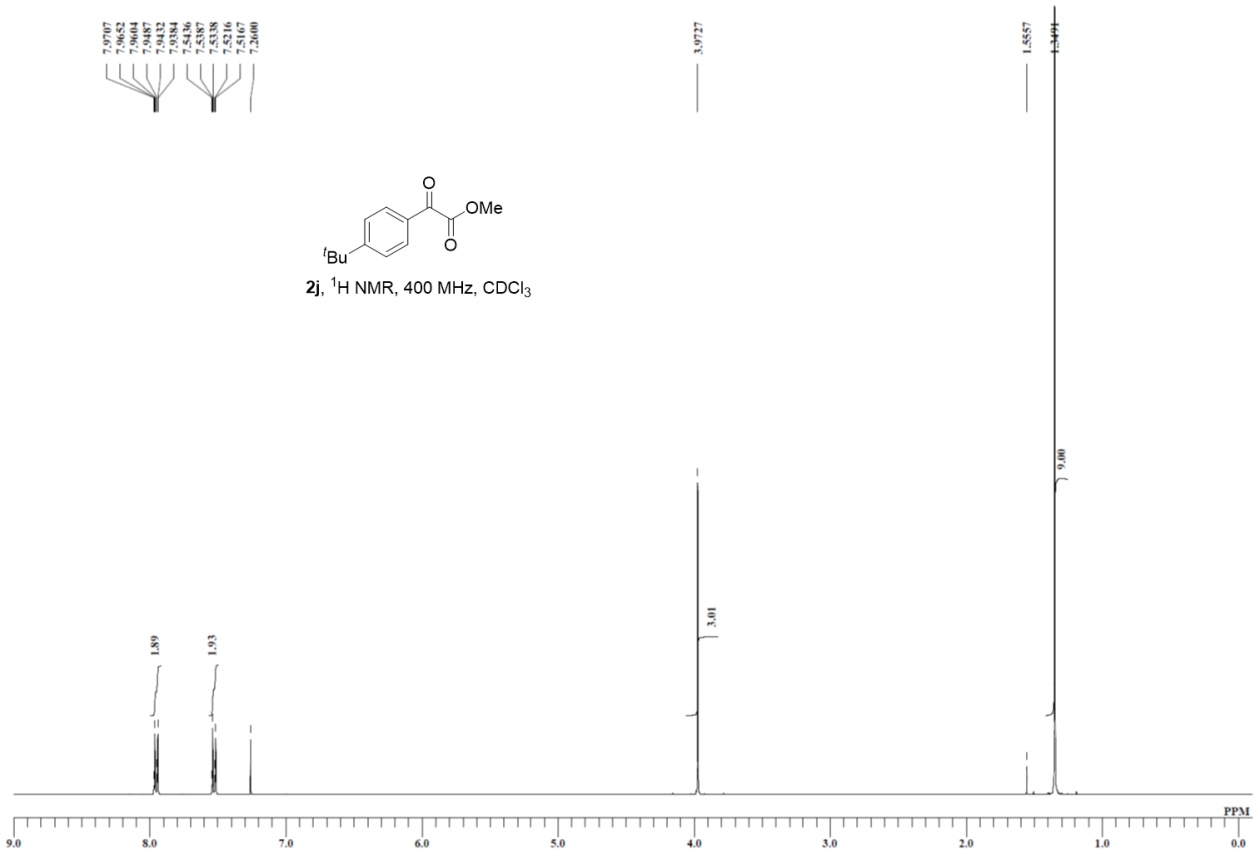
K. ^{1}H and ^{13}C NMR Spectra



2d, ^{1}H NMR, 400 MHz, $CDCl_3$



2d, ^{13}C NMR, 100 MHz, $CDCl_3$



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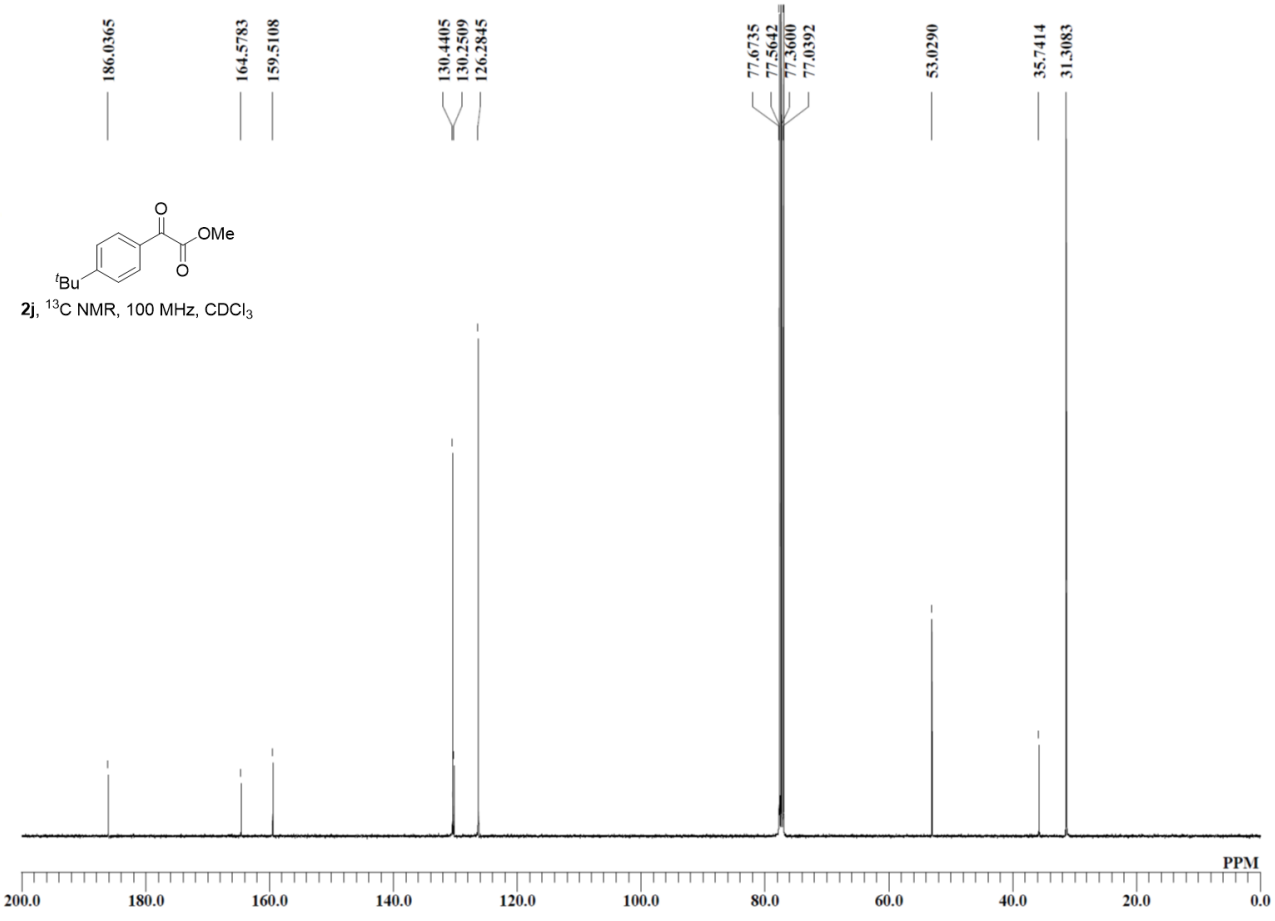

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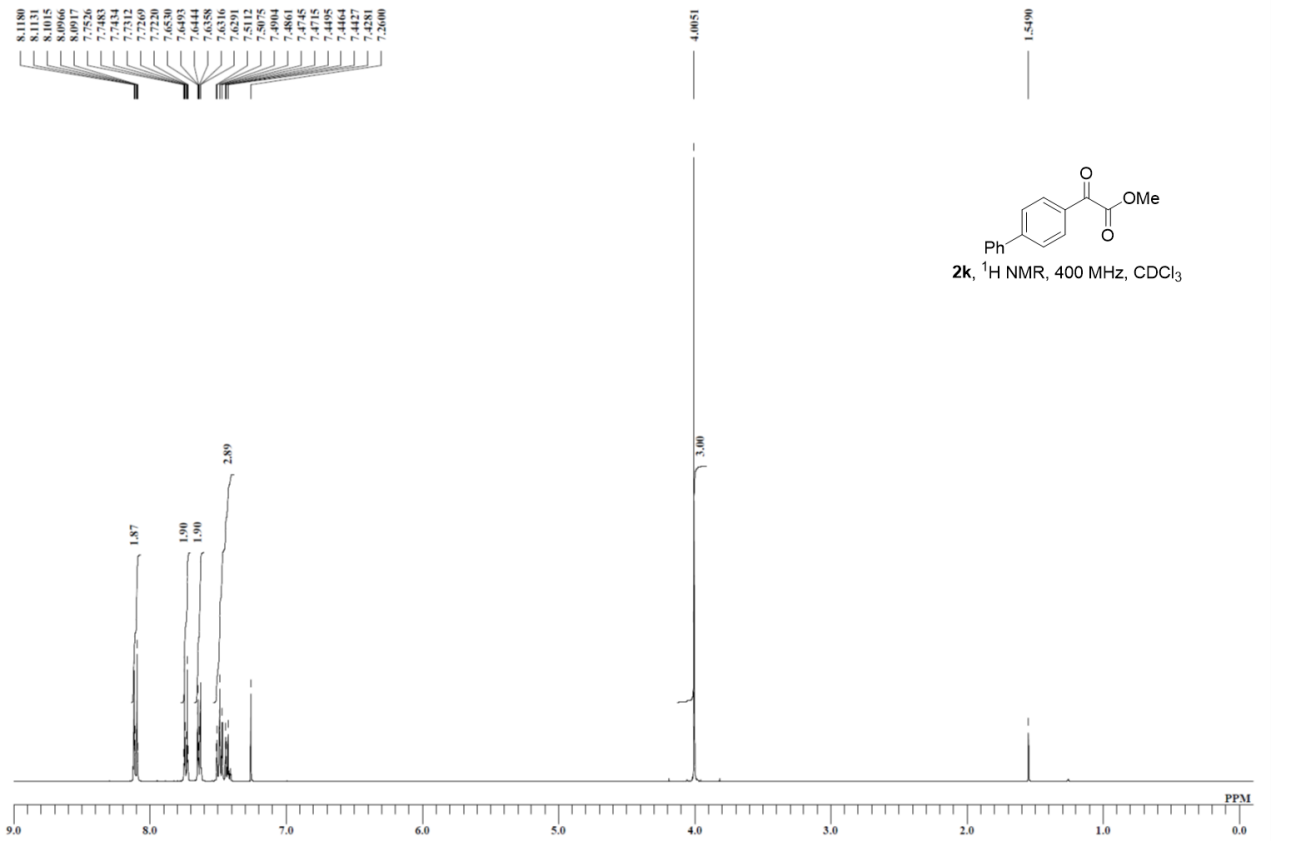

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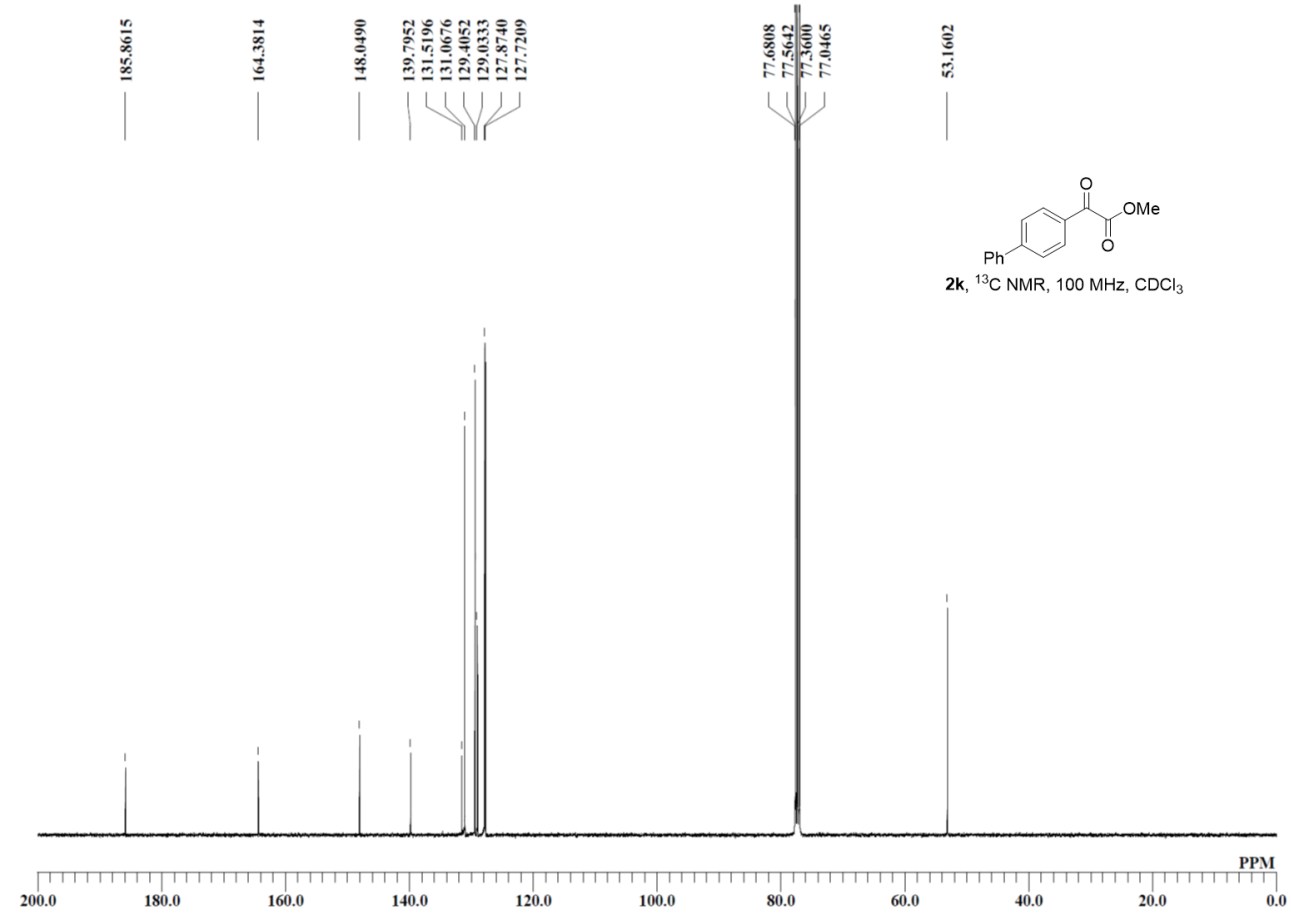

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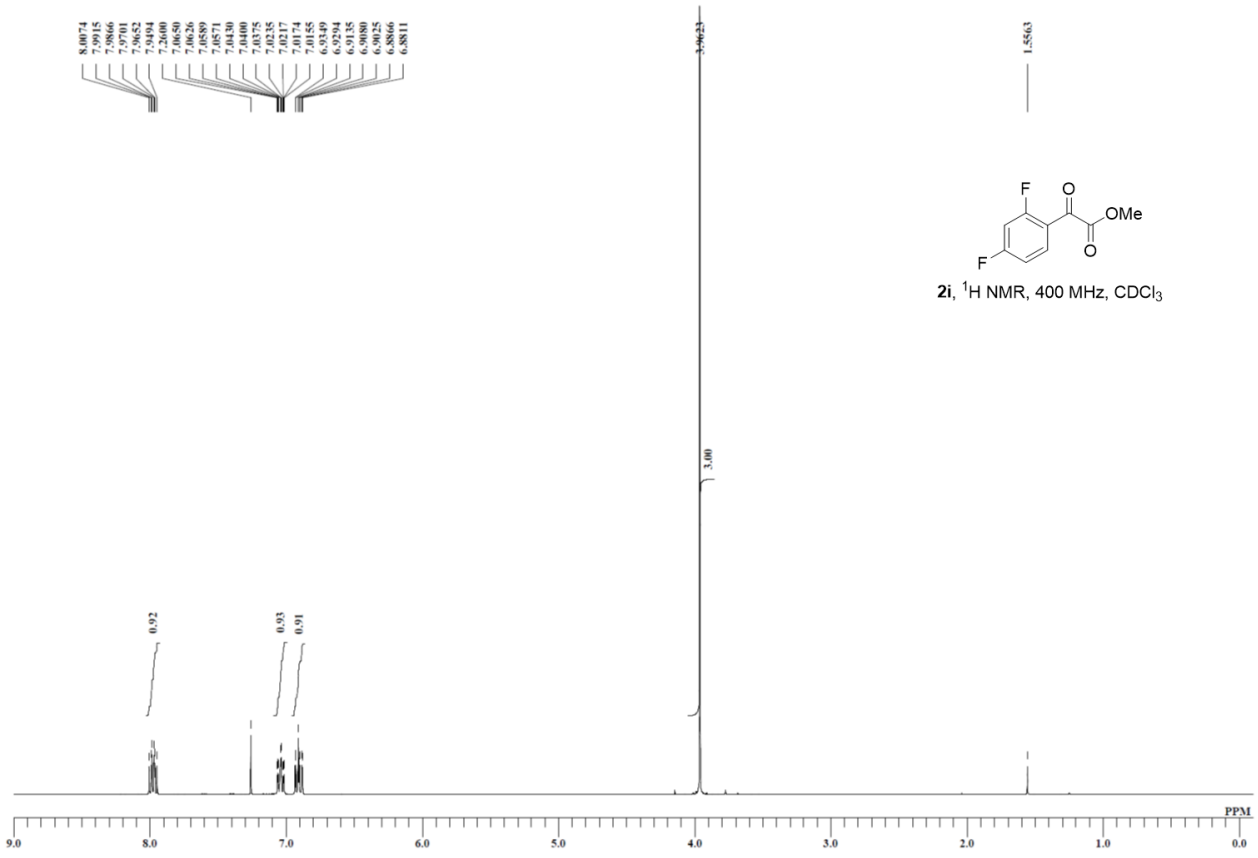

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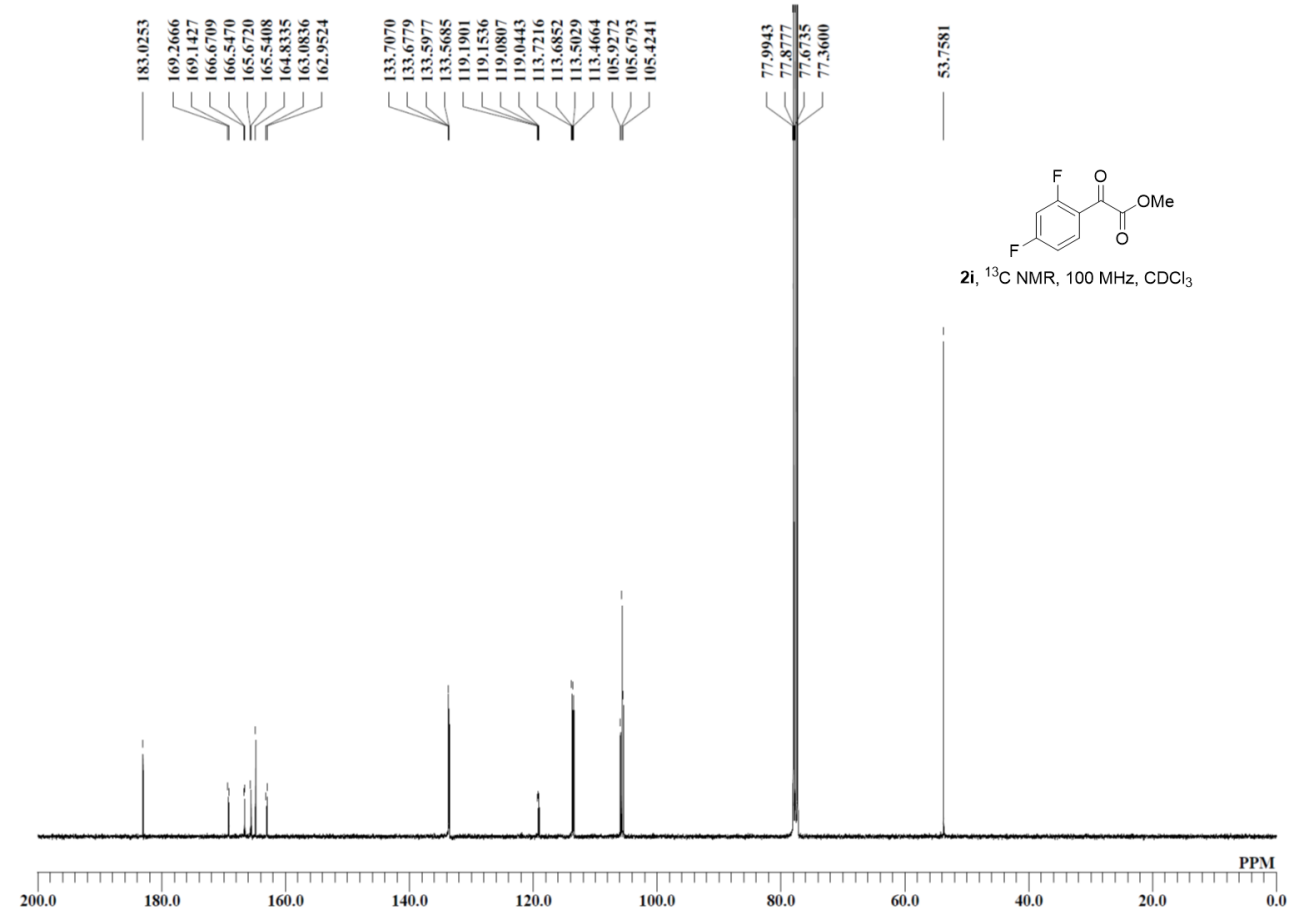

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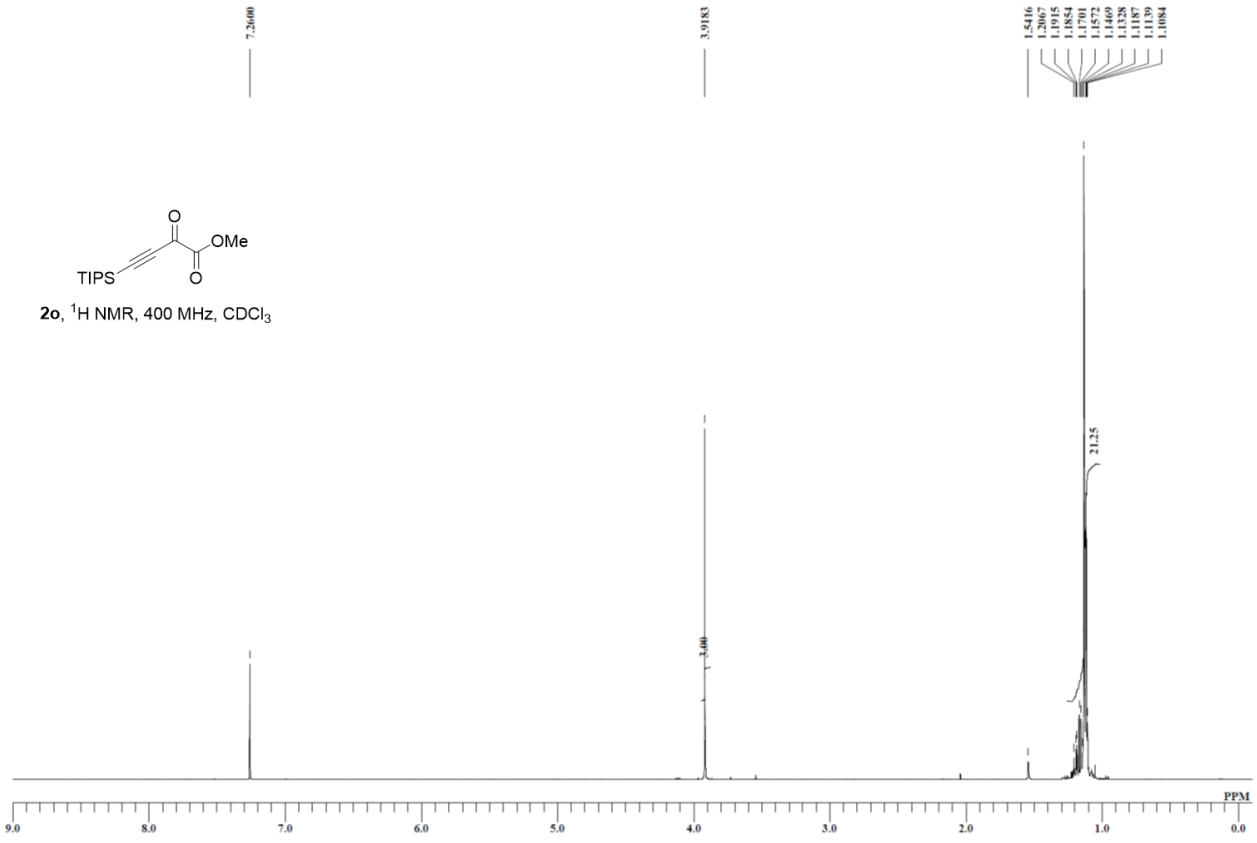
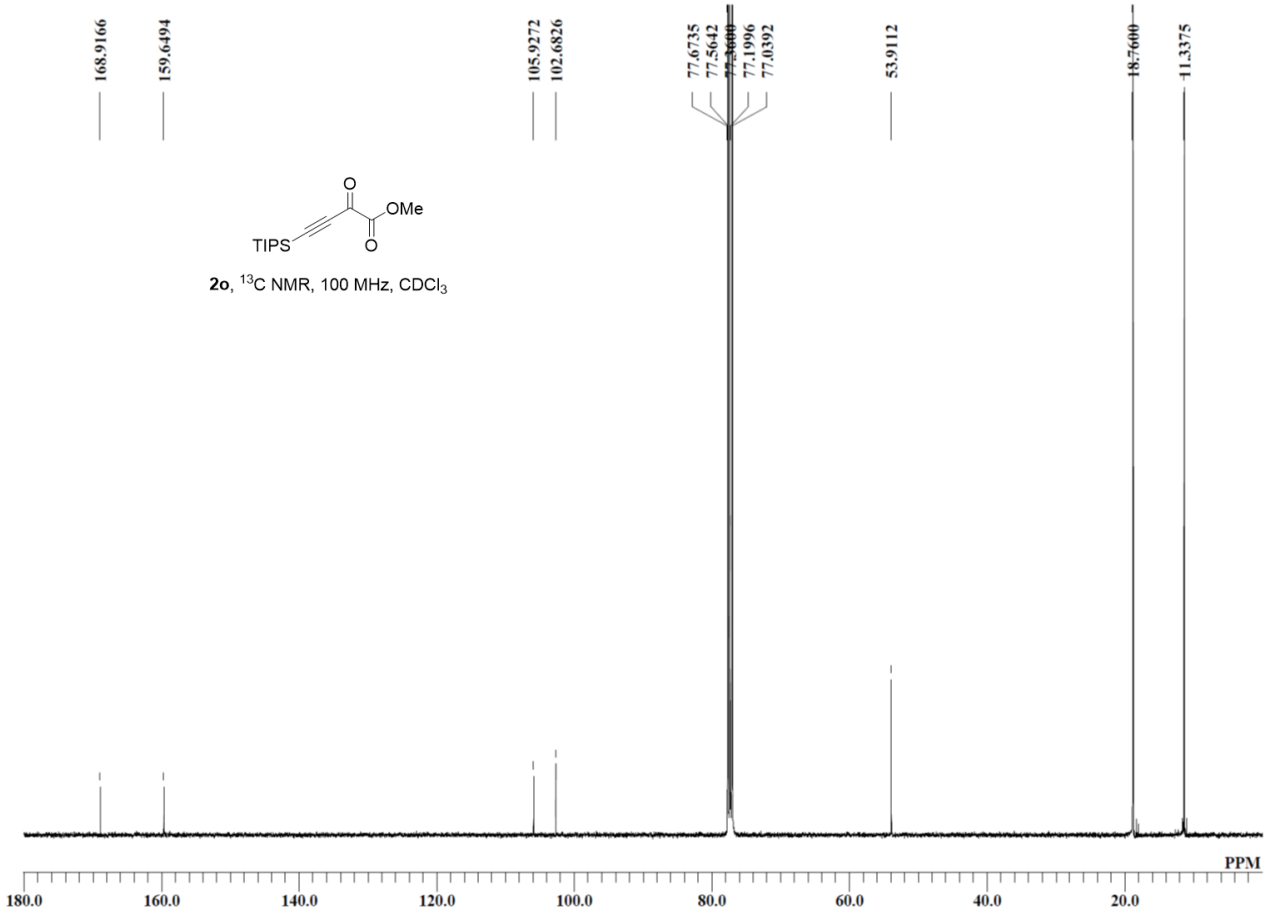


2o, ^{1}H NMR, 400 MHz, $CDCl_3$



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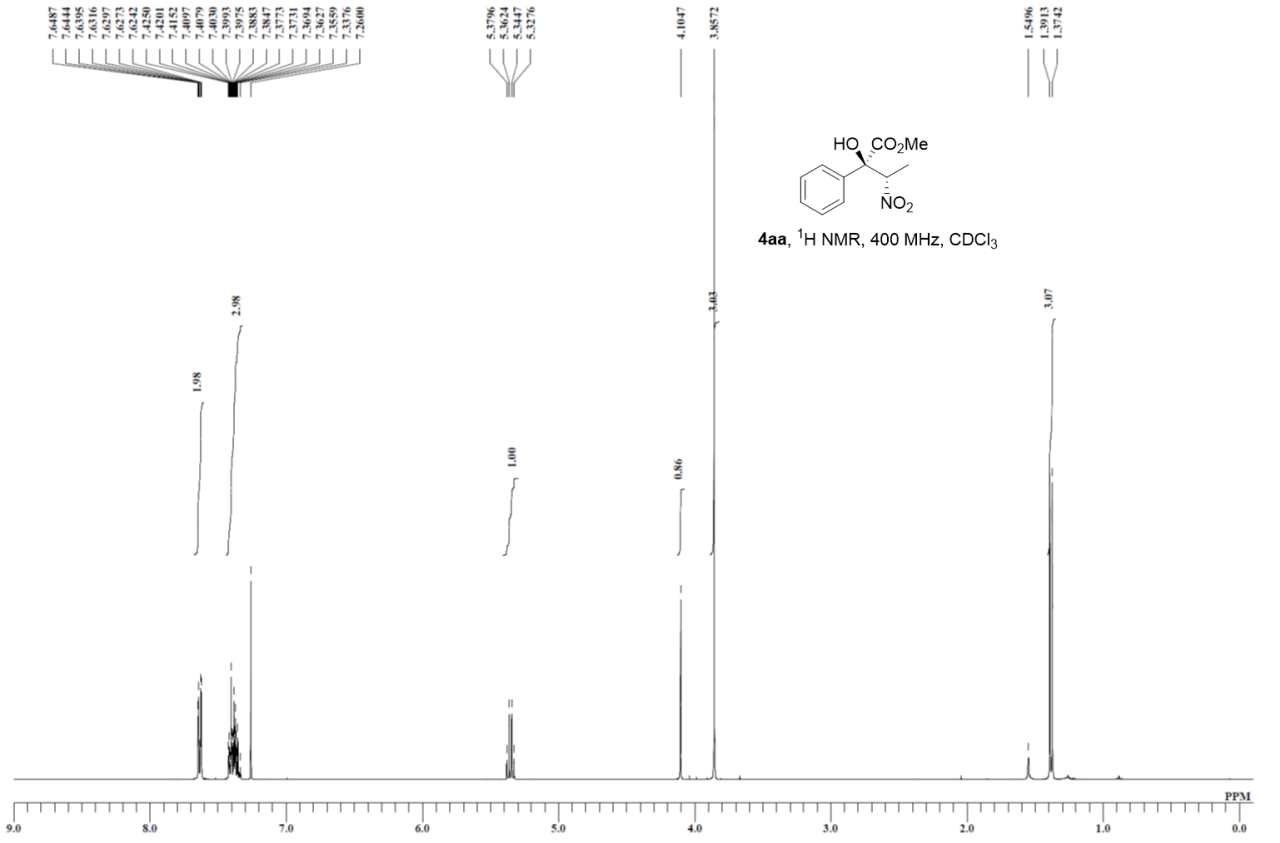

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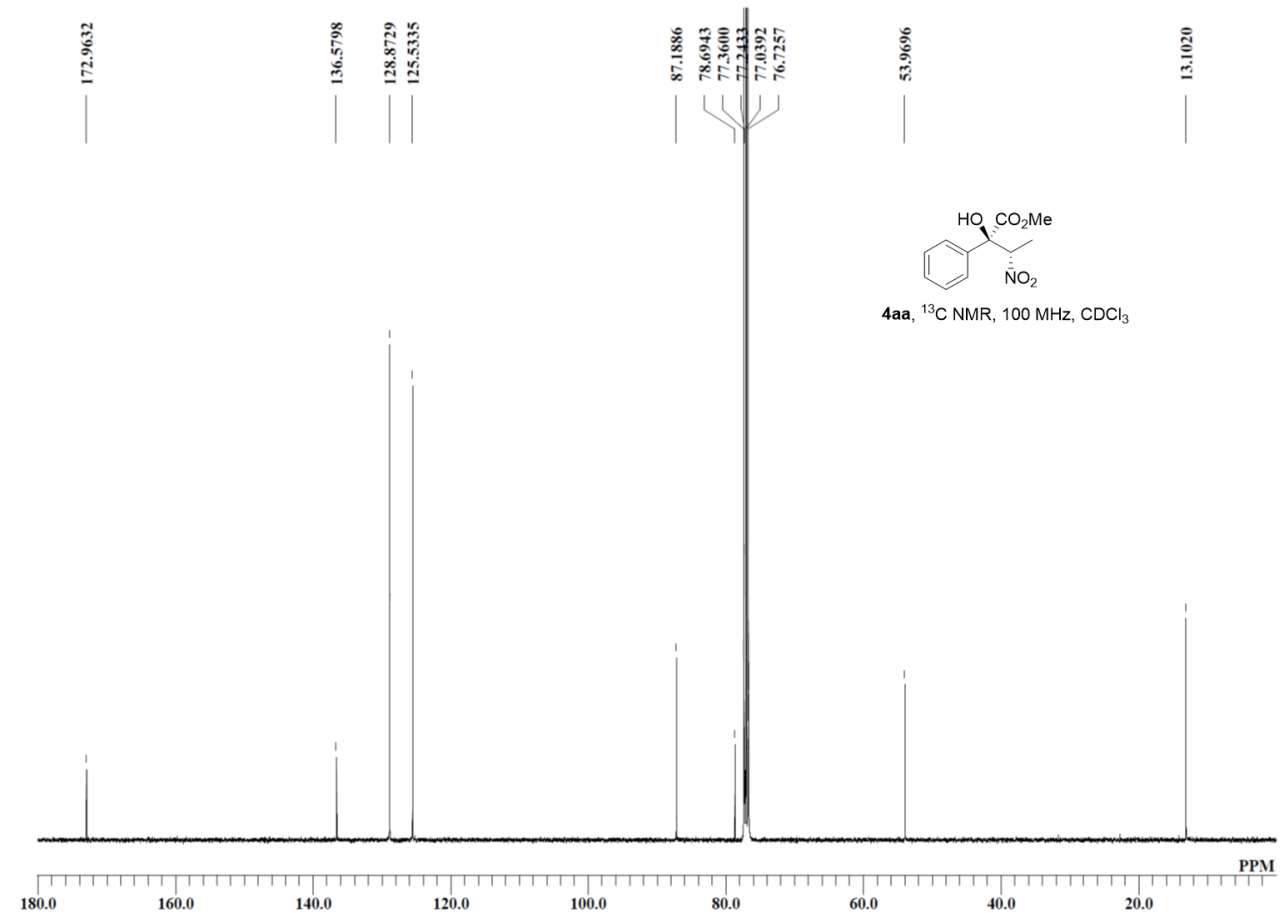

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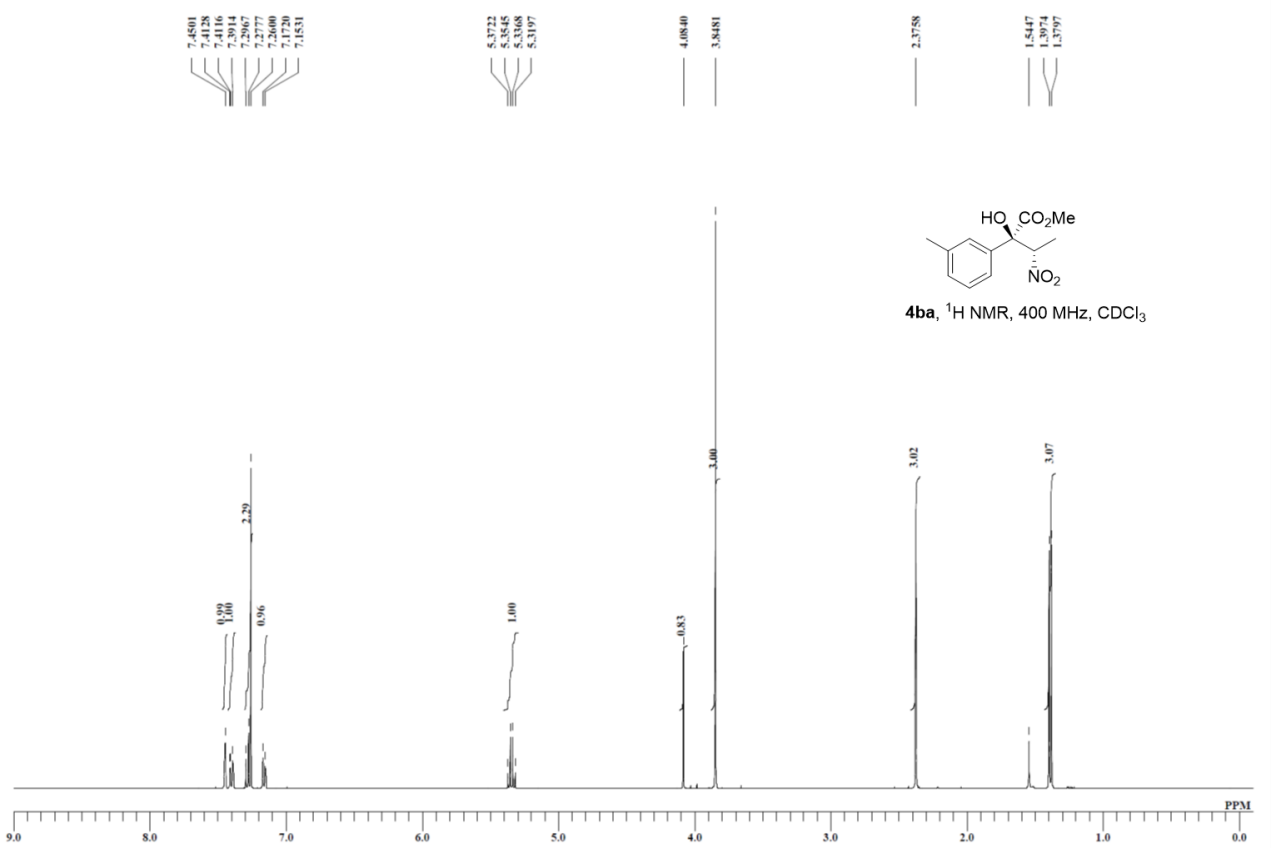
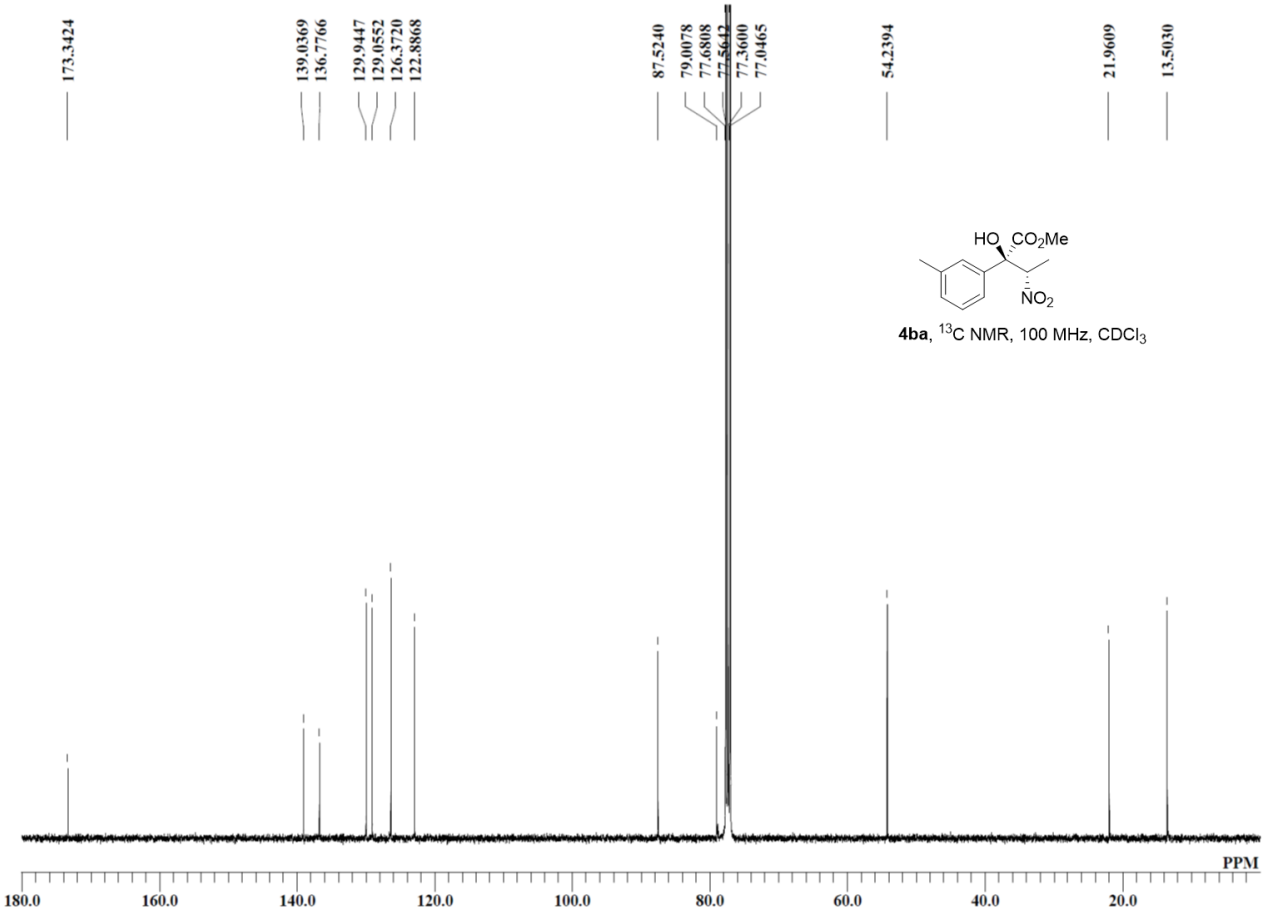


4ba, ^{1}H NMR, 400 MHz, $CDCl_3$



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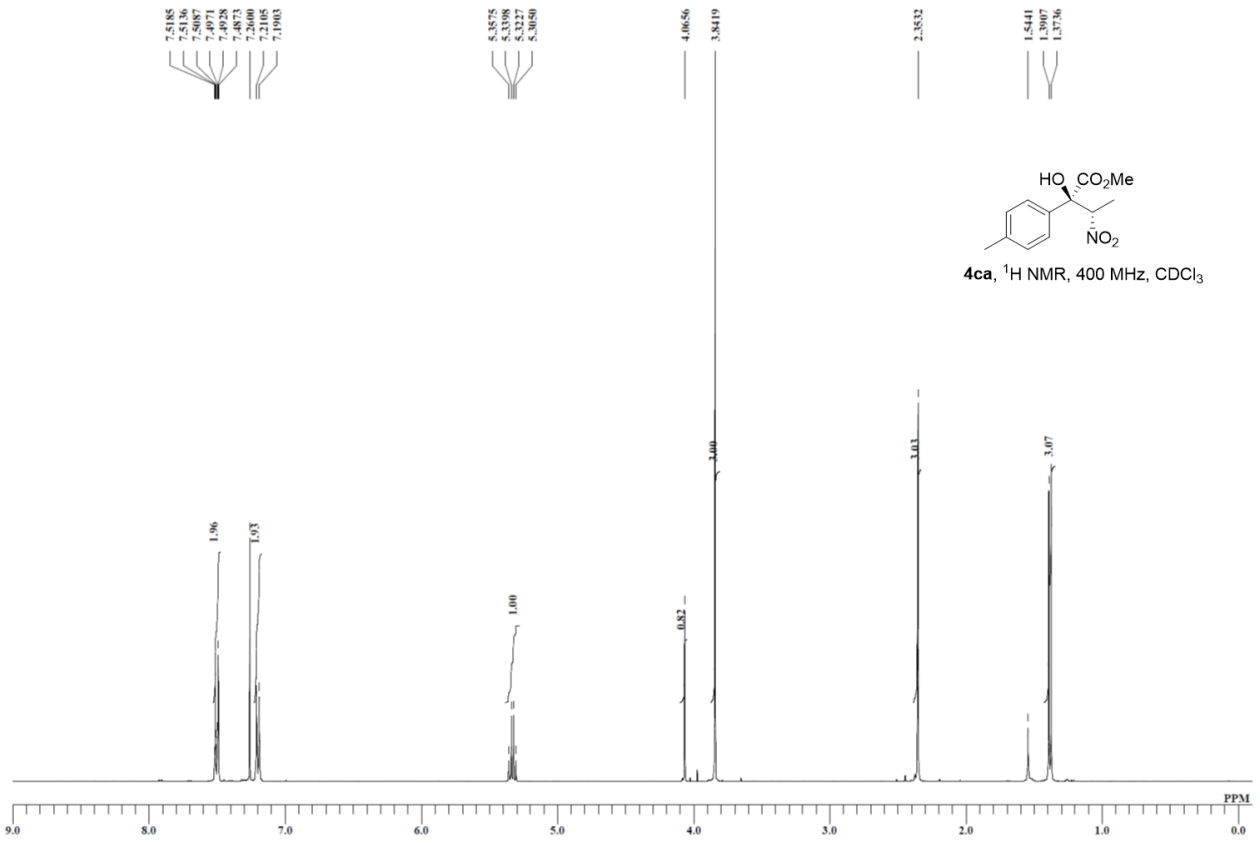

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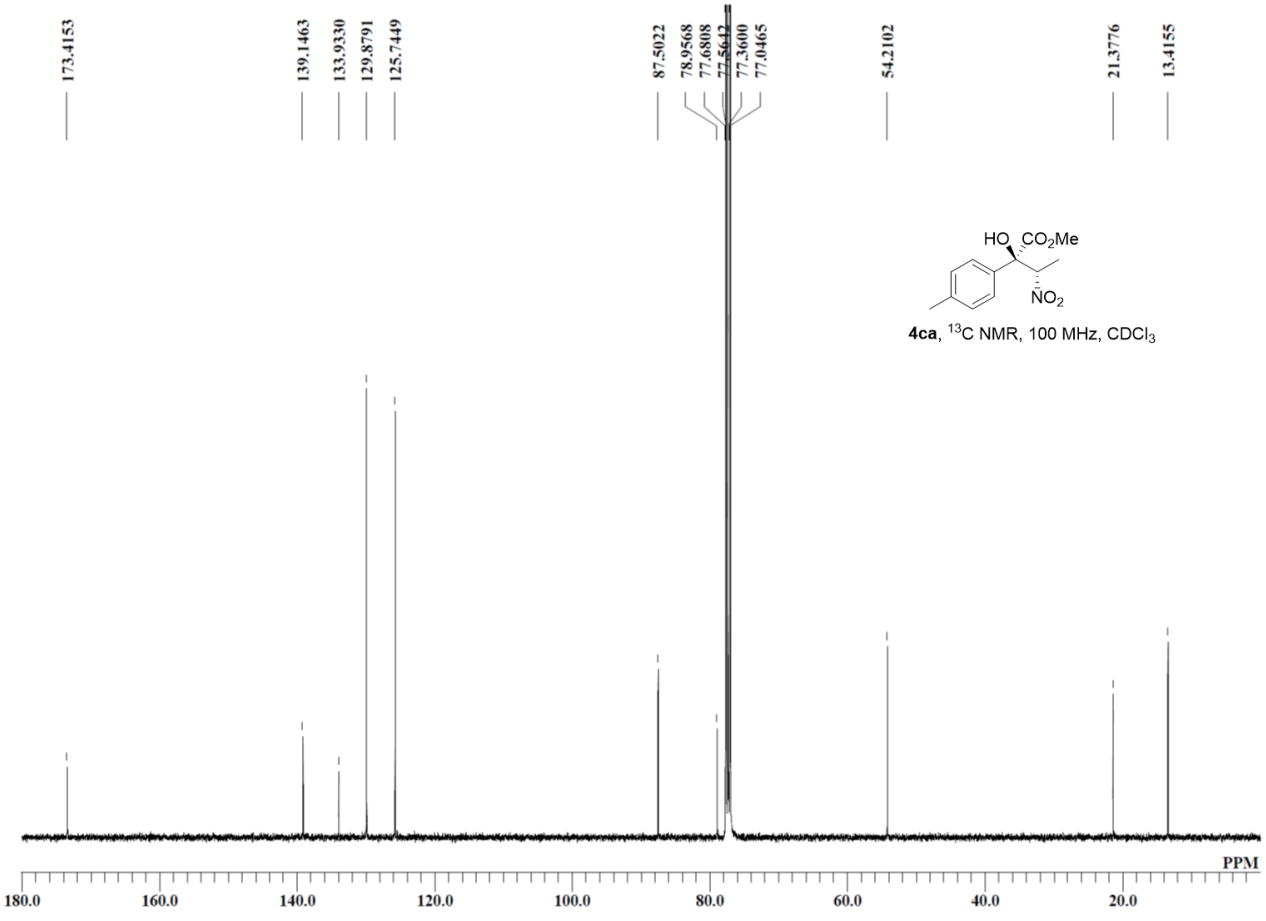

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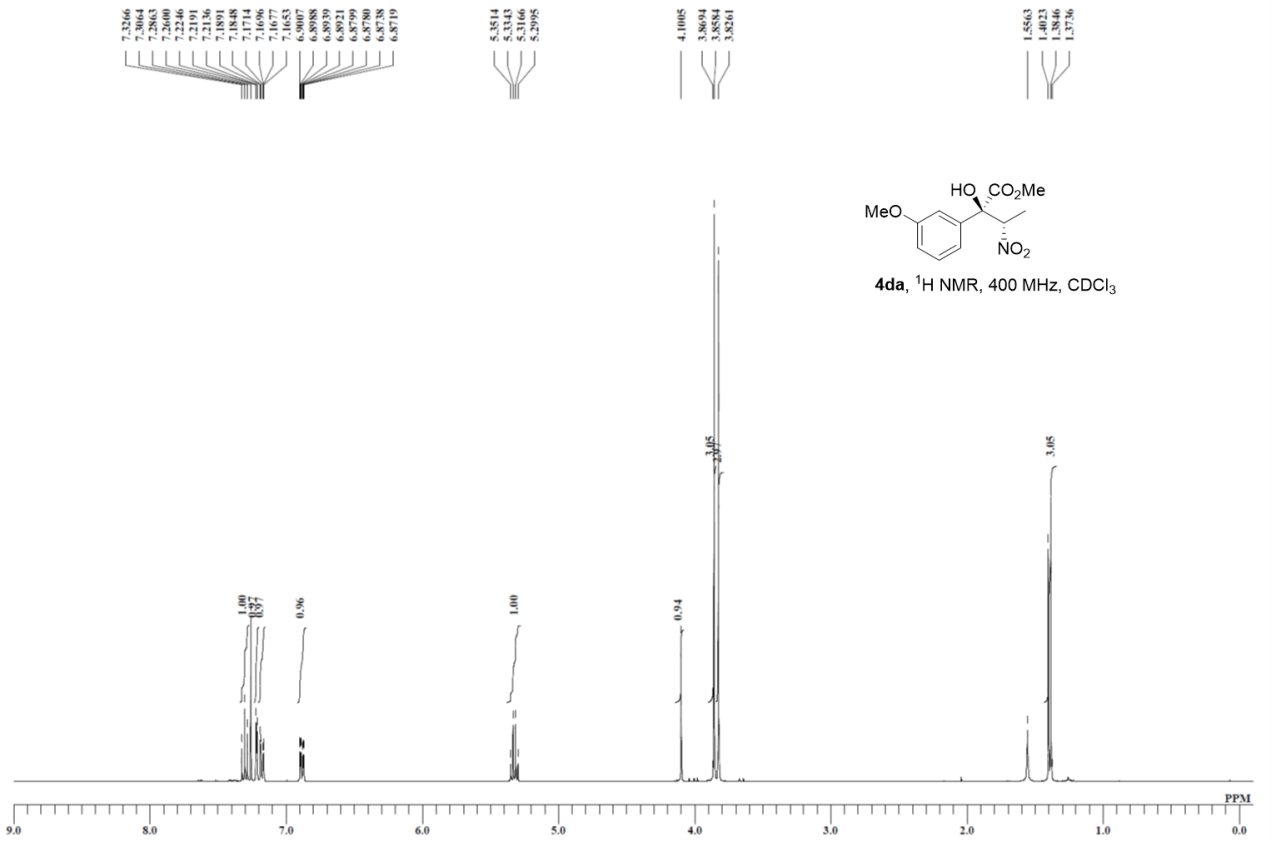
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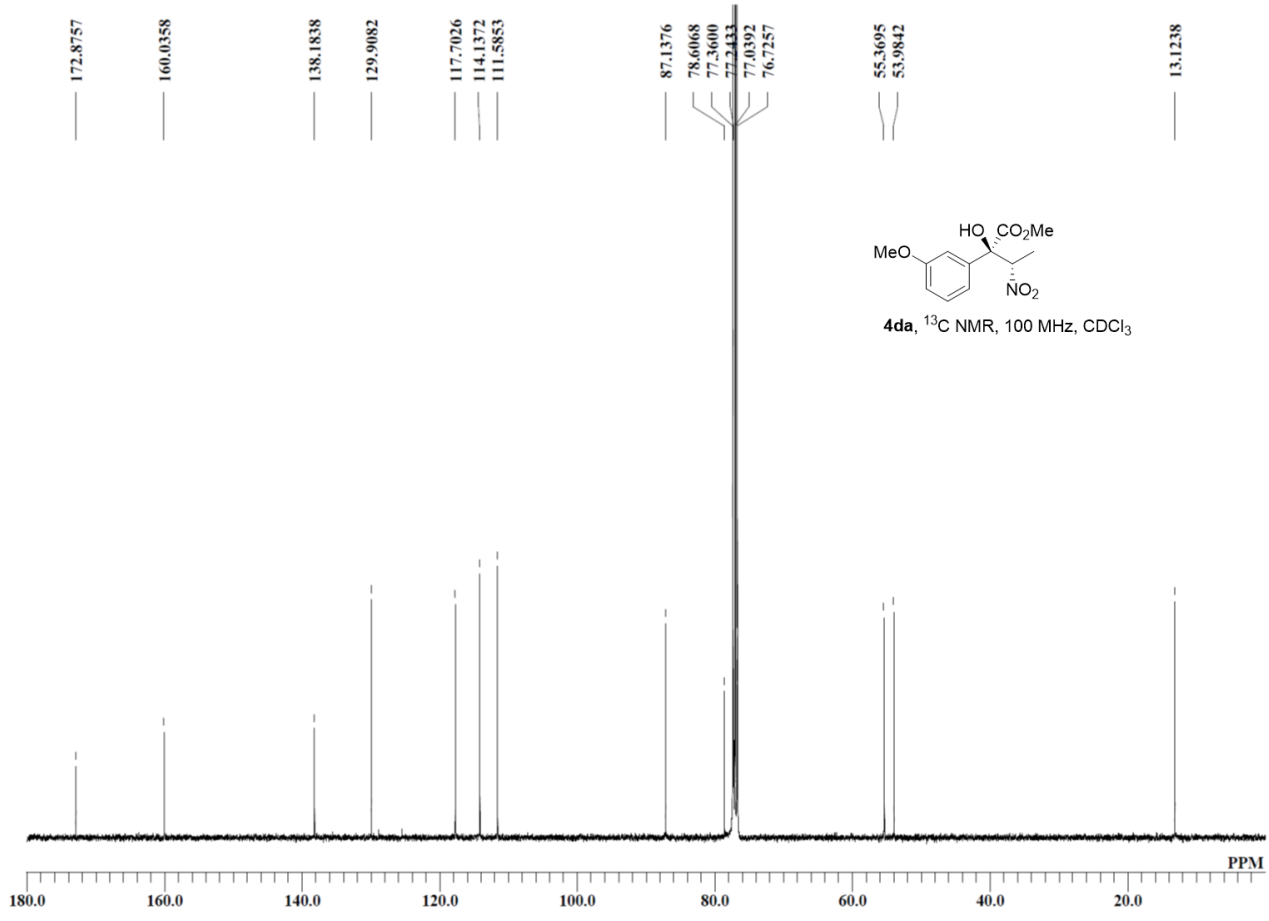
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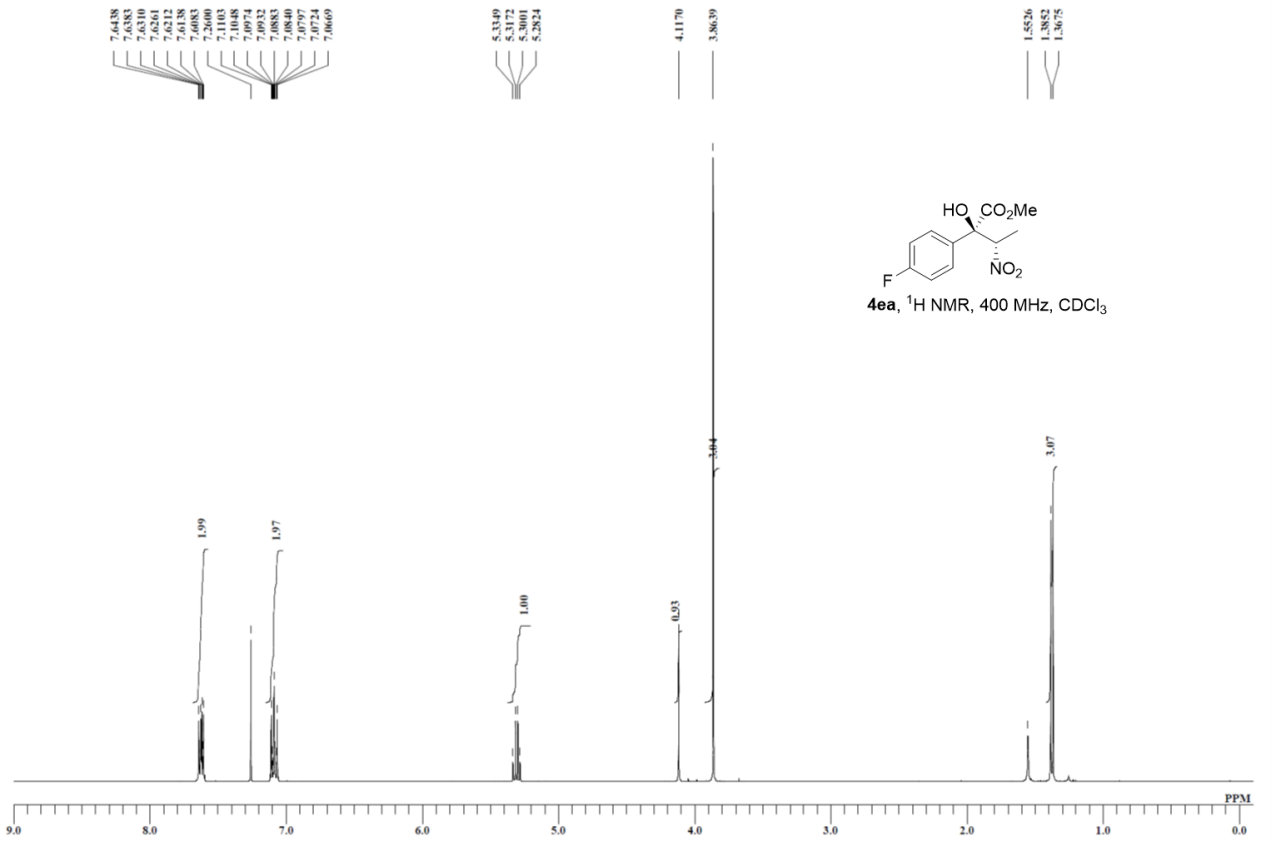

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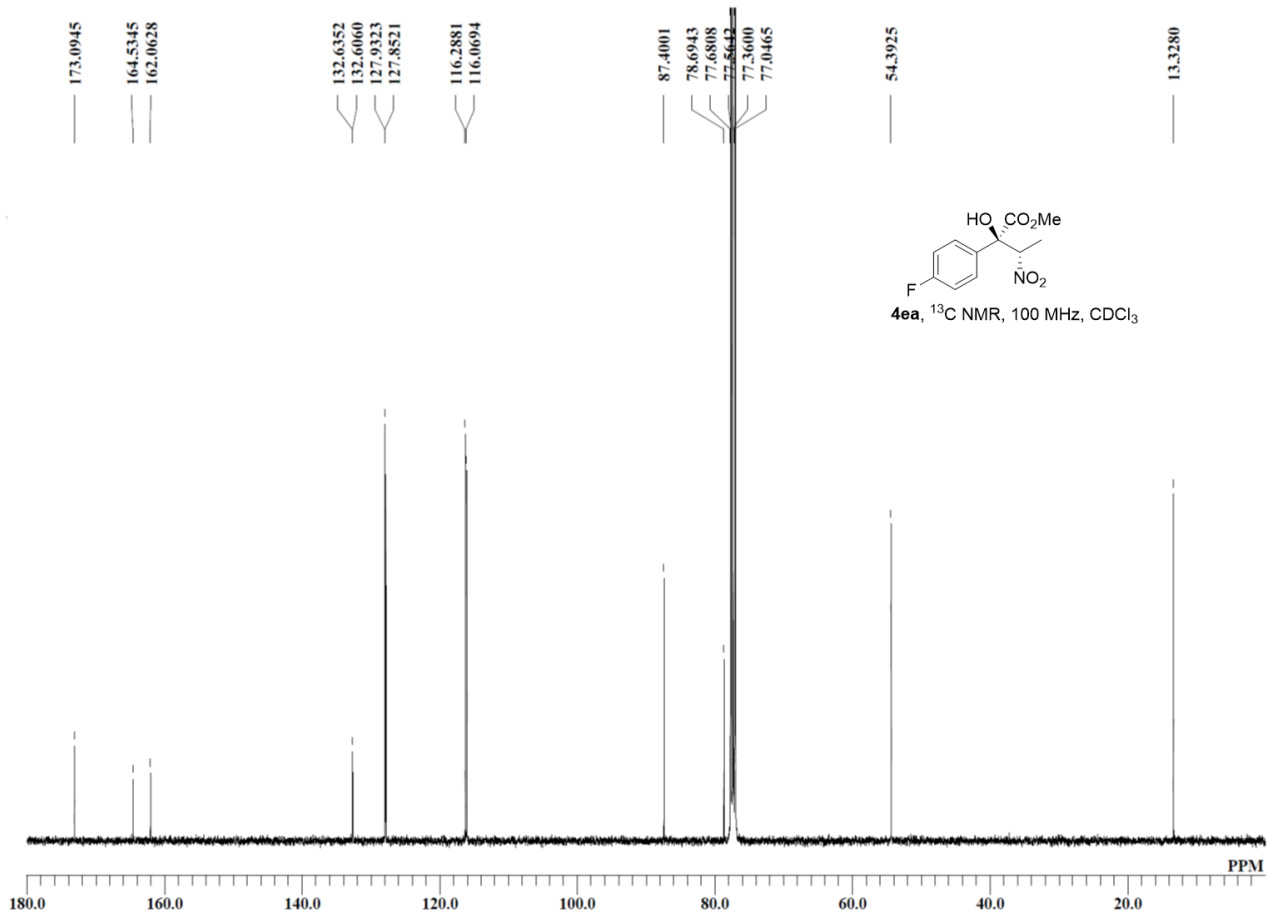

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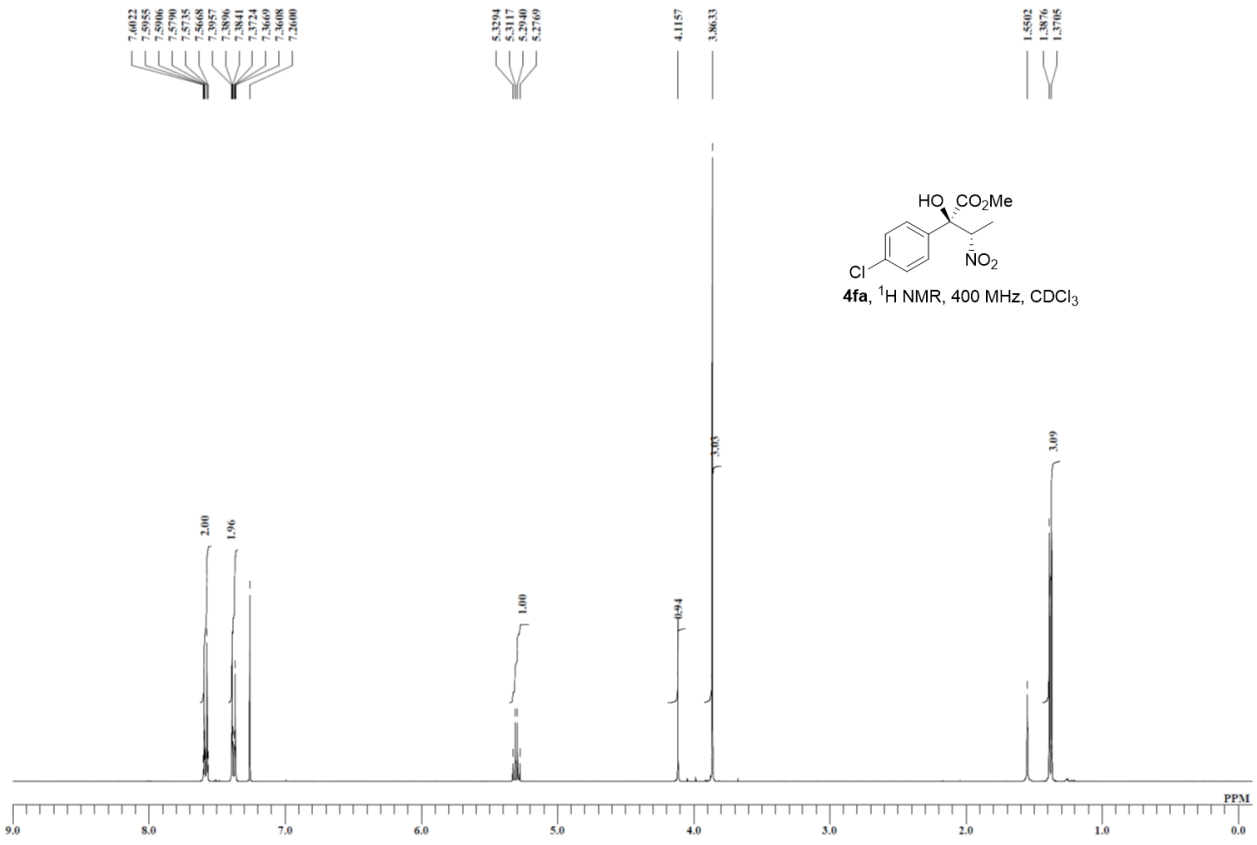

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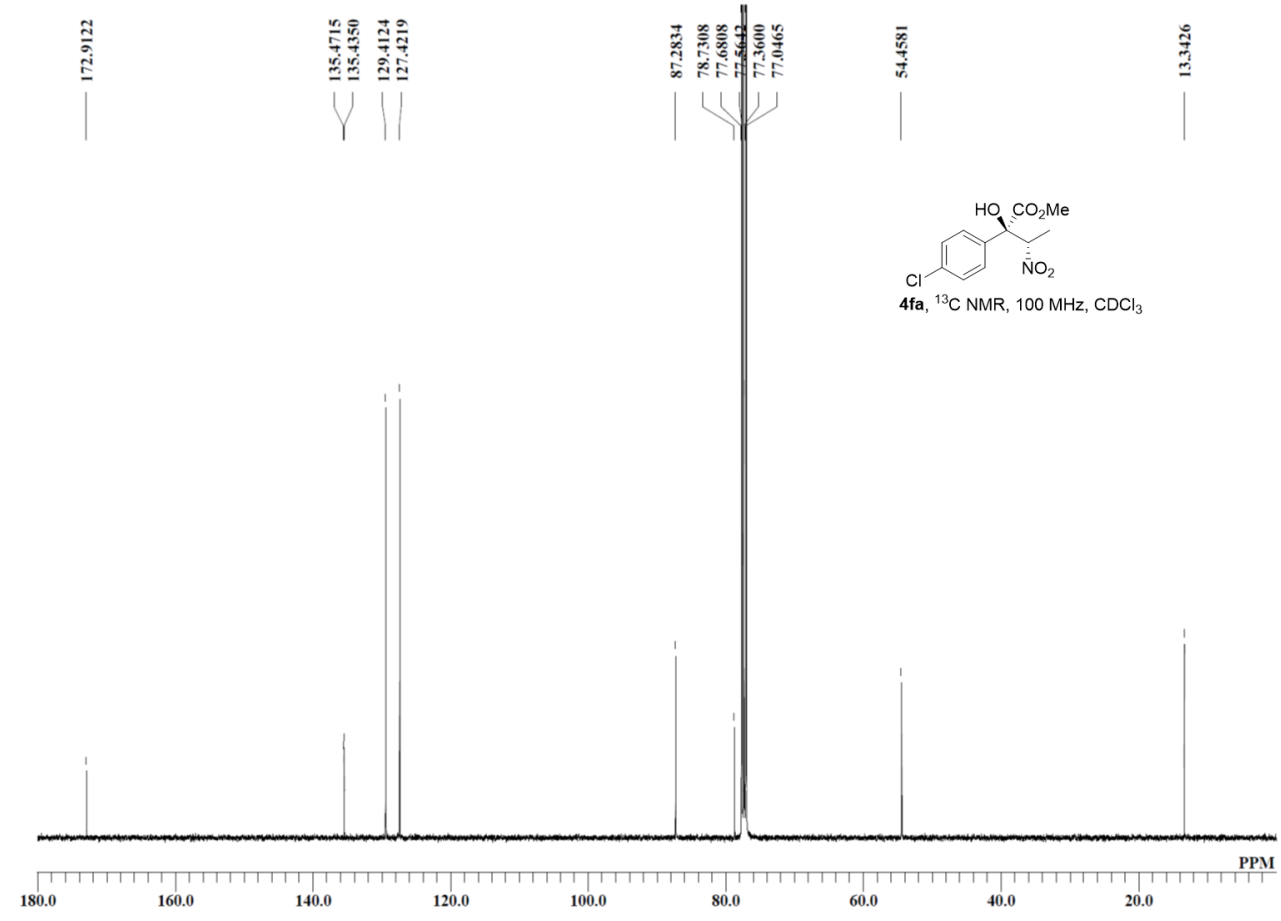

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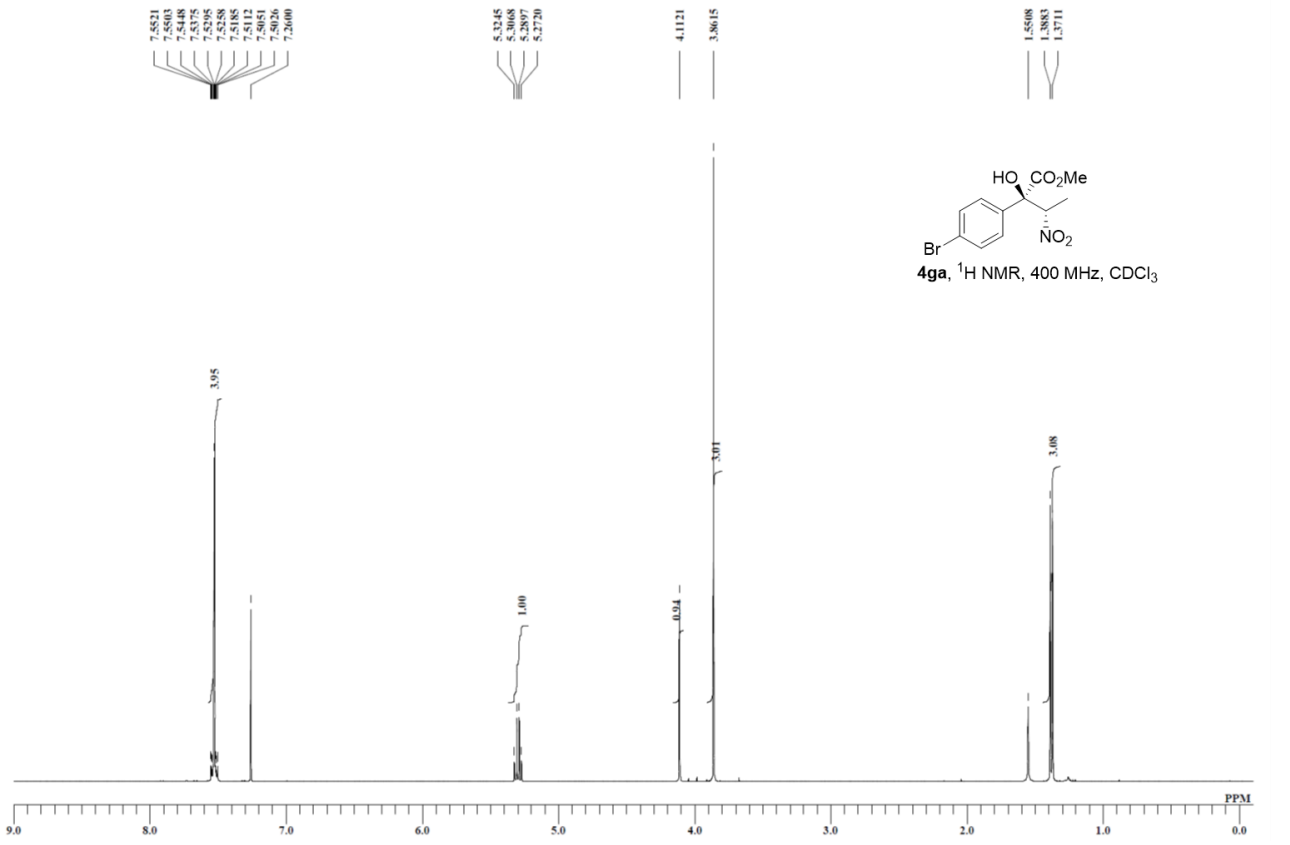

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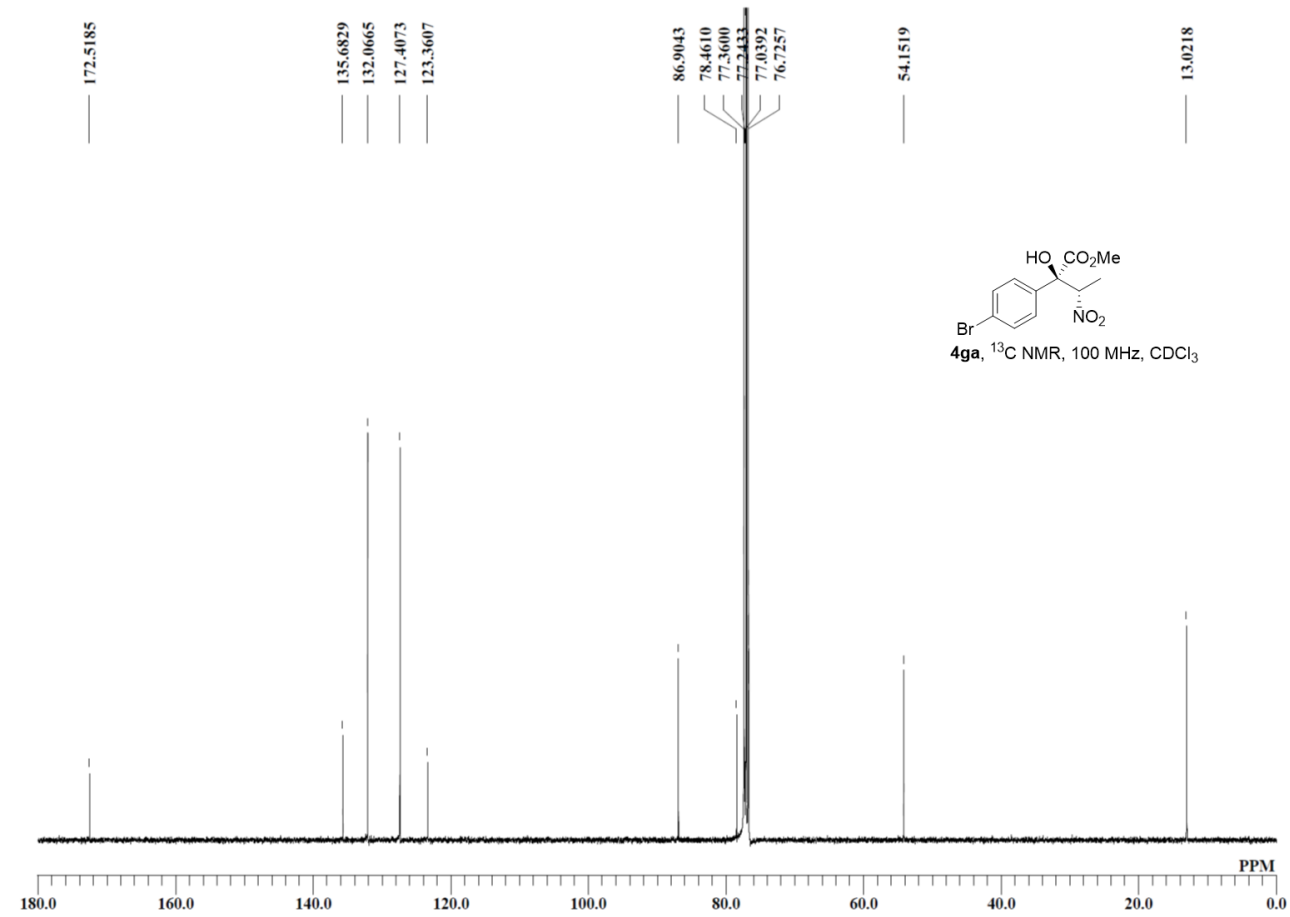

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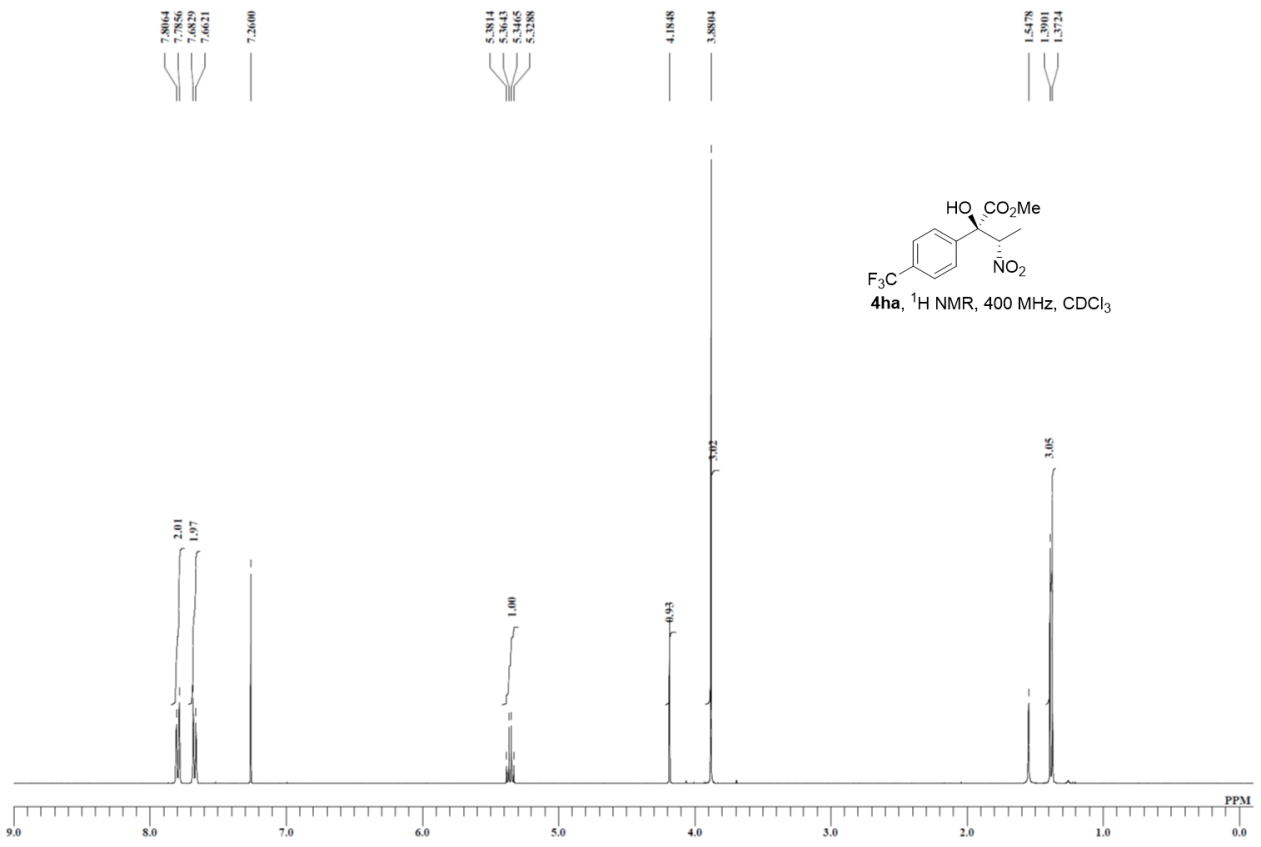

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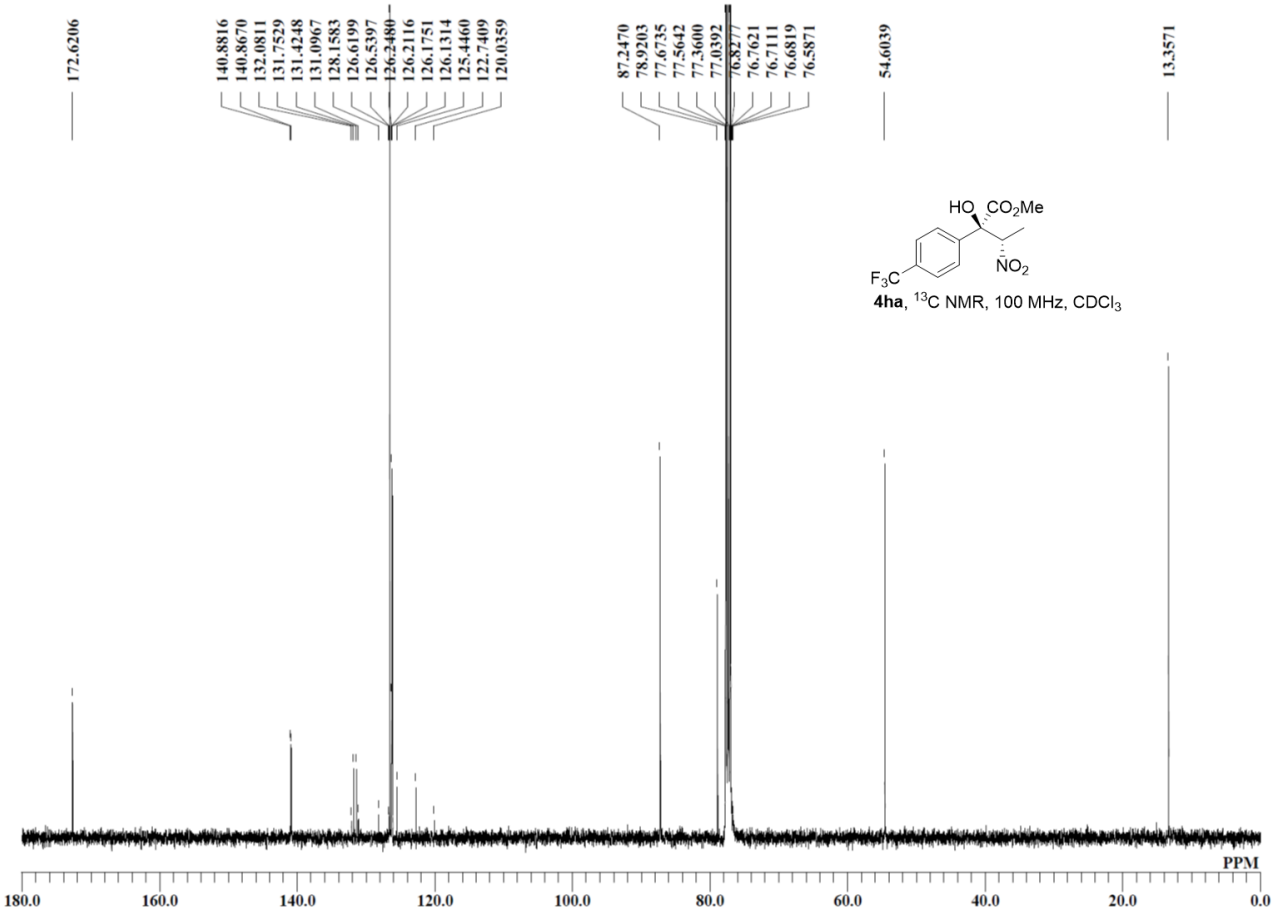

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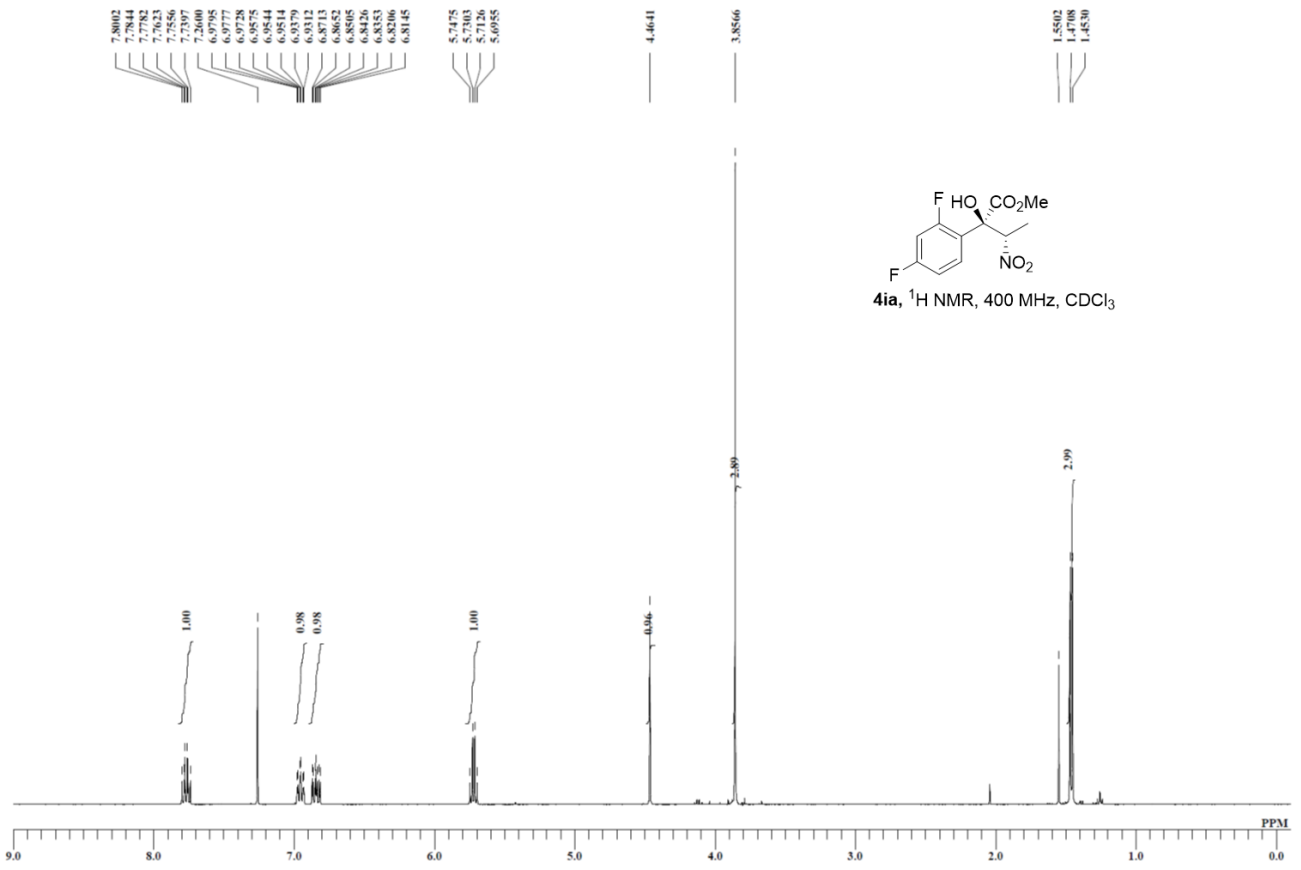

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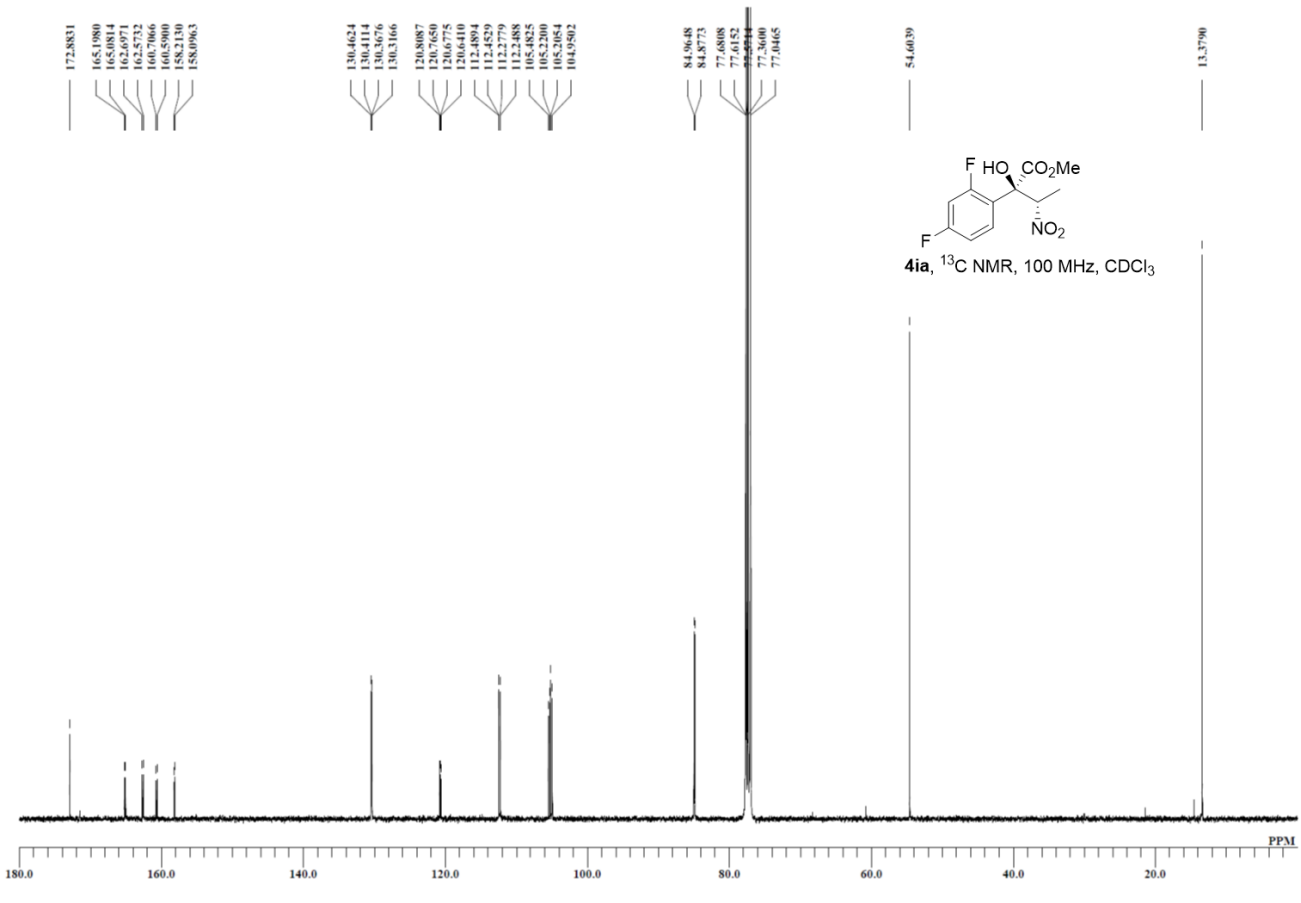

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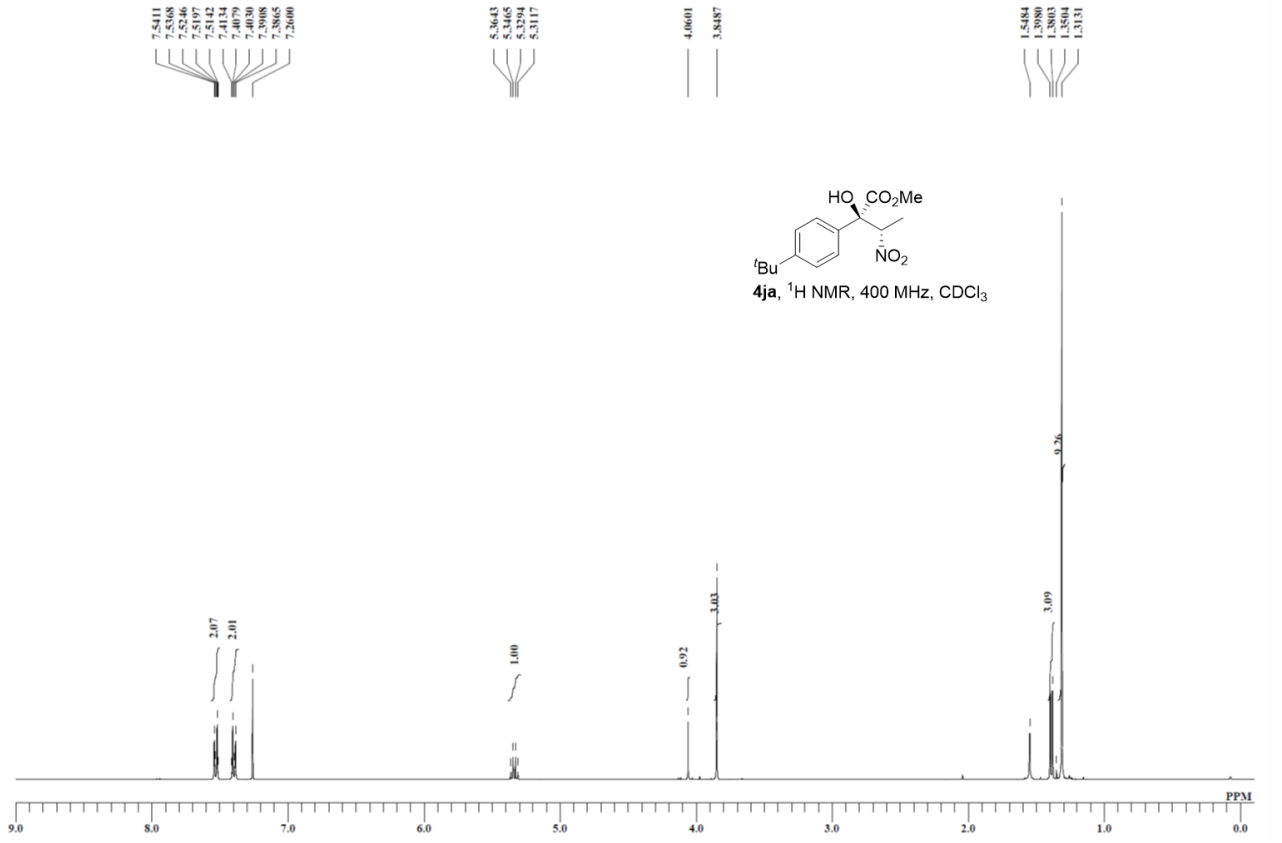
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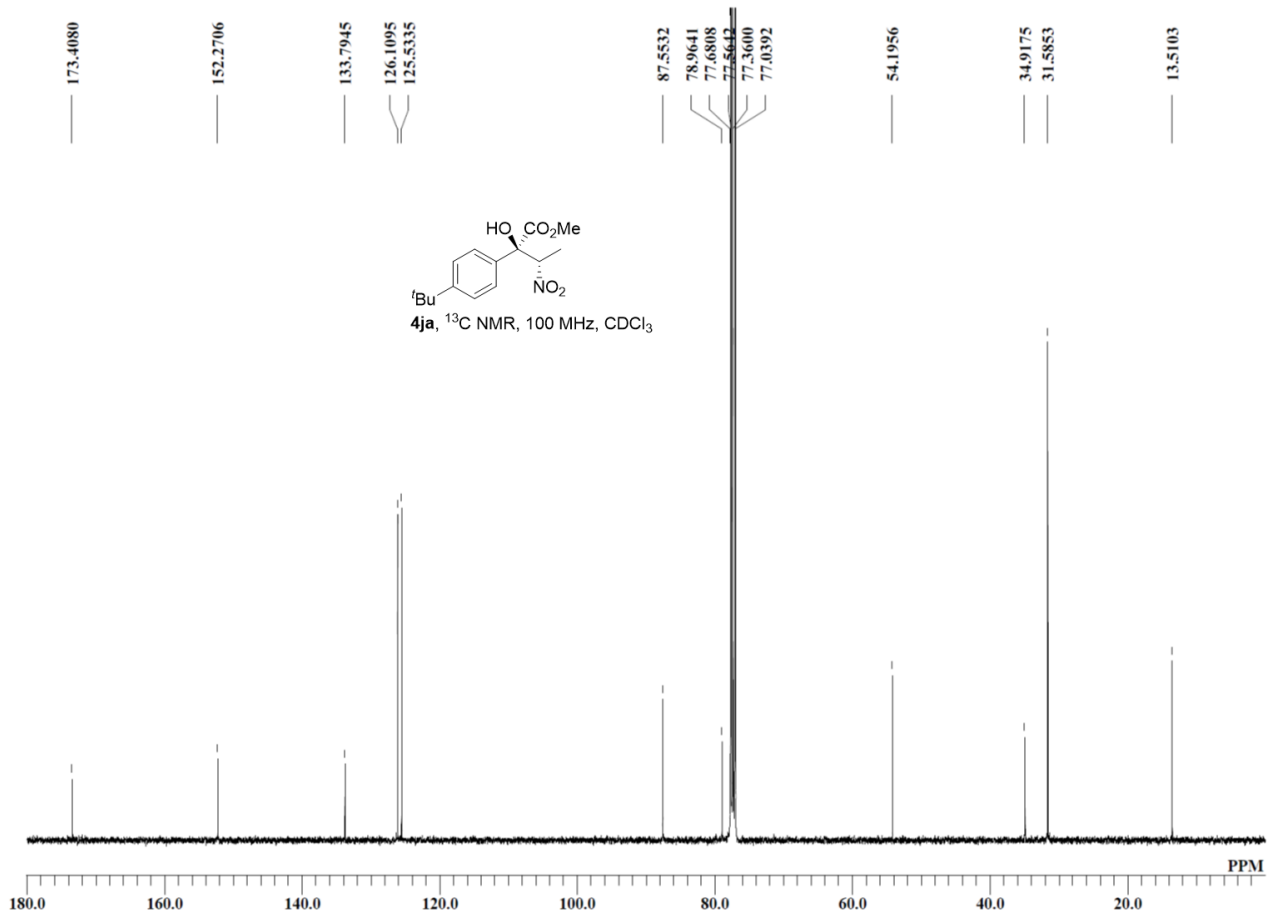
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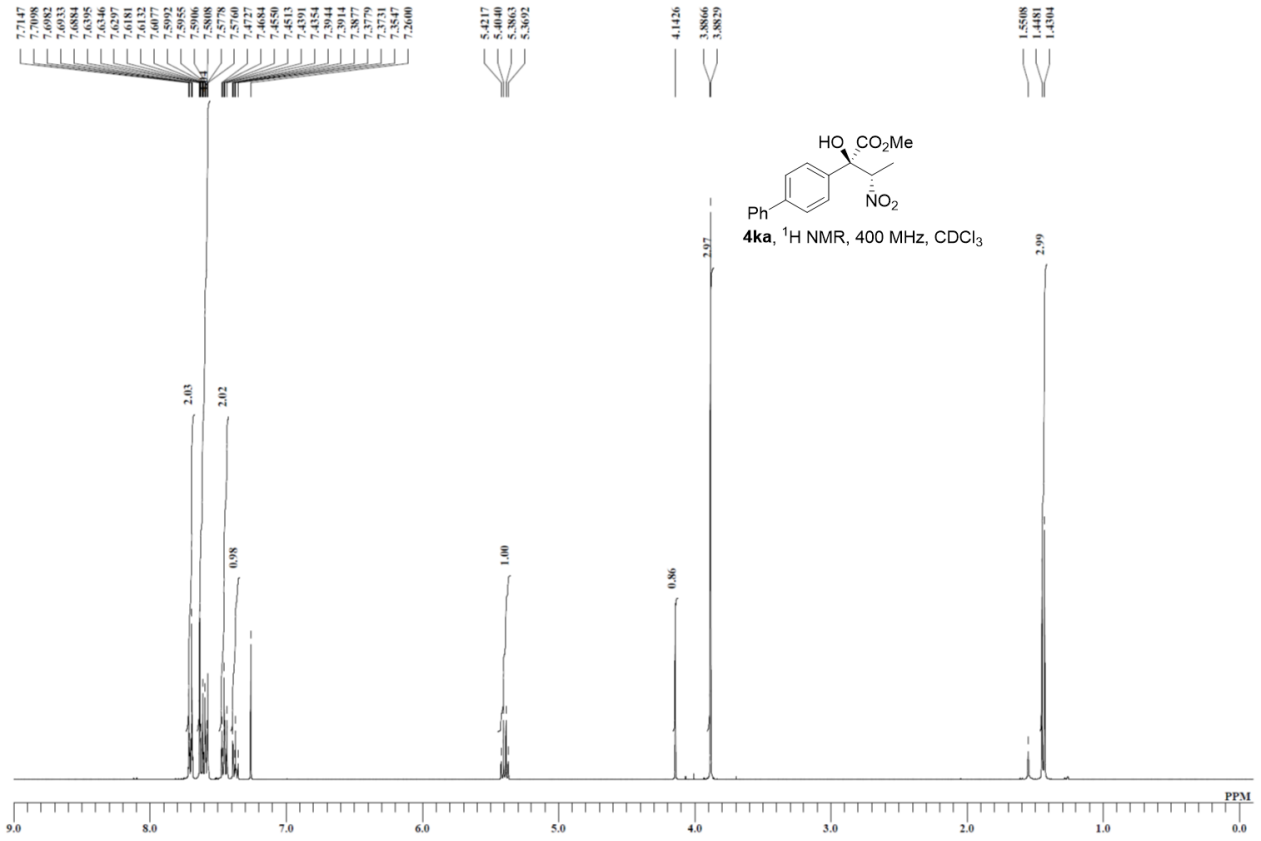

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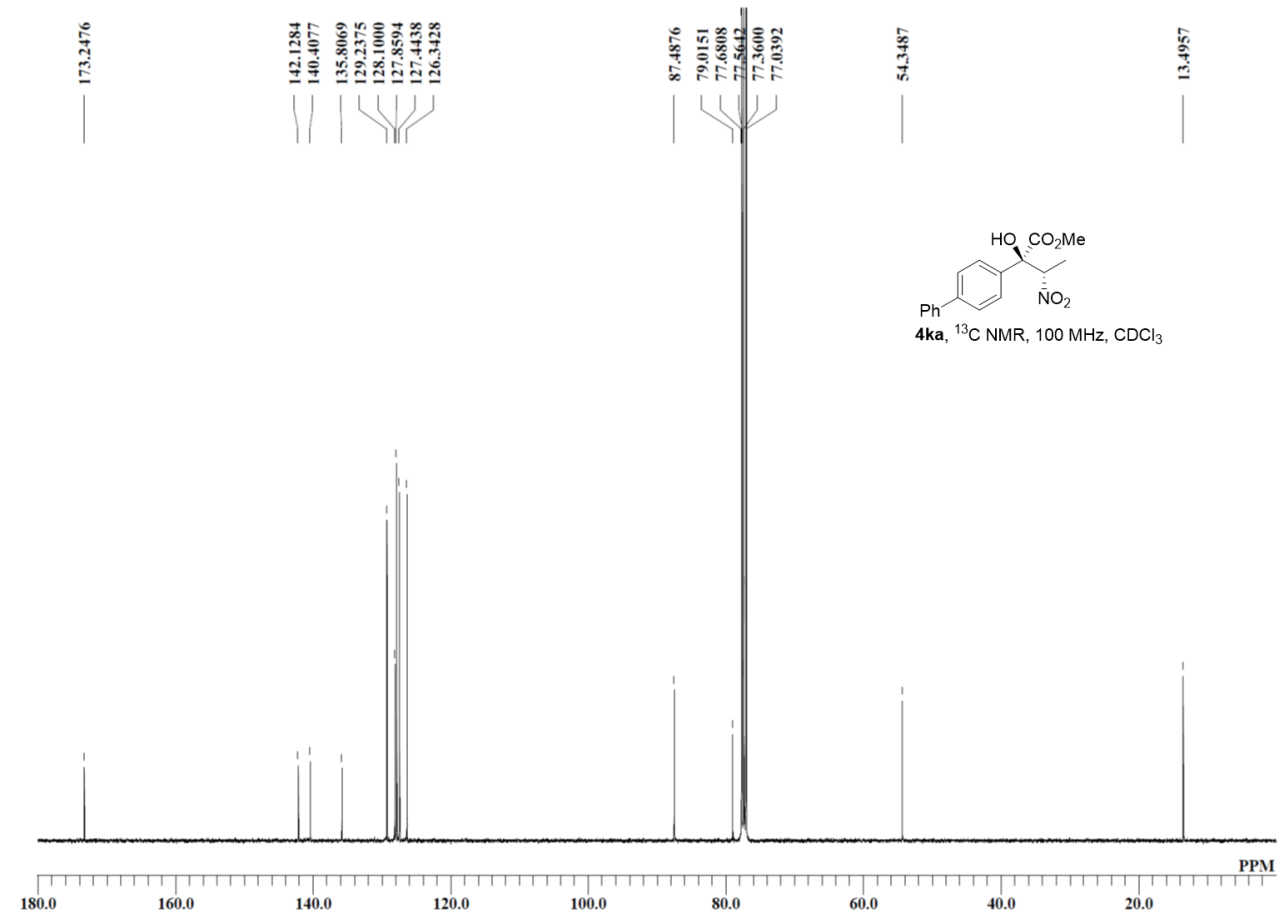
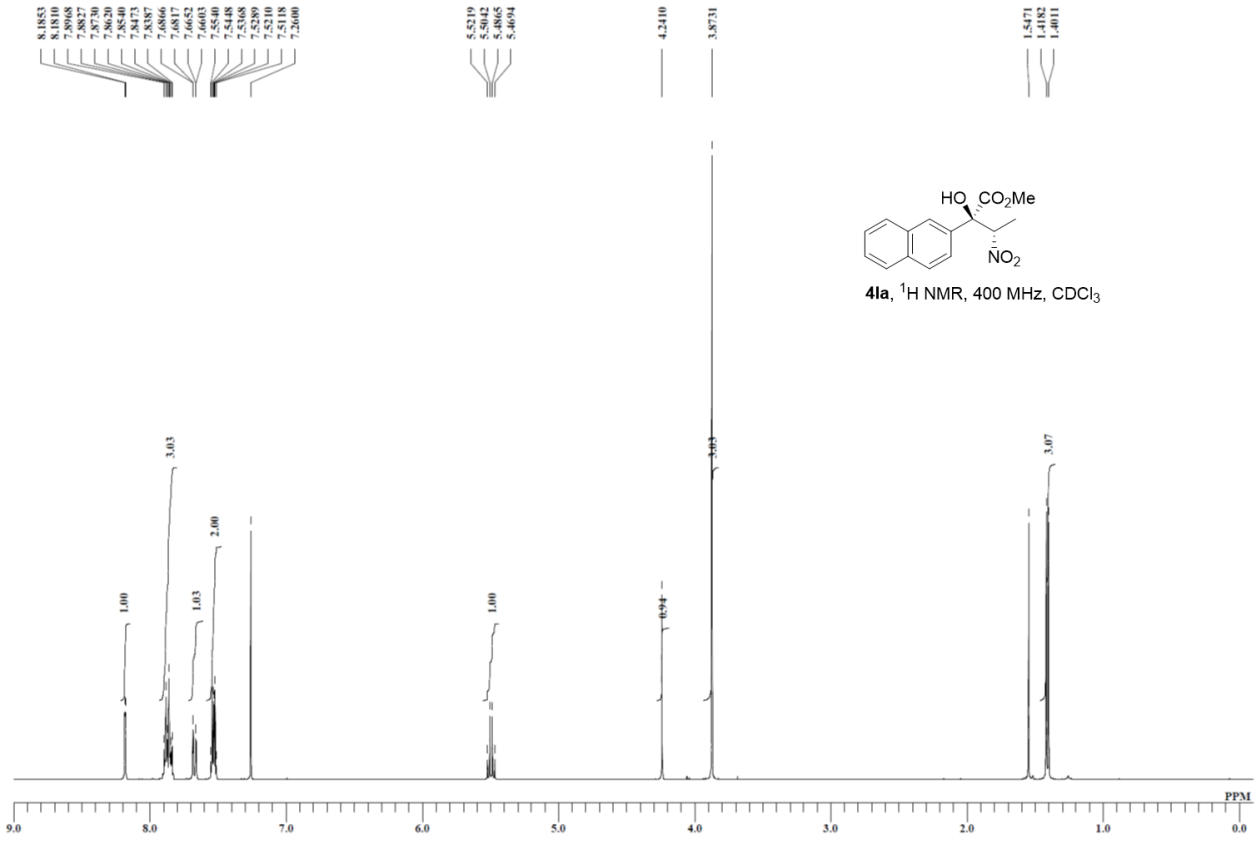


4ka, ^{13}C NMR, 100 MHz, $CDCl_3$



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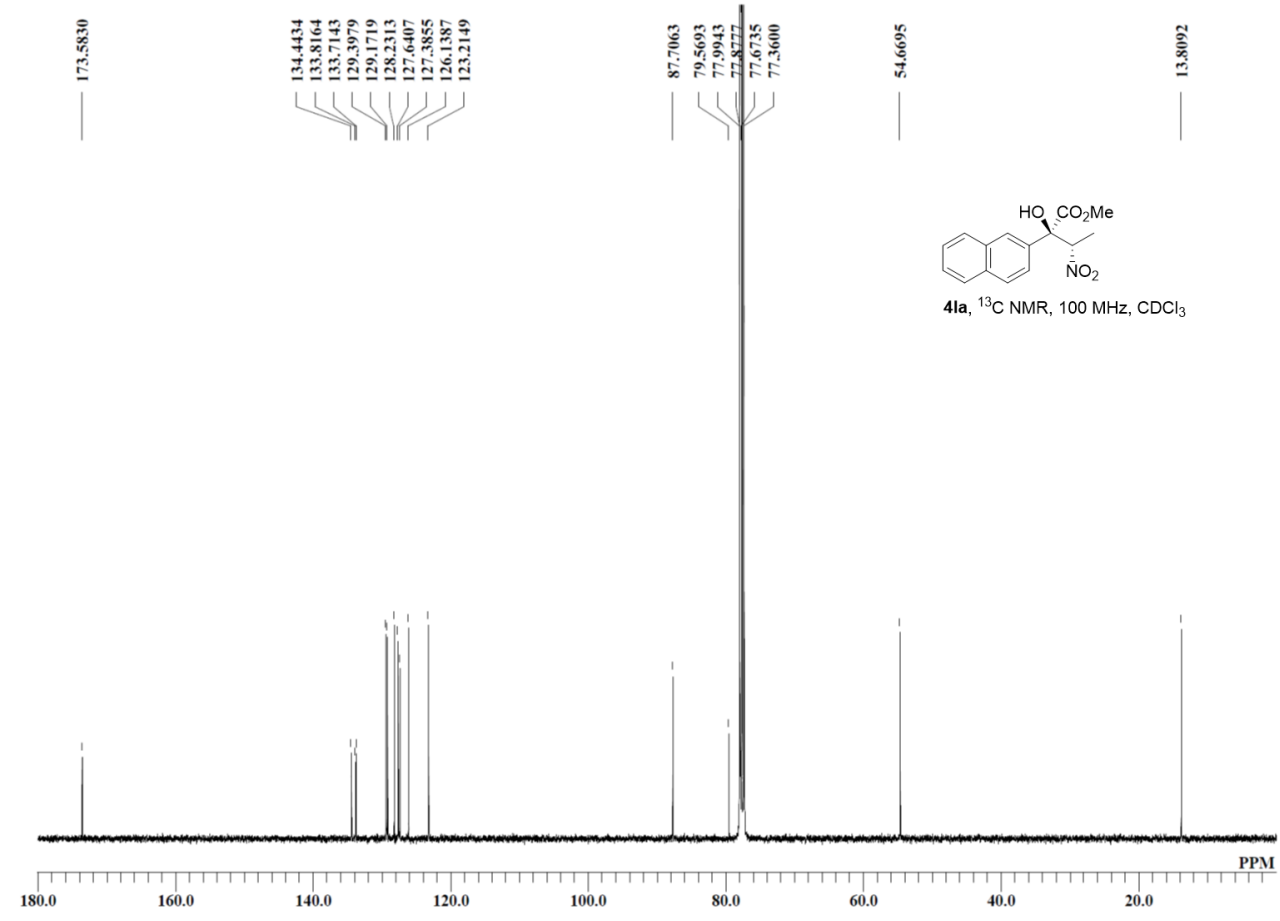

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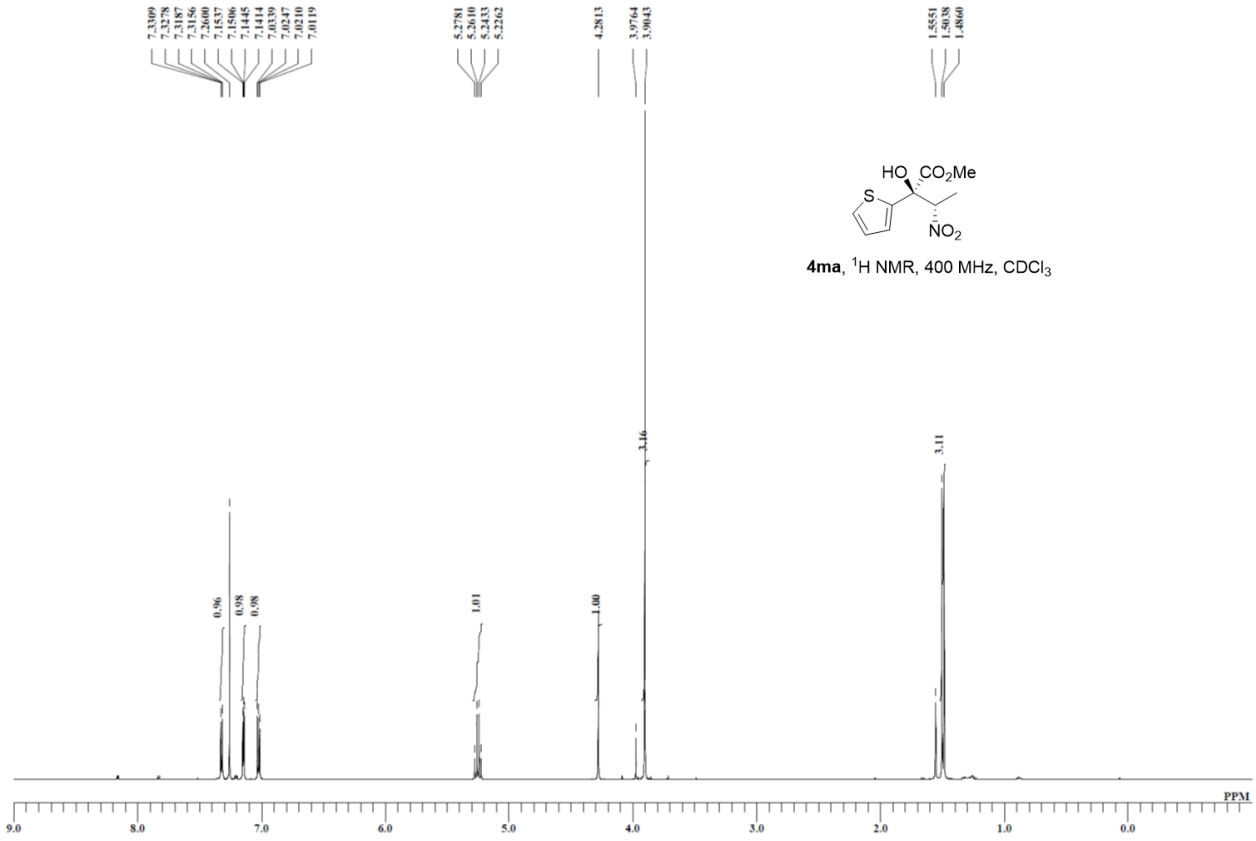

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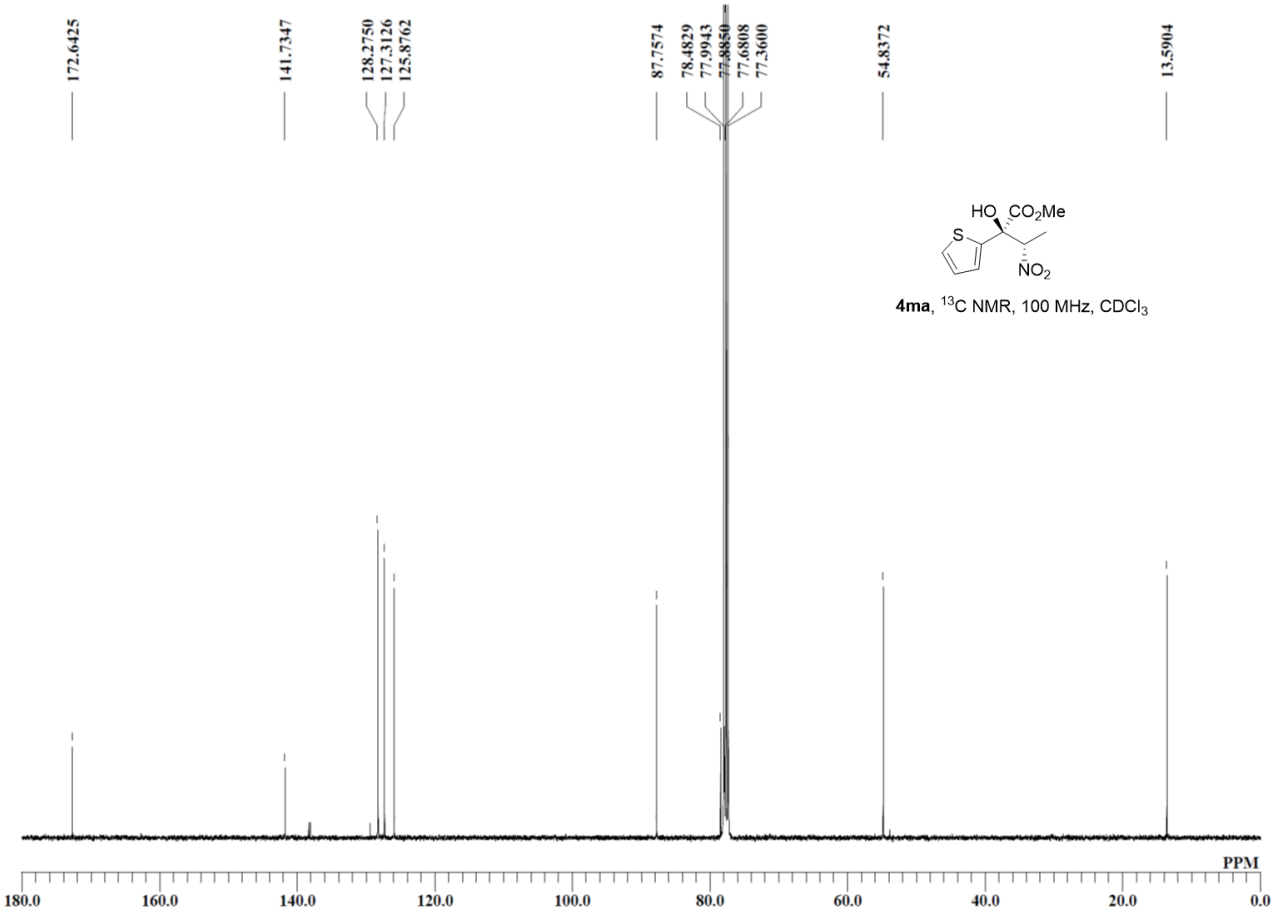
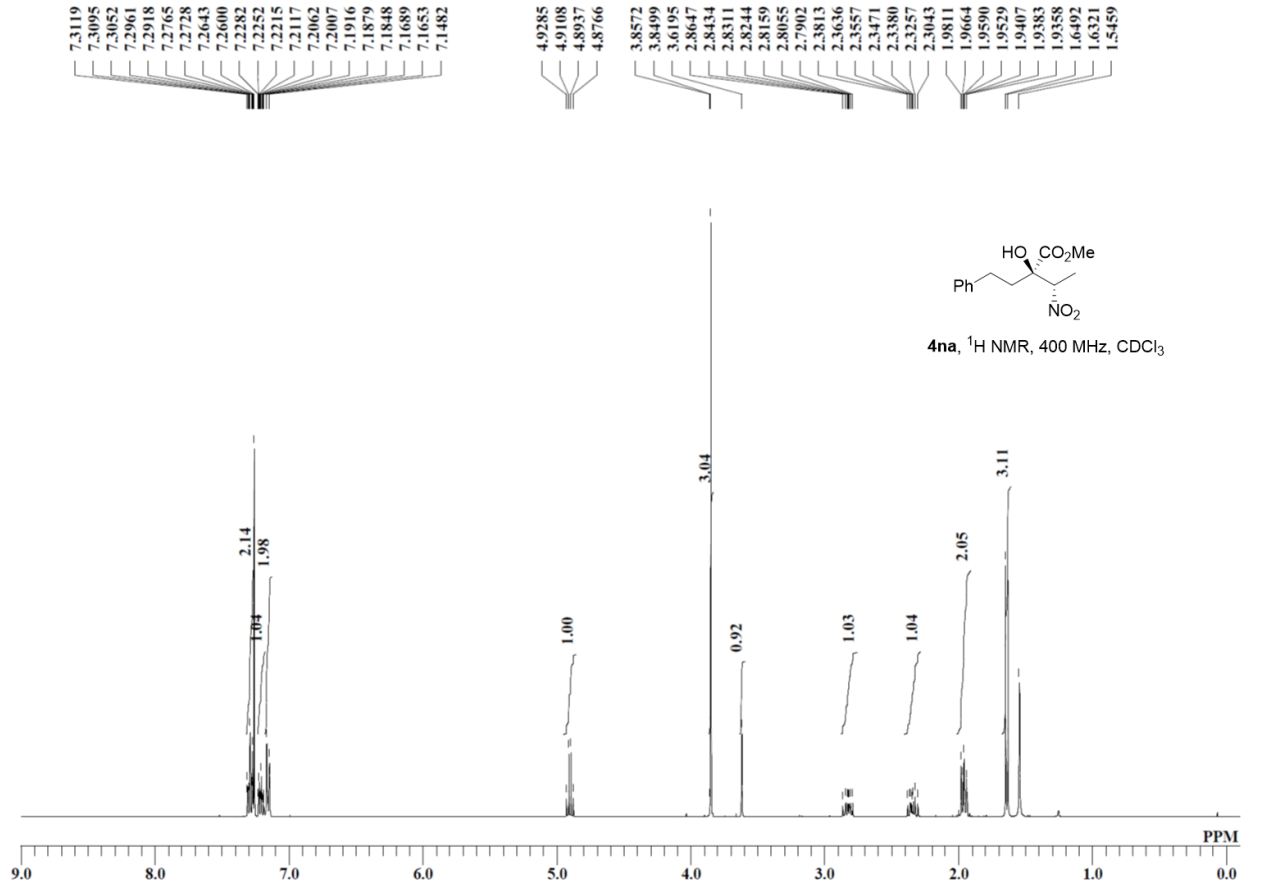


4ma, ^{13}C NMR, 100 MHz, $CDCl_3$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2.8159
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HO
CO2Me
Ph
NO2
4na, 1H NMR, 400 MHz, CDCl3
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3.04
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1.03
1.04
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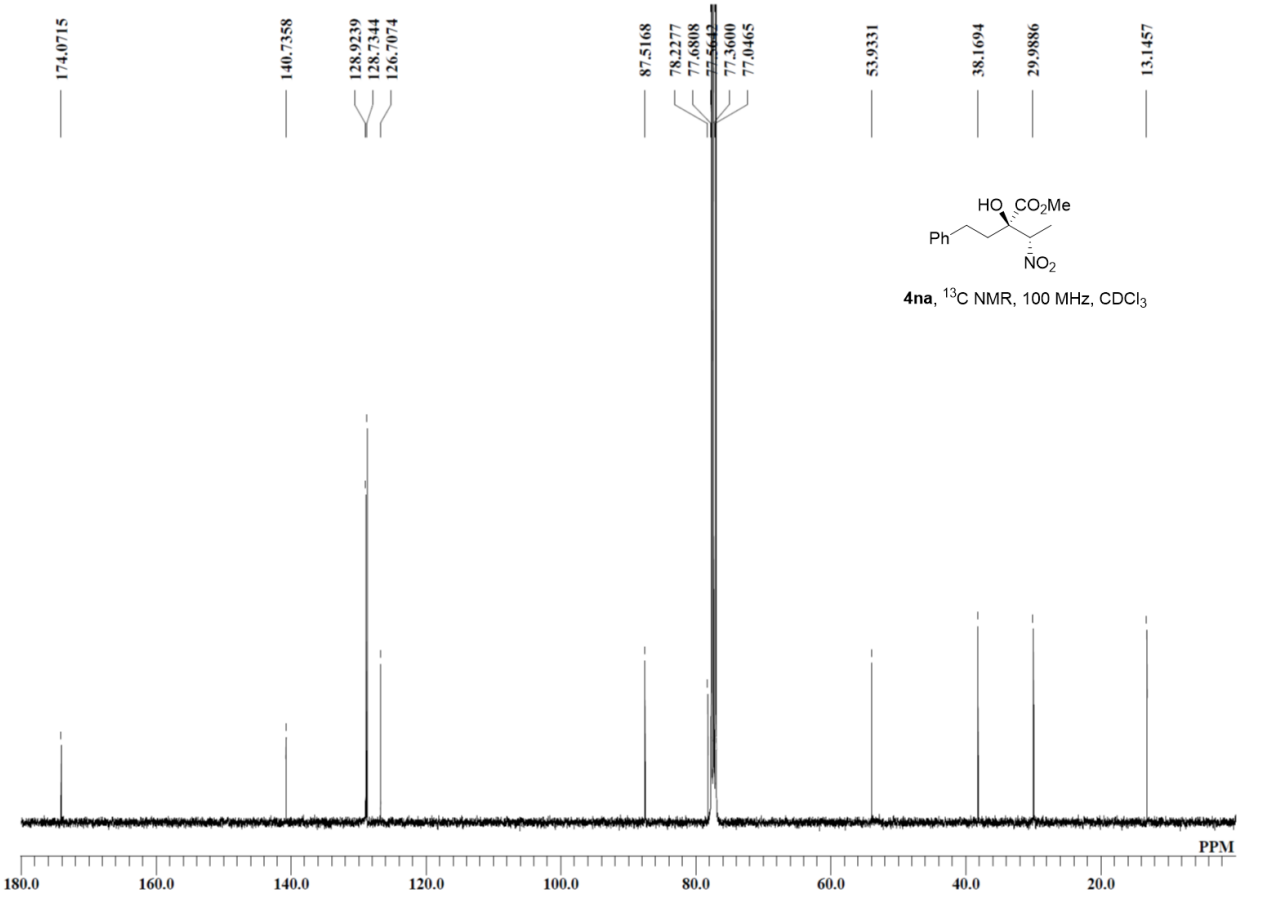
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Ph
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4na, 13C NMR, 100 MHz, CDCl3
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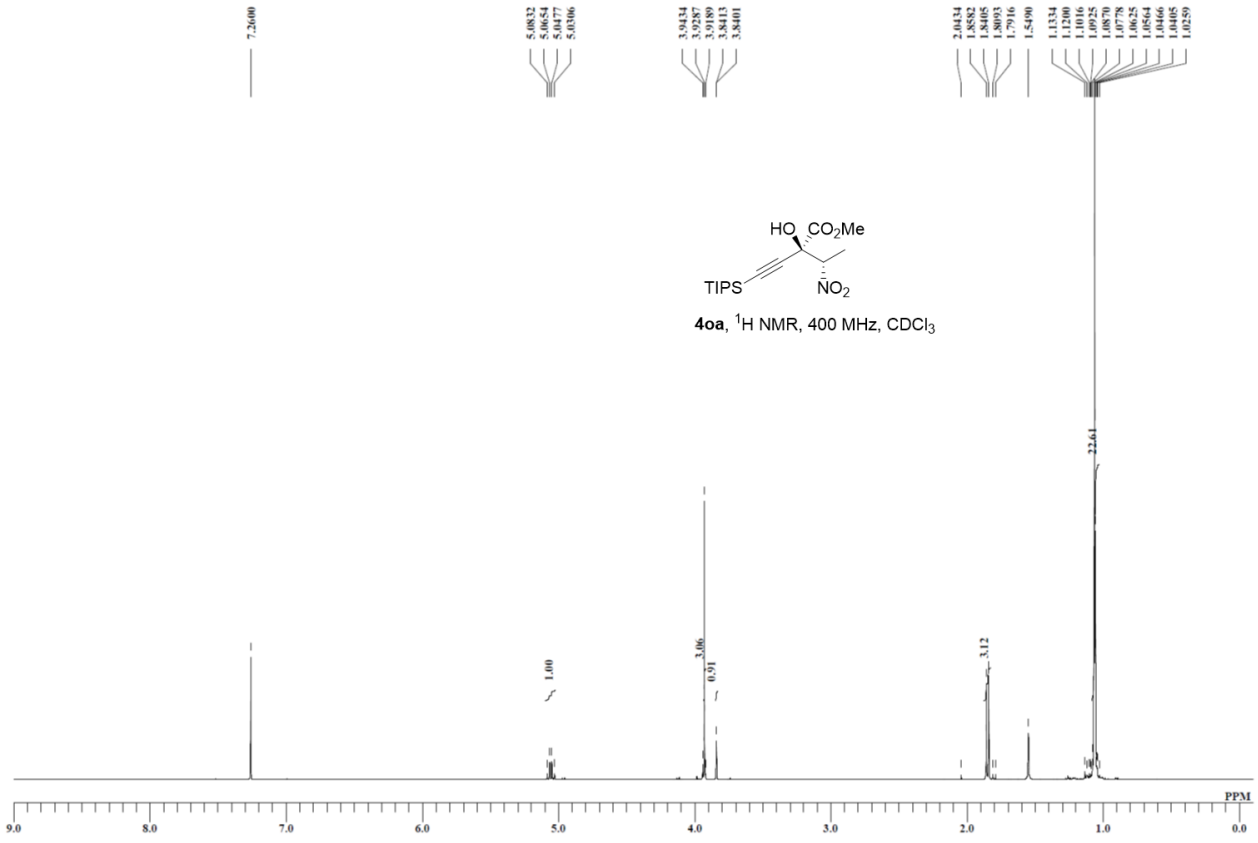

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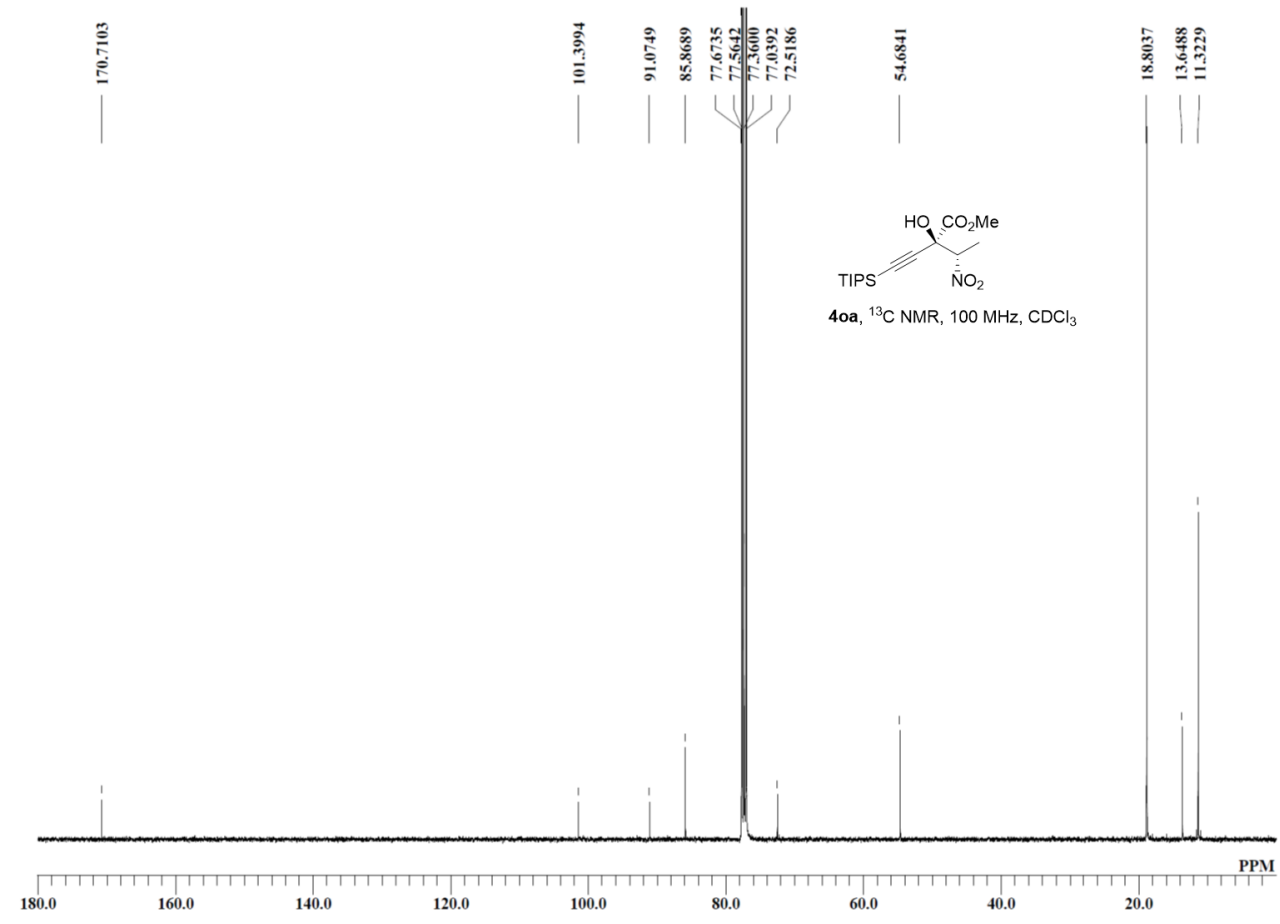

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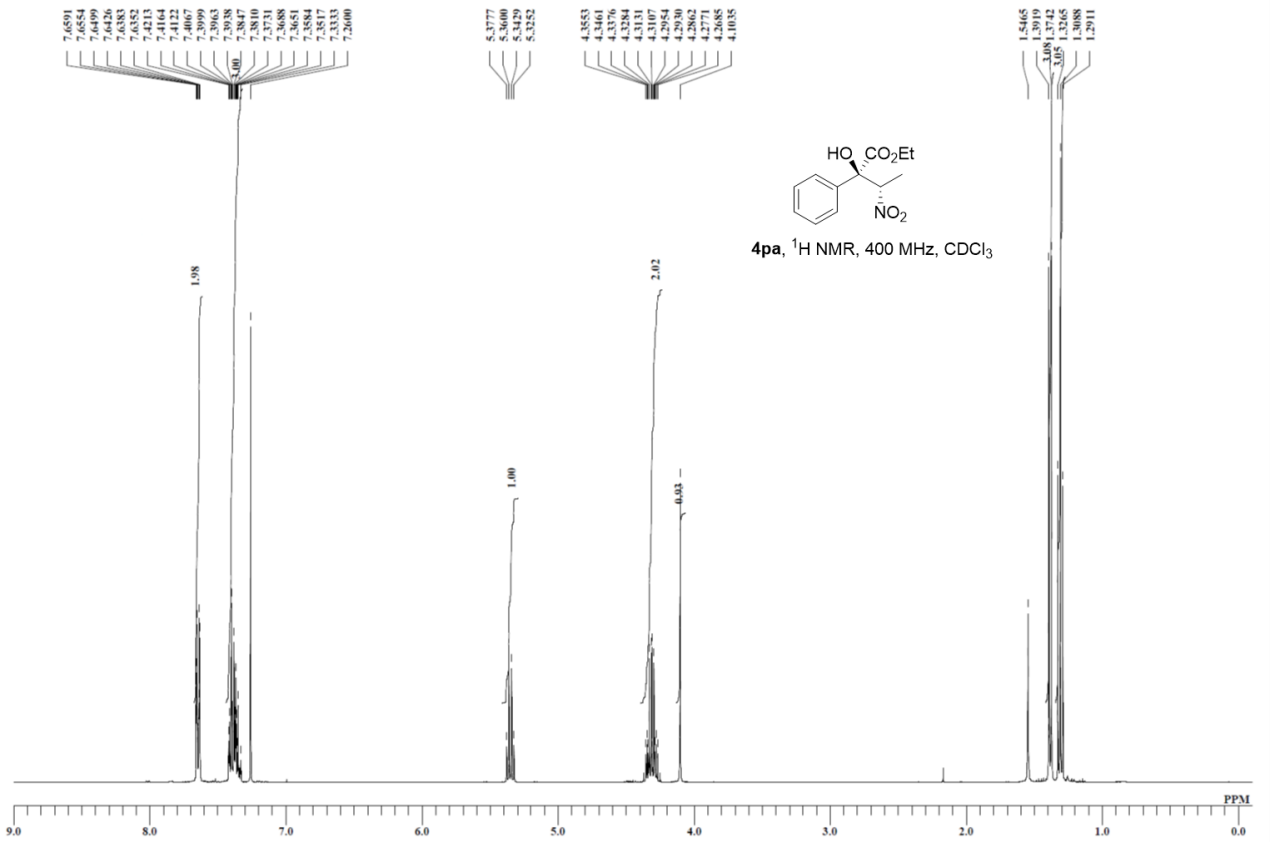

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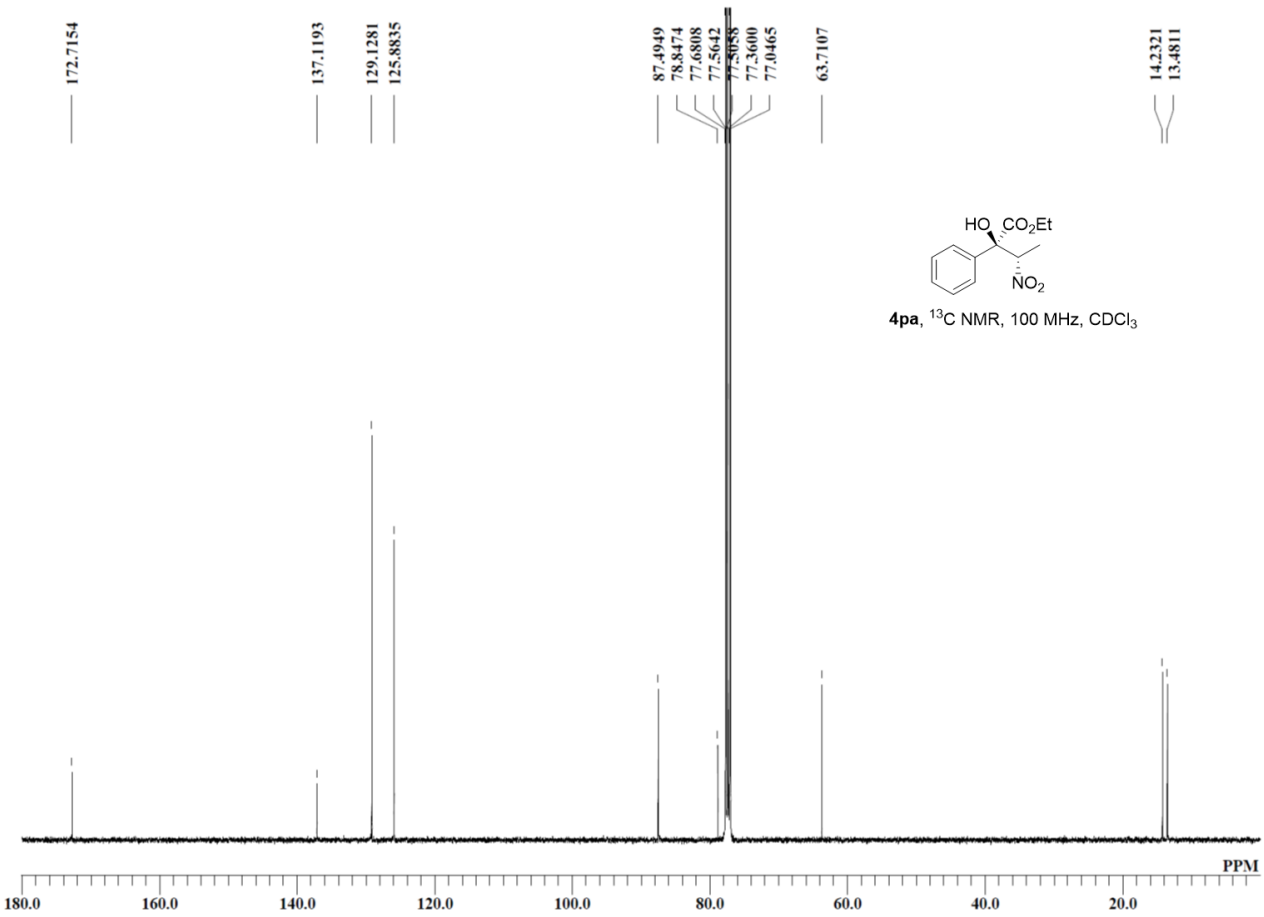

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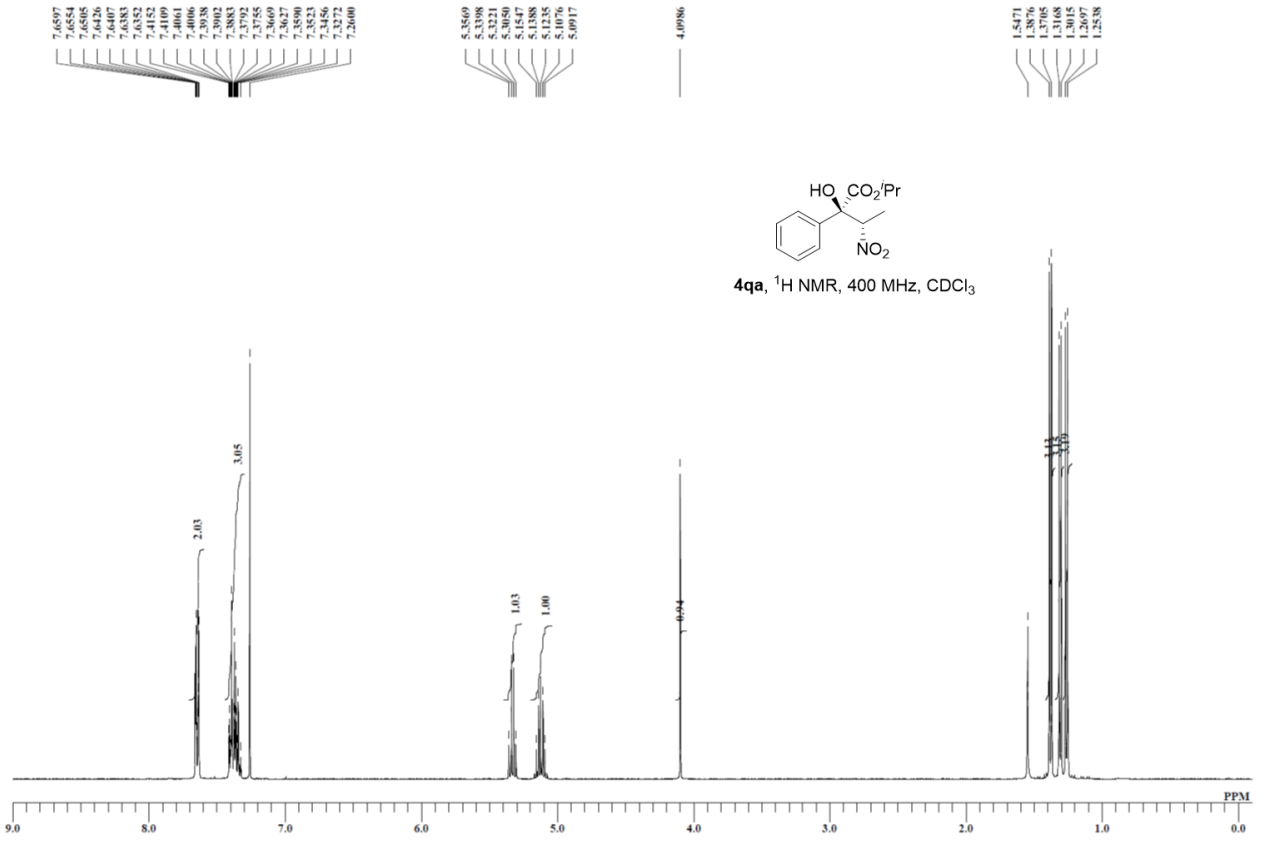
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5.1076
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4.0986
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1.3705
1.3168
1.3015
1.2697
1.2538
HO
CO2iPr
NO2
4qa, 1H NMR, 400 MHz, CDCl3
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1.03
1.00
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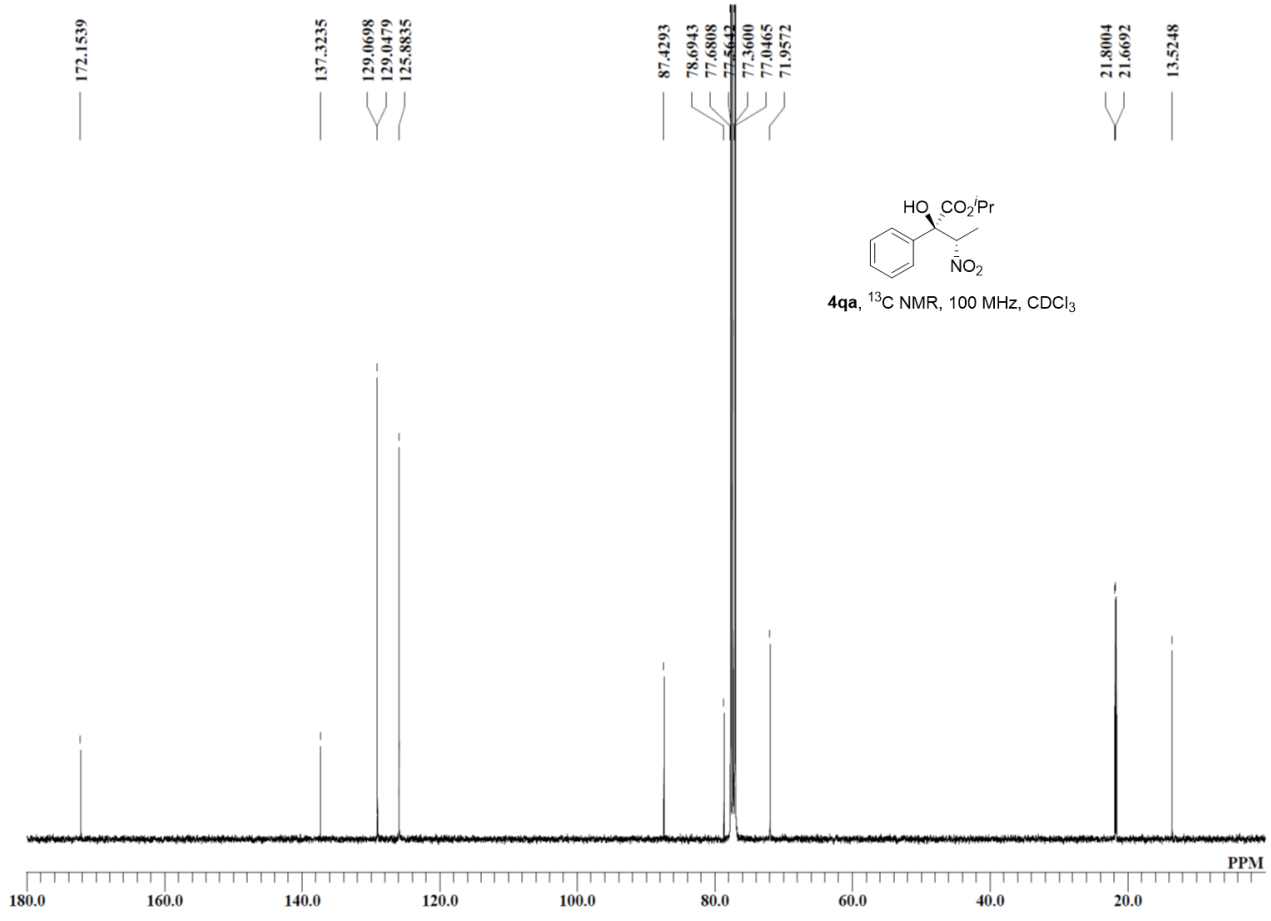
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21.6692
13.5248
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CO2iPr
NO2
4qa, 13C NMR, 100 MHz, CDCl3
PPM
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100.0
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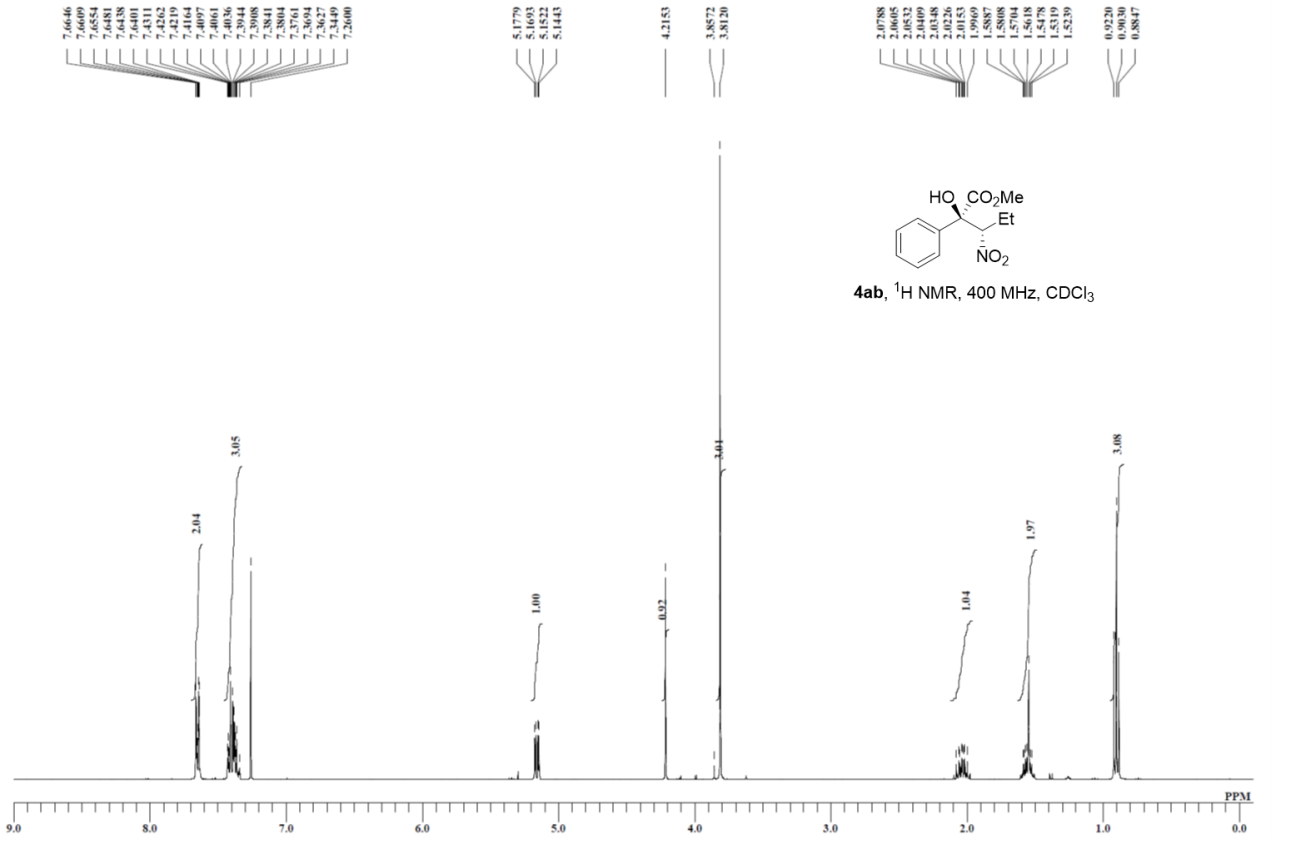
40.0
20.0



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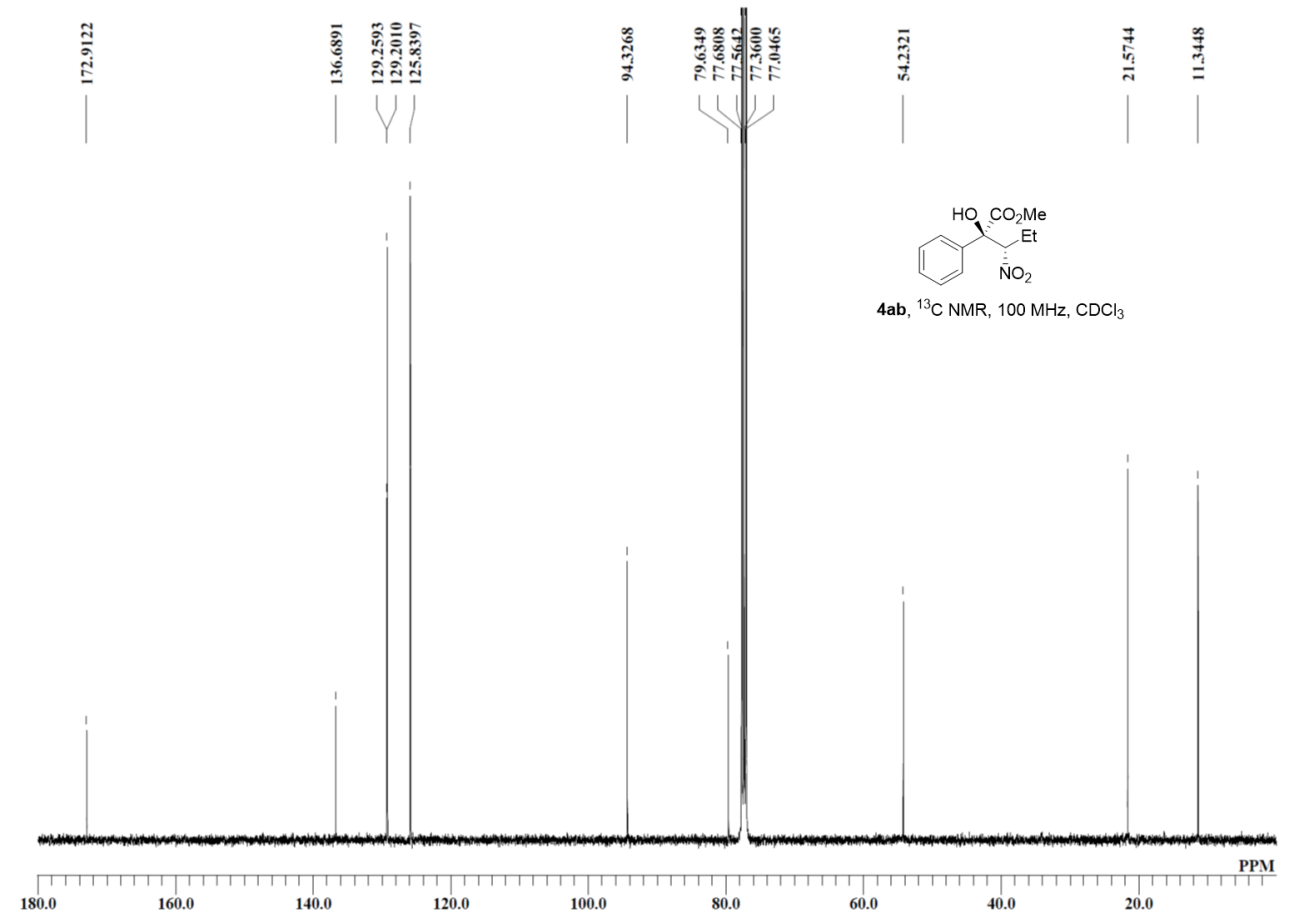

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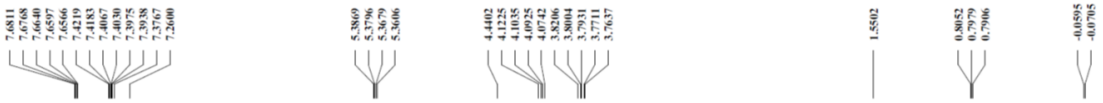

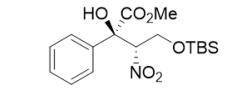

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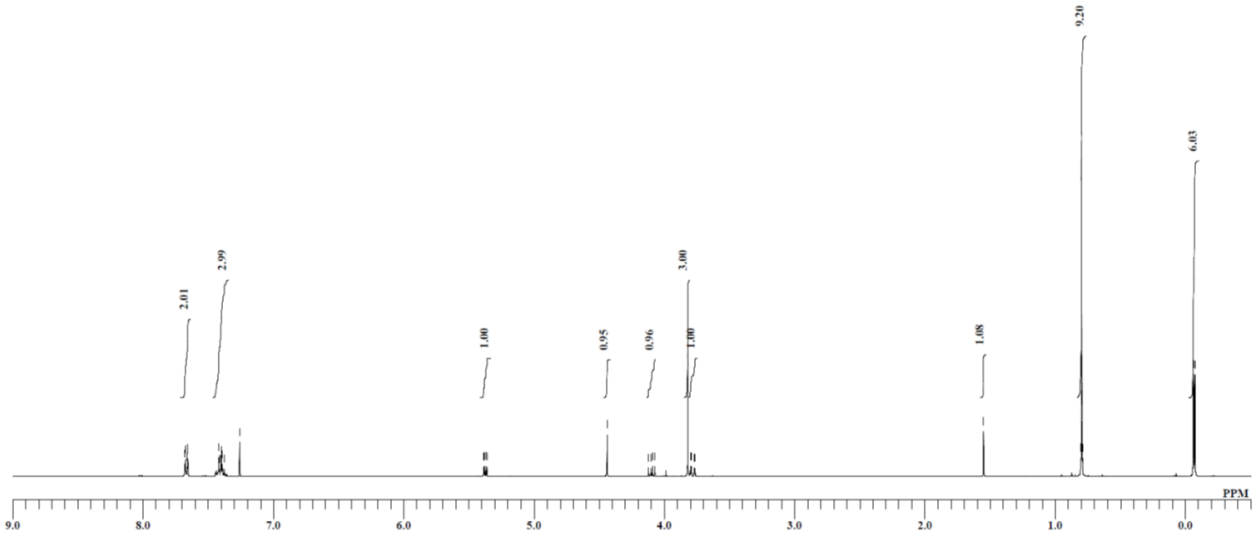

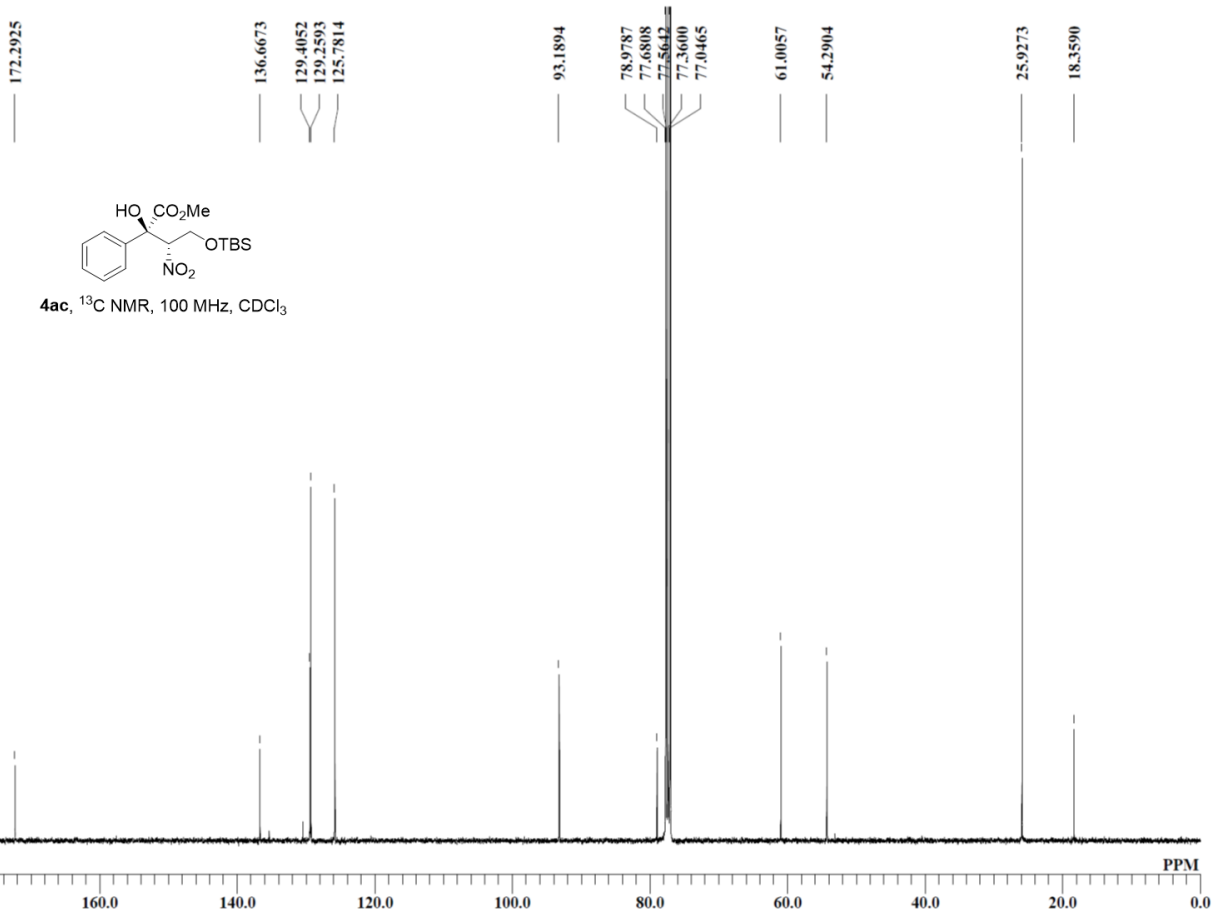

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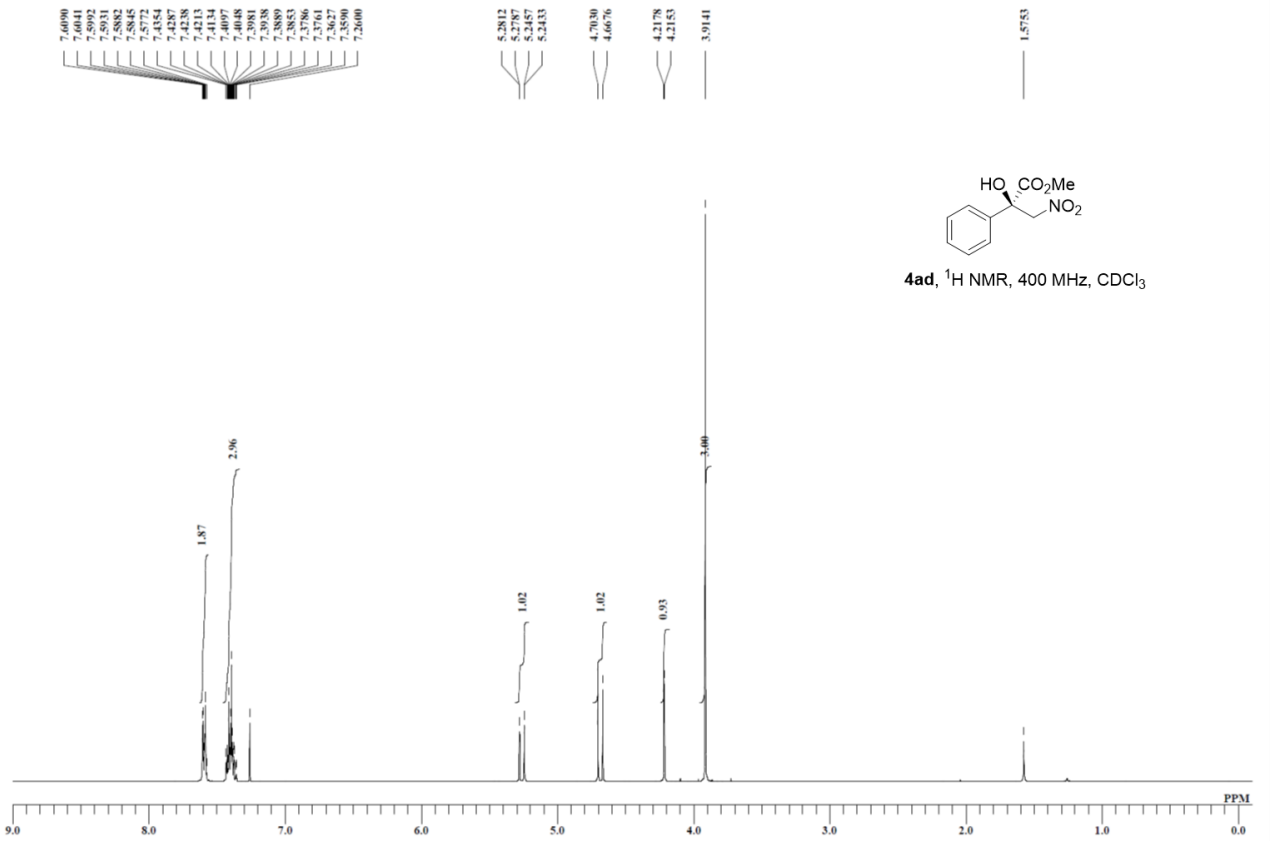

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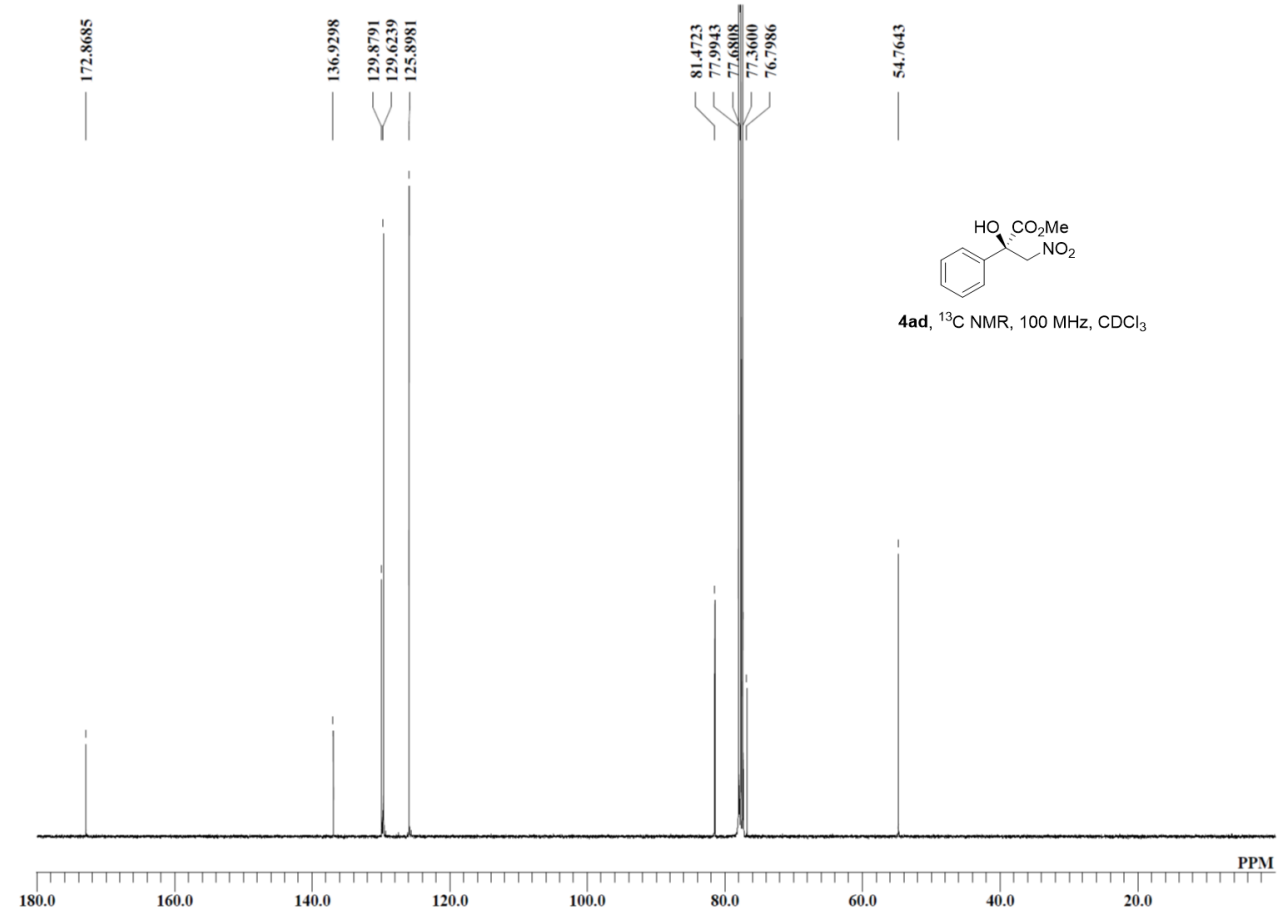

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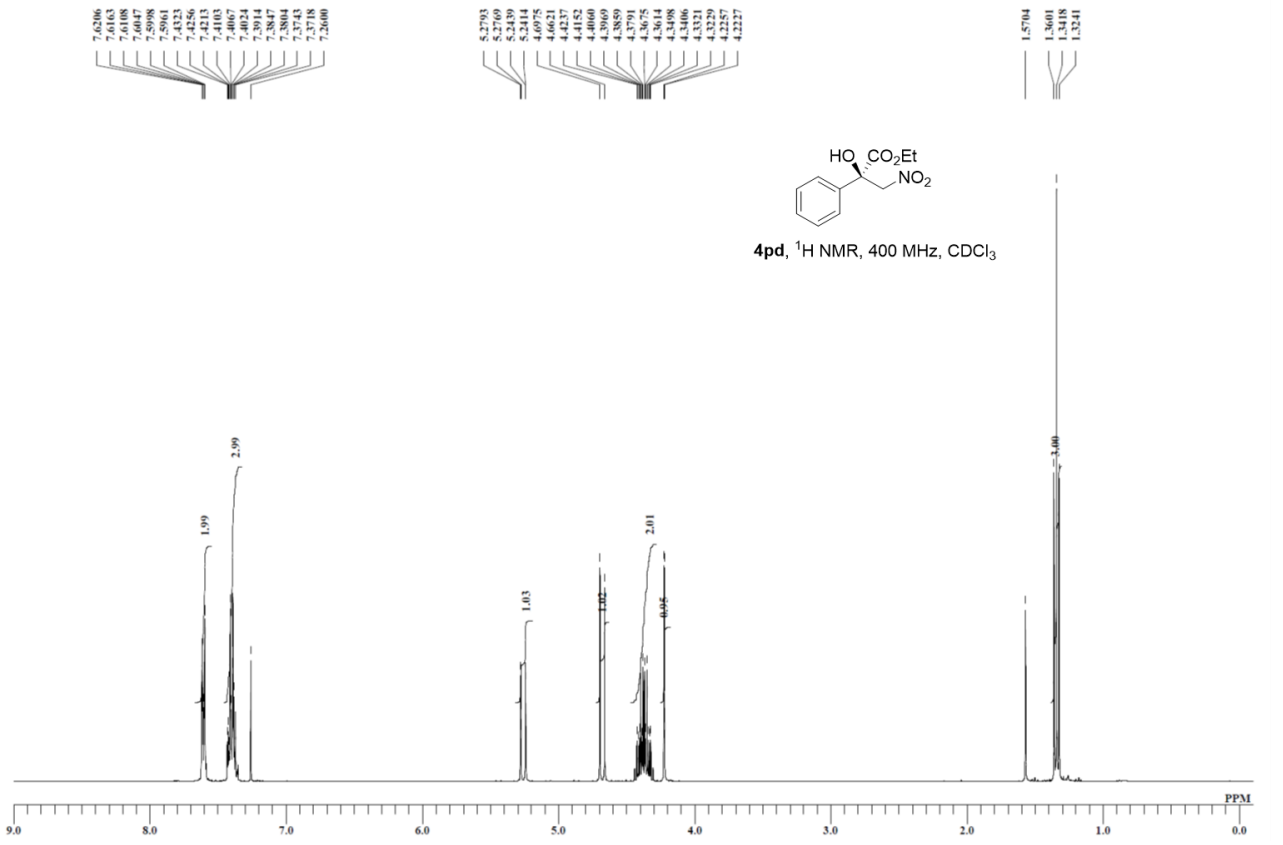

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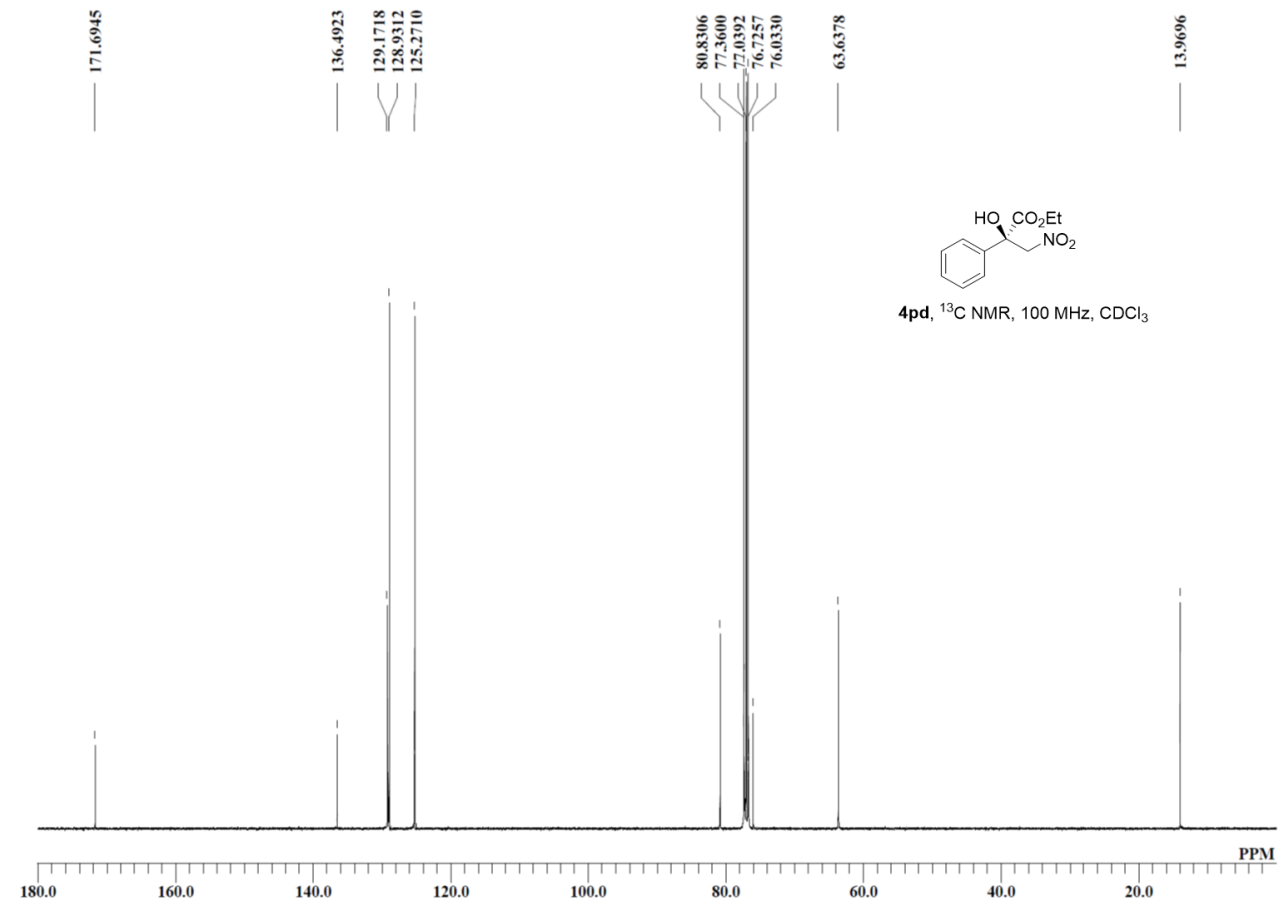

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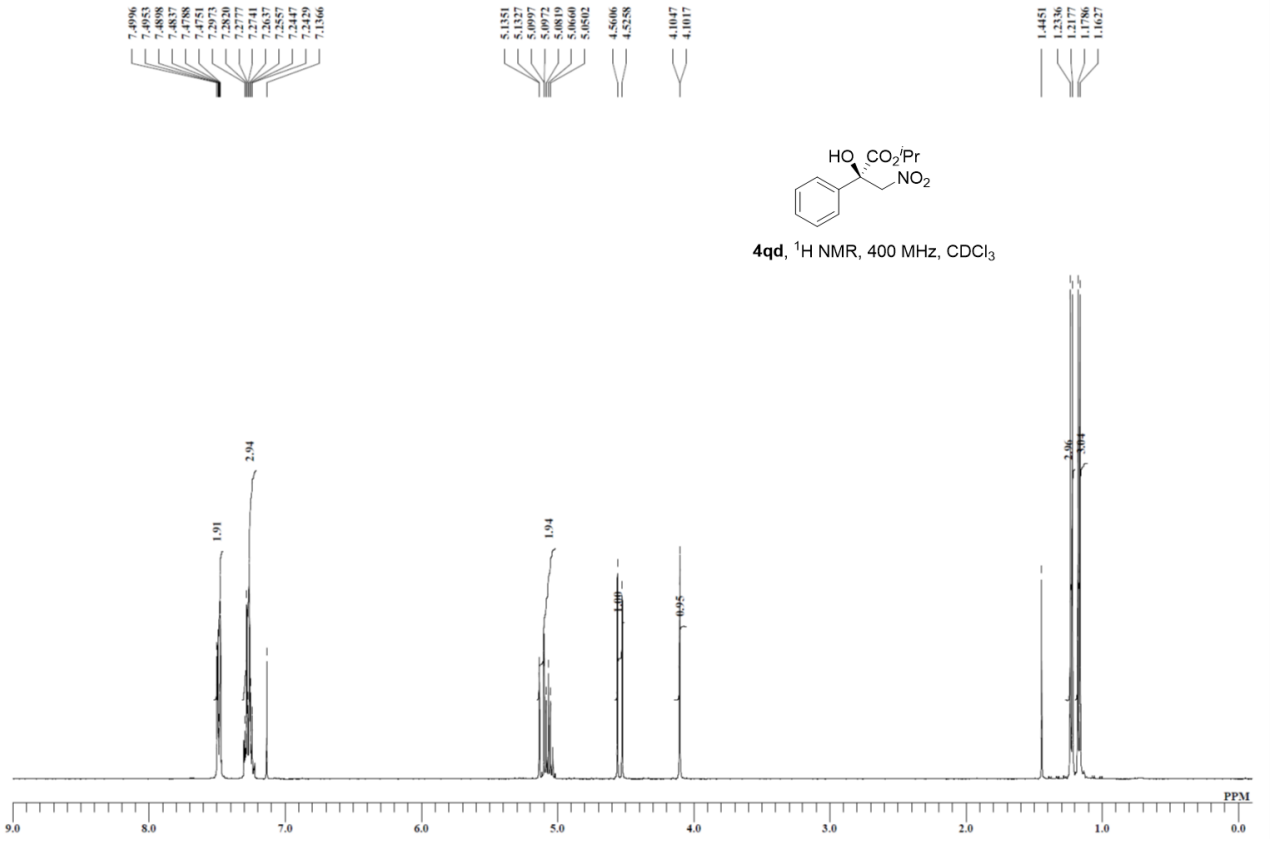

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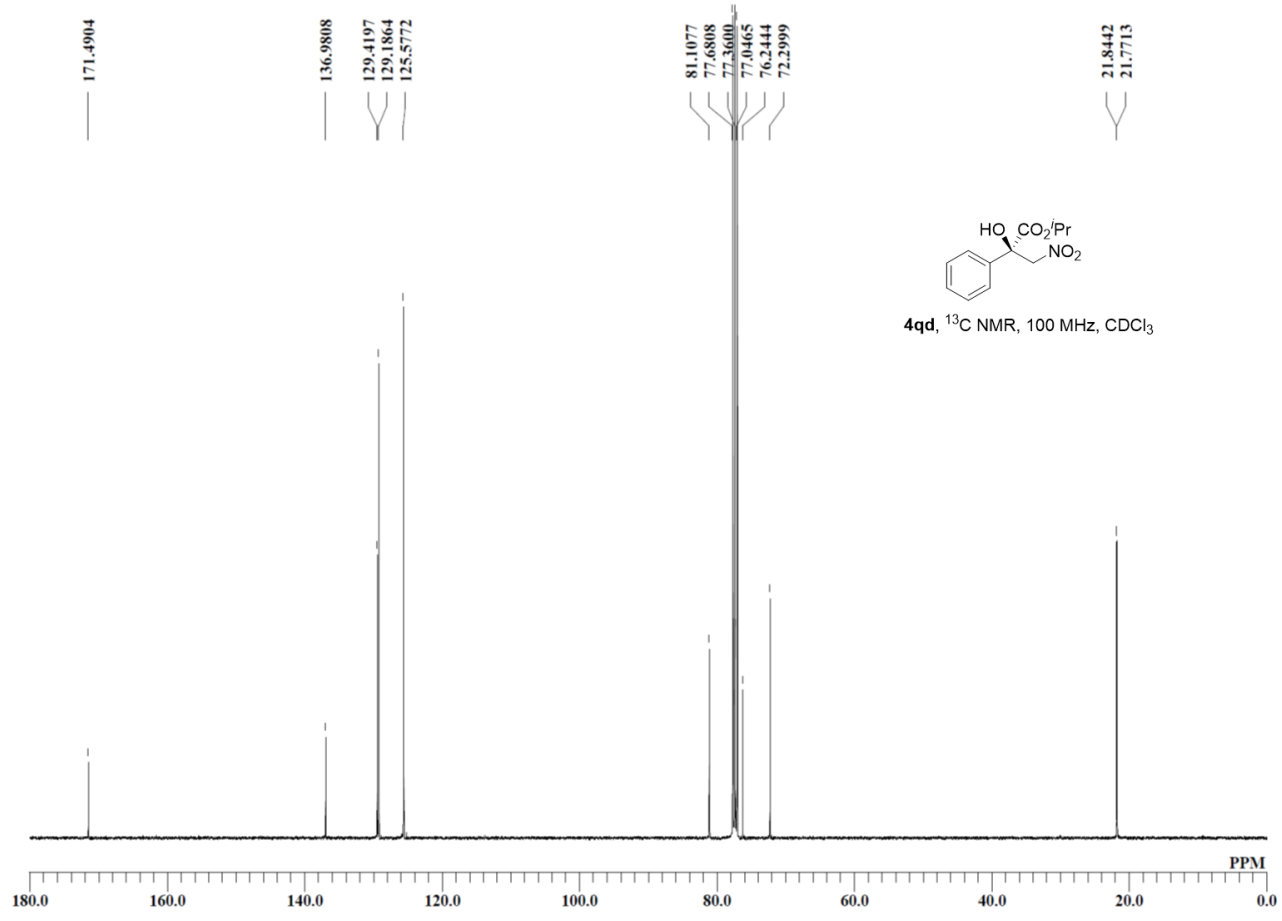

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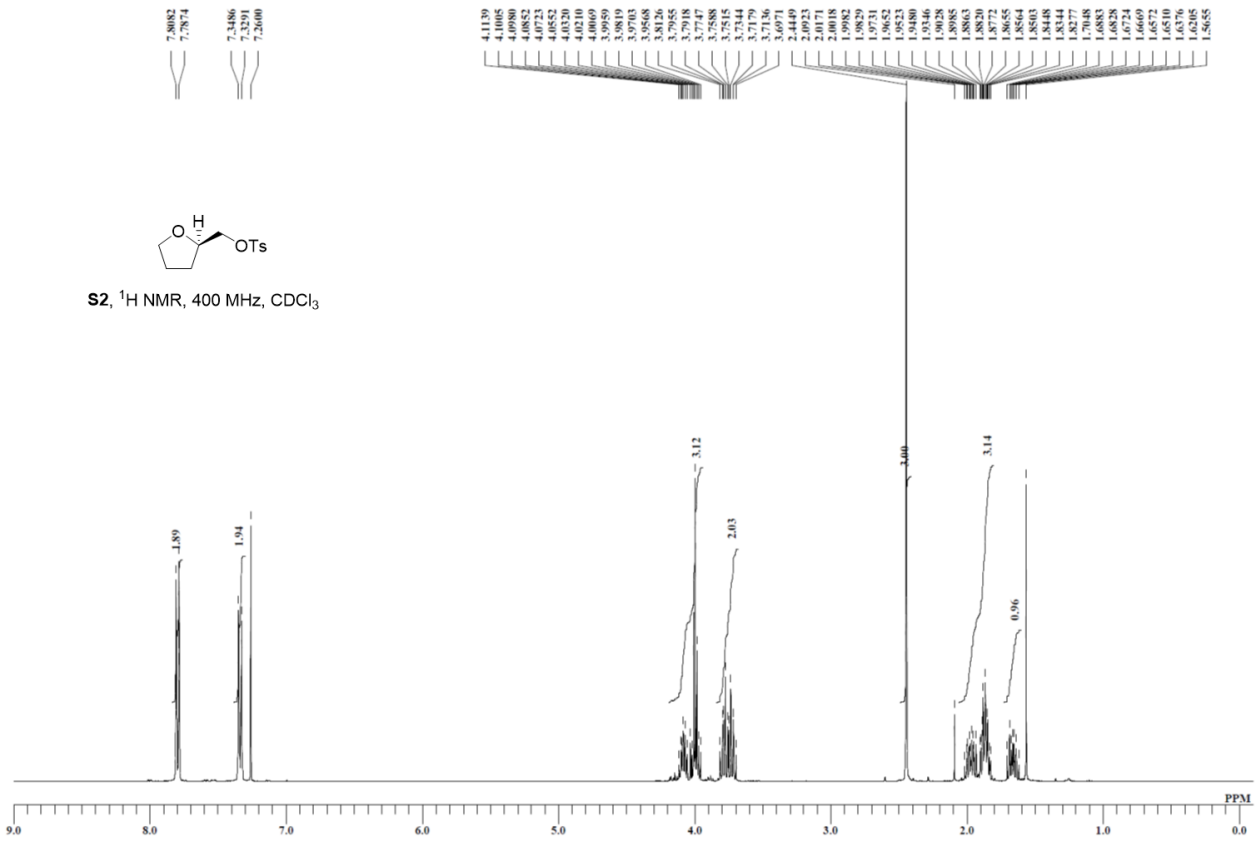

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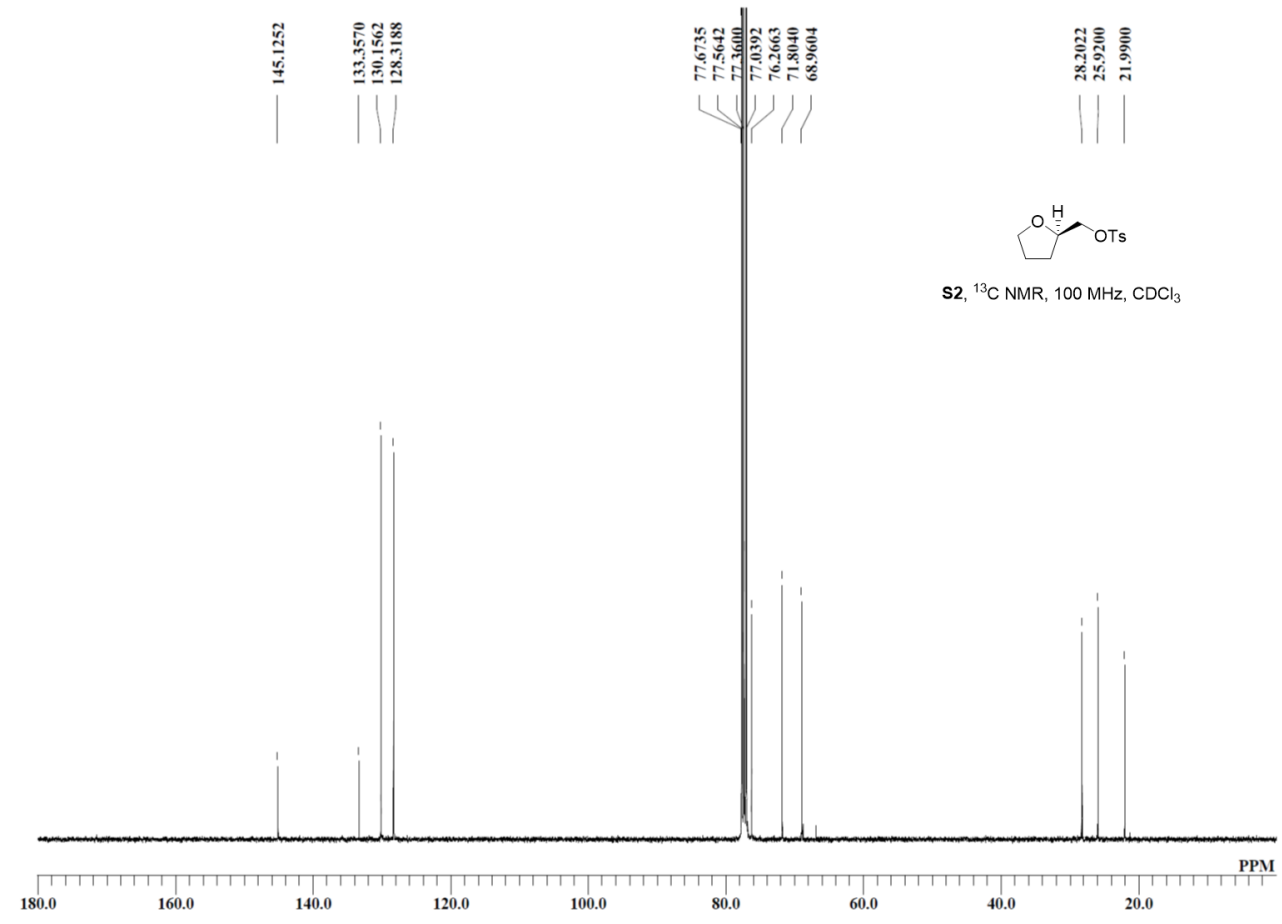

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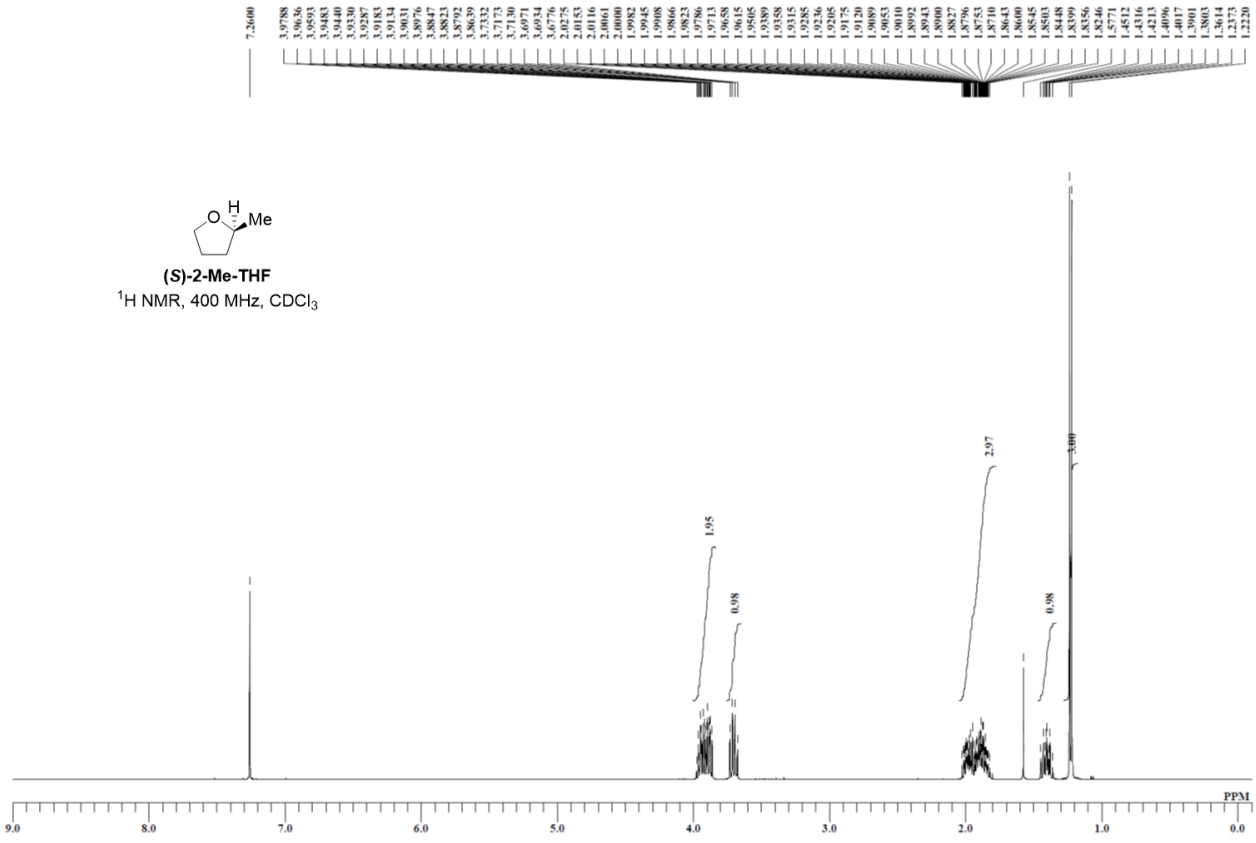
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2.0000
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1.3803
1.3614
1.2373
1.2220
O
H
Me
(S)-2-Me-THF
1H NMR, 400 MHz, CDCl3
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2.97
0.98
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PPM
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8.0
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6.0
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4.0
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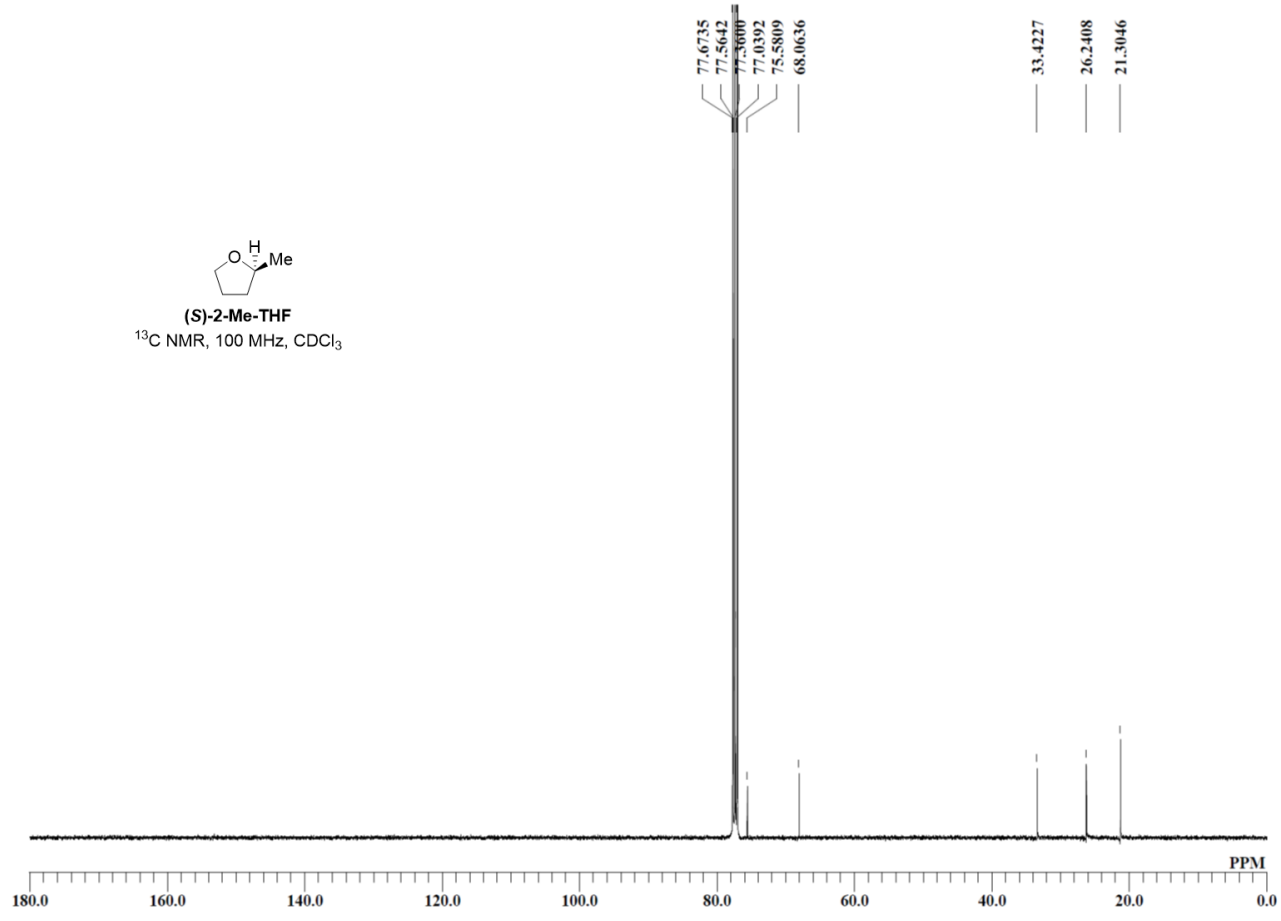
1.0
0.0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Me
(S)-2-Me-THF
13C NMR, 100 MHz, CDCl3
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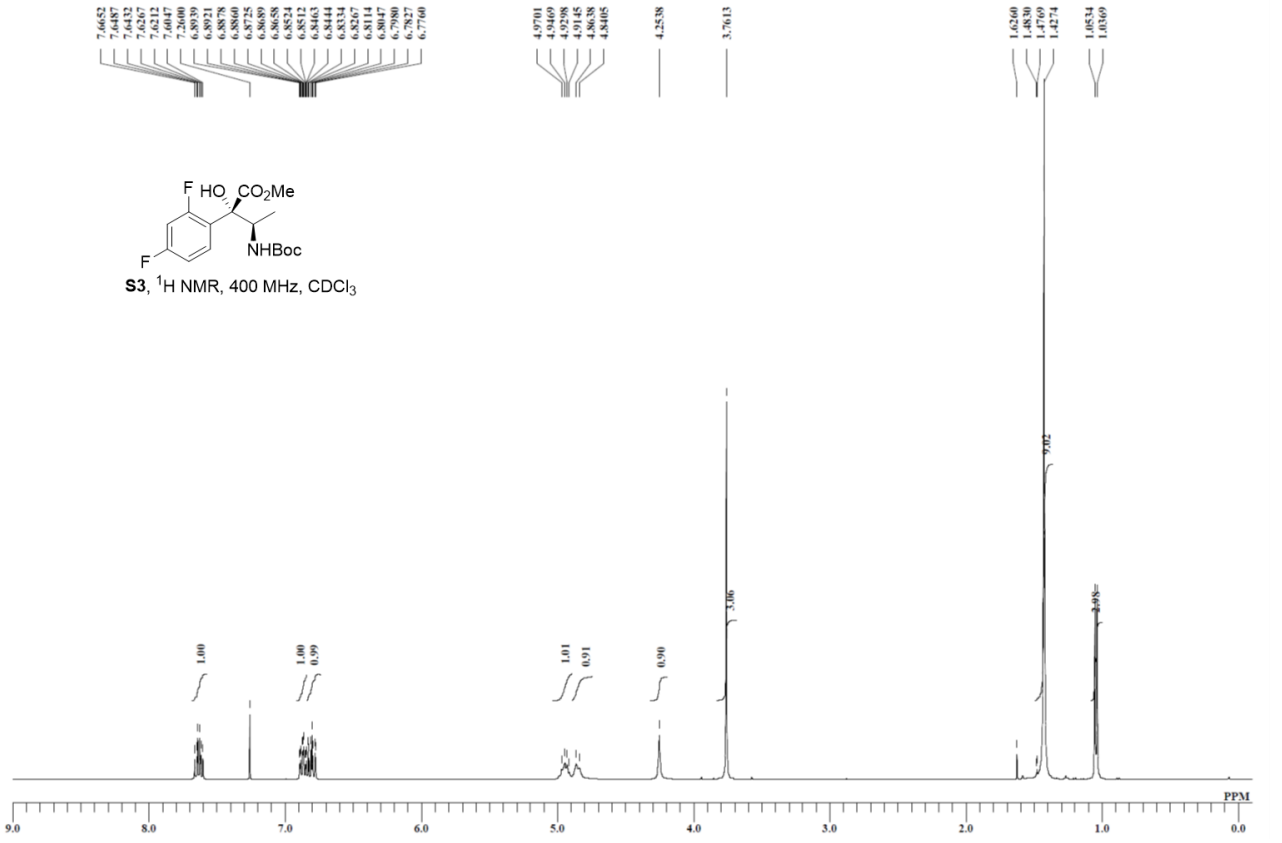
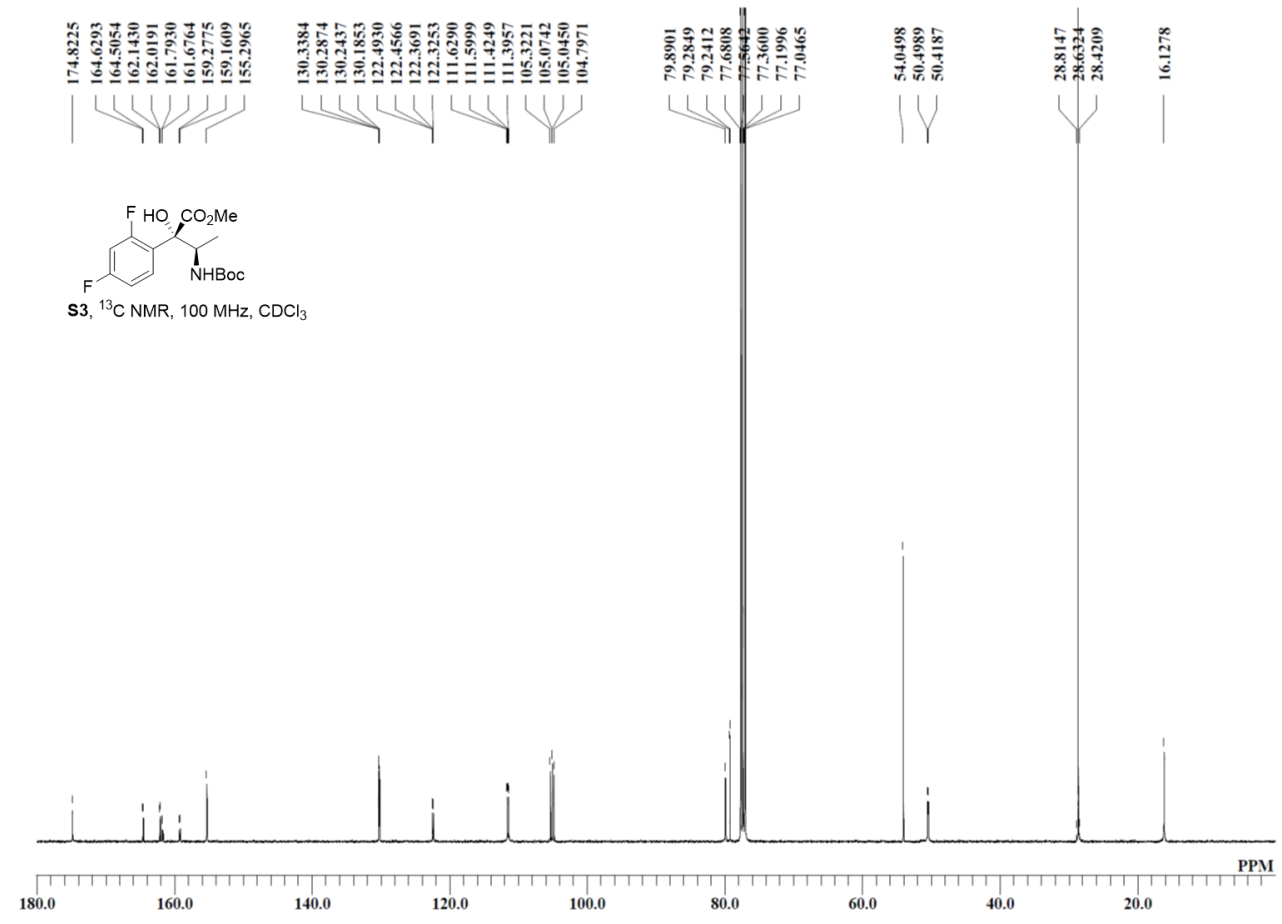
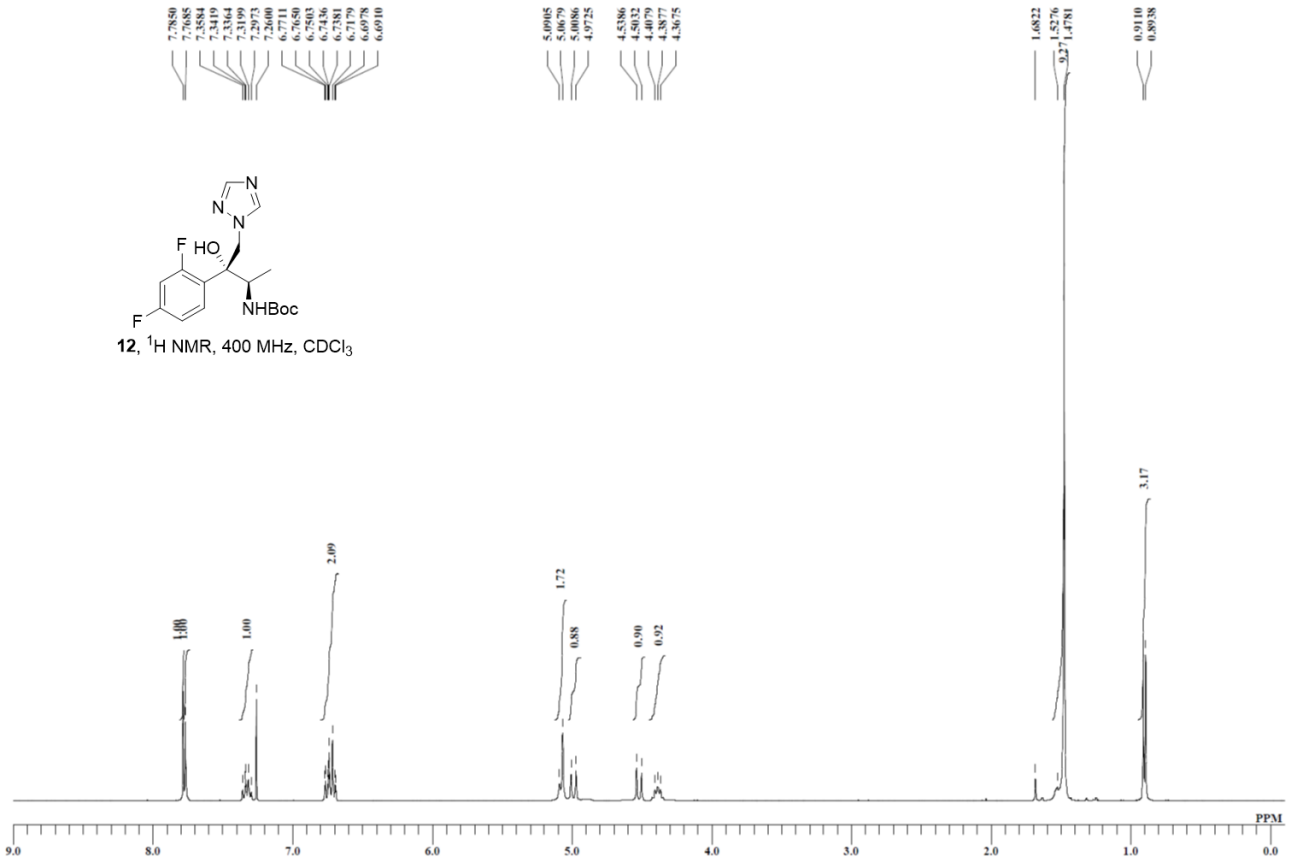


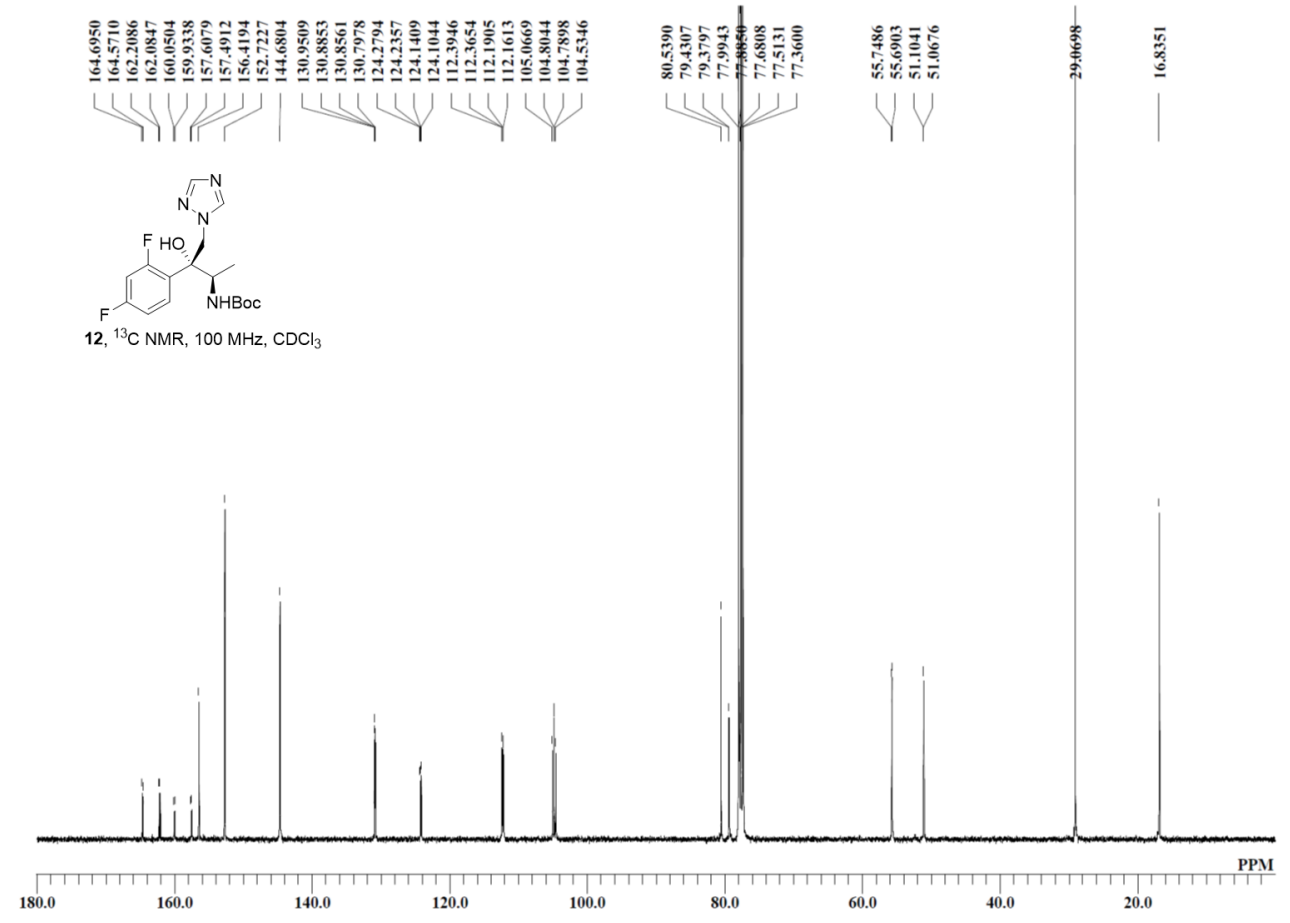
S3, ^{1}H NMR, 400 MHz, $CDCl_3$



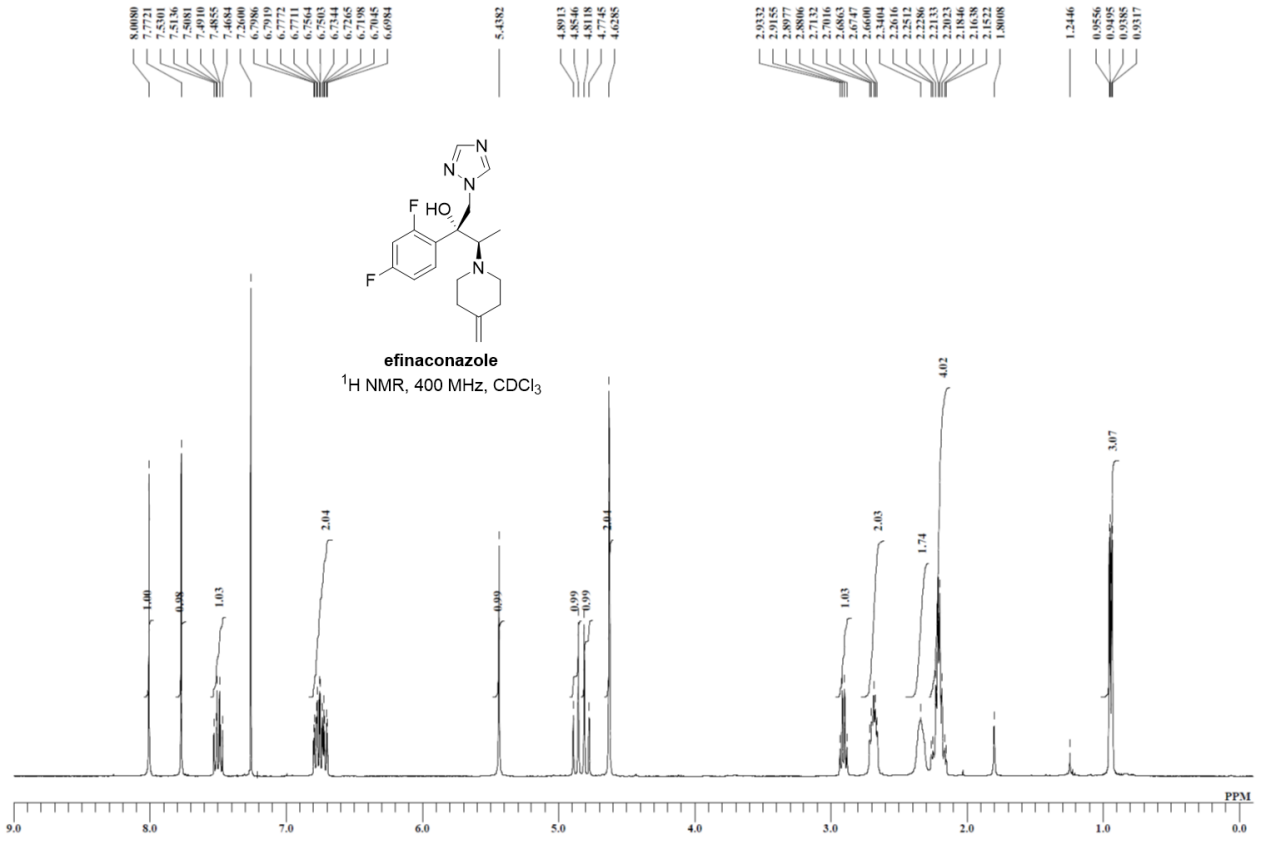
S3, ^{13}C NMR, 100 MHz, $CDCl_3$



12, ^{1}H NMR, 400 MHz, $CDCl_3$



12, ^{13}C NMR, 100 MHz, $CDCl_3$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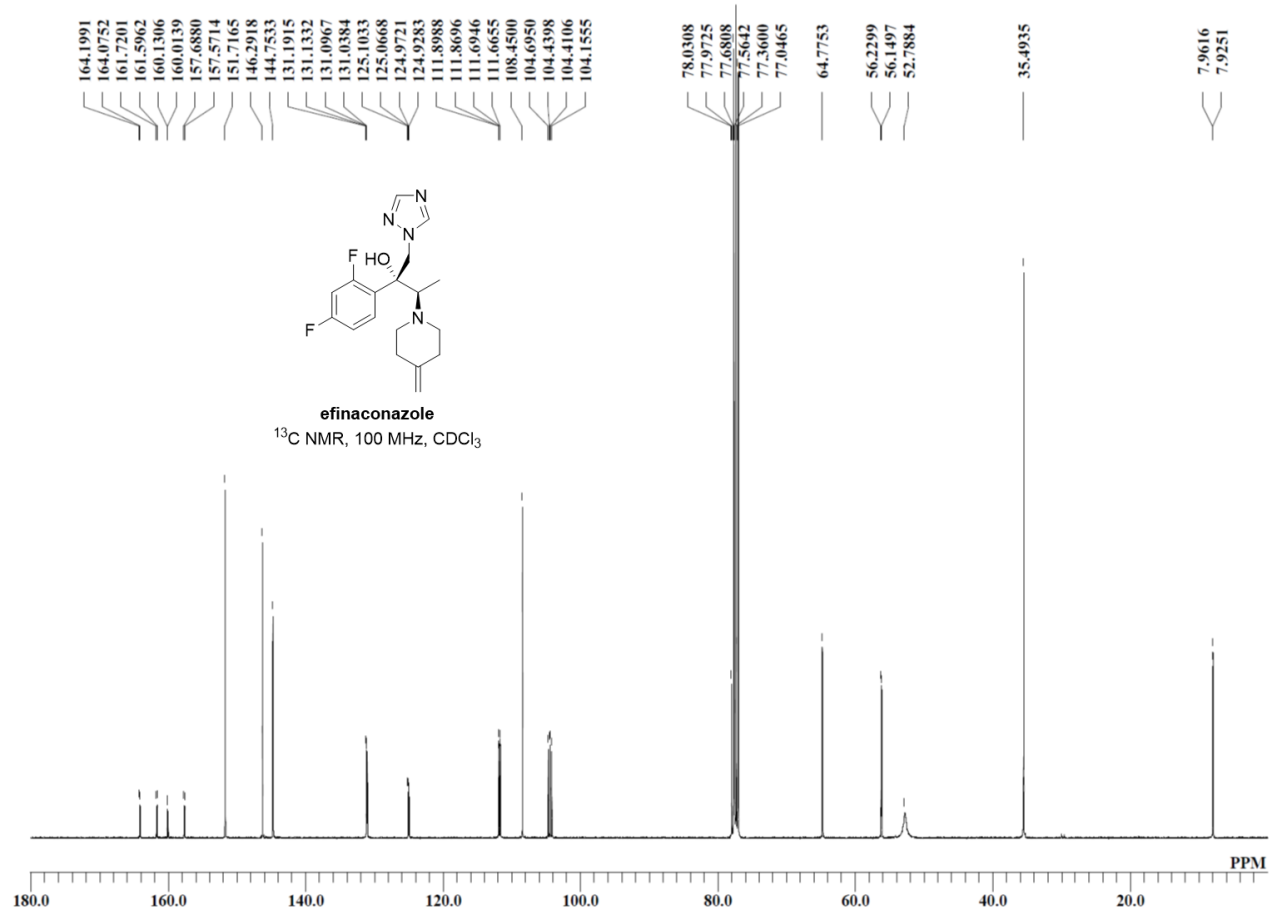
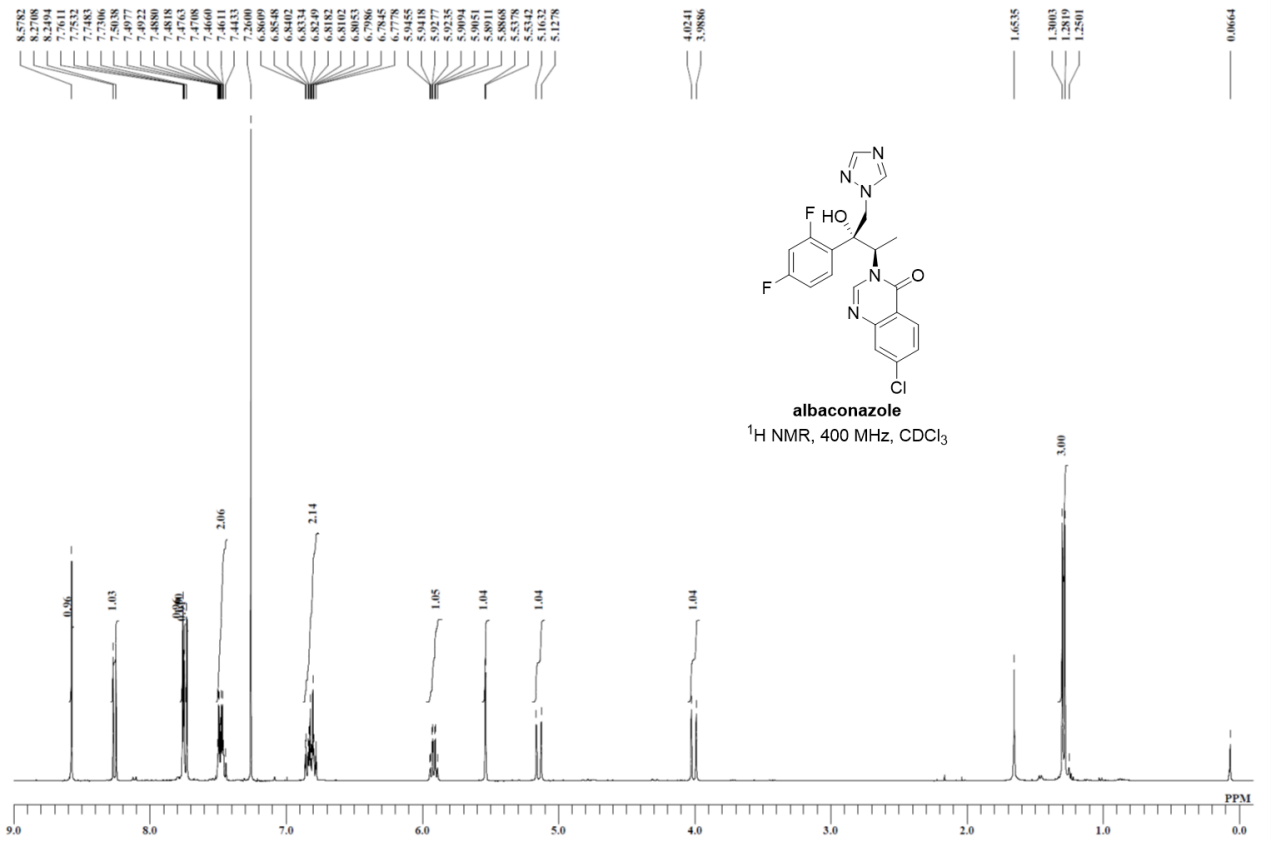
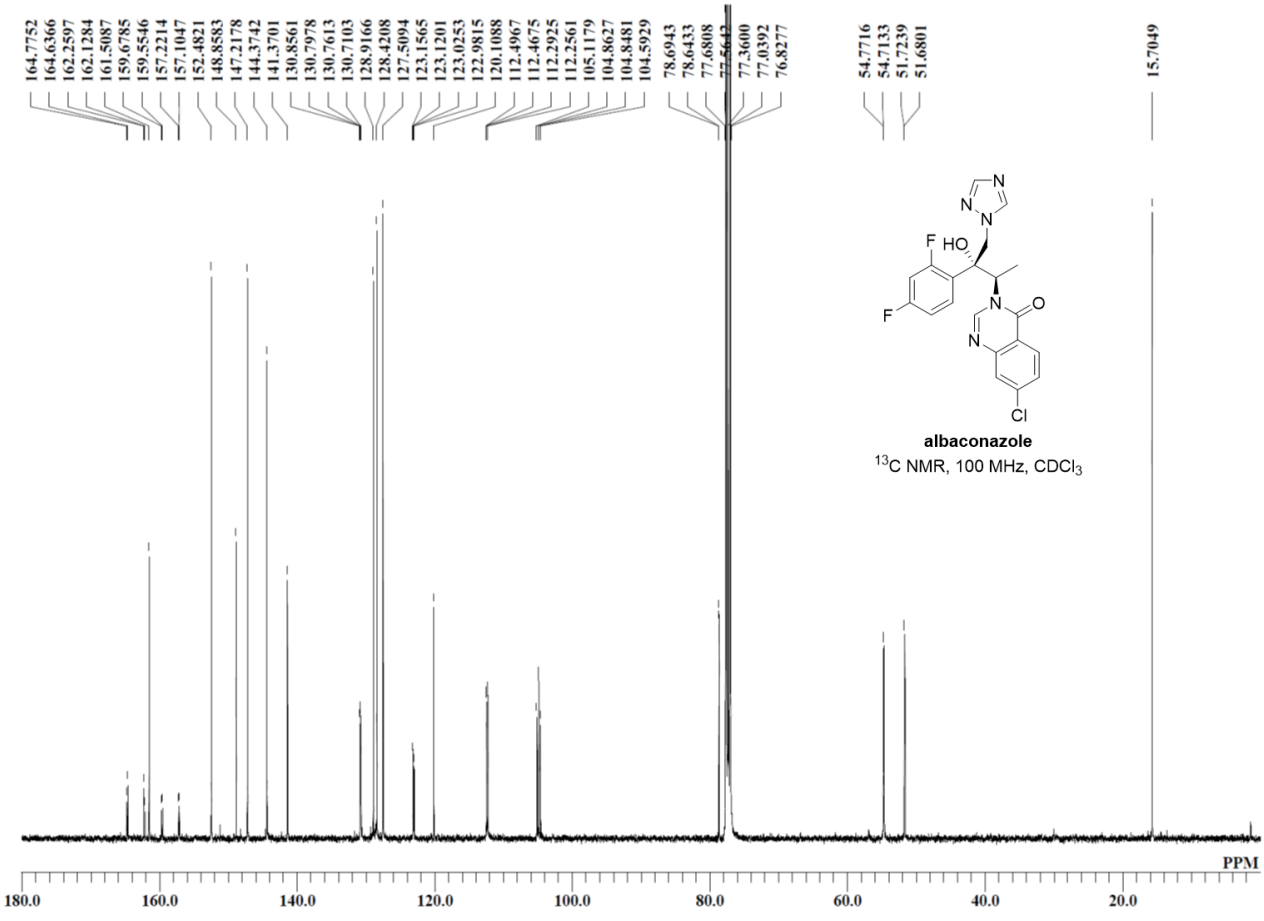
1H NMR, 400 MHz, CDCl3
PPM


efinaconazole
13C NMR, 100 MHz, CDCl3
PPM


albaconazole
^{1}H NMR, 400 MHz, $CDCl_3$
PPM


albaconazole
^{13}C NMR, 100 MHz, $CDCl_3$
PPM

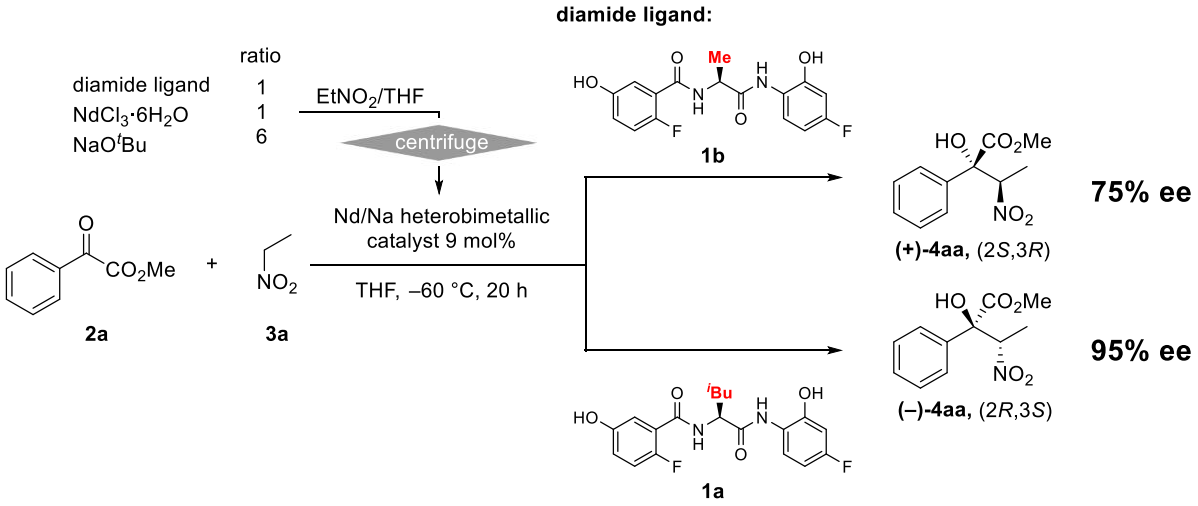
第 3 章

溶媒依存性エナンチオ選択的不斉ニトロアルドール反応

3 － 1　　はじめに

2 章で述べた α-ケトエステルの *anti* 選択的触媒的不斉ニトロアルドール反応の検討において、L-アラニンから誘導したジアミド型配位子 **1b** が従来の L-ロイシンから誘導した **1a** とは逆のエナンチオ選択性を示す興味深い結果を得た(Scheme 1、配位子検討の詳細は 3 － 2 参照)。本結果は安価な L-アミノ酸由来の配位子から両鏡像異性体を作り分けできる可能性を示唆しており、本章で詳細に検討した。

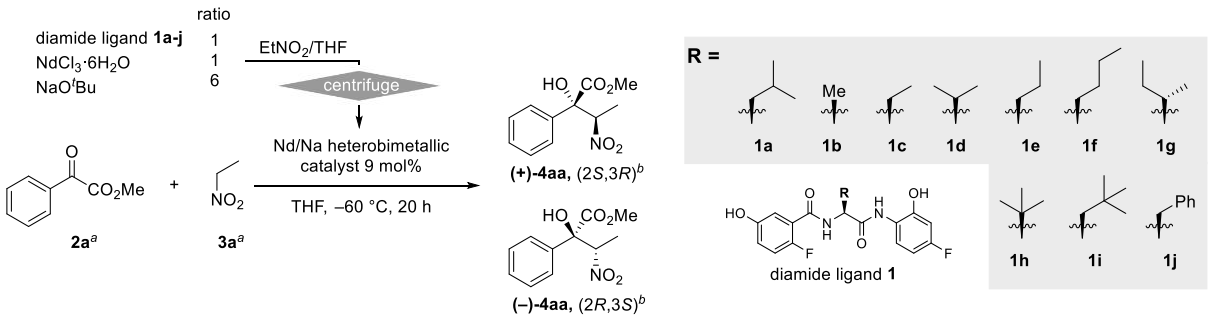
Scheme 1. Enantiodivergence in *anti*-selective catalytic nitroaldol reaction



３－２　　配位子の検討

L-アミノ酸部位を様々に変化させた配位子 **1a-j** から調製された異種 2 核金属触媒を用いて、α-ケトエステル **2a** とニトロエタンの反応を行い、エナンチオ選択性を比較した(Table 1)。まず、従来の L-ロイシンから誘導した配位子 **1a** (R = ^{i}Bu)は**(–)-4aa** を 95% ee のエナンチオ選択性で与えた(entry 1)。一方、L-アラニンから誘導した配位子 **1b** (R = Me)は逆の鏡像異性体である**(+)-4aa** を 75% ee で与えた(entry 2)。その他の配位子(**1c-f**)から調製した触媒は **1a** と同じ**(–)-4aa** が中程度の選択性(33-72% ee)で与え(entry 3-7)、(+)体を与えた **1b** から一炭素分だけ大きい **1c** (R = Et)由来の触媒も選択性は低いものの(–)体を主生成物と与えた(entry 3)[a]。以上の結果より、1) 本反応の不斉は配位子の不斉中心のみを単純に認識している訳ではなく、触媒クラスターの高次構造に起因する不斉を認識して誘起されていること、2) 触媒の立体構造は配位子上の置換基のサイズに大きな影響を受け、サイズが最も小さい **1b** からは他の配位子とは異なる立体選択性を与える触媒構造が誘起されることが明らかになった。

Table 1. Ligand screening



Entry	Ligand	Self-assembly[c]	Product[d] (**4aa**)	Yield[e] (%)	*anti*/*syn*[e]	%ee[f] (*anti*)	Entry	Ligand	Self-assembly[c]	Product[d] (**4aa**)	Yield[e] (%)	*anti*/*syn*[e]	%ee[f] (*anti*)
1	**1a**	++	**(–)**	97	> 98/2	95	6	**1f**	++	**(–)**	99	95/5	56
2	**1b**	++	**(+)**	99	> 98/2	75	7	**1g**	++	**(–)**	99	94/6	0
3	**1c**	++	**(–)**	84	94/6	41	8	**1h**	+	**(–)**	31	90/10	5
4	**1d**	+	**(–)**	97	92/8	33	9	**1i**	–	**-**	trace	-	-
5	**1e**	++	**(–)**	99	96/4	72	10	**1j**	–	**-**	trace	-	-

[a] **2a**: 0.12 mmol, **3a**: 1.2 mmol. [b] The absolute configration of nitroaldol product **4aa** was determined by comparing its chiral HPLC retention time with published data. [c] Amount of precipitation by self-assembly; ++: high, +: moderate, –: low. [d] Optical rotation. [e] Determined by ^{1}H NMR analysis. [f] Determined by chiral HPLC analysis.

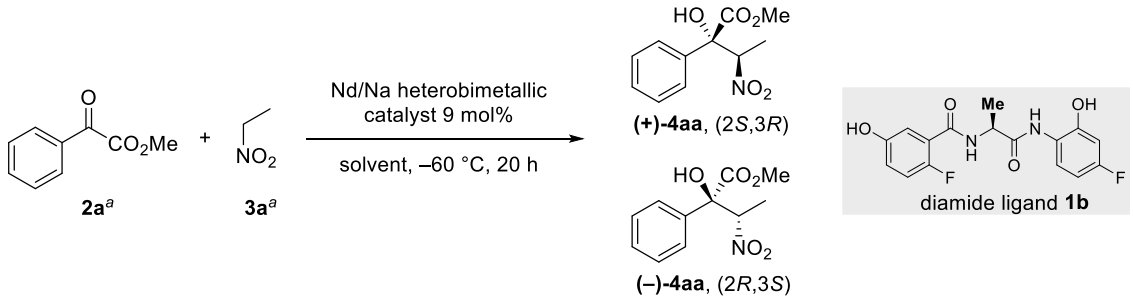
[a] 嵩高い置換基を持つ配位子 **1h-1j** を用いた場合は反応がほとんど進行しなかった。これらの配位子からは触媒調製時に白色沈殿が見られず、適切な触媒構造が構築されなかったと考えている。

3－3　反応溶媒の検討

前項でエナンチオ選択性の逆転が見られた配位子 **1b** を用い、反応溶媒の検討を行った(Table 2)。Entry1-8でエーテル系溶媒を検討したところ、THF 中で反応した場合のみ高いエナンチオ選択性で**(+)-4aa** が得られた。$^{i}Pr_2O$ もわずかなエナンチオ選択性で**(+)-4aa** を与えたものの、それ以外のすべてのエーテル系溶媒中で**(–)-4aa** を主生成物として与えた。特に MTBE を溶媒として用いた場合は 70% ee と比較的高いエナンチオ選択性で**(–)-4aa** が得られた。同じエーテル系溶媒である THF と MTBE 中で異なるエナンチオ選択性を与えた結果は興味深い[b]。なお、エーテル系以外の溶媒からも**(–)-4aa** が主生成物として得られた(entry 11-14)。

THF 中でのみエナンチオ選択性の逆転が見られた結果は、小さな置換基に持つ配位子 **1b** から調製される触媒はコンパクトな THF を配位子として取り込む余地があり、THF を取り込んだ結果、触媒の高次構造が逆のエナンチオマーを与える配座に変化し、**(+)-4aa** を主生成物として与えたと考えている。

Table 2. Solvent screening



entry	solvent[b]	product[c] (**4aa**)	yield[d] (%)	*anti*/*syn*[d]	%ee[e] (*anti*)	entry	solvent[b]	product[c] (**4aa**)	yield[d] (%)	*anti*/*syn*[d]	%ee[e] (*anti*)
1	THF	**(+)**	99	> 98/2	75	8	CPME	**(–)**	99	97/3	50
2	2-Me-THF	**(–)**	99	> 98/2	20	9	MTBE	**(–)**	97	97/3	70
3	2,5-Me_2-THF	**(–)**	97	96/4	26	10	toluene	**(–)**	79	94/6	67
4	Et_2O	**(–)**	99	94/6	35	11	EtOAc	**(–)**	88	96/4	31
5	$^{i}Pr_2O$	**(+)**	66	93/7	2	12	^{i}PrOAc	**(–)**	74	96/4	54
6	4-Me-THP	**(–)**	96	97/3	55	13	CH_2Cl_2	**(–)**	96	84/16	70
7	DME	**(–)**	89	97/3	65	14	EtCN	**(–)**	30	87/13	49

[a] **2a**: 0.12 mmol, **3a**: 1.2 mmol. [b] 2,5-Me_2-THF: 2,5-dimethyltetrahydrofuran (mixture of isomers), 4-Me-THP: 4-methyltetrahydropyran, CPME: cyclopentyl methyl ether, MTBE: *tert* -butyl methyl ether. [c] Optical rotation. [d] Determined by ^{1}H NMR analysis. [e] Determined by chiral HPLC analysis.

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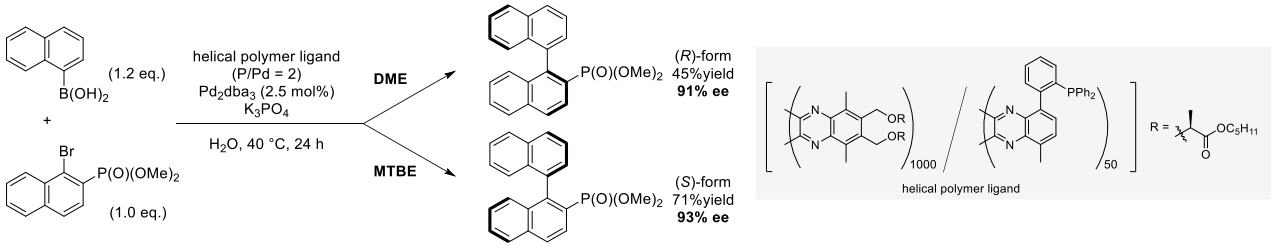
[b] 溶媒種に依存してエナンチオ選択性が逆転する反応は多数知られている[1,2]が、エーテル系の溶媒同士で選択性が逆転する反応はこれまでに下記の 1 例しか知られていない。長田、杉野目らはキノキサリンが連なったらせん状高分子を配位子とした Pd 触媒を用いた溶媒依存性エナンチオ選択的不斉鈴木カップリングを報告している[2d]。この反応では反応溶媒が DME と MTBE の場合でエナンチオ選択性が逆転し、それぞれ *R*体、*S*体が高い立体選択性で得られる。

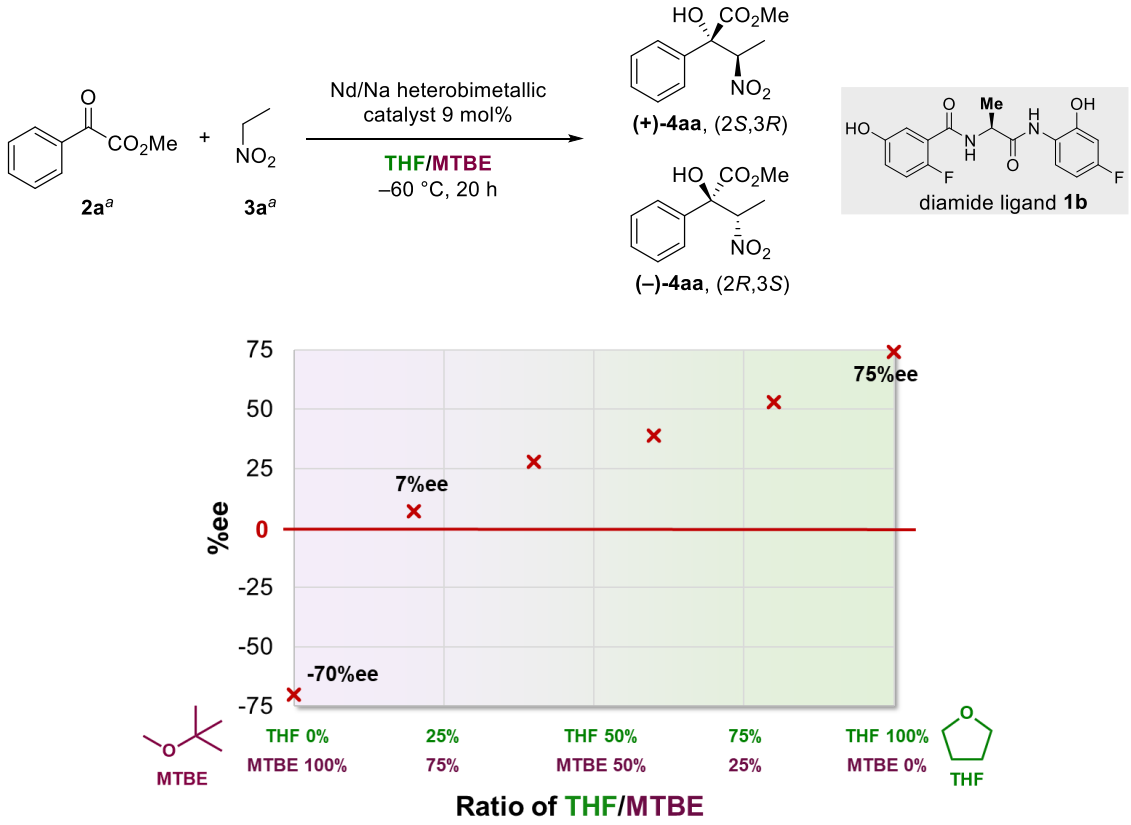
Nagata, Suginome et al. (2014)



３－４　混合溶媒中の反応

前項で紹介した溶媒効果の理解を深めるために、(+)体を与える THF と(–)体を与える MTBE を様々な比で混合した溶媒中で反応を行い、エナンチオ選択性を比較した(Figure 1)。その結果、MTBE が過剰であっても、THF が 20%存在すれば、(+)体を主生成物として与えることがわかった(+7% ee)。本結果は、コンパクトで配位能の高い THF が MTBE に優先して触媒に配位していることを示しており、THF の触媒へ配位がエナンチオ選択性に影響を与えている大きな証拠である。

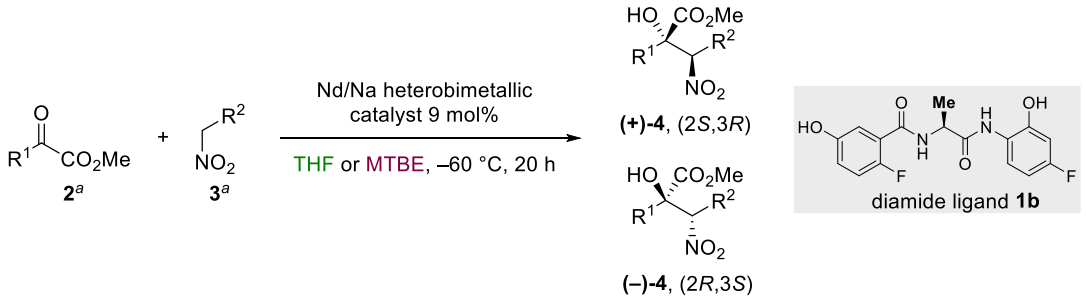
Figure 1. Enantioselectivity of reactions in combined solvent (THF/MTBE)

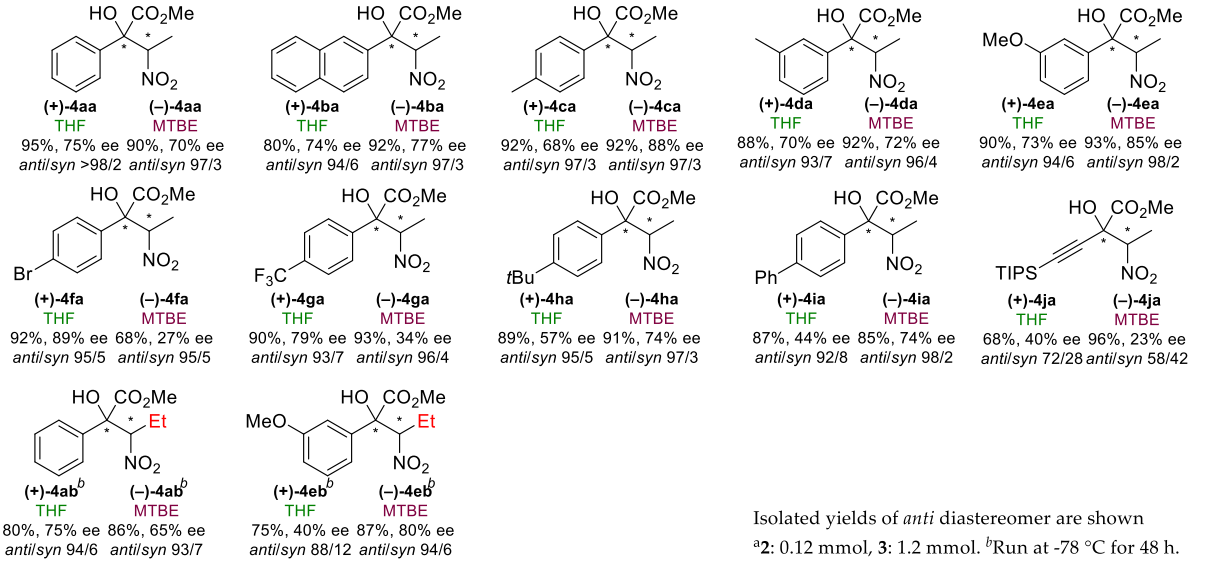


3 − 5　基質一般性の検討

配位子 **1b** の本溶媒依存性反応の基質一般性を調べた(Scheme 2)。THF と MTBE 中で反応を行ったところ、すべての基質でエナンチオ選択性の逆転が見られた。フェニルケトンや 2-ナフチルケトンは両溶媒中で良好なエナンチオ選択性を与え、それぞれ(+)体、(−)体を与えた。電子供与性基である Me 基や OMe 基が置換したフェニルケトンからは(−)体が得られる MTBE 中で高いエナンチオ選択性を与えた。一方、電子求引性基である Br 基や CF_3 基が置換したフェニルケトンからは(+)体を与える THF 中で高いエナンチオ選択性を与えた。嵩高い置換基を持つケトンやアルキニルケトン、ニトロプロパンの反応はエナンチオ選択性の低下が見られたものの、溶媒に依存したエナンチオ選択性の逆転現象は維持した。

Scheme 2. Reaction scope





Isolated yields of *anti* diastereomer are shown
[a]**2**: 0.12 mmol, **3**: 1.2 mmol. [b]Run at -78 °C for 48 h.

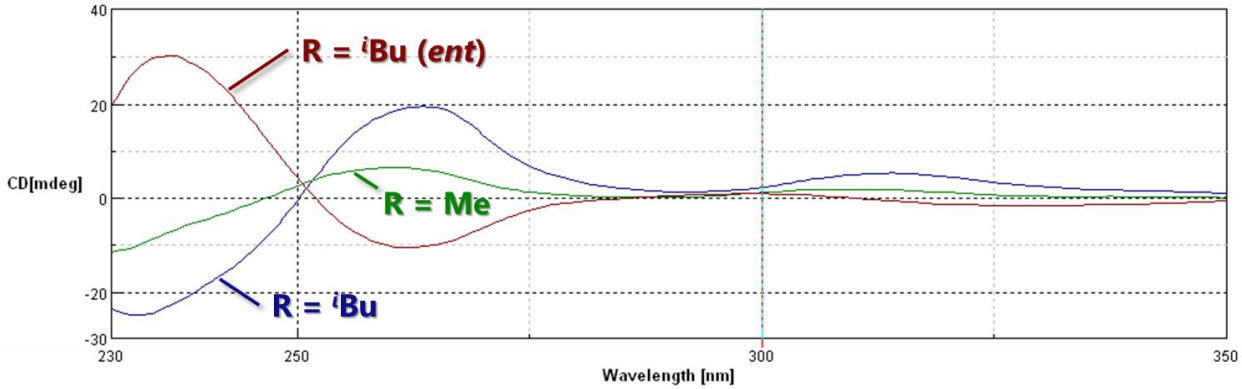
３－６　CD による触媒構造の解析

触媒の高次構造ならびにエナンチオ選択性の逆転現象の理解を深めるために、配位子 **1a**(R = ^{i}Bu)、**1b**(R = Me)および ***ent*-1a**(R = ^{i}Bu)から調製した触媒の CD スペクトルを測定した。３－２で述べたように配位子 **1a** と **1b** は THF 中で逆のエナンチオ選択性を与えることから、正負が逆の CD スペクトルが観測されることを期待した。

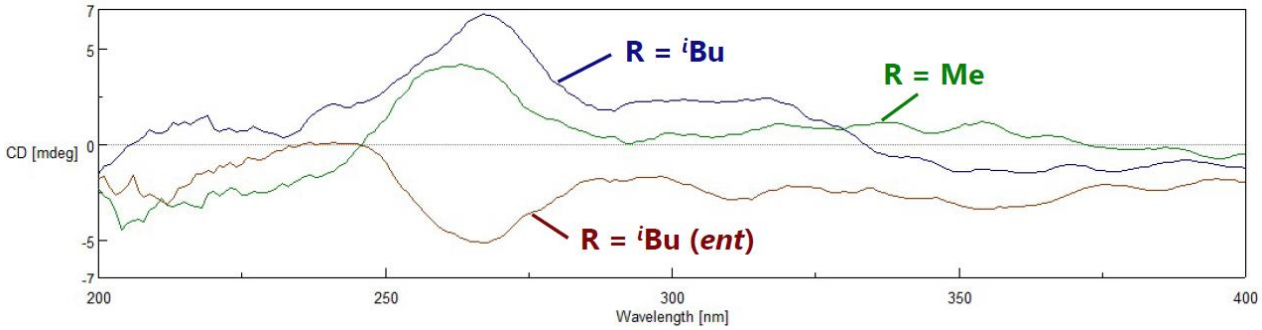
触媒の飽和 THF 溶液の CD スペクトル(透過法)と乾燥させた触媒粉末の CD スペクトル(拡散反射法)を Figure 2 に示す。どちらの場合も配位子 **1a** と **1b** は正負が同一の CD スペクトルを与え、本結果から立体選択性に影響を与える触媒構造の相違に関する情報を得ることは出来なかった。

Figure 2. CD spectra of Nd/Na heterobimetallic catalyst

Nd/Na 異種二核金属触媒の飽和 THF 溶液の CD スペクトル(透過法)



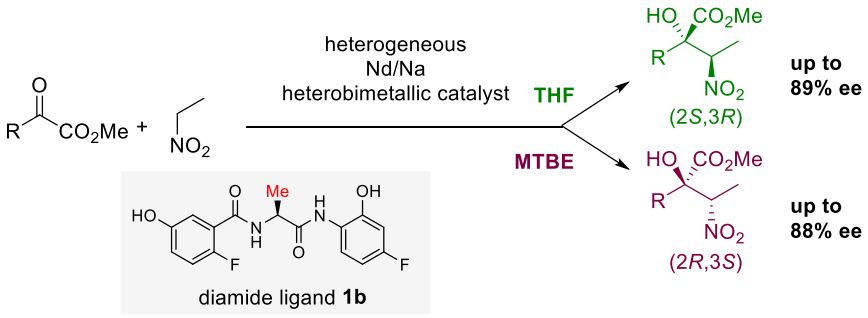
乾燥させた Nd/Na 異種二核金属触媒粉末の CD スペクトル(拡散反射法)



3－7　まとめ

3 章では L-アラニン由来のジアミド型配位子 **1b** から調製される Nd/Na 異種 2 核金属触媒による α-ケトエステルの溶媒依存性エナンチオ選択的不斉ニトロアルドール反応について述べた [3]。溶媒依存性反応は最も小さいメチル基を置換基として持つ配位子 **1b** からのみ誘導され、同じエーテル系の溶媒である THF と MTBE 中で異なるエナンチオ選択性を与える興味深い結果を与えた。本結果は、1) 本触媒反応の不斉が配位子の不斉中心のみを単純に認識している訳ではなく、触媒の高次構造により構築される不斉を認識して誘起されていること、2) コンパクトな配位子 **1b** から調製される触媒はコンパクトで配位性の THF を取り込むと、その高次構造が変化し、エナンチオ選択性の逆転が引き起こされることを示唆している。今後も触媒構造や不斉発現機構を解明に向けた研究を継続する。

Scheme 3. Summary of chapter 3



References

1. For reviews of stereodivergent reactions, see: (a) Bartók, M. *Chem. Rev.* **2010**, *110*, 1663. (b) Beletskaya, I. P.; Nájera, C.; Yus, M. *Chem. Rev.* **2018**, *118*, 5080.
2. For selected examples of solvent-dependent enantiodivergent reactions, see: (a) Sohtome, Y.; Shin, B.; Horitsugi, N.; Takagi, R.; Noguchi, K.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 7299. (b) Sohtome, Y.; Tanaka, S.; Takada, K.; Yamaguchi, T.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 9254. (c) Garzan, A.; Jaganathan, A.; Marzijarani, N. S.; Yousefi, R.; Whitehead, D. C.; Jackson, J. E.; Borhan, B. *Chem. Eur. J.* **2013**, *19*, 9015. (d) Nagata, Y.; Kuroda, T.; Takagi, K.; Suginome, M. *Chem. Sci.* **2014**, *5*, 4953. (e) Nagata, Y.; Nishikawa, T.; Suginome, M. *J. Am. Chem. Soc.* **2014**, *136*, 15901. (f) Abadie, M.; Trivelli, X.; Medina, F.; Duhal, N.; Kouach, M.; Linden, B.; Génin, E.; Vandewalle, M.; Capet, F.; Roussel, P.; Rosal, I. D.; Maron, L.; Agbossou-Niedercorn, F.; Michon, C. *Chem. Eur. J.* **2017**, *23*, 10777.
3. Karasawa, T.; Saito, A.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2019**, *21*, 3581.

Experimental Section for chapter 3 entitled

Solvent-Dependent Enantiodivergence in *anti*-Selective Catalytic Asymmetric Nitroaldol Reactions

Table of Contents:

A. General Methods

A-1. Reactions and purifications

Unless otherwise noted, all reactions were carried out in an oven-dried glassware fitted with a 3-way glass stopcock under an argon atmosphere with magnetically stirred chips. All work-up and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Thin layer chromatography (TLC) was performed on Merck TLC plates (0.25 mm) pre-coated with silica gel 60 F254 and visualized by UV quenching and staining with $KMnO_4$ or ninhydrine. Flash column chromatography was performed on a Biotage Isolera Spektra One with a Redisep column.

A-2. Characterizations

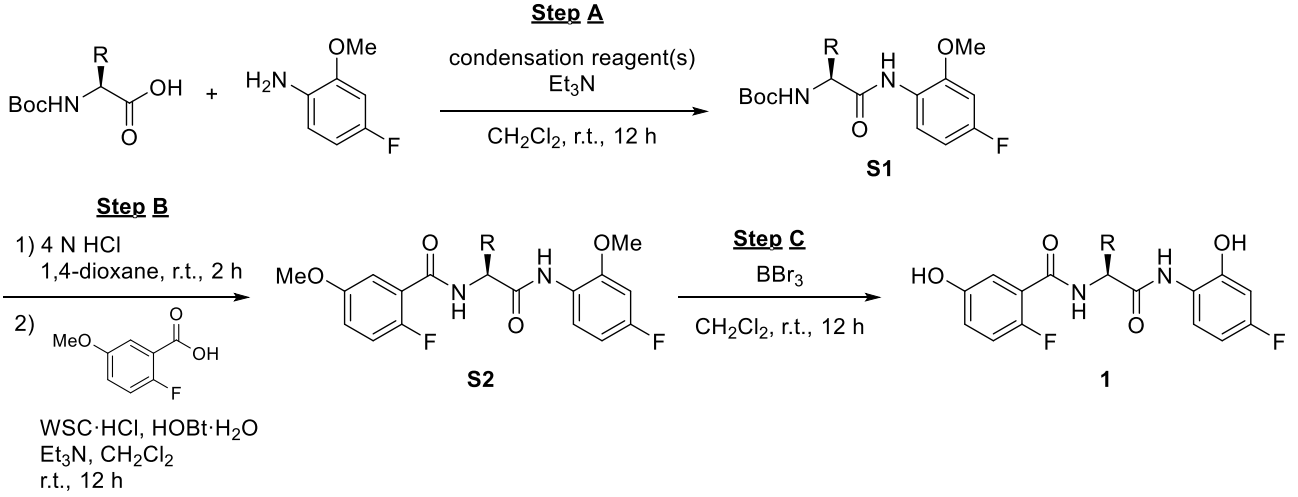
Infrared (IR) spectra were recorded on a HORIBA FT210 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL ECS-400. Chemical shifts (δ) are given in ppm relative to residual solvent peaks.[1] Data for ^{1}H NMR are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet), q (quartet), m (multiplet), br (broad). For ^{19}F NMR, chemical shifts were reported in the scale relative to $PhCF_3$ (δ –62.7680 ppm in $CDCl_3$) as an external reference. High performance liquid chromatography (HPLC) analysis was performed on Jasco analytical instruments with single pump and UV detector. Optical rotation was measured using a 1 mL cell with a 10 cm path length on a JASCO polarimeter P-1030. High-resolution mass spectra were measured on a Thermo Fisher Scientific LTQ Orbitrap XL.

A-3. Solvents and reagents

THF, Et_2O, DME, CPME, toluene, EtOAc, CH_2Cl_2 and DMF were purified by passing through a solvent purification system (Glass Contour). 2-Me-THF was purchased from Aldrich (anhydrous and inhibitor-free). MTBE was purchased from Wako Pure Chemical Co. Ltd (anhydrous and inhibitor-free). 2,5-Me_2-THF, $^{i}Pr_2O$, 4-Me-THP, ^{i}PrOAc, EtCN, nitroethane (**3a**), nitropropane (**3b**) and methyl benzoylformate (**2a**) were purchased from TCI Co. Ltd. and nitroethane was used after distillation. Amide-based ligand were prepared by the procedure described below. $NdCl_3 \bullet 6H_2O$ was purchased from Wako Pure Chemical Co. Ltd. and used after grinding with a mortar. 2.0 M $NaO^{t}Bu$/THF was purchased from Aldrich. α-Keto esters **2b**,[2] **2c**,[2] **2d**,[2] **2e**,[3] **2f**,[4] **2g**,[2] **2h**,[3] **2i**[3] and **2j**[3] were prepared by the known procedures. All other starting materials were used as supplied by commercial venders.

B. Preparation of amide-based ligands

Amide-based ligands **1a**,[5] **1e**,[6] **1i**[6] and **1j**[6] were prepared according to the known procedure. Amide-based ligands **1b**, **1c**, **1d**, **1f**, **1g**, and **1h** were prepared by general procedure described below.

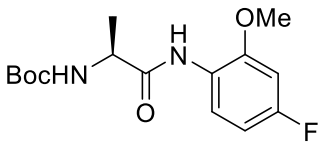


General procedure for step A: To a solution of *N*-Boc-protected L-amino acid (1.0 eq.) and 4-fluoro-2-methoxyaniline (1.0 eq.) in CH_2Cl_2 (0.25 M) were added condensation reagent(s) (1.2 eq. (each)) and Et_3N (3.6 eq.) at 0 °C and the mixture was stirred at room temperature for 12 h. After quench with 1 N HCl aq., the resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with sat. $NaHCO_3$ aq. and brine, and dried over Na_2SO_4. After concentration in *vacuo*, the resulting crude product was purified by silica gel chromatography (EtOAc/*n*-hexane) to give monoamide **S1**.

General procedure for step B: **S1** was added to 4 N HCl/1,4-dioxane (5 eq.) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was concentrated in *vacuo*. To a solution of the above residue in CH_2Cl_2 (0.25 M) were added 2-fluoro-5-methoxybenzoic acid (1.1 eq.), HOBt•H_2O (1.5 eq.), Et_3N (3.5 eq.) and WSC•HCl (1.5 eq.) at 0 °C and the mixture was stirred at room temperature for 12 h. After quench with 1 N HCl aq., the resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with sat. $NaHCO_3$ aq. and brine, and dried over Na_2SO_4. After concentration in *vacuo*, the resulting crude product was purified by silica gel chromatography (EtOAc/*n*-hexane) to give amide-based ligand precursor **S2**.

General procedure for step C: To a solution of **S2** in CH_2Cl_2 (0.25 M) was added 1.0 M BBr_3/ CH_2Cl_2 (6.0 eq.) at 0 °C and the mixture was stirred at room temperature for 12 h. After concentration in *vacuo*, H_2O was added to the residue and the resulting mixture was extracted with EtOAc twice. The combined organic layers were washed with sat. $NaHCO_3$ aq. and brine, and dried over Na_2SO_4. After concentration in *vacuo*, the resulting crude product was purified by recrystallization or reslurry from toluene/IPA/hexane (13 WR/ 0.75 WR/13 WR to crude product, WR = weight ratio) to give amide-based ligand **1**.

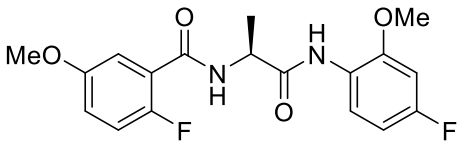
***tert*-Butyl (*S*)-(1-((4-fluoro-2-methoxyphenyl)amino)-1-oxopropan-2-yl)carbamate (S1b):**



Prepared by the general procedure for step A (HATU was used as a condensation reagent) from (*tert*-butoxycarbonyl)-L-alanine (1.34 g, 7.1 mmol) and isolated as a white solid (2.17 g, 6.9 mmol, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (brs, 1H), 8.28 (dd, *J* = 8.8, 6.1 Hz, 1H), 6.67-6.60 (m, 2H), 5.02 (brs, 1H), 4.32 (brs, 1H), 3.86 (s, 3H), 1.46 (s, 9H), 1.44 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 159.4 (d, *J* = 241.3 Hz), 155.7, 149.4 (d, *J* = 10.2 Hz), 123.7, 120.7 (d, *J* = 8.8 Hz), 106.8 (*J* = 21.2 Hz), 98.9 (d, *J* = 27.0 Hz), 80.5, 56.1, 51.1, 28.4, 18.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.3; IR (thin film) *ν* 2979, 1682, 1615, 1532, 1454, 1414, 1367, 1279, 1164, 1109 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{22}FN_2O_4$ *m*/*z* 313.1558 $[M+H]^+$, found 313.1557; $[\alpha]_D^{25}$

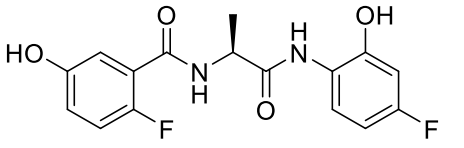
−44.6 (*c* 1.02, $CHCl_3$)

(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-methoxyphenyl)amino)-1-oxopropan-2-yl)-5-methoxybenzamide (S2b):



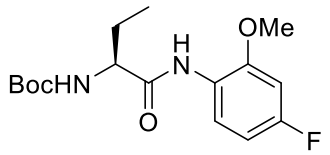
Prepared by the general procedure for step B from **S1b** (2.10 g, 6.7 mmol) and isolated as a white solid (2.40 g, 6.6 mmol, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (brs, 1H), 8.27 (dd, *J* = 9.0, 6.4 Hz, 1H), 7.57 (dd, *J* = 6.1, 3.4 Hz, 1H), 7.36 (dd, *J* = 12.7, 7.1 Hz, 1H), 7.07 (dd, *J* = 11.0, 9.1 Hz, 1H), 7.01 (ddd, *J* = 9.0, 4.2, 3.4 Hz, 1H), 6.68-6.60 (m, 2H), 4.86 (dt, *J* = 2.0, 7.1 Hz, 1H), 1.59 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 163.3 (d, *J* = 3.7 Hz), 159.5 (d, *J* = 241.3 Hz), 156.2, 155.4 (d, *J* = 239.9 Hz), 149.5 (d, *J* = 9.5 Hz), 123.5 (d, *J* = 2.9 Hz), 121.0 (d, *J* = 9.5 Hz), 120.8 (d, *J* = 12.4 Hz), 120.4 (d, *J* = 9.5 Hz), 117.2 (d, *J* = 26.3 Hz), 114.8 (d, *J* = 2.2 Hz), 106.9 (d, *J* = 21.9 Hz), 98.9 (d, *J* = 27.0 Hz), 56.2, 56.1 50.5, 18.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.0, 123.2; IR (thin film) *ν* 2940, 1652, 1615, 1521, 1492, 1454, 1415, 1279, 1193, 1033 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}O_4N_2F_2$ *m*/*z* 365.1307 $[M+H]^+$, found 365.1310; $[\alpha]_D^{25}$ −28.1 (*c* 0.91, $CHCl_3$)

(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-hydroxyphenyl)amino)-1-oxopropan-2-yl)-5-hydroxybenzamide (1b):



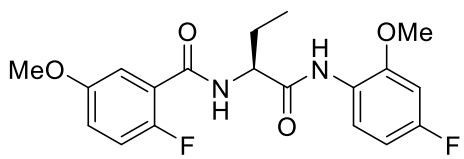
Prepared by the general procedure for step C from **S2b** (2.02 g, 5.5 mmol), purified by reslurry and isolated as a white solid (1.72 g, 5.1 mmol, 92%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (dd, *J* = 8.8, 6.1 Hz, 1H), 7.17 (dd, *J* = 5.8, 3.2 Hz, 1H), 7.04 (dd, *J* = 10.5, 8.8 Hz, 1H), 6.91 (ddd, *J* = 8.8, 3.9, 3.2 Hz, 1H), 6.59 (dd, *J* = 10.0, 2.7 Hz, 1H), 6.54 (ddd, J = 8.6, 8.6, 3.0 Hz), 4.76 (q, *J* = 7.1 Hz, 1H), 1.54 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.1, 166.5 (d, *J* = 2.2 Hz), 161.7 (d, *J* = 240.6 Hz), 155.1 (d, *J* = 1.5 Hz), 155.1 (d, *J* = 238.4), 151.2 (d, *J* = 10.9 Hz), 124.5 (d, *J* = 9.5 Hz), 123.7 (d, *J* = 15.3 Hz), 123.2 (d, *J* = 2.9 Hz), 120.7 (d, *J* = 8.0 Hz), 117.9 (d, *J* = 24.8 Hz), 117.0 (d, *J* = 2.9 Hz), 106.4 (d, *J* = 22.6 Hz), 103.7 (d, *J* = 25.5 Hz), 51.6, 18.3; ^{19}F NMR (376 MHz, CD_3OD) δ −118.4, −128.2; IR (thin film) *ν* 3270, 1658, 1642, 1547, 1527, 1501, 1434, 1192, 974, 767 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{15}F_2N_2O_4$ *m*/*z* 337.0994 $[M+H]^+$, found 337.0998; $[\alpha]_D^{25}$ −6.2 (*c* 0.97, CH_3OH)

***tert*-Butyl (*S*)-(1-((4-fluoro-2-methoxyphenyl)amino)-1-oxobutan-2-yl)carbamate(S1c):**



Prepared by the general procedure for step A (HATU was used as a condensation reagent) from (*S*)-2-((*tert*-butoxycarbonyl)amino)butanoic acid (720 mg, 3.5 mmol) and isolated as a white solid (1.14 g, 3.5 mmol, quant.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.8, 6.1 Hz, 1H), 8.15 (brs, 1H), 6.68-6.60 (m, 2H), 5.04 (brs, 1H), 4.16-4.13 (m, 1H), 3.86 (s, 3H), 2.03-1.91 (m, 1H), 1.77-1.58 (m, 1H), 1.46 (s, 9H), 1.01 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 159.4 (d, *J* = 242.1 Hz), 155.8, 149.4 (d, *J* = 9.5 Hz), 123.6, 120.8 (d, *J* = 8.8 Hz), 106.9 (d, *J* = 21.9 Hz), 98.9 (d, *J* = 27.7 Hz), 80.4, 56.8 (d, *J* = 2.2 Hz), 56.1, 28.4, 25.8, 10.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.2; IR (thin film) *ν* 2973, 1673, 1536, 1499, 1455, 1414, 1366, 1279, 1153, 1109 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{24}FN_2O_4$ *m*/*z* 327.1715 $[M+H]^+$, found 327.1719; $[\alpha]_D^{25}$ −37.9 (*c* 1.07, $CHCl_3$)

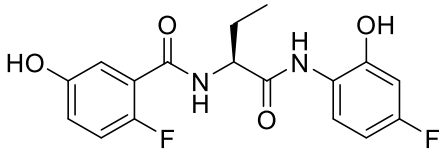
(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-methoxyphenyl)amino)-1-oxobutan-2-yl)-5-methoxybenzamide (S2c):



Prepared by the general procedure for step B from **S1c** (1.06 g, 3.3 mmol) and isolated as a white solid (1.19 g, 3.1 mmol, 97%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.8, 6.1 Hz, 1H), 8.19 (brs, 1H), 7.56 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.35 (dd, *J* = 12.7, 7.6 Hz, 1H), 7.07 (dd, *J* = 11.0, 9.0 Hz, 1H), 7.00 (ddd, *J* = 9.0, 4.4, 3.4 Hz, 1H), 6.67-6.60 (m, 2H), 4.78-4.72 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.16-2.06 (m, 1H), 1.93-1.82 (m, 1H), 1.06 (dd, *J* = 7.3, 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 163.4 (d, *J* = 3.7 Hz), 159.5 (d, *J* = 241.3 Hz), 156.2 (d, *J* = 2.2 Hz), 155.3 (d, *J* = 239.2 Hz), 149.5 (d, *J* = 9.5 Hz), 123.4 (d, *J* = 2.9 Hz), 121.0 (d, *J* = 9.5 Hz), 120.8, 120.3 (d, *J* = 9.5 Hz), 117.2 (d, *J* = 26.2 Hz), 114.8 (d, *J* = 2.2 Hz), 106.9 (d, *J* = 21.2 Hz), 98.9 (d, *J* = 27.0 Hz), 56.2, 56.1, 56.0, 25.8, 10.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.9, −123.3; IR (thin film) *ν* 2970, 1652, 1615, 1523, 1492, 1464, 1415, 1280, 1193, 1034 cm^{-1};

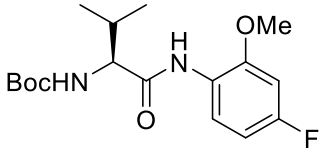
HRMS (ESI) calcd. for $C_{19}H_{21}O_4N_2F_2$ *m/z* 379.1464 $[M+H]^+$, found 379.1470; $[\alpha]_D^{25}$ −20.9 (*c* 1.00, $CHCl_3$)

(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-hydroxyphenyl)amino)-1-oxobutan-2-yl)-5-hydroxybenzamide (1c):



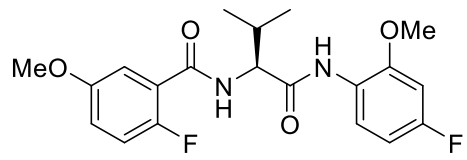
Prepared by the general procedure for step C from **S2c** (1.30 g, 3.5 mmol), purified by reslurry and isolated as a white solid (1.03 g, 2.9 mmol, 84%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (dd, *J* = 9.1, 6.4 Hz, 1H), 7.15 (dd, *J* = 5.6, 3.0 Hz, 1H), 7.05 (dd, *J* = 10.5, 9.1 Hz, 1H), 6.91 (ddd, *J* = 8.8, 4.2, 3.2 Hz, 1H), 6.59 (dd, *J* = 12.7, 1.7 Hz, 1H), 6.55 (ddd, *J* = 8.6, 8.6, 3.0 Hz, 1H), 4.66 (dd, *J* = 8.3, 5.6 Hz, 1H), 2.04 (dq, *J* = 5.6, 7.3 Hz, 1H), 1.86 (dq, *J* = 8.3, 7.3 Hz, 1H), 1.07 (dd, *J* = 7.3, 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.5, 166.8 (d, *J* = 1.5 Hz), 161.8 (d, *J* = 240.6 Hz), 155.2 (d, *J* = 2.2 Hz), 155.1 (d, *J* = 238.4 Hz), 151.4 (d, *J* = 10.9 Hz), 124.8 (d, *J* = 10.2 Hz), 123.8 (d, *J* = 14.6 Hz), 123.1 (d, *J* = 2.9 Hz), 120.7 (d, *J* = 8.0 Hz), 118.0 (d, *J* = 25.5 Hz), 117.1 (d, *J* = 2.2 Hz), 106.5 (d, *J* = 27.6 Hz), 103.8 (d, *J* = 24.8 Hz), 57.3, 26.5, 10.6; ^{19}F NMR (376 MHz, CD_3OD) δ −118.2, −128.3; IR (thin film) *ν* 3280, 1658, 1642, 1547, 1528, 1501, 1434, 1309, 976, 770 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{17}F_2N_2O_4$ *m/z* 351.1151 $[M+H]^+$, found 351.1146; $[\alpha]_D^{25}$ −12.1 (*c* 1.01, CH_3OH)

***tert*-Butyl (*S*)-(1-((4-fluoro-2-methoxyphenyl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (S1d):**



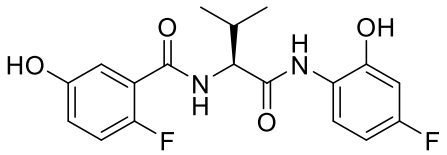
Prepared by the general procedure for step A (WSC•HCl and HOBt•H_2O were used as condensation reagents) from (*tert*-butoxycarbonyl)-L-valine (3.85 g, 17.7 mmol) and isolated as a white solid (2.83 g, 8.3 mmol, 47%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.8, 6.1 Hz, 1H), 8.05 (brs, 1H), 6.68-6.60 (m, 2H), 5.11 (brs, 1H), 4.05 (brs, 1H), 3.86 (s, 3H), 2.27-2.22 (m, 1H), 1.46 (s, 9H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 159.5 (d, *J* = 242.1 Hz), 156.0, 149.4 (d, *J* = 9.5 Hz), 123.4, 120.9 (d, *J* = 8.8 Hz), 106.9 (d, *J* = 21.1 Hz), 98.9 (d, *J* = 27.0 Hz), 80.2, 61.0, 56.1, 31.1, 28.5, 19.5, 17.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.1; IR (thin film) *ν* 2969, 1702, 1665, 1608, 1540, 1291, 1170, 1152, 1035, 1011 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{26}FN_2O_4$ m/z 341.1871 $[M+H]^+$, found 341.1870; $[\alpha]_D^{25}$ −25.6 (*c* 1.07, $CHCl_3$)

(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-methoxyphenyl)amino)-3-methyl-1-oxobutan-2-yl)-5-methoxybenzamide (S2d):



Prepared by the general procedure for step B from **S1d** (2.00 g, 5.9 mmol) and isolated as a white solid (2.27 g, 5.9 mmol, quant.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 9.0, 6.2 Hz, 1H), 8.05 (brs, 1H), 7.56 (dd, *J* = 6.1, 3.2 Hz, 1H), 7.36 (dd, *J* = 13.1, 8.2 Hz, 1H), 7.08 (dd, *J* = 11.0, 9.0 Hz, 1H), 7.01 (ddd, *J* = 9.0, 4.4, 3.4 Hz, 1H), 6.67-6.60 (m, 2H), 4.66-4.62 (m, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 2.35 (ddd, *J* = 2.2, 2.7, 2.7 Hz, 1H), 1.09 (d, *J* = 2.7 Hz, 3H), 1.07 (d, *J* = 2.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 163.5 (d, *J* = 2.9 Hz), 159.6 (d, *J* = 241.3 Hz), 156.2 (d, *J* = 1.5 Hz), 155.4 (d, *J* = 239.2 Hz), 149.4 (d, *J* = 9.5 Hz), 123.3 (d, *J* = 3.6 Hz), 121.0 (d, *J* = 9.5 Hz), 120.4 (d, *J* = 9.5 Hz), 117.3 (d, *J* = 27.0 Hz), 114.8 (d, *J* = 2.2 Hz), 106.9 (d, *J* = 21.1 Hz), 98.9 (d, *J* = 27.0 Hz), 60.2, 56.2, 56.1, 31.3, 19.5, 18.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.8, −123.5; IR (thin film) *ν* 2965, 1655, 1616, 1527, 1492, 1465, 1415, 1279, 1193, 1034 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{23}F_2N_2O_4$ *m/z* 393.1620 $[M+H]^+$, found 393.1617; $[\alpha]_D^{25}$ −4.3 (*c* 1.01, $CHCl_3$)

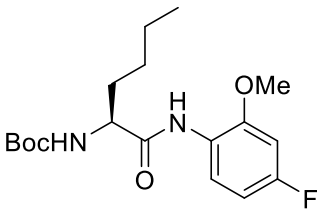
(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-hydroxyphenyl)amino)-3-methyl-1-oxobutan-2-yl)-5-hydroxybenzamide (1d):



Prepared by the general procedure for step C from **S2d** (2.00 g, 5.1 mmol), purified by recrystallization and isolated as a white solid (1.60 g, 4.4 mmol, 86%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.69 (dd, *J* = 9.0, 6.4 Hz, 1H), 7.19 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.09 (dd, *J* = 10.5, 8.8 Hz, 1H), 6.95 (ddd, *J* = 8.8, 3.9, 3.2 Hz, 1H), 6.64 (dd, *J* = 10.0, 2.7 Hz, 1H), 6.58 (ddd, *J* = 8.8, 8.8, 3.0 Hz, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 2.31 (dt, *J* = 6.8, 6.8 Hz, 1H), 1.11 (dd, *J* = 6.8, 6.8 Hz, 6H); ^{13}C NMR

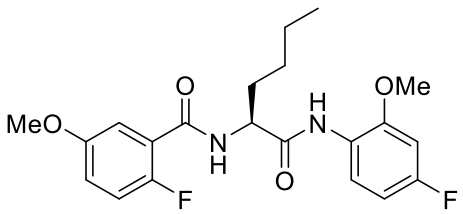
(100 MHz, CD_3OD) δ 173.0, 167.5 (d, *J* = 2.2 Hz), 162.8 (d, *J* = 240.6 Hz), 156.0 (d, *J* = 1.5 Hz), 156.0 (d = 237.7 Hz), 126.1 (d, *J* = 9.5 Hz), 124.5 (d, *J* = 14.6 Hz), 123.8 (d, *J* = 8.8 Hz), 118.8 (d, *J* = 25.5 Hz), 117.9 (d, *J* = 2.2 Hz), 107.4 (d, *J* = 22.6 Hz), 104.8 (d, *J* = 25.5 Hz), 62.0, 33.2, 20.6, 19.5; ^{19}F NMR (376 MHz, CD_3OD) δ −118.0, −128.3; IR (thin film) *ν* 3268, 1658, 1643, 1547, 1527, 1501, 1433, 1191, 973, 771 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{19}F_2N_2O_4$ *m*/*z* 365.1307 $[M+H]^+$, found 365.1298; $[\alpha]_D^{25}$ −8.6 (*c* 1.06, CH_3OH)

***tert*-Butyl (*S*)-(1-((4-fluoro-2-methoxyphenyl)amino)-1-oxohexan-2-yl)carbamate (S1f):**



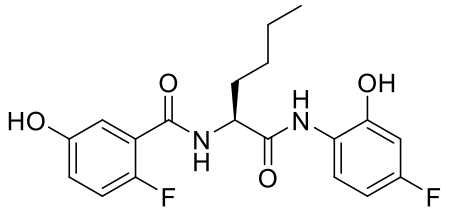
Prepared by the general procedure for step A (WSC•HCl and HOBt•H_2O were used as condensation reagents) from (*S*)-2-((*tert*-butoxycarbonyl)amino)hexanoic acid (1.00 g, 4.32 mmol) and isolated as a white solid (707 mg, 2.0 mmol, 46%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.8, 6.1 Hz, 1H), 8.22 (brs, 1H), 6.67-6.60 (m, 2H), 5.03 (brs, 1H), 4.20 (brs, 1H), 1.97-1.88 (m, 1H), 1.71-1.62 (m, 1H), 1.46 (s, 9H), 1.39-1.32 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 159.4 (d, *J* = 241.3 Hz), 155.8, 149.4 (d, *J* = 9.5 Hz), 123.6, 120.8 (d, *J* = 8.8 Hz), 106.8 (d, *J* = 21.9 Hz), 98.9 (d, *J* = 27.0 Hz), 80.3, 56.1, 55.6, 32.3, 28.4, 27.9, 22.6, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.2; IR (thin film) *ν* 2959, 2934, 1671, 1536, 1500, 1455, 1414, 1171, 1153 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{28}O_4N_2F$ *m*/*z* 355.2028 $[M+H]^+$, found 355.2026; $[\alpha]_D^{25}$ −30.1 (*c* 1.12, $CHCl_3$)

(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-methoxyphenyl)amino)-1-oxohexan-2-yl)-5-methoxybenzamide (S2f):



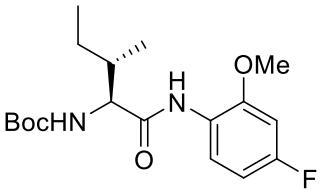
Prepared by the general procedure for step B from **S1f** (685 mg, 1.9 mmol) and isolated as a white solid (745 mg, 1.8 mmol, 95%); ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 9.0, 6.1 Hz, 1H), 8.20 (brs, 1H), 7.57 (dd, *J* = 6.1, 3.2 Hz, 1H), 7.31 (dd, *J* = 13.2, 7.8 Hz, 1H), 7.07 (dd, *J* = 10.8, 9.0 Hz, 1H), 7.00 (ddd, *J* = 8.8, 4.2, 3.2 Hz, 1H), 6.68-6.60 (m, 2H), 4.80-4.75 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.09-2.02 (m, 1H), 1.88-1.79 (m, 1H), 1.48-1.35 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 163.4 (d, *J* = 2.9 Hz), 159.5 (d, *J* = 241.3 Hz), 156.2 (d, *J* = 1.5 Hz), 155.4 (d, *J* = 239.2 Hz), 149.5 (d, *J* = 10.2 Hz), 123.5 (d, *J* = 2.9 Hz), 121.0 (d, *J* = 8.7 Hz), 120.9 (d, *J* = 13.1 Hz), 120.4 (d, *J* = 8.8 Hz), 117.2 (d, *J* = 26.2 Hz), 114.8 (d, *J* = 2.2 Hz), 106.9 (d, *J* = 21.9 Hz), 98.9 (d, *J* = 27.0 Hz), 56.2, 56.1, 54.9, 32.2, 27.8, 22.6, 14.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.9, −123.3; IR (thin film) *ν* 2957, 1652, 1615, 1530, 1493, 1465, 1415, 1279, 1192, 1034 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{25}F_2N_2O_4$ *m*/*z* 407.1777 $[M+H]^+$, found 407.1777; $[\alpha]_D^{25}$ −15.9 (*c* 1.08, $CHCl_3$)

(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-hydroxyphenyl)amino)-1-oxohexan-2-yl)-5-hydroxybenzamide (1f):



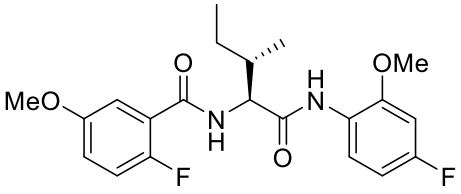
Prepared by the general procedure for step C from **S2f** (700 mg, 1.7 mmol), purified by recrystallization and isolated as a white solid (488 mg, 1.3 mmol, 75%); ^1H NMR (400 MHz, CD_3OD) δ 7.73 (dd, *J* = 9.0, 6.4 Hz, 1H), 7.15 (dd, *J* = 5.6, 2.9 Hz, 1H), 7.05 (dd, *J* = 10.0, 8.8 Hz, 1H), 6.91 (ddd, *J* = 9.0, 4.2, 3.2 Hz, 1H), 6.60 (dd, *J* = 10.0, 2.9 Hz, 1H), 6.55 (ddd, *J* = 8.6, 8.6, 2.9 Hz, 1H), 4.71 (dd, *J* = 8.3, 5.6 Hz, 1H), 2.03-1.97 (m, 1H), 1.96-1.82 (m, 1H), 1.51-1.38 (m, 4H), 0.95 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.7, 166.8, 161.8 (d, *J* = 240.6 Hz), 155.1 (d, *J* = 2.2 Hz), 155.0 (d, *J* = 238.4 Hz), 151.3 (d, *J* = 10.9 Hz), 124.7 (d, *J* = 10.2 Hz), 123.8 (d, *J* = 14.6 Hz), 123.1 (d, *J* = 2.9 Hz), 120.7 (d, *J* = 8.0 Hz), 117.9 (d, *J* = 24.8 Hz), 117.0 (d, *J* = 2.2 Hz), 106.4 (d, *J* = 22.6 Hz), 103.8 (d, *J* = 24.8 Hz), 55.9, 32.9, 29.1, 23.4, 14.3; ^{19}F NMR (376 MHz, CD_3OD) δ −118.3, −128.3; IR (thin film) *ν* 3268, 1658, 1642, 1547, 1528, 1501, 1434, 1221, 976, 771 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}F_2N_2O_4$ *m*/*z* 379.1464 $[M+H]^+$, found 379.1460; $[\alpha]_D^{25}$ −10.7 (*c* 0.99, CH_3OH)

***tert*-Butyl ((2*S*,3*S*)-1-((4-fluoro-2-methoxyphenyl)amino)-3-methyl-1-oxopentan-2-yl)carbamate (S1g):**



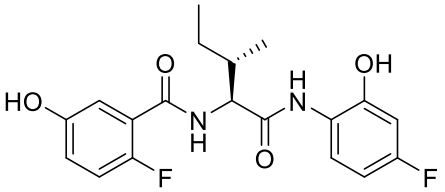
Prepared by the general procedure for step A (WSC•HCl and HOBt•H_2O were used as condensation reagents) from (*tert*-butoxycarbonyl)-L-isoleucine (1.00 g, 4.32 mmol) and isolated as a white solid (536 mg, 1.5 mmol, 35%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.8, 6.1 Hz, 1H), 8.07 (brs, 1H), 6.68-6.60 (m, 2H), 5.11 (brs, 1H), 4.11 (brs, 1H), 3.86 (s, 3H), 2.03-1.93 (m, 1H), 1.61-1.49 (m, 1H), 1.45 (s, 3H), 1.28-1.14 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 159.5 (d, *J* = 241.3 Hz), 155.9, 149.4 (d, *J* = 9.5 Hz), 123.4 (d, *J* = 2.9 Hz), 120.8 (d, *J* = 9.5 Hz), 106.9 (d, *J* = 21.9 Hz), 98.9 (d, *J* = 27.0 Hz), 80.2 (d, *J* = 1.4 Hz), 60.3, 56.1, 37.5, 28.5, 24.9, 15.9, 11.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.1; IR (thin film) *ν* 2969, 1700, 1664, 1538, 1497, 1464, 1416, 1170, 1152, 1034 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{28}O_4N_2F$ *m*/*z* 355.2028 $[M+H]^+$, found 355.2025; $[\alpha]_D^{25}$ −21.9 (*c* 0.97, $CHCl_3$)

2-Fluoro-*N*-((2*S*,3*S*)-1-((4-fluoro-2-methoxyphenyl)amino)-3-methyl-1-oxopentan-2-yl)-5-methoxybenzamide (S2g):



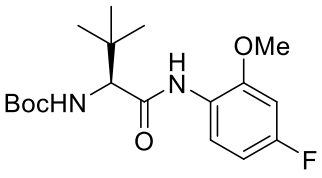
Prepared by the general procedure for step B from **S1g** (500 mg, 1.4 mmol) and isolated as a white solid (572 mg, 1.4 mmol, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.8, 6.1 Hz, 1H), 8.06 (brs, 1H), 7.56 (dd, *J* = 6.1, 3.4 Hz, 1H), 7.37 (dd, J = 13.0, 8.3 Hz, 1H), 7.07 (dd, *J* = 10.8, 8.8 Hz, 1H), 7.00 (ddd, 9.0, 4.2, 3.2 Hz, 1H), 6.67-6.60 (m, 2H), 4.71-4.66 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.17-2.07 (m, 1H), 1.72-1.62 (m, 1H), 1.34-1.23 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 163.4 (d, *J* = 3.6 Hz), 159.6 (d, *J* = 241.3 Hz), 156.2 (d, *J* = 1.2 Hz), 155.4 (d, *J* = 238.8 Hz), 149.4 (d, *J* = 9.5 Hz), 123.3 (d, *J* = 3.7 Hz), 121.0 (d, *J* = 9.5 Hz), 120.9, 120.4 (d, *J* = 8.8 Hz), 117.2 (d, *J* = 27.0 Hz), 114.8 (d, *J* = 1.5 Hz), 106.9 (d, *J* = 21.9 Hz), 98.9 (d, *J* = 27.7 Hz), 59.4, 56.2, 56.1, 37.6, 25.3, 15.8, 11.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.9, −123.4; IR (thin film) *ν* 2965, 1651, 1616, 1531, 1493, 1464, 1415, 1279, 1193, 1034 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{25}O_4N_2F_2$ *m*/*z* 407.1777 $[M+H]^+$, found 407.1775; $[\alpha]_D^{25}$ −0.25 (*c* 1.07, $CHCl_3$)

2-Fluoro-*N*-((2*S*,3*S*)-1-((4-fluoro-2-hydroxyphenyl)amino)-3-methyl-1-oxopentan-2-yl)-5-hydroxybenzamide (1g):



Prepared by the general procedure for step C from **S2g** (550 mg, 1.4 mmol), purified by recrystallization and isolated as a white solid (483 mg, 1.3 mmol, 94%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.65 (dd, *J* = 8.8, 6.1 Hz, 1H), 7.15 (dd, *J* = 5.9, 2.9 Hz, 1H), 7.05 (dd, *J* = 10.5, 9.0 Hz, 1H), 6.91 (ddd, *J* = 8.8, 4.1, 3.2 Hz, 1H), 6.60 (dd, *J* = 10.5, 2.9 Hz, 1H), 6.55 (ddd, *J* = 8.3, 8.3, 2.9 Hz), 4.64 (d, *J* = 6.4 Hz, 1H), 2.08-2.01 (m, 1H), 1.71-1.65 (m, 1H), 1.35-1.29 (m, 1H), 1.06 (d, *J* = 6.9 Hz), 0.98 (t, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 171.2, 166.6 (*J* = 2.2 Hz), 161.9 (d, *J* = 240.6 Hz), 155.2 (d, *J* = 2.2 Hz), 155.1 (d, *J* = 237.7 Hz), 151.7 (d, *J* = 10.9 Hz), 125.2 (d, *J* = 10.2 Hz), 123.7 (d, *J* = 15.3 Hz), 122.9 (d, *J* = 2.9 Hz), 120.7 (d, *J* = 8.8 Hz), 117.9 (d, *J* = 24.8 Hz), 117.0 (d, *J* = 2.7 Hz), 106.5 (d, *J* = 22.6 Hz), 104.0 (d, *J* = 25.5 Hz), 60.3, 38.5, 26.1, 16.0, 11.5; ^{19}F NMR (376 MHz, CD_3OD) δ −118.0, −128.3; IR (thin film) *ν* 3269, 1658, 1642, 1547, 1528, 1501, 1434, 1191, 770 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}F_2N_2O_4$ *m*/*z* 379.1464 $[M+H]^+$, found 379.1461; $[\alpha]_D^{25}$ −6.4 (*c* 1.03, CH_3OH)

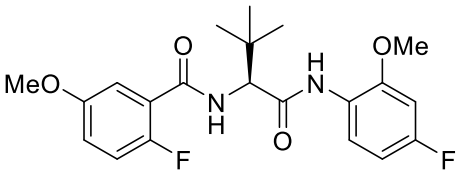
***tert*-Butyl (*S*)-(1-((4-fluoro-2-methoxyphenyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (S1h):**



Prepared by the general procedure for step A (HATU was used as a condensation reagent) from (*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-dimethylbutanoic acid (819 mg, 3.5 mmol) and isolated as an orange oil (1.23 g, 3.5 mmol, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.8, 6.1 Hz, 1H), 8.05 (brs, 1H), 6.68-6.60 (m, 2H), 5.11 (brs, 1H), 4.05 (brs, 1H), 3.86 (s, 3H), 2.27-2.22 (m, 1H), 1.46 (s, 9H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 159.5 (d, *J* = 242.1 Hz), 156.0, 149.4 (d, *J* = 9.5 Hz), 123.4, 120.9 (d, *J* = 8.8 Hz), 106.9 (d, *J* = 21.1 Hz), 98.9 (d, *J* = 27.0 Hz), 80.2,

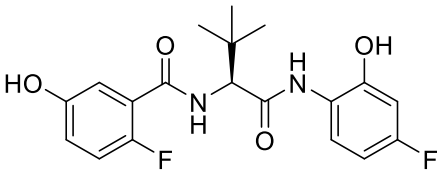
61.0, 56.1, 31.1, 28.5, 19.5, 17.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.1; IR (thin film) *ν* 2969, 1702, 1665, 1608, 1540, 1291, 1170, 1152, 1035, 1011 cm^{-1}; HRMS (ESI) calcd. for $C_{17}H_{26}FN_2O_4$ *m*/*z* 341.1871 $[M+H]^+$, found 341.1870; $[\alpha]_D^{25}$ −25.6 (*c* 1.07, $CHCl_3$)

(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-methoxyphenyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-5-methoxybenzamide (S2h):



Prepared by the general procedure for step B from **S1h** (1.07 mg, 3.0 mmol) and isolated as a white solid (1.08 g, 2.7 mmol, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.6, 6.1 Hz, 1H), 7.86 (brs, 1H), 7.55-7.50 (m, 2H), 7.07 (dd, *J* = 10.8, 8.8 Hz, 1H), 7.00 (ddd, *J* = 9.1, 4.2, 3.4 Hz, 1H), 6.67-6.61 (m, 2H), 4.61 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 1.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 163.3 (d, *J* = 3.6 Hz), 159.6 (d, *J* = 242.1 Hz), 156.2 (d, *J* = 1.5 Hz), 155.4 (d, *J* = 239.2 Hz), 139.4 (d, *J* = 10.2 Hz), 123.2 (d, *J* = 2.9 Hz), 121.1 (d, *J* = 13.1 Hz), 121.0 (d, *J* = 9.4 Hz), 120.3 (d, *J* = 8.7 Hz), 117.3 (d, *J* = 27.0 Hz), 106.9 (d, *J* = 21.9 Hz), 98.9 (d, *J* = 27.0 Hz), 62.5, 56.2, 56.1, 35.4, 26.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.8, −123.4; IR (thin film) *ν* 2963, 1653, 1615, 1524, 1492, 1415, 1280, 1193, 1034, 951 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{25}O_4N_2F_2$ *m*/*z* 407.1777 $[M+H]^+$, found 407.1768; $[\alpha]_D^{25}$ 11.3 (*c* 0.81, $CHCl_3$)

(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-hydroxyphenyl)amino)-3,3-dimethyl-1-oxobutan-2-yl)-5-hydroxybenzamide (1h):

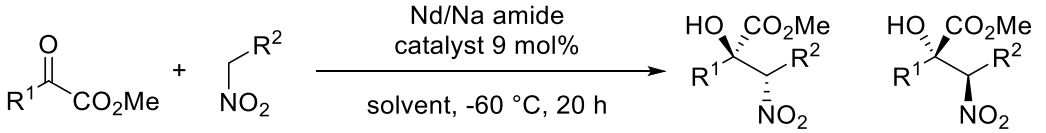


Prepared by the general procedure for step C from **S2h** (1.00 g, 2.5 mmol), purified by reslurry and isolated as a white solid (468 mg, 1.2 mmol, 46%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.56 (dd, *J* = 8.8, 6.4 Hz, 1H), 7.22 (dd, *J* = 6.1, 3.2 Hz, 1H), 7.07 (dd, *J* = 11.0, 9.0 Hz, 1H), 6.93 (ddd, *J* = 9.0, 4.2, 3.2 Hz, 1H), 6.61 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.56 (ddd, *J* = 8.3, 8.3, 2.7 Hz, 1H), 4.71 (s, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.4, 166.0 (d, *J* = 2.9 Hz), 162.2 (d, *J* = 241.3 Hz), 155.4 (d, *J* = 237.7 Hz), 155.3 (d, *J* = 1.5 Hz), 152.2 (d, *J* = 10.9 Hz), 125.9 (d, *J* = 10.2 Hz), 123.3 (d, *J* = 13.9 Hz), 122.7 (d, *J* = 2.9 Hz), 121.0 (d, *J* = 8.7 Hz), 118.0 (d, J = 25.5), 117.3 (d, *J* = 2.2 Hz), 106.7 (d, *J* = 21.9 Hz), 104.2 (d, *J* = 25.5 Hz), 63.0, 36.0, 27.7; ^{19}F NMR (376 MHz, CD_3OD) δ −117.7, −128.2; IR (thin film) *ν* 3267, 1658, 1643, 1547, 1528, 1502, 1222, 1190, 974, 770 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{21}F_2N_2O_4$ *m*/*z* 379.1464 $[M+H]^+$, found 379.1461; $[\alpha]_D^{25}$ 1.6 (*c* 1.02, CH_3OH)

C. Preparation of catalyst for anti-selective catalytic asymmetric nitroaldol reaction

A flame-dried test tube (20 mL) was charged with $NdCl_3 \bullet 6H_2O$ (8.6 mg, 0.024 mmol) and amide based ligand **1a-j** (0.024 mmol), and dried under vacuum at room temperature at least for 5 min. Ar was backfilled (evacuation/backfill was repeated 5 times) to the test tube, then THF (600 μL) was added at room temperature. After stirring the resulting slightly cloudy suspension at 60 °C for 30 min, 2.0 M NaO^tBu/THF (72 μL, 0.144 mmol) was added slowly at the same temperature. After stirring the resulting mixture at 60 °C for 1 h (white precipitate appeared), the mixture was cooled to room temperature and nitroethane (172 μL, 2.4 mmol) was added. Self-assembly of Nd/Na catalyst initiated in a few minutes and the resulting mixture was stirred at room temperature for 12 h to give a thick white suspension. The whole suspension was transferred to an Eppendorf tube with THF washing (0.5 mL x 2). The tube was centrifuged at ca. 10,000 rpm for 30 sec. The supernatant was decanted and THF (1.6 mL) was added. The tube was agitated using a vortex mixer for 30 sec and centrifuged again, then the supernatant was decanted (washing process). This washing process was repeated again. The resulting precipitate was agitated with reaction solvent (1.6 mL) and a part of resulting suspension (0.015 mmol/1000 μL) was used for *anti*-selective catalytic asymmetric nitroaldol reaction. (Note: THF and nitroethane were essential for formation of the heterogeneous catalyst. Self-assembly did not proceed well with a solvent other than THF nor a nitroalkane other than nitroethane.)

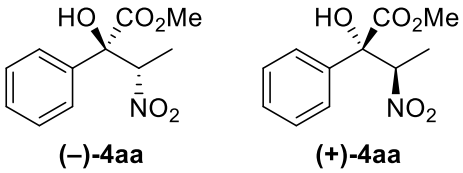
D. General procedure for anti-selective catalytic asymmetric nitroaldol reaction.



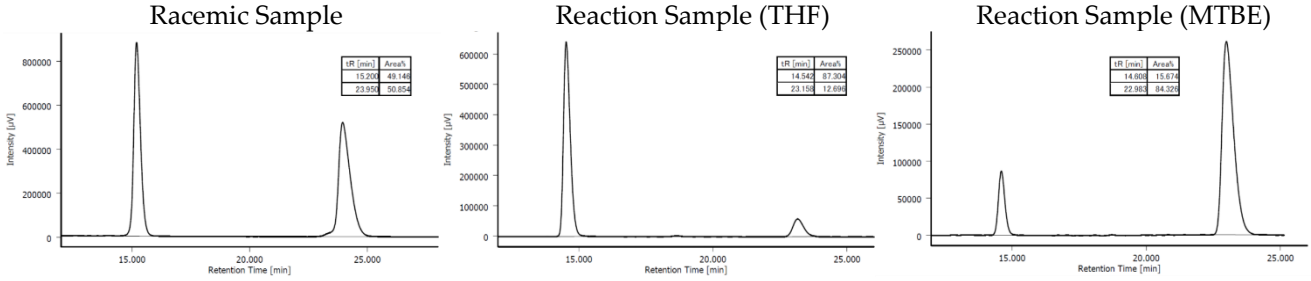
A flame-dried 20 mL test tube was charged with a reaction solvent (480 μL) and catalyst suspension prepared in above section (720 μL, 0.0108 mmol, 9 mol%). After adding nitroalkane (1.2 mmol, 10 eq.) at room temperature, the mixture was cooled to -60 °C and then α-keto ester in reaction solvent (146 μL, 0.12 mmol) was added dropwise for 1 min. After stirring the reaction mixture at the same temperature for 20 h, 0.2 M AcOH/THF (500 μL) was added slowly and warmed to room temperature. H_2O (1 mL) was added and the resulting mixture was extracted with EtOAc (2 mL). The organic layer was dried over Na_2SO_4. After removal of volatiles under reduced pressure, the resulting residue was analyzed by ^{1}H NMR to determine diastereomeric ratio of product. The crude product was purified by silica gel column chromatography (EtOAc/*n*-hexane) to give a product as a single diastereomer. Enantiomeric excess was determined by chiral HPLC analysis.

E. Characterizations of Nitroaldol Products.

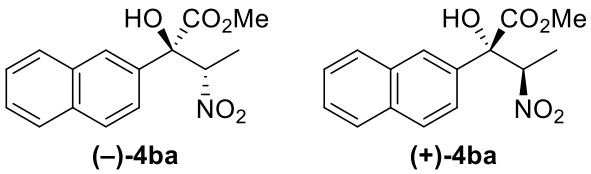
Methyl (2*R*,3*S*)-2-hydroxy-3-nitro-2-phenylbutanoate ((−)-4aa)
Methyl (2*S*,3*R*)-2-hydroxy-3-nitro-2-phenylbutanoate ((+)-4aa):



4aa *is known compounds.*[3]
White solid; 27.3 mg (95%, reaction in THF), 25.7 mg (90%, reaction in MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.63 (m, 2H), 7.43-7.34 (m, 3H), 5.35 (q, *J* = 6.8 Hz, 1H), 4.10 (s, 1H), 3.86 (s, 3H), 1.38 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 136.6, 128.9, 128.9, 125.5, 87.2, 78.7, 54.0, 13.1; $[\alpha]_D^{25}$ 36.7 (*c* 1.04, $CHCl_3$, 75% ee, Reaction Sample (THF), (2*S*,3*R*) isomer major), $[\alpha]_D^{25}$ -35.0 (*c* 0.91, $CHCl_3$, 70% ee, Reaction Sample (MTBE), (2*R*,3*S*) isomer major); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 15.2 min (2*S*,3*R*), 24.0 min (2*R*,3*S*):

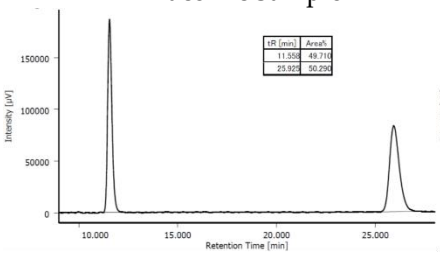


Methyl (2R,3S)-2-hydroxy-2-(naphthalen-2-yl)-3-nitrobutanoate ((−)-4ba)
Methyl (2S,3R)-2-hydroxy-2-(naphthalen-2-yl)-3-nitrobutanoate ((+)-4ba):

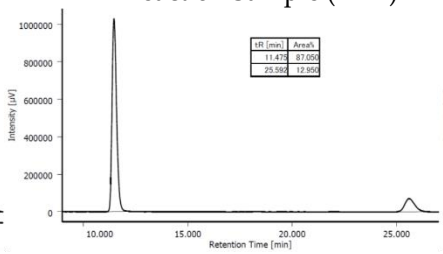


4ba *is known compounds.*[3]
White solid; 27.8 mg (80%, reaction in THF), 31.8 mg (92%, reaction in MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 1.7 Hz, 1H), 7.90-7.84 (m, 3H), 7.67 (dd, *J* = 2.0, 8.6 Hz, 1H), 7.55-7.51 (m, 2H), 5.49 (q, *J* = 7.1 Hz, 1H), 4.24 (s, 1H), 3.87 (s, 3H), 1.41 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 134.4, 133.8, 133.7, 129.4, 129.2, 128.2, 127.6, 127.4, 126.1, 123.2, 87.7, 79.6, 54.7, 13.8; HPLC analysis: CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 11.6 min (2*S*,3*R*), 25.9 min (2*R*,3*S*):

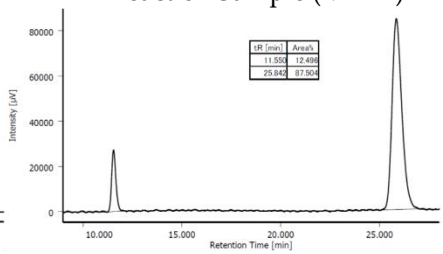
Racemic Sample



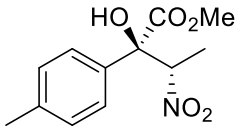
Reaction Sample (THF)



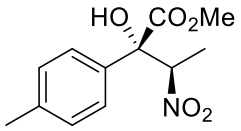
Reaction Sample (MTBE)



Methyl (2*R*,3*S*)-2-hydroxy-3-nitro-2-(*p*-tolyl)butanoate ((−)-4ca)
Methyl (2*S*,3*R*)-2-hydroxy-3-nitro-2-(*p*-tolyl)butanoate ((+)-4ca):



(–)-4ca

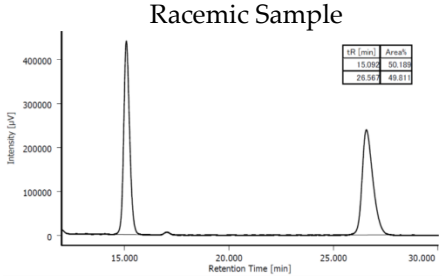


(+)-4ca

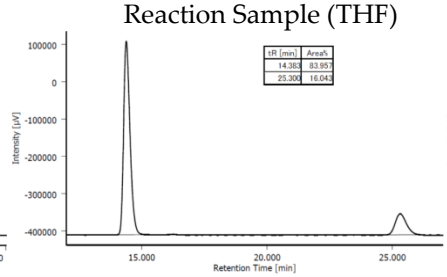
4ca *is known compounds.*[3]

White solid; 27.9 mg (92%, reaction in THF), 28.1 mg (92%, reaction in MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 5.33 (q, *J* = 7.1 Hz, 1H), 4.07 (s, 1H), 3.84 (s, 3H), 2.35 (s, 3H), 1.38 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 139.1, 133.9, 129.9, 125.7, 87.5, 79.0, 54.2, 21.4, 13.4;; HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 15.1 min (2*S*,3*R*), 26.6 min (2*R*,3*S*):

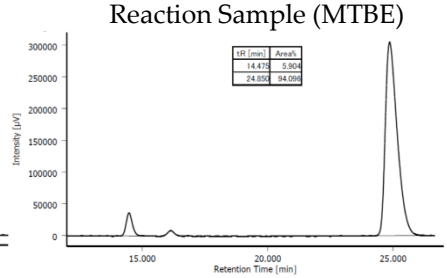
Racemic Sample



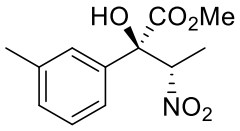
Reaction Sample (THF)



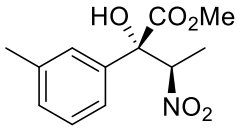
Reaction Sample (MTBE)



Methyl (2*S*,3*R*)-2-hydroxy-3-nitro-2-(*m*-tolyl)butanoate ((−)-4da)
Methyl (2*S*,3*R*)-2-hydroxy-3-nitro-2-(*m*-tolyl)butanoate ((+)-4da):



(–)-4da

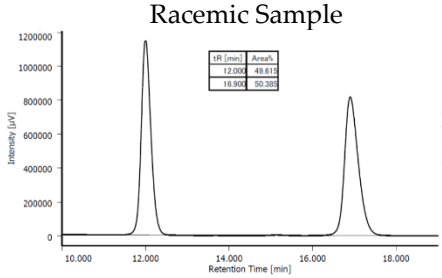


(+)-4da

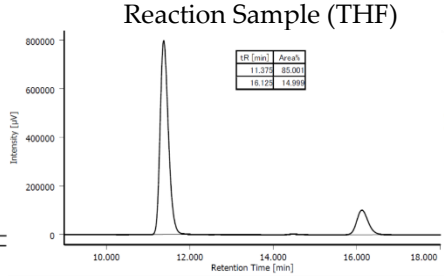
4da *is known compounds.*[3]

White solid; 26.7 mg (88%, reaction in THF), 28.1 mg (92%, reaction in MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.28 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 5.34 (q, *J* = 7.1 Hz, 1H), 4.08 (s, 1H), 3.85 (s, 3H), 2.38 (s, 3H), 1.39 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 139.0, 136.8, 129.9, 129.1, 126.4, 122.9, 87.5, 79.0, 54.2, 22.0, 13.5; HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 12.0 min (2*S*,3*R*), 16.9 min (2*R*,3*S*):

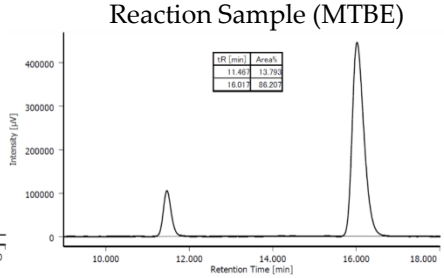
Racemic Sample



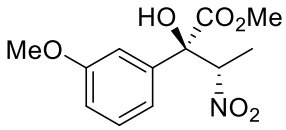
Reaction Sample (THF)



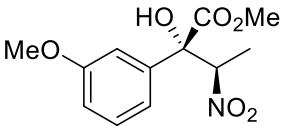
Reaction Sample (MTBE)



Methyl (2*R*,3*S*)-2-hydroxy-2-(3-methoxyphenyl)-3-nitrobutanoate ((−)-4ea)
Methyl (2*S*,3*R*)-2-hydroxy-2-(3-methoxyphenyl)-3-nitrobutanoate ((+)-4ea):



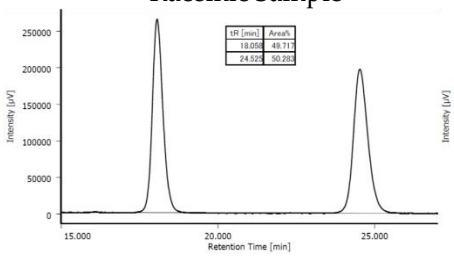
(−)-4ea



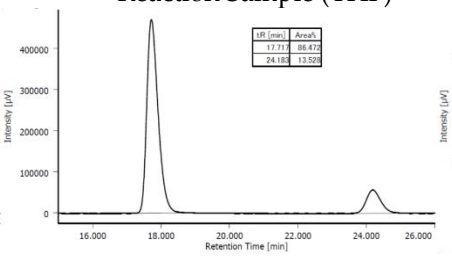
(+)-4ea

4ea *is known compounds.*[3]
White solid; 29.0 mg (90%, reaction in THF), 30.1 mg (93%, reaction in MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.22 (dd, *J* = 2.2, 2.2 Hz, 1H), 7.18 (ddd, *J* = 0.7, 2.2, 8.0 Hz, 1H), 6.89 (ddd, *J* = 0.7, 2.2, 8.0 Hz, 1H), 5.33 (q, *J* = 6.8 Hz, 1H), 4.10 (s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 1.38 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 160.0, 138.2, 129.9, 117.7, 114.1, 111.6, 87.1, 78.6, 55.4, 54.0, 13.1; HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 18.1 min (2*S*,3*R*), 24.5 min (2*R*,3*S*):

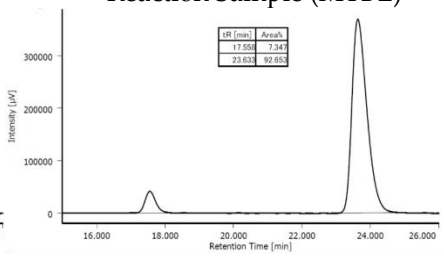
Racemic Sample



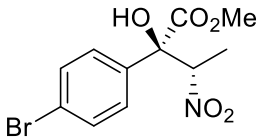
Reaction Sample (THF)



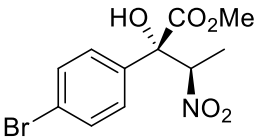
Reaction Sample (MTBE)



Methyl (2*R*,3*S*)-2-(4-bromophenyl)-2-hydroxy-3-nitrobutanoate ((−)-4fa)
Methyl (2*R*,3*S*)-2-(4-bromophenyl)-2-hydroxy-3-nitrobutanoate ((+)-4fa):



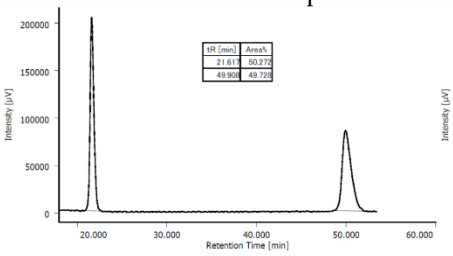
(−)-4fa



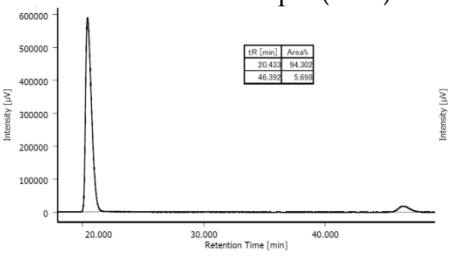
(+)-4fa

4fa *is known compounds.*[3]
White solid; 35.2 mg (92% reaction in THF), 26.0 mg (68%, reaction in MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.50 (m, 4H), 5.30 (q, *J* = 7.1 Hz, 1H), 4.11 (s, 1H), 3.86 (s, 3H), 1.38 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 135.7, 132.1, 127.4, 123.3, 86.9, 78.5, 54.2, 13.0; HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 21.6 min (2*S*,3*R*), 49.9 min (2*R*,3*S*):

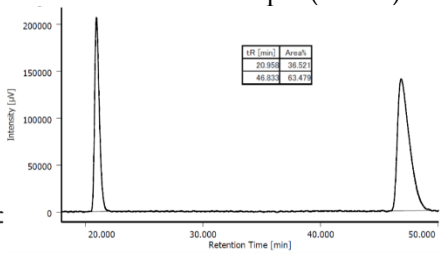
Racemic Sample



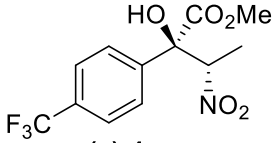
Reaction Sample (THF)



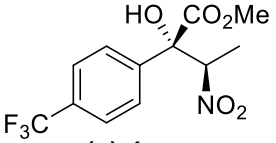
Reaction Sample (MTBE)



Methyl (2*R*,3*S*)-2-hydroxy-3-nitro-2-(4-(trifluoromethyl)phenyl)butanoate ((−)-4ga)
Methyl (2*S*,3*R*)-2-hydroxy-3-nitro-2-(4-(trifluoromethyl)phenyl)butanoate ((+)-4ga):



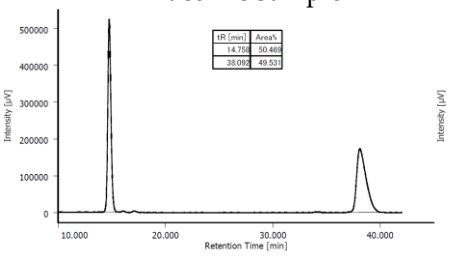
(−)-4ga



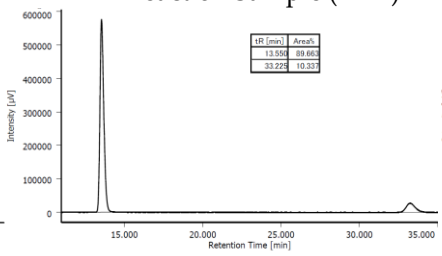
(+)-4ga

4ga *is known compounds.*[3]
White solid; 33.1 mg (90%, reaction in THF), 34.3 mg (93%, reaction in MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 5.36 (q, *J* = 6.8 Hz, 1H), 4.18 (s, 1H), 3.88 (s, 3H), 1.38 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 140.9, 131.6 (q, *J* = 31.8 Hz), 126.5, 126.2 (q, *J* = 3.6 Hz), 124.1 (q, *J* = 270.5 Hz), 87.2, 78.9, 54.6, 13.4; ^{19}F NMR (376 MHz, $CDCl_3$) -62.8; HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 14.8 min (2*S*,3*R*), 38.1 min (2*R*,3*S*):

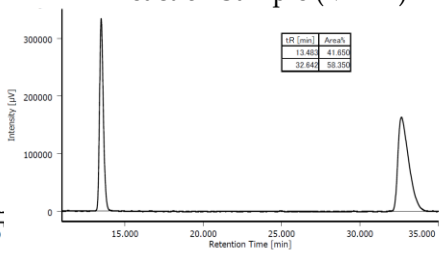
Racemic Sample



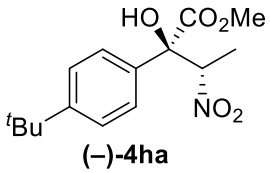
Reaction Sample (THF)



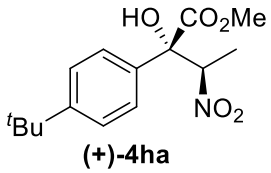
Reaction Sample (MTBE)



Methyl (2*R*,3*S*)-2-(4-(*tert*-butyl)phenyl)-2-hydroxy-3-nitrobutanoate ((−)-4ha)
Methyl (2*S*,3*R*)-2-(4-(*tert*-butyl)phenyl)-2-hydroxy-3-nitrobutanoate ((+)-4ha):



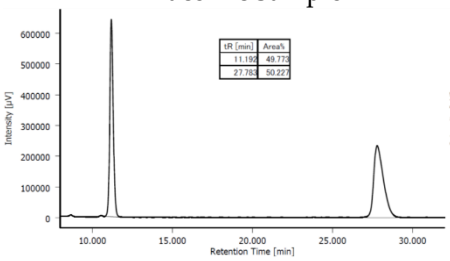
(–)-4ha



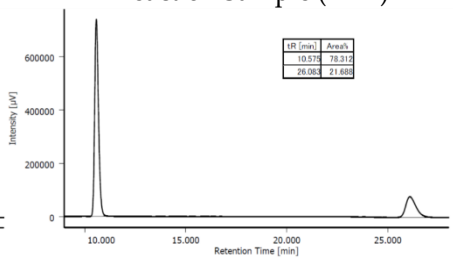
(+)-4ha

4ha *is known compounds.*[3]
White solid; 31.5 mg (89%, reaction in THF), 32.3 mg (91%, reaction in MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (ddd, *J* = 2.2, 2.2, 6.8 Hz, 2H), 7.40 (ddd, *J* = 2.2, 2.2, 6.8 Hz, 2H), 5.34 (q, *J* = 7.1 Hz, 1H), 4.06 (s, 1H), 3.85 (s, 3H), 1.39 (d, *J* = 7.1 Hz, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 152.3, 133.8, 126.1, 125.5, 87.6, 79.0, 54.2, 34.9, 31.6, 13.5; HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 11.2 min (2*S*,3*R*) , 27.8 min (2*R*,3*S*):

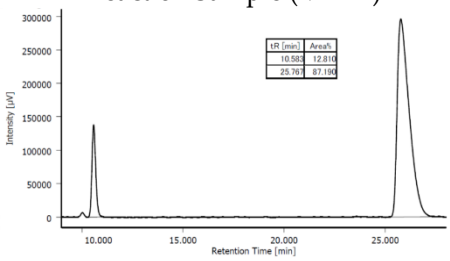
Racemic Sample



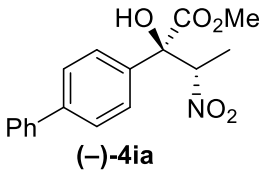
Reaction Sample (THF)



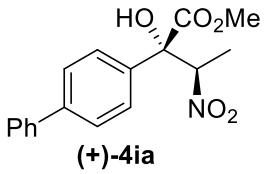
Reaction Sample (MTBE)



Methyl (2*R*,3*S*)-2-([1,1'-biphenyl]-4-yl)-2-hydroxy-3-nitrobutanoate ((−)-4ia)
Methyl (2*S*,3*R*)-2-([1,1'-biphenyl]-4-yl)-2-hydroxy-3-nitrobutanoate ((+)-4ia):



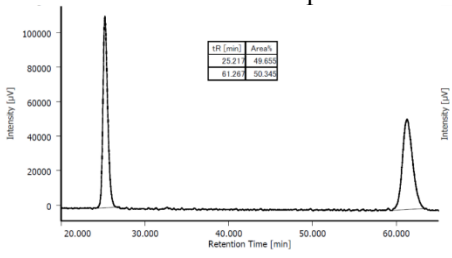
(–)-4ia



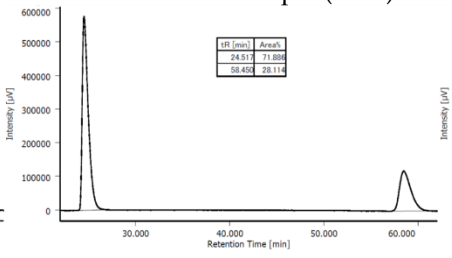
(+)-4ia

4ia *is known compounds.*[3]
White solid; 32.9 mg (87%, reaction in THF), 32.0 mg (85%, reaction in MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.69 (m, 2H), 7.64-7.58 (m, 4H), 7.47-7.44 (m, 2H), 7.39-7.36 (m, 1H), 5.39 (q, *J* = 7.1 Hz, 1H), 4.14 (s, 1H), 3.88 (s, 3H), 1.44 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 142.1, 140.4, 135.8, 129.2, 128.1, 127.9, 127.4, 126.3, 87.5, 79.0, 54.3, 13.5; HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 25.2 min (2*S*,3*R*), 61.3 min (2*R*,3*S*):

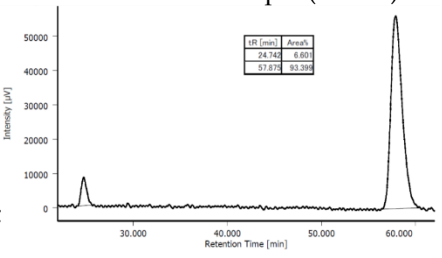
Racemic Sample



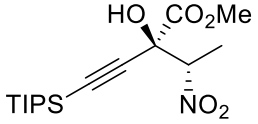
Reaction Sample (THF)



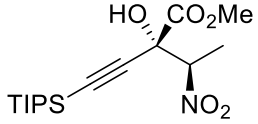
Reaction Sample (MTBE)



Methyl (*R*)-2-hydroxy-2-((*S*)-1-nitroethyl)-4-(triisopropylsilyl)but-3-ynoate ((−)-4ja)
Methyl (*S*)-2-hydroxy-2-((*R*)-1-nitroethyl)-4-(triisopropylsilyl)but-3-ynoate ((+)-4ja):



(−)-4ja

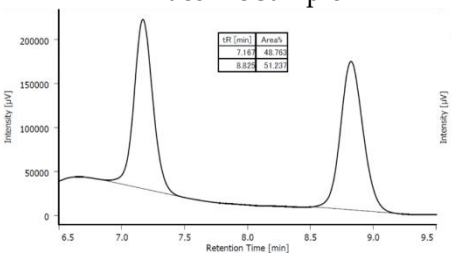


(+)-4ja

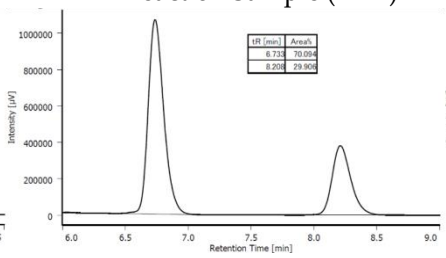
4ja *is known compounds.*[3]

Colorless oil; 28.1 mg (68%, reaction in THF), 39.7 mg (96%, reaction in MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.05 (q, *J* = 7.1 Hz, 1H), 3.92 (s, 3H), 3.84 (s, 1H), 1.85 (d, *J* = 7.1 Hz, 3H), 1.07-1.04 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 101.4, 91.1, 85.9, 72.5, 54.7, 18.8, 13.6, 11.3; HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 7.2 min (2*S*,3*R*), 8.8 min (2*R*,3*S*):

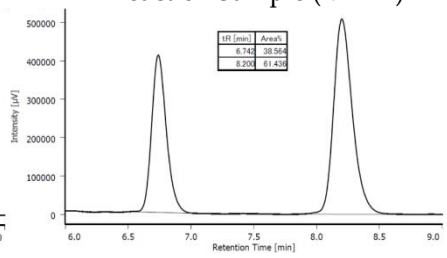
Racemic Sample



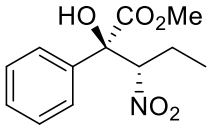
Reaction Sample (THF)



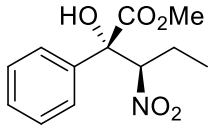
Reaction Sample (MTBE)



Methyl (2*R*,3*S*)-2-hydroxy-3-nitro-2-phenylpentanoate ((−)-4ab)
Methyl (2*S*,3*R*)-2-hydroxy-3-nitro-2-phenylpentanoate ((+)-4ab):



(−)-4ab

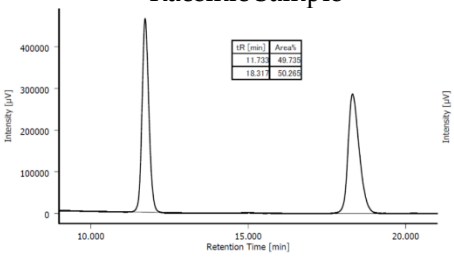


(+)-4ab

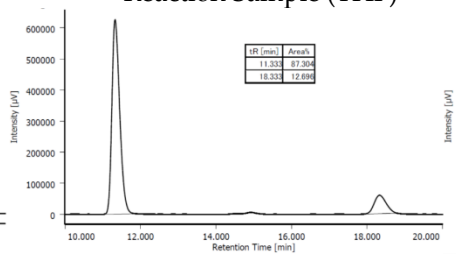
4ab *is known compounds.*[3]

White solid; 24.3 mg (80%, reaction in THF), 26.0 mg (86%, reaction in MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.64 (m, 2H), 7.43-7.34 (m, 3H), 5.16 (dd, *J* = 3.2, 10.3 Hz, 1H), 4.21 (s, 1H), 3.81 (s, 3H), 2.04 (ddq, *J* = 3.2, 7.6, 10.3 Hz, 1H), 1.56 (ddq, *J* = 3.2, 4.4, 7.6 Hz, 1H), 0.90 (dd, *J* = 7.6, 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 136.7, 129.3, 129.2, 125.8, 94.3, 79.6, 54.2, 21.6, 11.3; HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 11.7 min (2*S*,3*R*), 18.3 min (2*R*,3*S*):

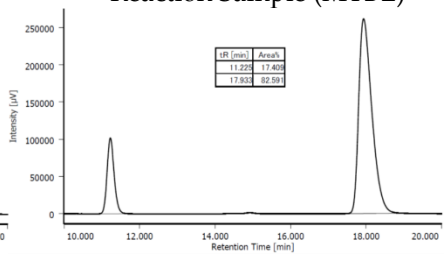
Racemic Sample



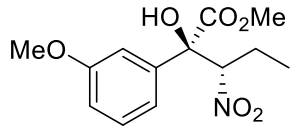
Reaction Sample (THF)



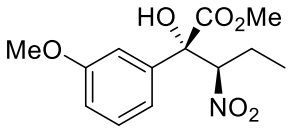
Reaction Sample (MTBE)



Methyl (2*R*,3*S*)-2-hydroxy-2-(3-methoxyphenyl)-3-nitropentanoate ((−)-4eb)
Methyl (2*S*,3*R*)-2-hydroxy-2-(3-methoxyphenyl)-3-nitropentanoate ((+)-4eb):



(−)-4eb

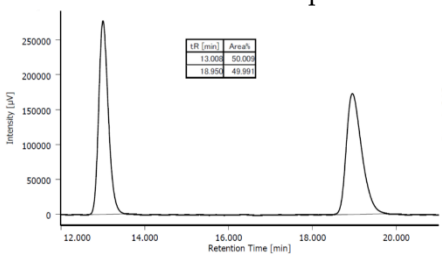


(+)-4eb

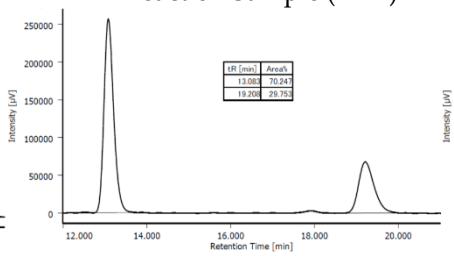
Colorless oil; 25.6 mg (75%, reaction in THF), 29.7 mg (87%, reaction in MTBE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 8.1, 8.1 Hz, 1H), 7.23 (dd, *J* = 2.0, 2.0 Hz, 1H), 7.19 (ddd, *J* = 0.8, 1.7, 7.8 Hz, 1H), 6.89 (ddd, *J* = 1.0, 2.7, 8.3 Hz, 1H), 5.14 (dd, *J* = 3.2, 10.3 Hz), 4.21 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.09-1.98 (m, 1H), 1.63-1.53 (m, 1H), 0.91 (dd, J = 7.3, 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 160.2, 138.1, 130.0, 117.8, 114.4, 111.6, 94.1, 79.4, 55.5, 54.0, 21.4, 11.2; IR (thin film) *ν* 3490, 2956, 1737, 1600, 1551, 1435, 1258, 1155, 1040, 763 cm^{-1}; HRMS (ESI) calcd. for $C_{13}H_{17}O_6NNa$ *m*/*z* 306.0948 [M+Na]$^+$, found 306.0948; $[\alpha]_D^{25}$ 15.4 (*c* 1.11, $CHCl_3$, 40% ee, Reaction Sample (THF), (2*S*,3*R*) isomer major), $[\alpha]_D^{25}$ -28.6 (*c* 1.46, $CHCl_3$, 80% ee, Reaction Sample (MTBE), (2*R*,3*S*) isomer major); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate =

1.0 mL/min, detection at 210 nm, flow rate = 1.0 mL/min, t_R = 13.0 min (2*S*,3*R*), 18.9 min (2*R*,3*S*):

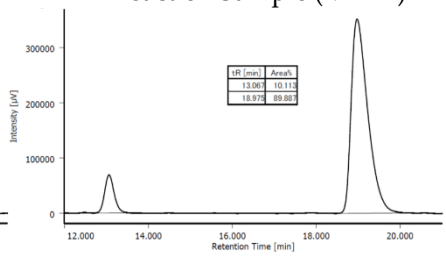
Racemic Sample



Reaction Sample (THF)



Reaction Sample (MTBE)



F. References for Experimental Section of Chapter 3

1 Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176.

2 Kurono, N.; Uemura, M.; Ohkuma, T. *Eur. J. Org. Chem.* **2010**, *8*, 1455.

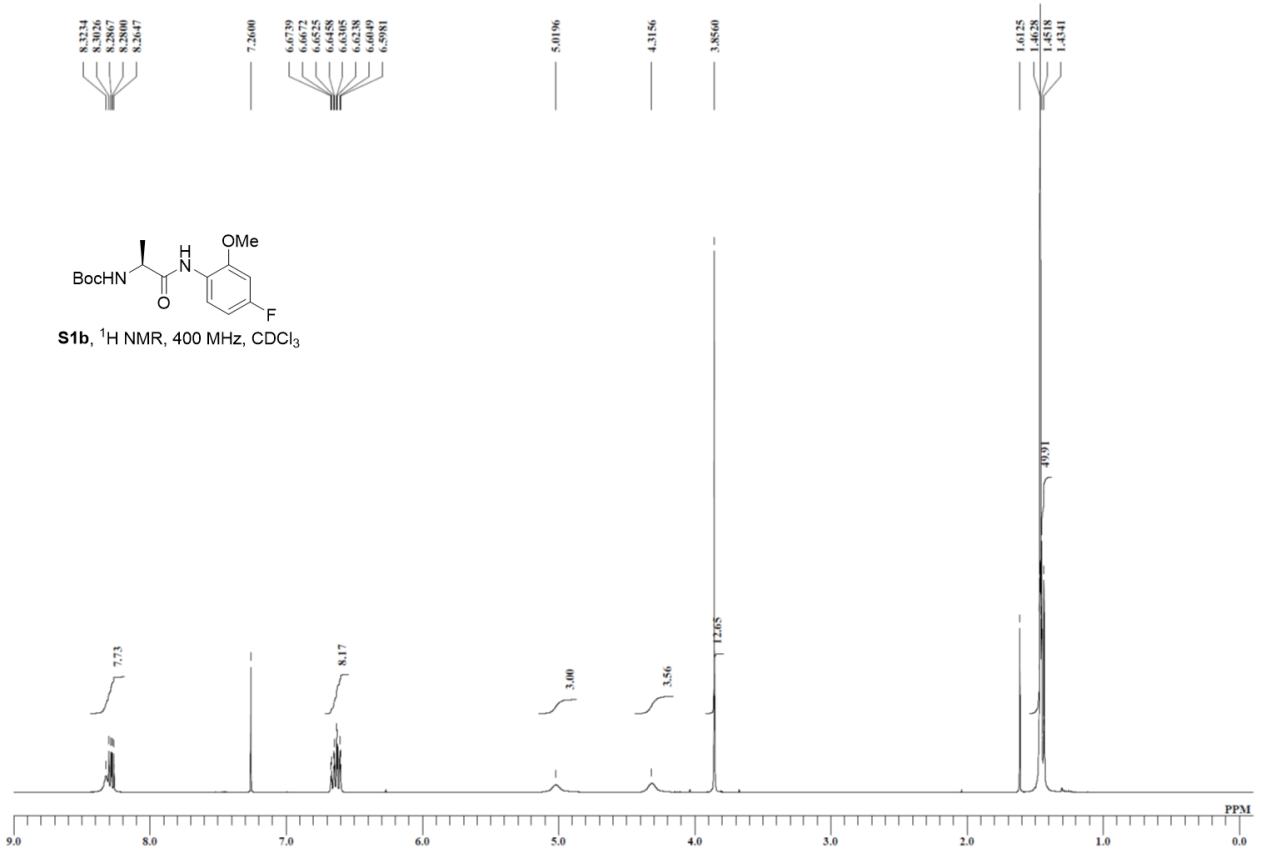
3 Karasawa, T.; Oriez, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2018**, *140*, 12290.

4 Zhuang, J.; Wang, C.; Xie, F.; Zhang, W. *Tetrahedron* **2009**, *65*, 9797.

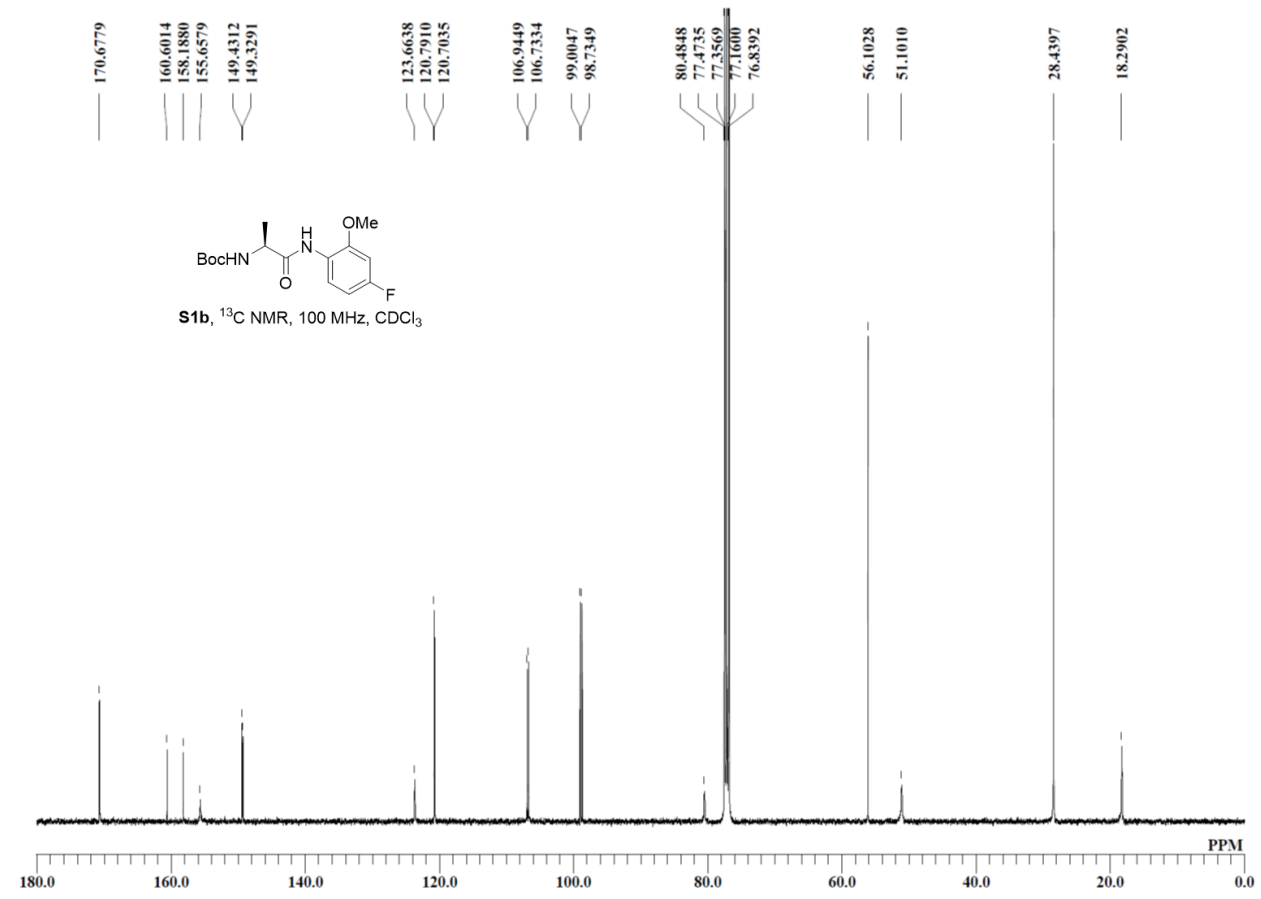
5 Nitabaru, T.; Nojiri, A.; Kobayashi, M.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 13860.

6 Nonoyama, A.; Kumagai, N.; Shibasaki, M. *Tetrahedron* **2017**, *73*, 1517.

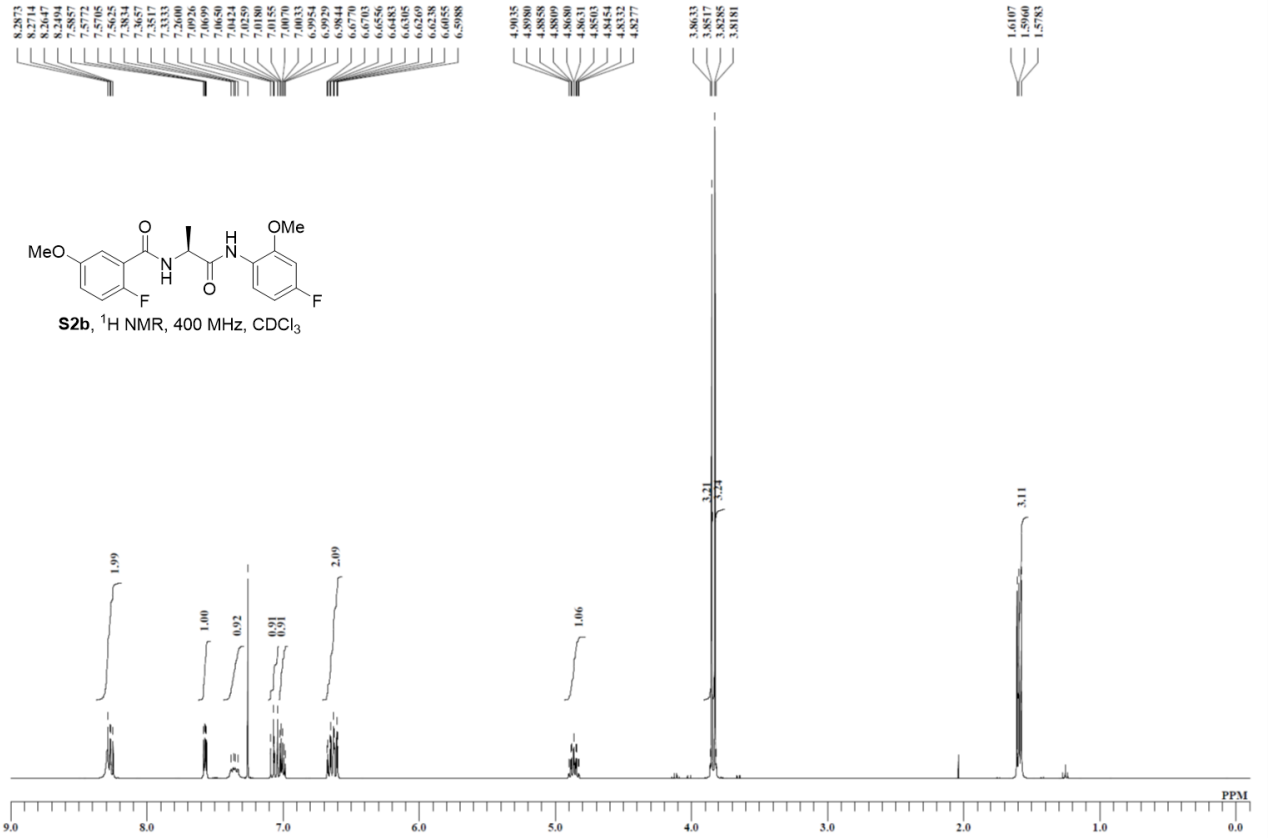
G. ^{1}H and ^{13}C NMR Spectra.



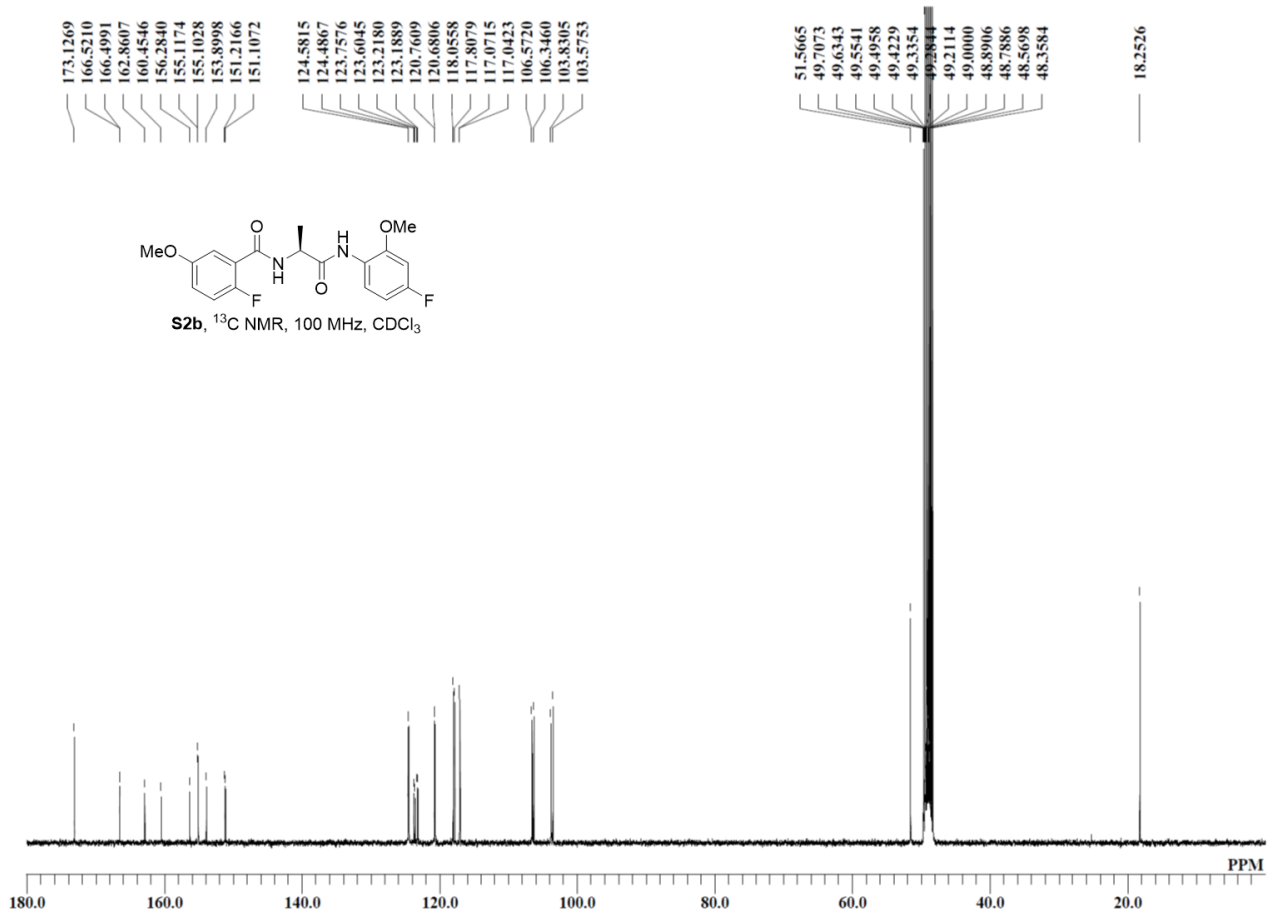
S1b, ^{1}H NMR, 400 MHz, $CDCl_3$



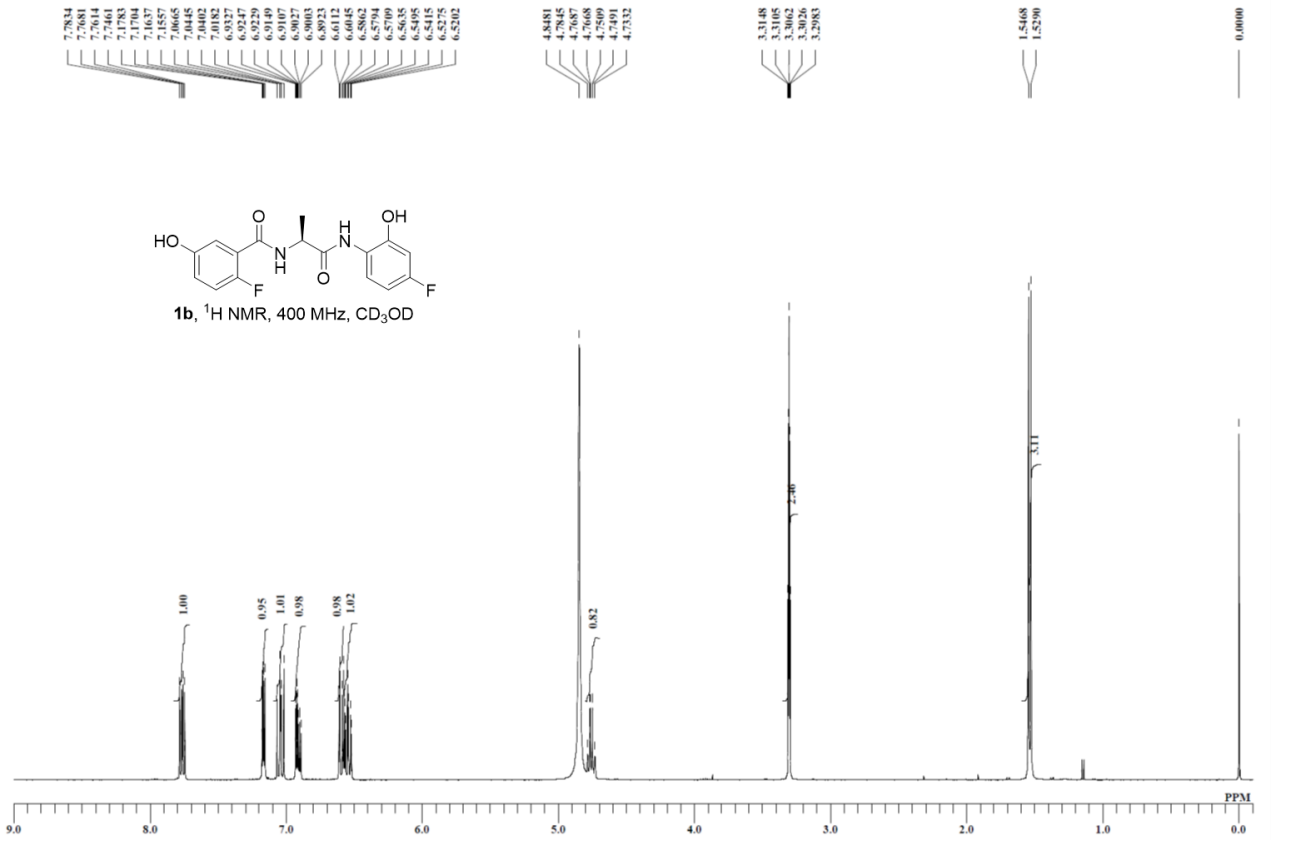
S1b, ^{13}C NMR, 100 MHz, $CDCl_3$



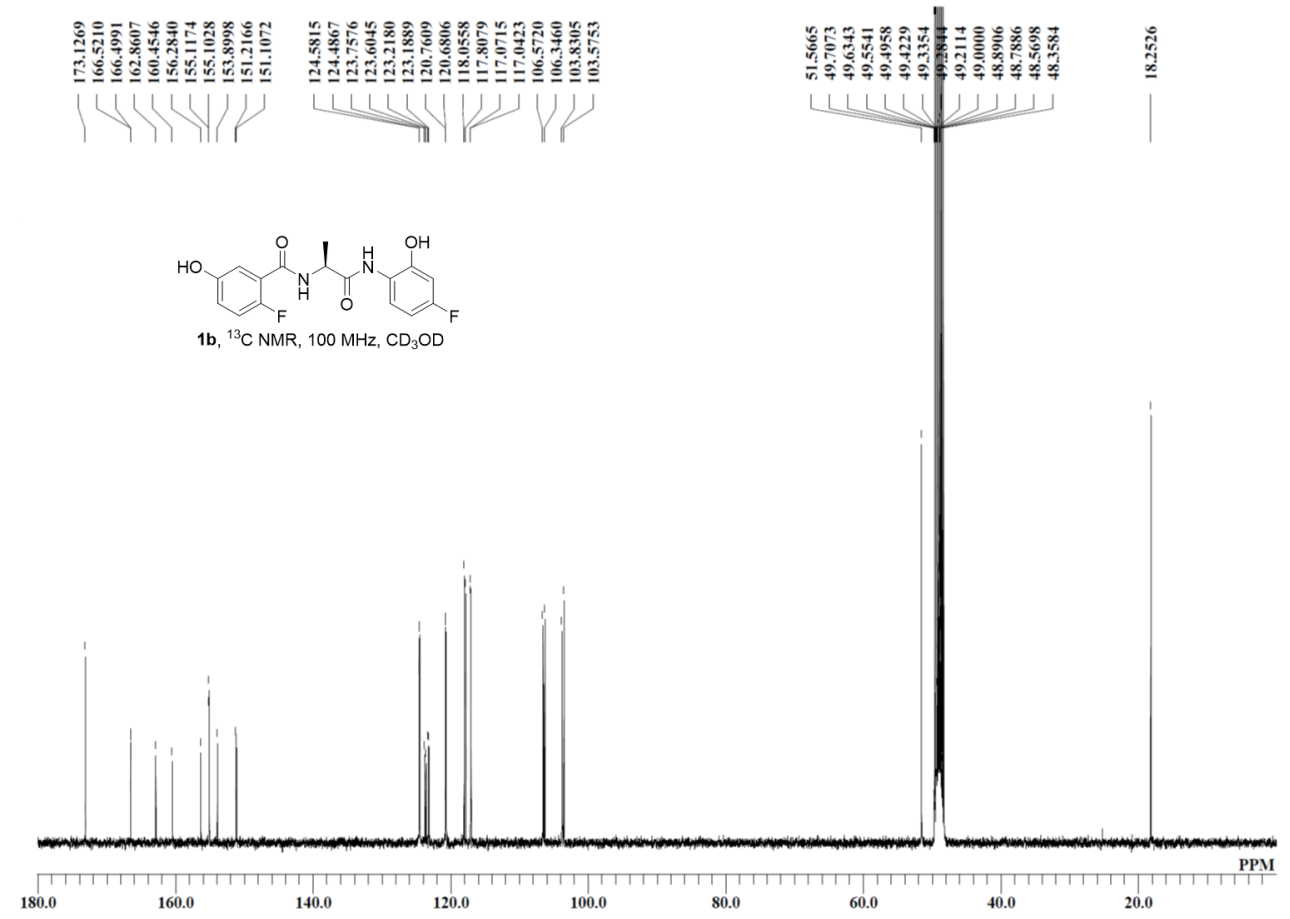
S2b, ^{1}H NMR, 400 MHz, $CDCl_3$



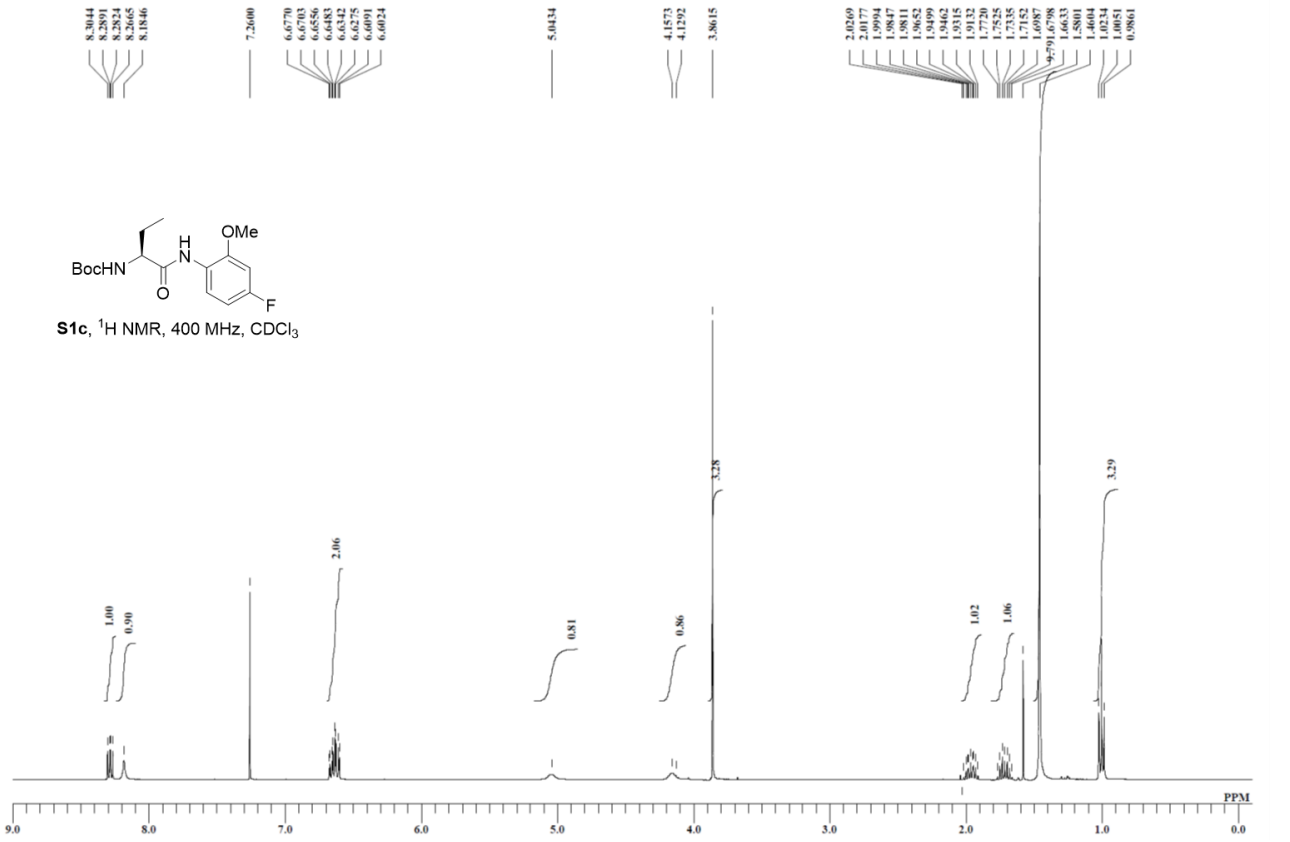
S2b, ^{13}C NMR, 100 MHz, $CDCl_3$



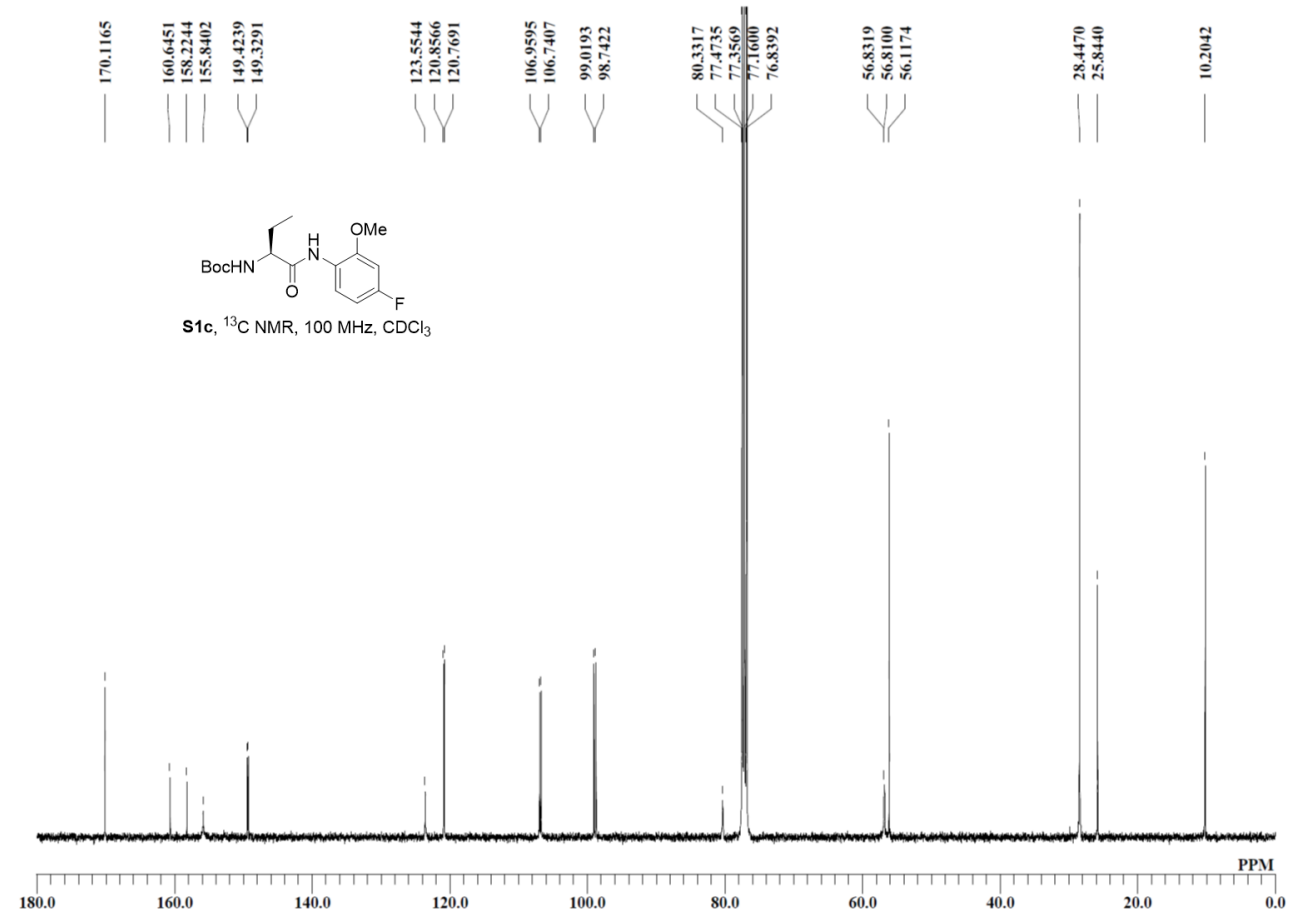
1b, ^{1}H NMR, 400 MHz, CD_3OD



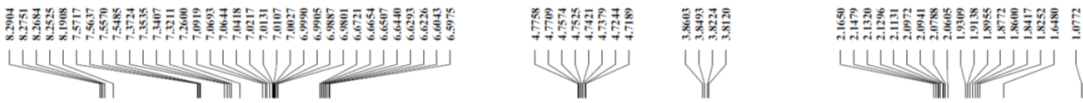
1b, ^{13}C NMR, 100 MHz, CD_3OD

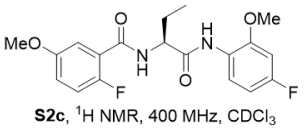


S1c, ^{1}H NMR, 400 MHz, $CDCl_3$

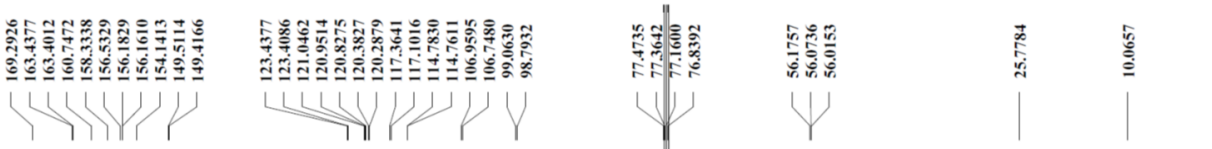


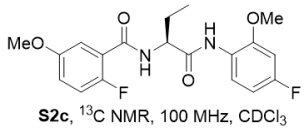
S1c, ^{13}C NMR, 100 MHz, $CDCl_3$



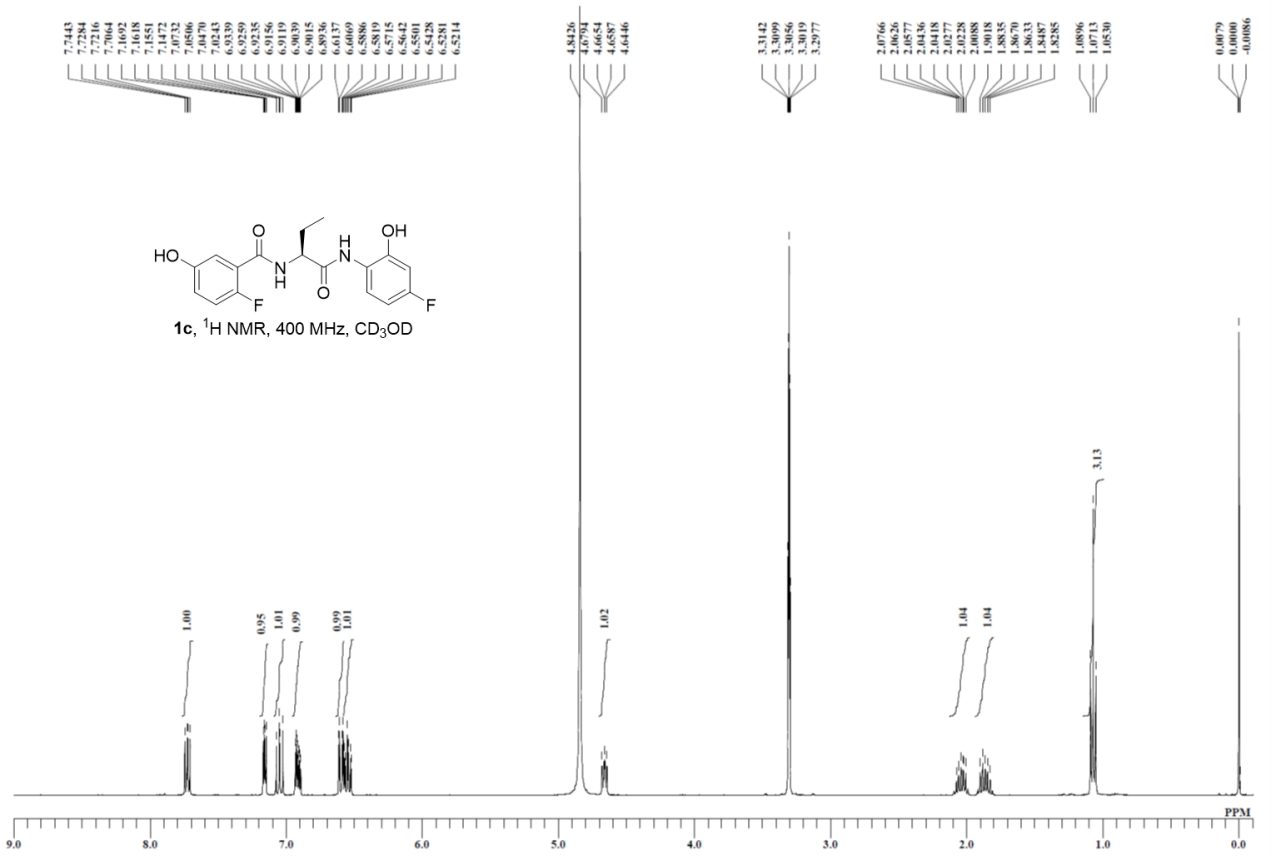


S2c, ^{1}H NMR, 400 MHz, $CDCl_3$

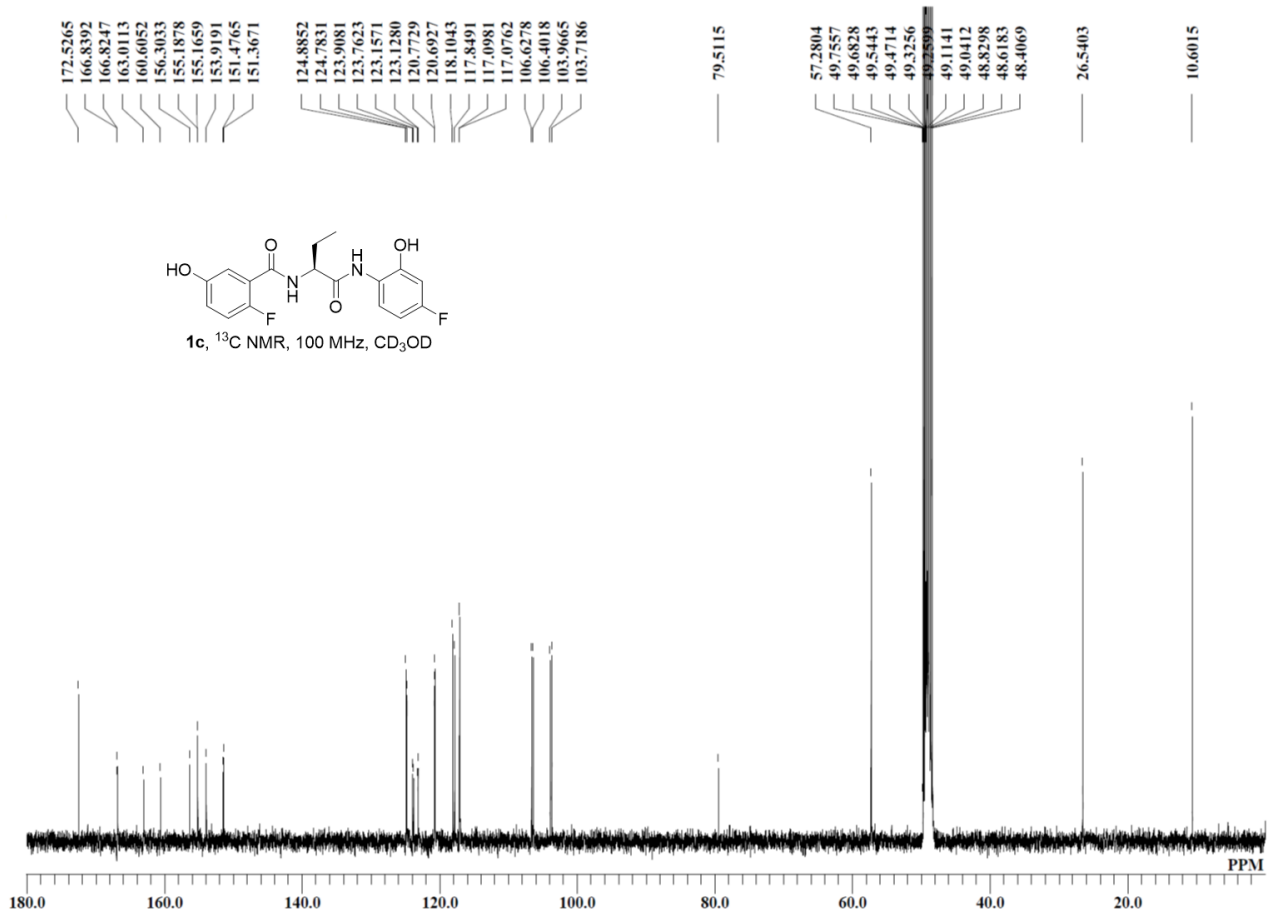




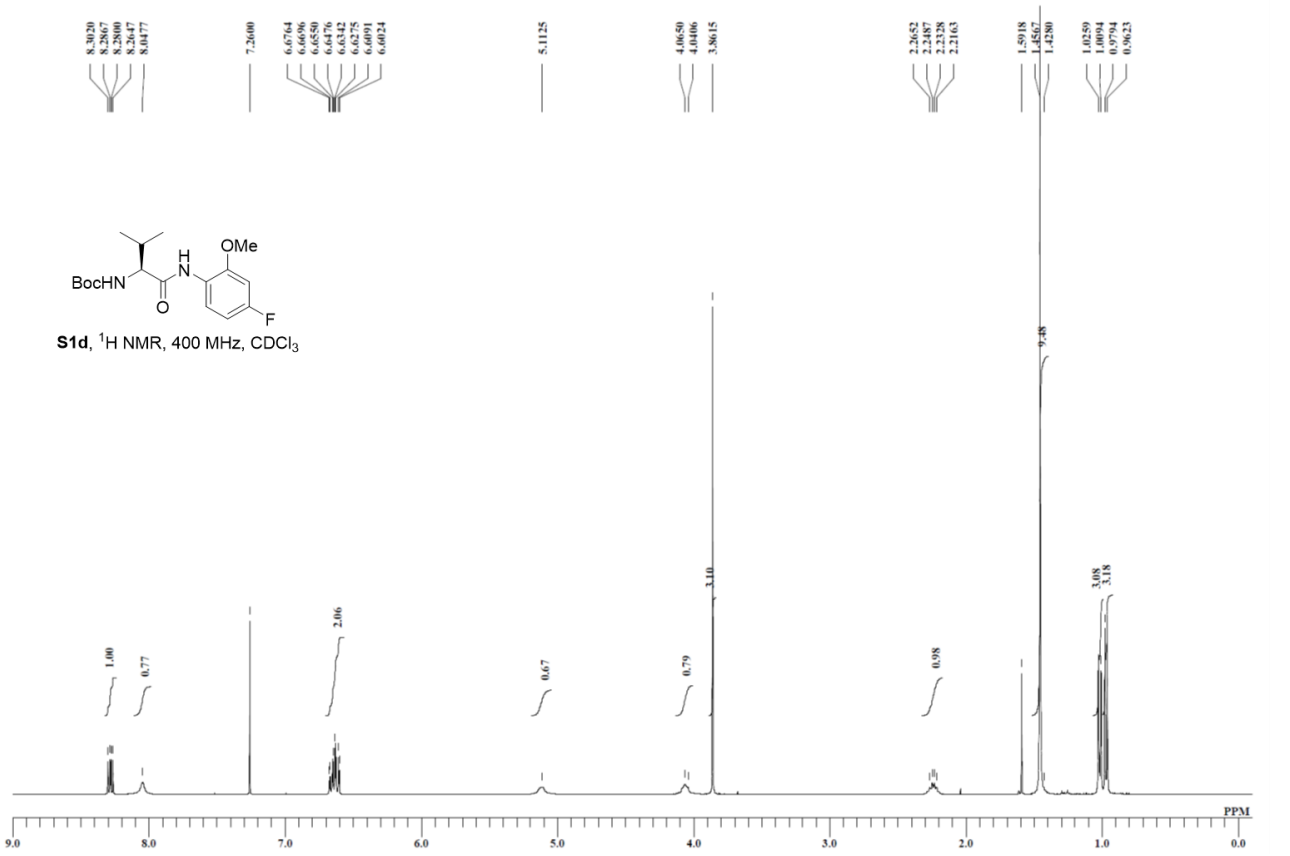
S2c, ^{13}C NMR, 100 MHz, $CDCl_3$



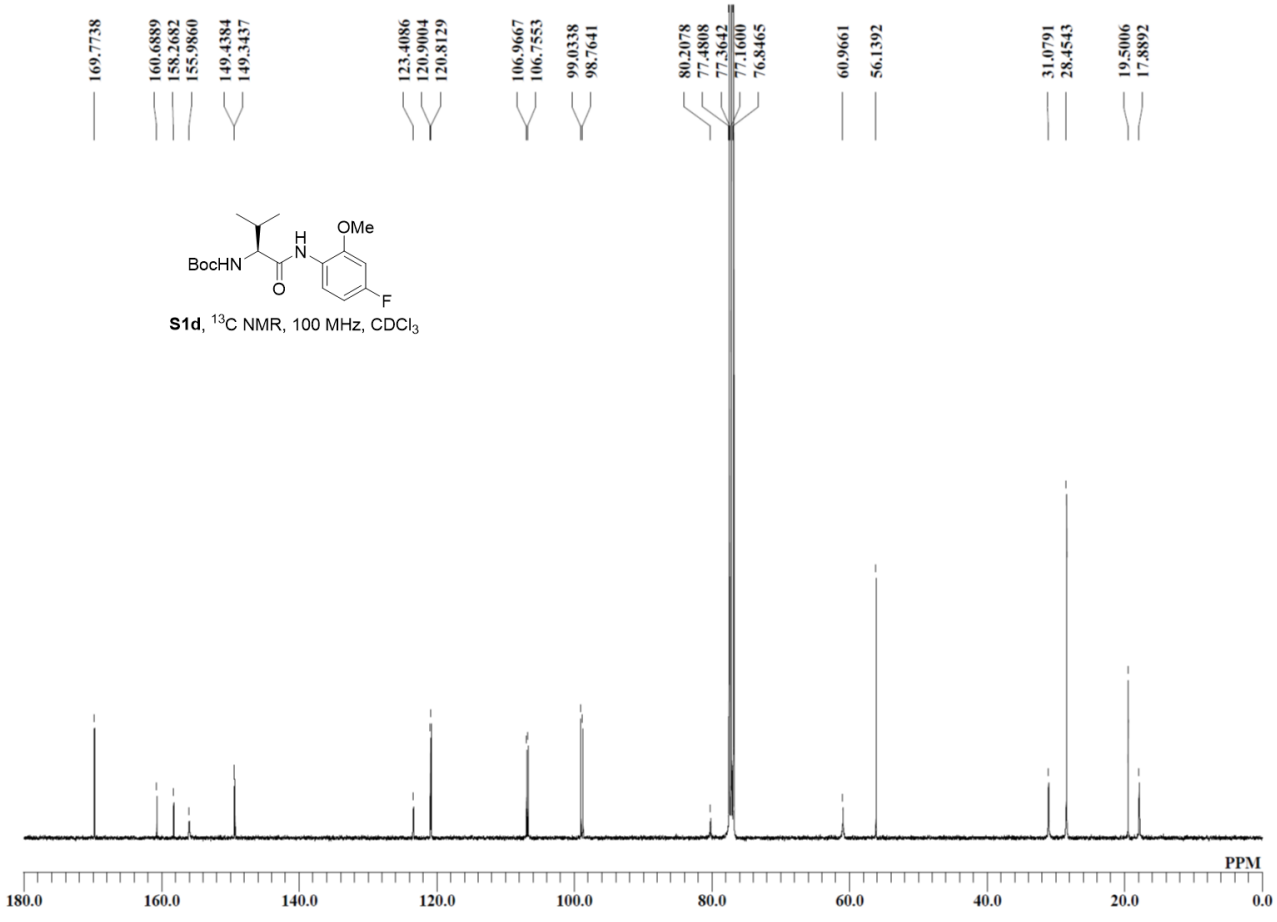
1c, ^{1}H NMR, 400 MHz, CD_3OD



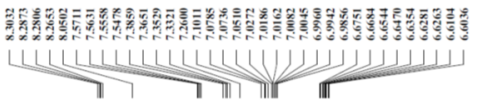
1c, ^{13}C NMR, 100 MHz, CD_3OD

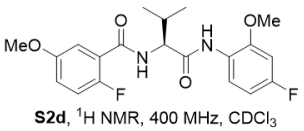


S1d, ^{1}H NMR, 400 MHz, $CDCl_3$

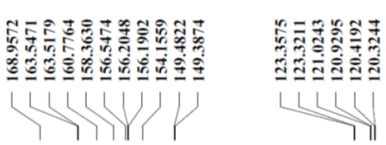


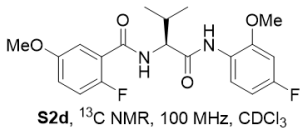
S1d, ^{13}C NMR, 100 MHz, $CDCl_3$



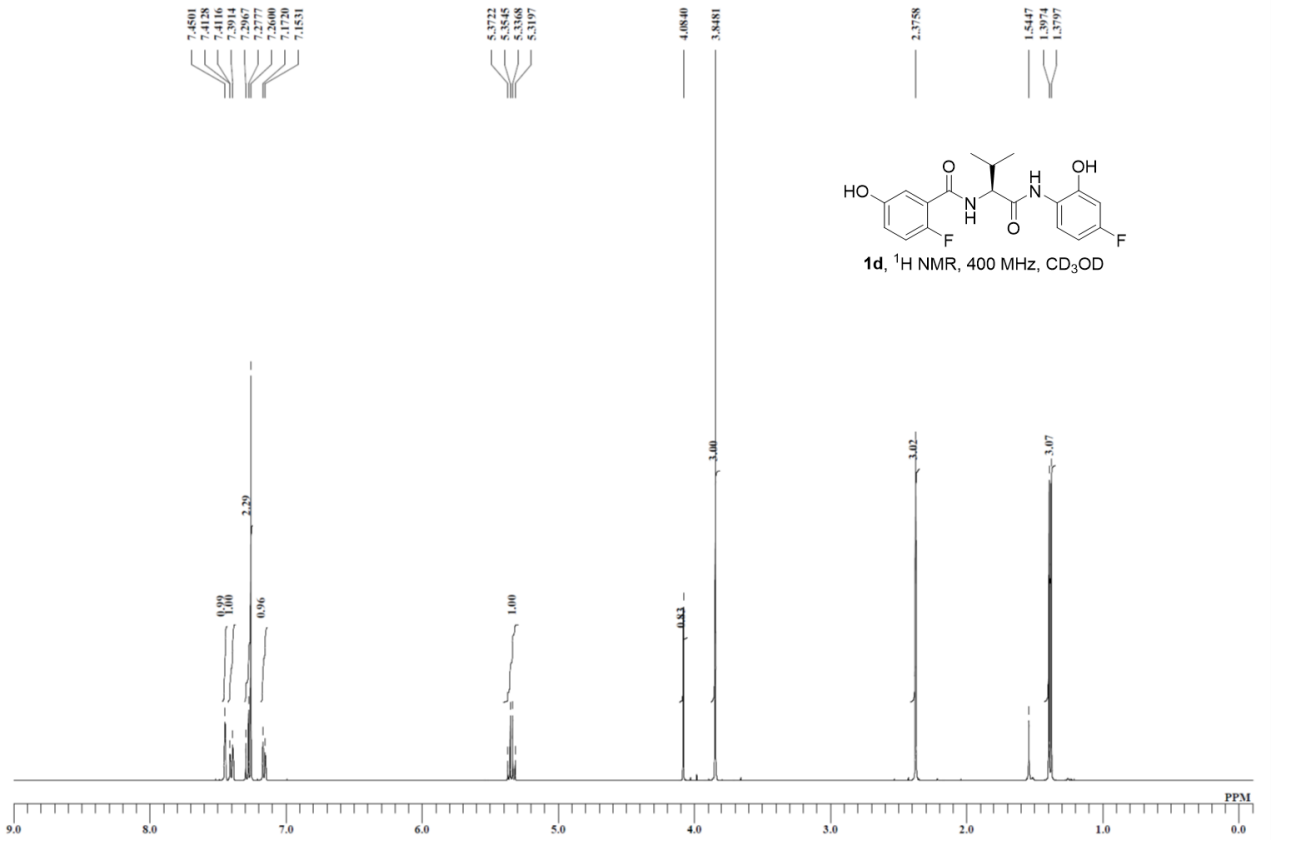


S2d, ^{1}H NMR, 400 MHz, $CDCl_3$

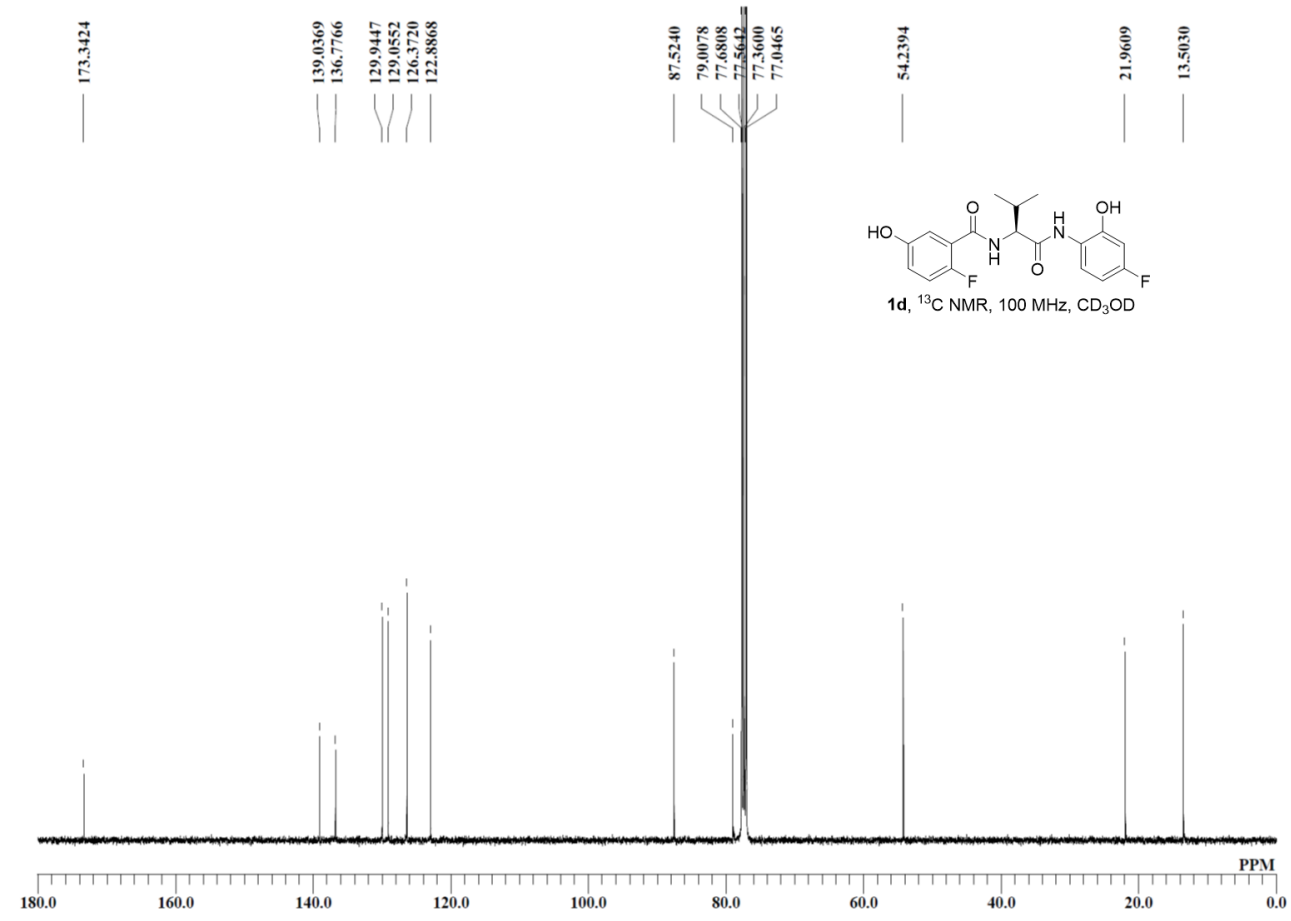




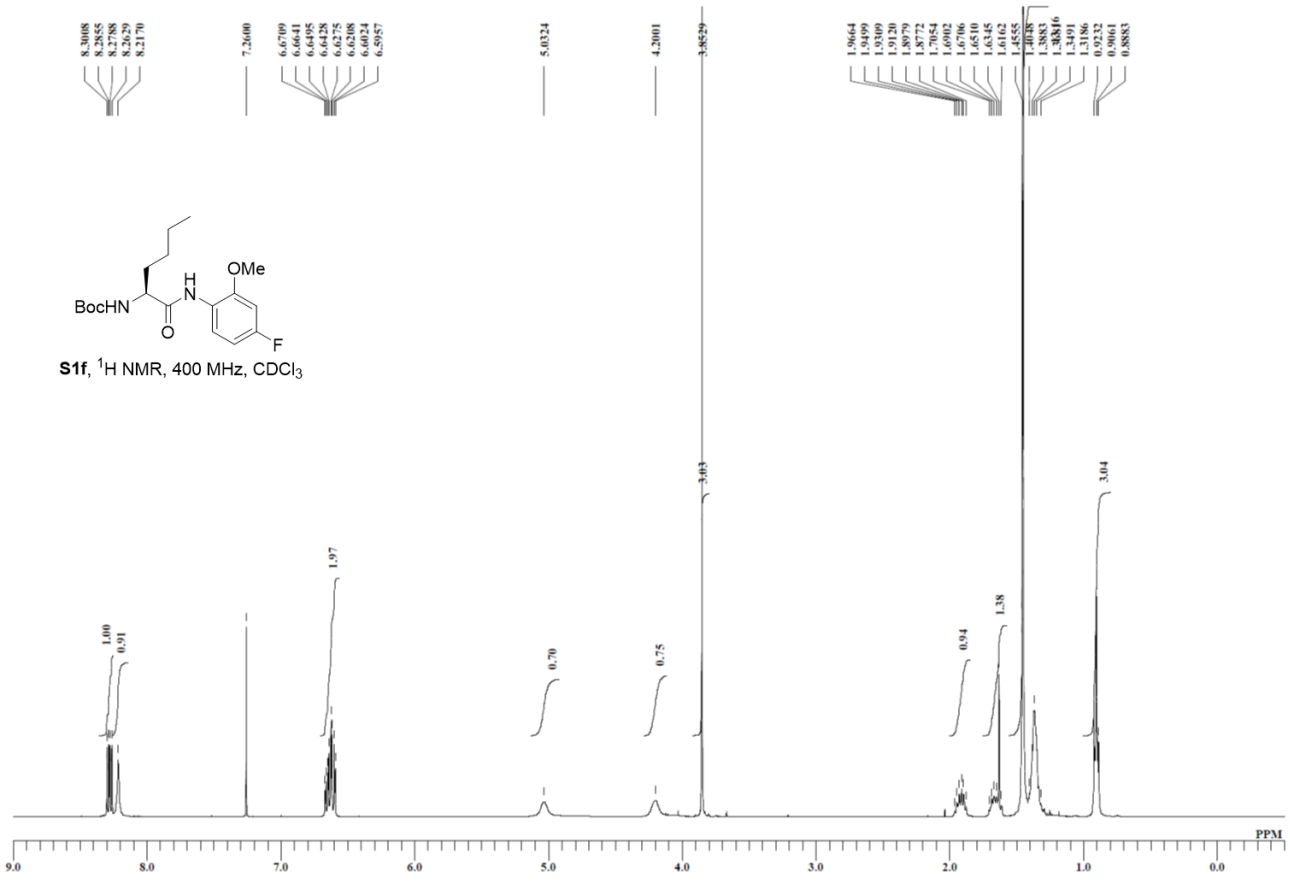
S2d, ^{13}C NMR, 100 MHz, $CDCl_3$



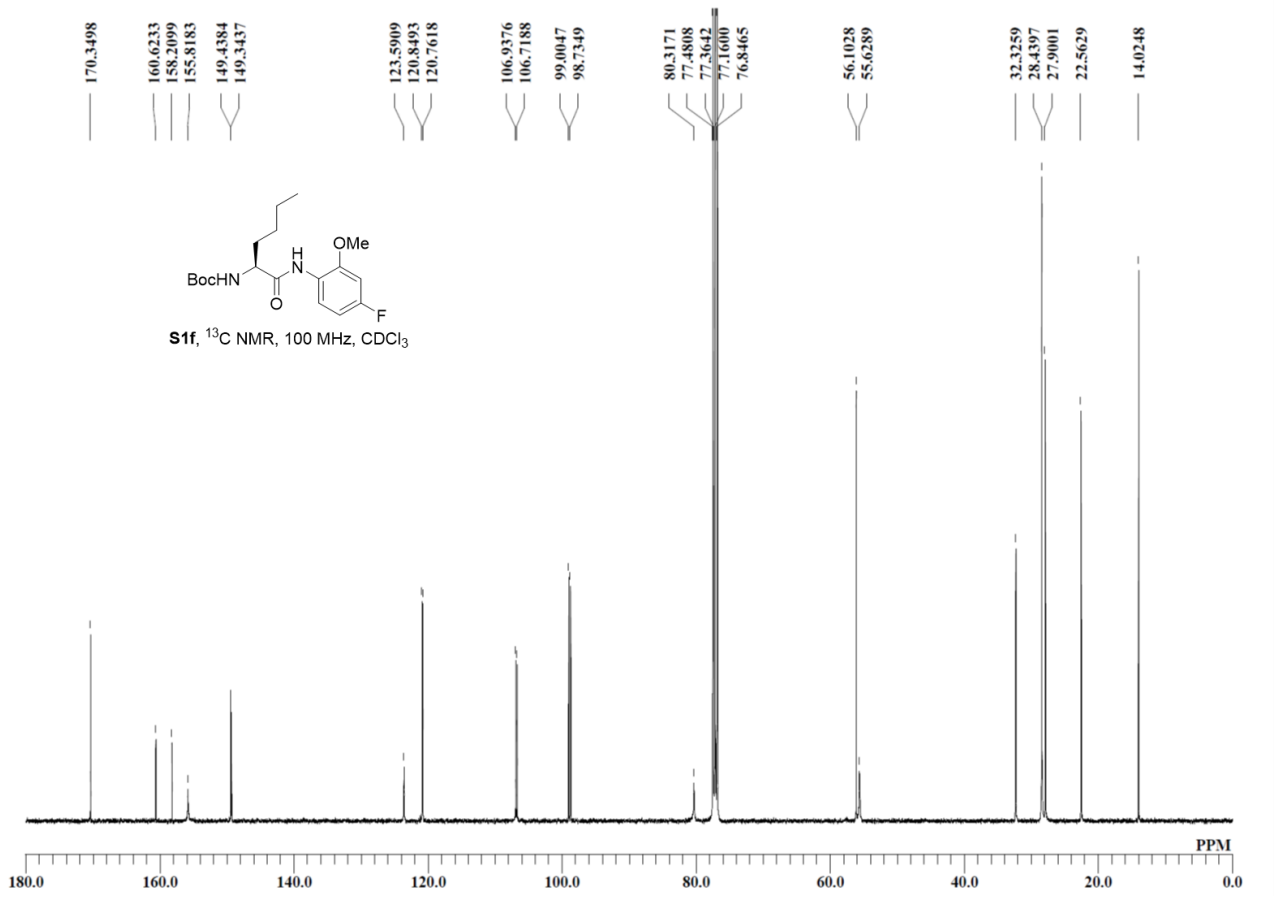
1d, ^{1}H NMR, 400 MHz, CD_3OD



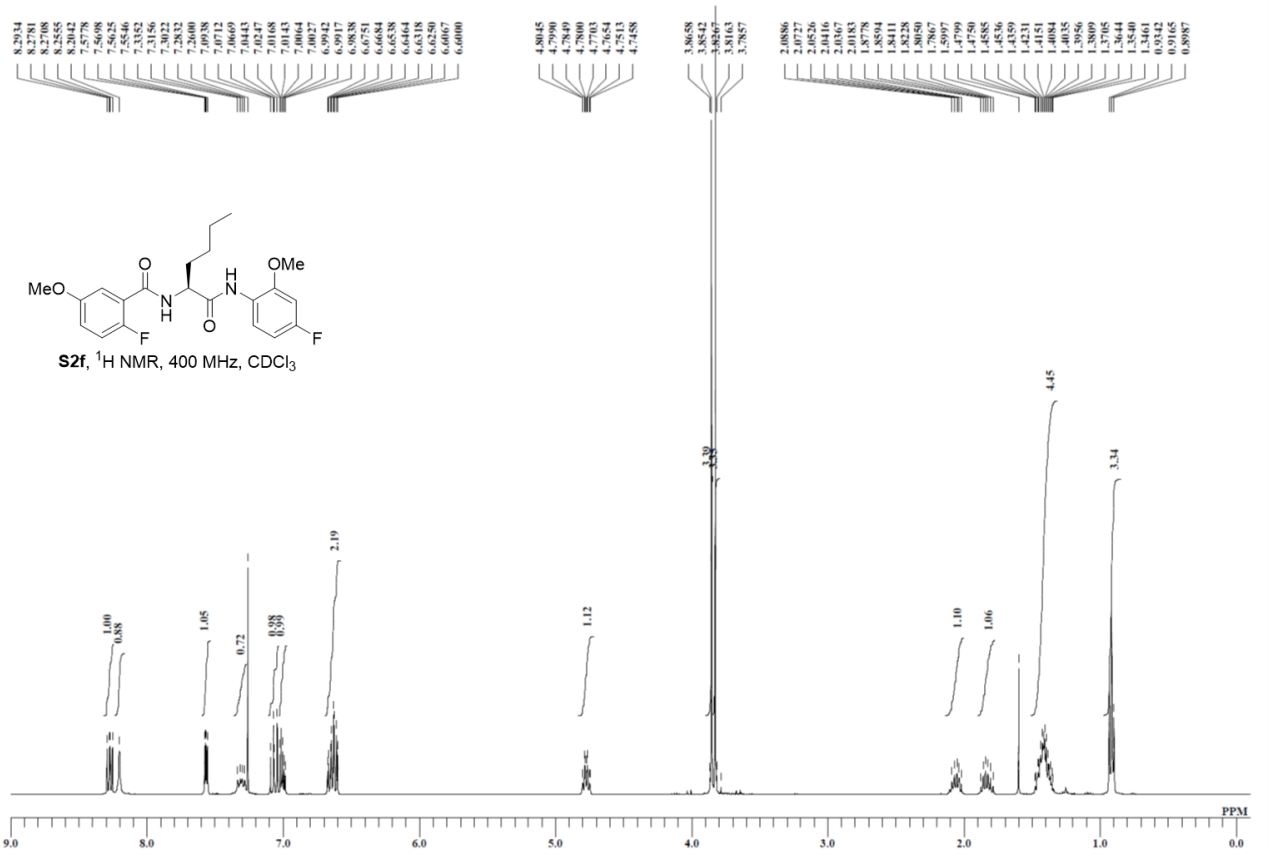
1d, ^{13}C NMR, 100 MHz, CD_3OD



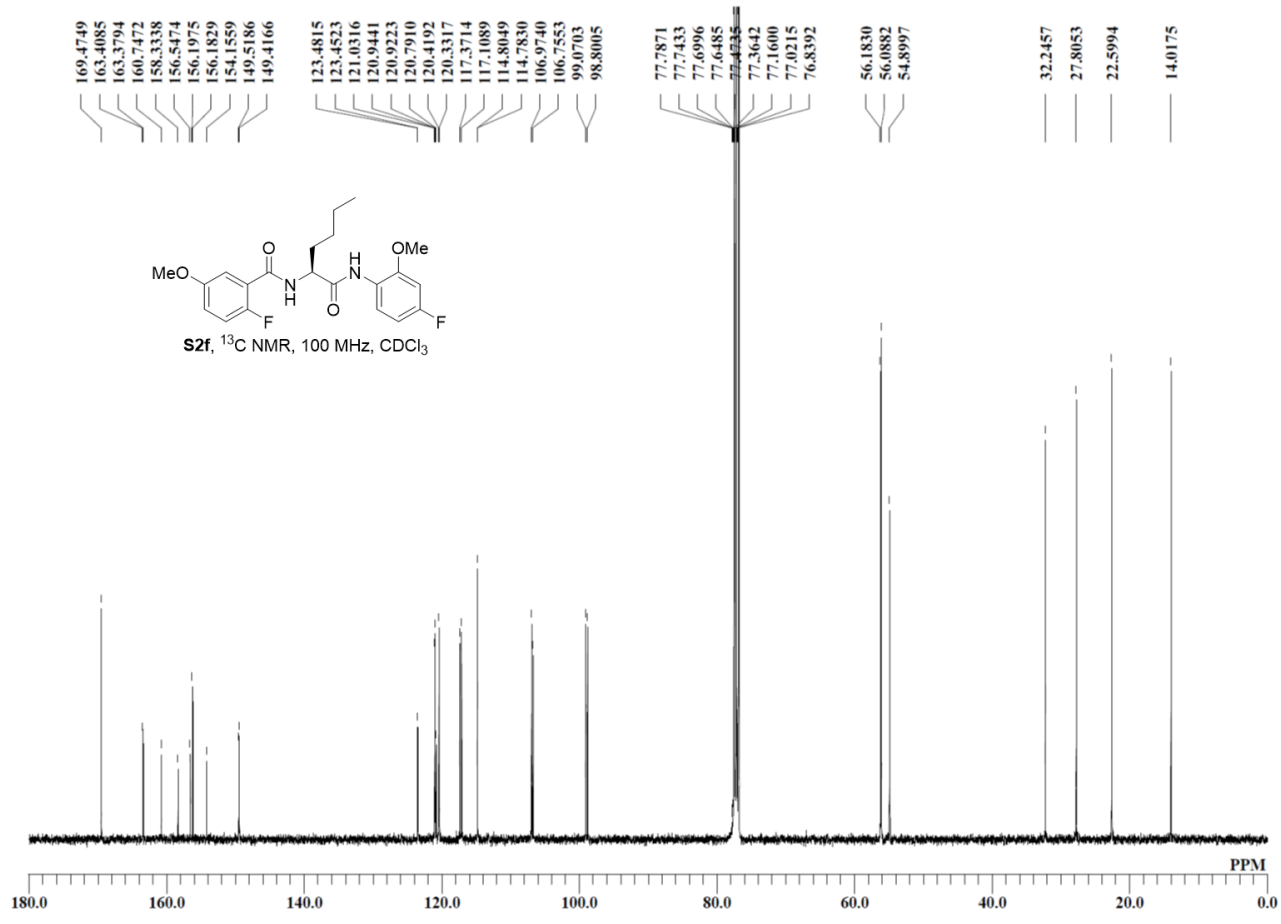
S1f, ^{1}H NMR, 400 MHz, $CDCl_3$



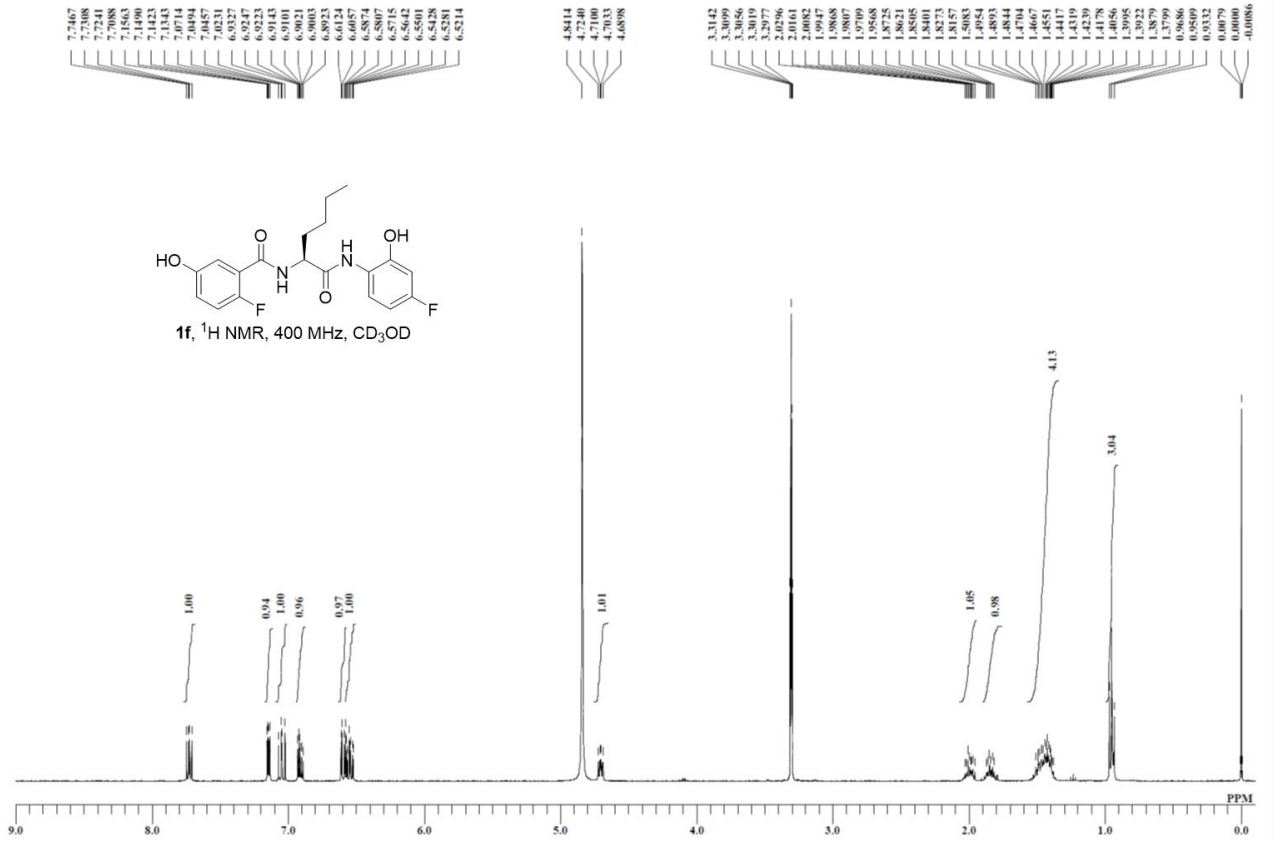
S1f, ^{13}C NMR, 100 MHz, $CDCl_3$

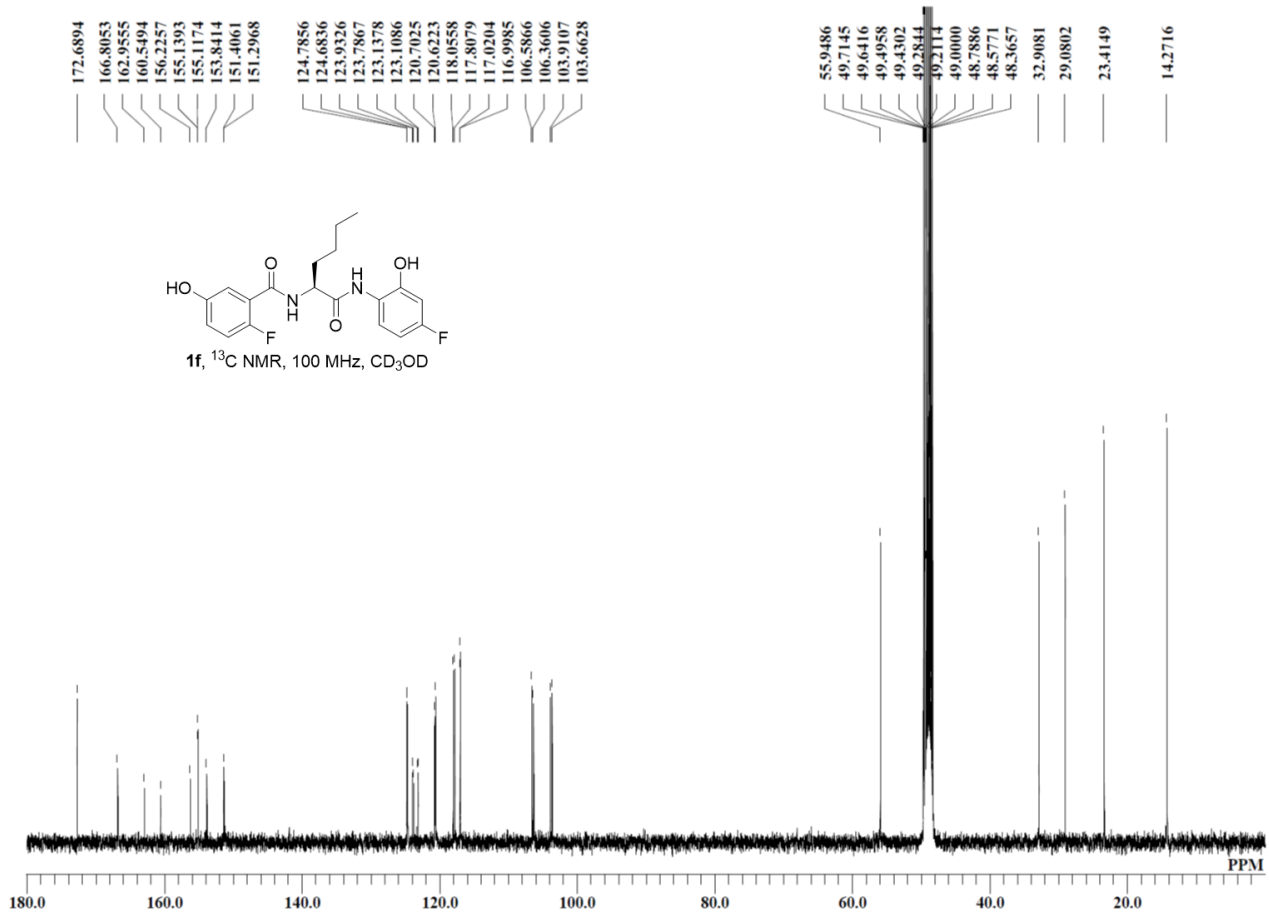


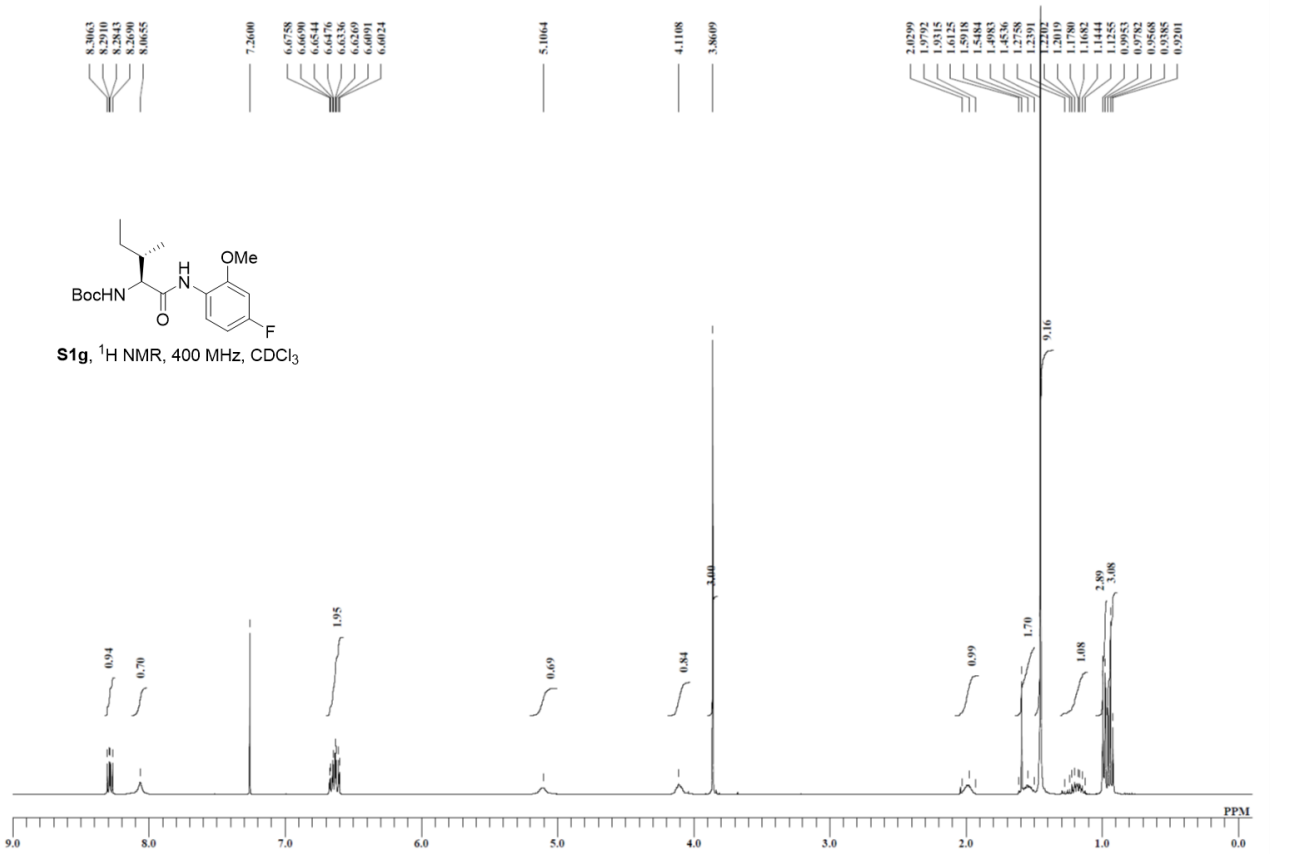
S2f, ^{1}H NMR, 400 MHz, $CDCl_3$



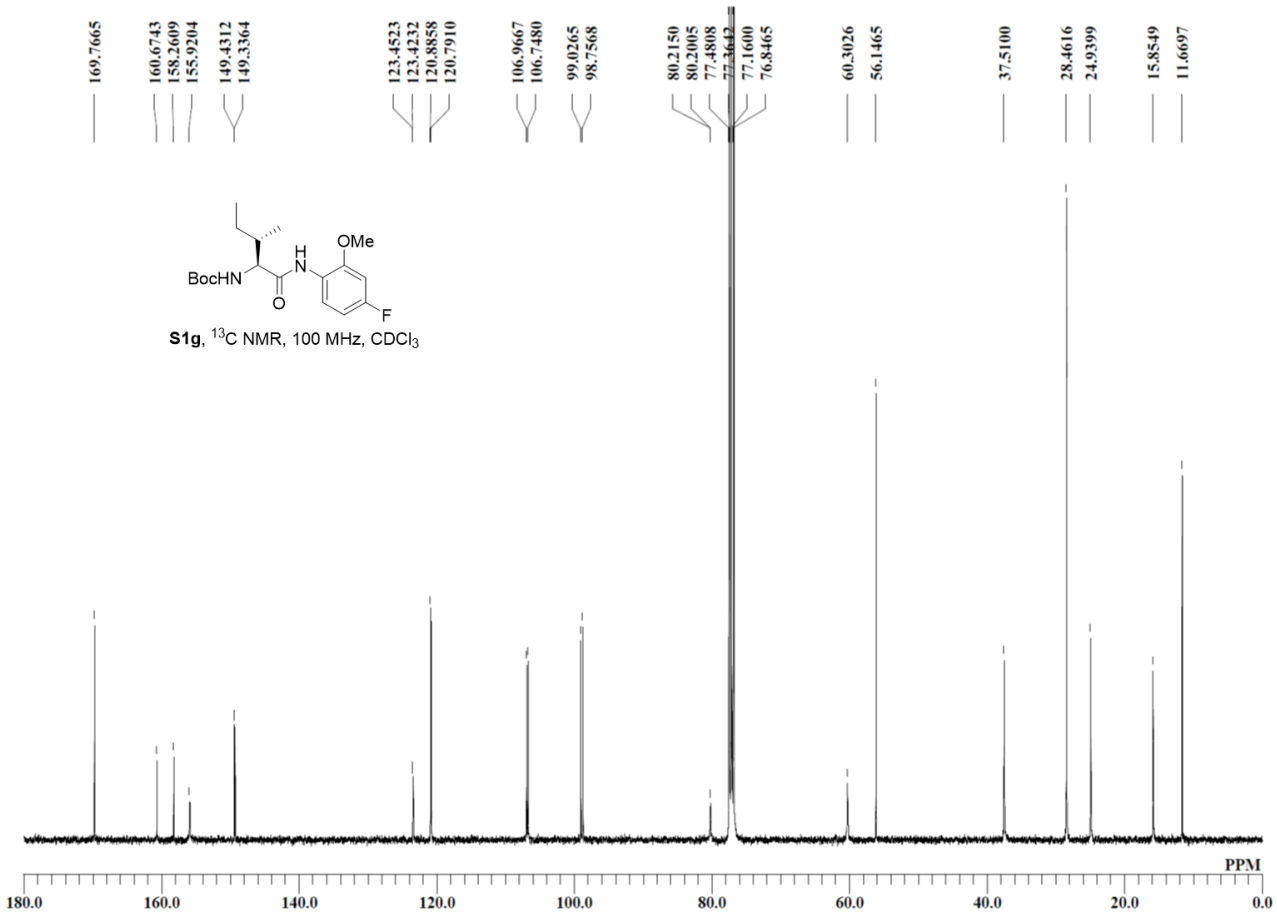
S2f, ^{13}C NMR, 100 MHz, $CDCl_3$


HO
O
N
H
O
H
N
OH
F
F
1f, 1H NMR, 400 MHz, CD3OD
PPM

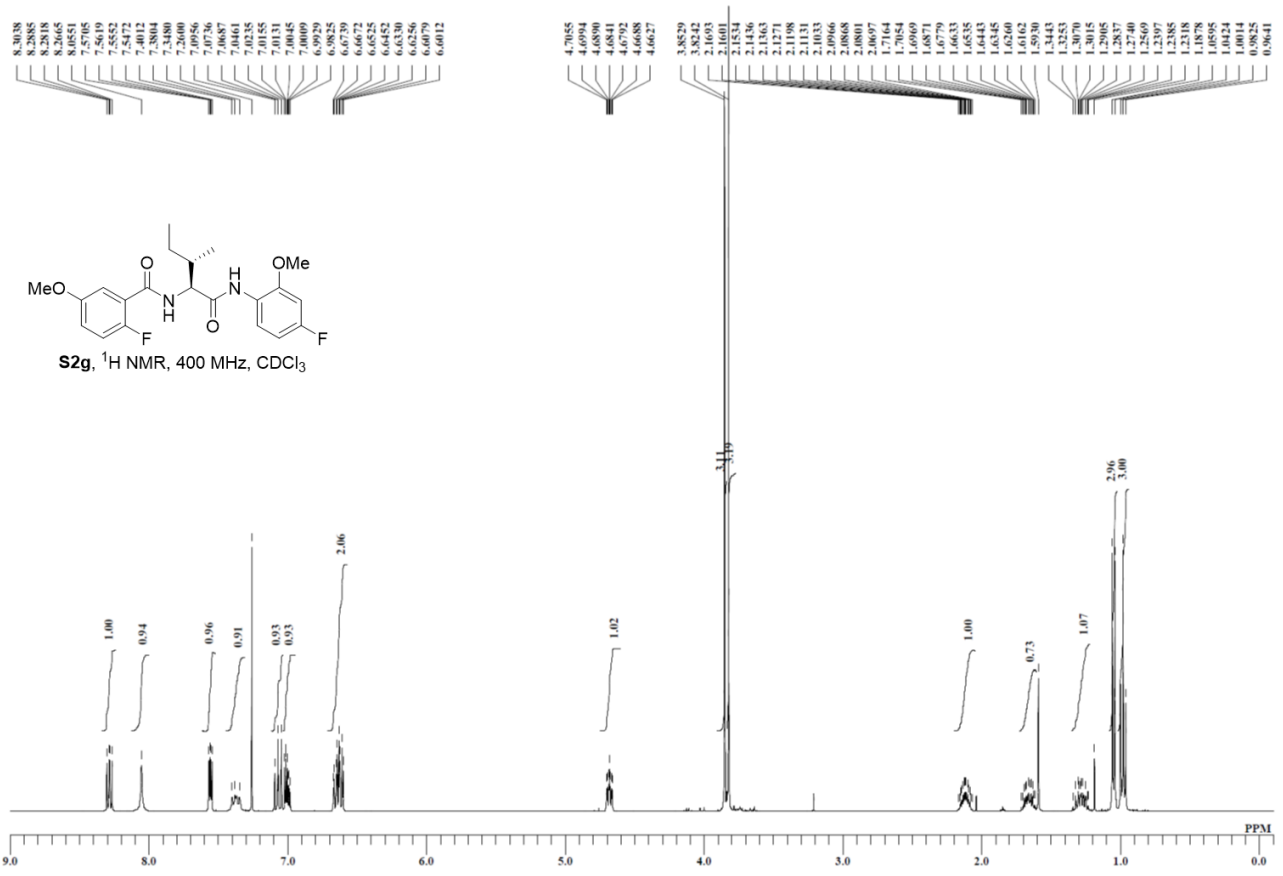

HO
O
N
H
O
H
N
OH
F
F
1f, 13C NMR, 100 MHz, CD3OD
PPM



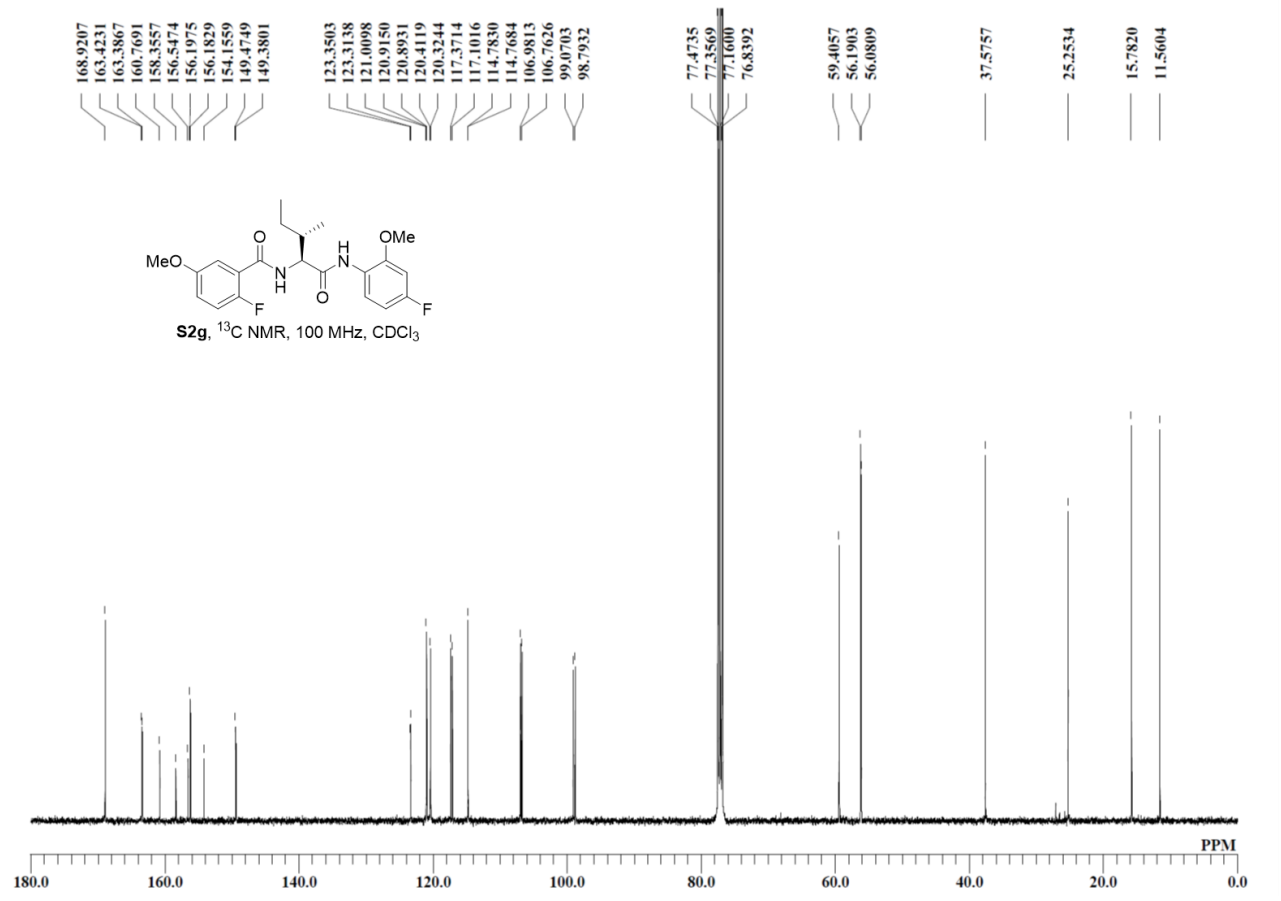
S1g, ^{1}H NMR, 400 MHz, $CDCl_3$



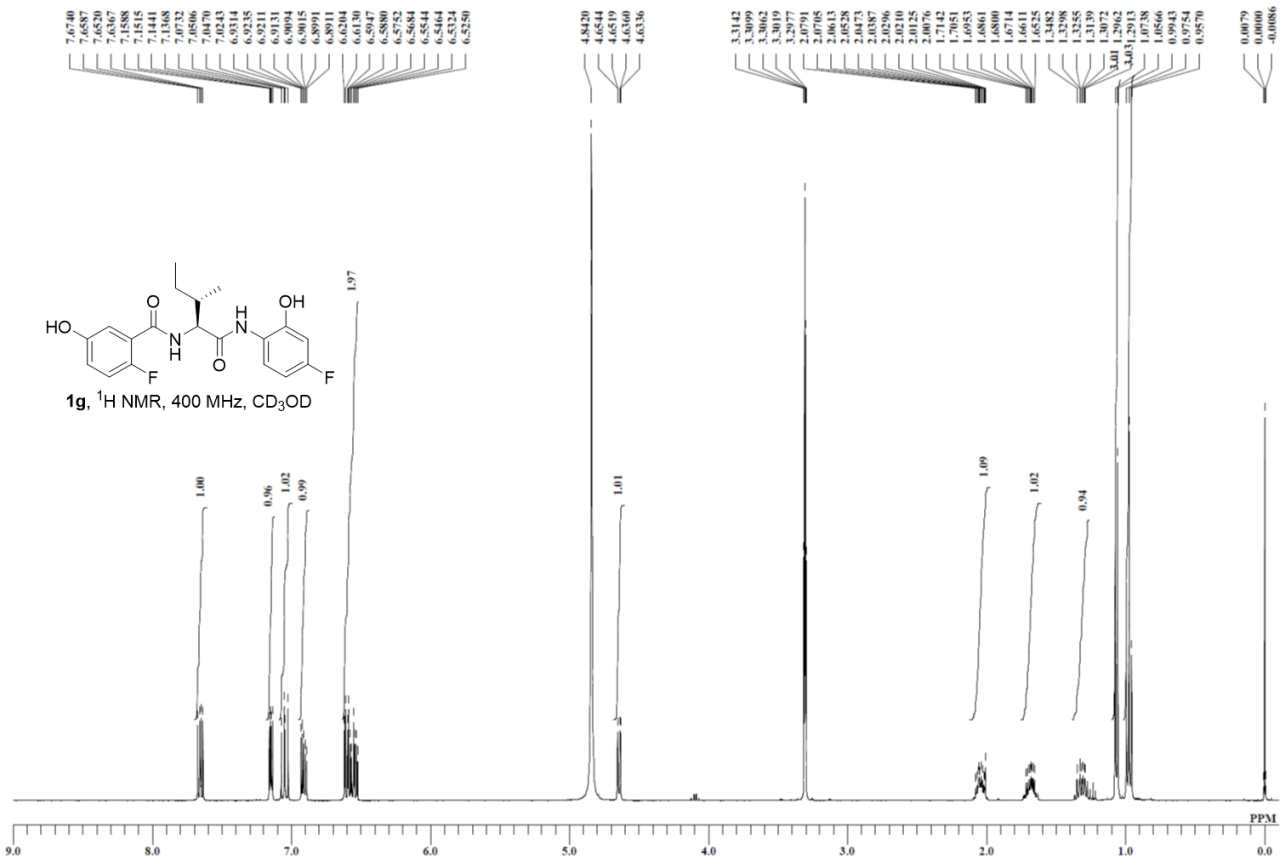
S1g, ^{13}C NMR, 100 MHz, $CDCl_3$



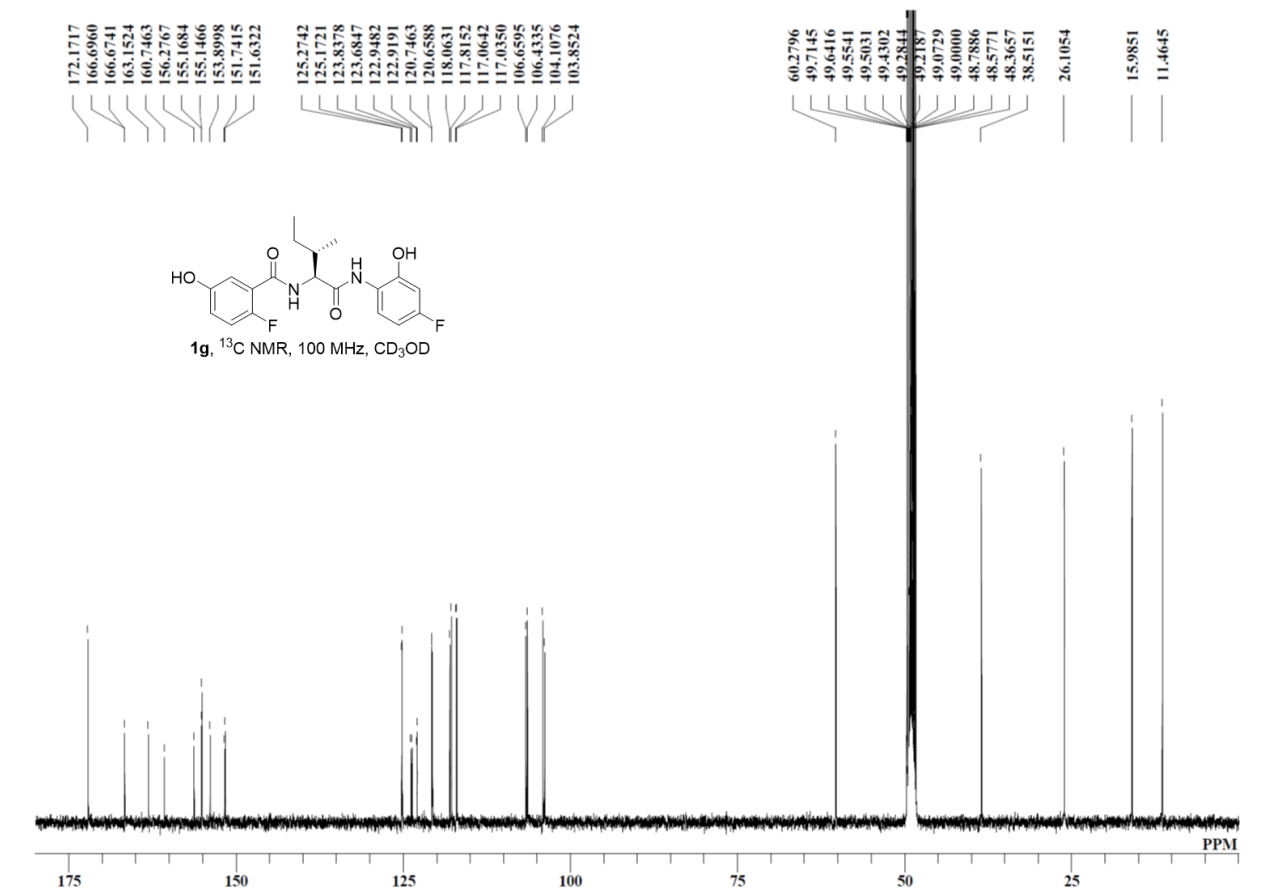
S2g, ^{1}H NMR, 400 MHz, $CDCl_3$



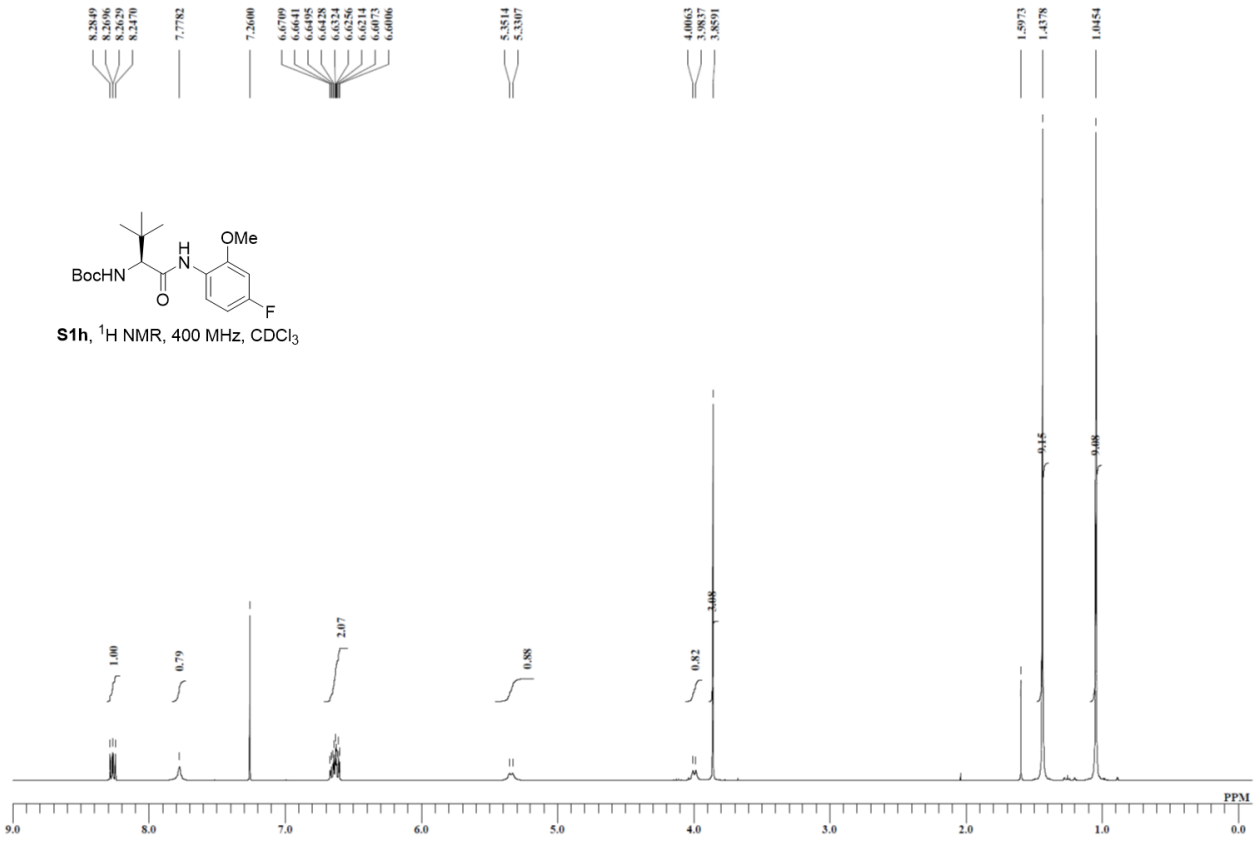
S2g, ^{13}C NMR, 100 MHz, $CDCl_3$



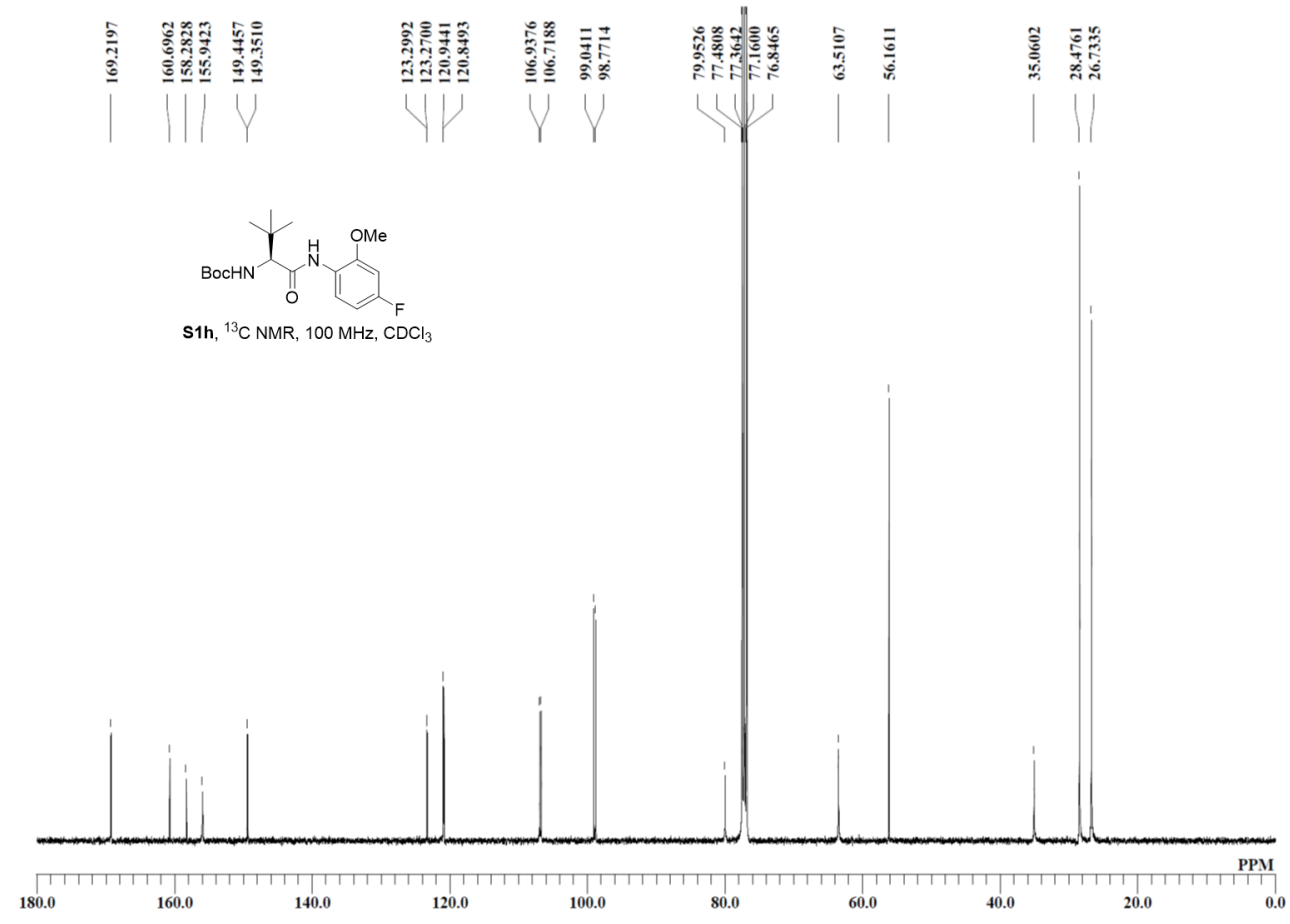
1g, ^{1}H NMR, 400 MHz, CD_3OD



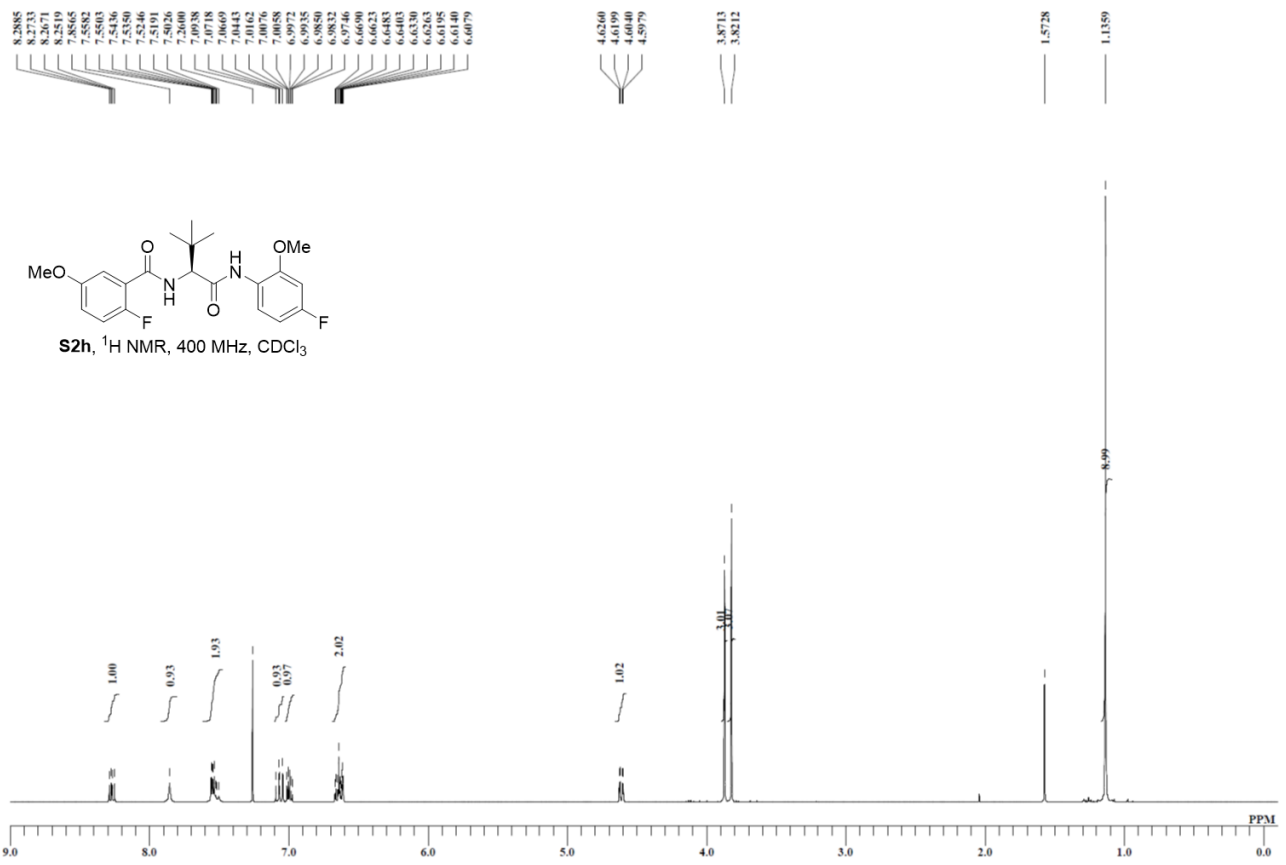
1g, ^{13}C NMR, 100 MHz, CD_3OD



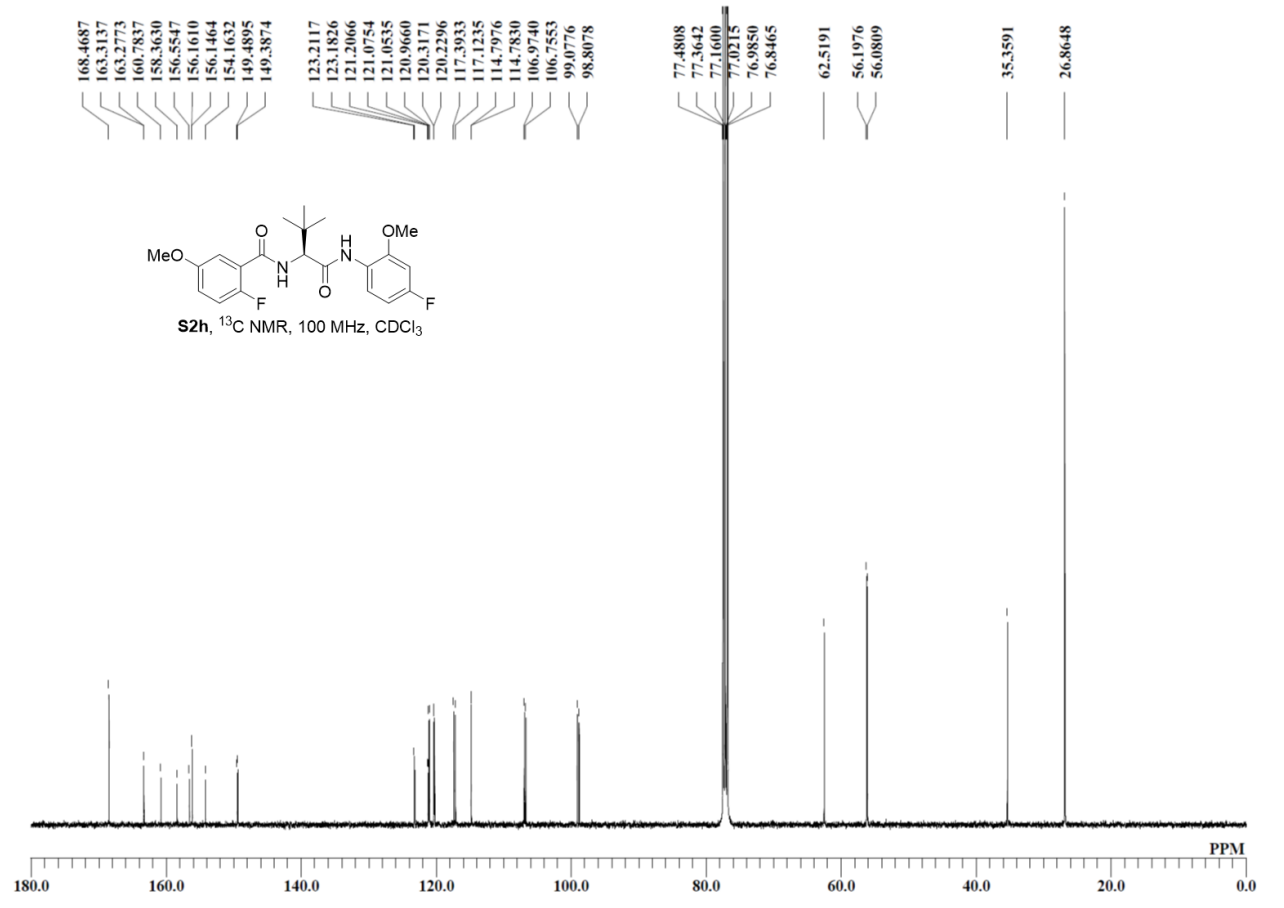
S1h, ^{1}H NMR, 400 MHz, $CDCl_3$



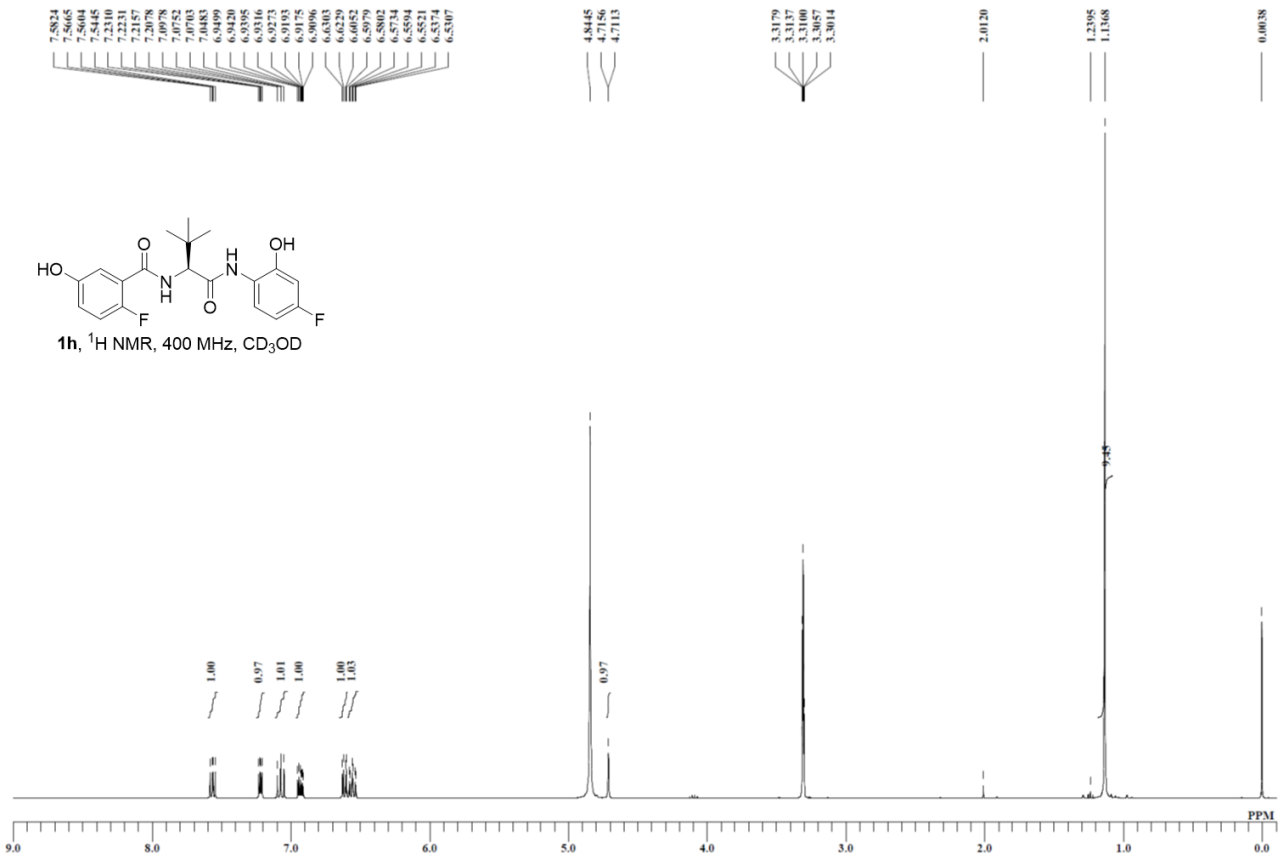
S1h, ^{13}C NMR, 100 MHz, $CDCl_3$



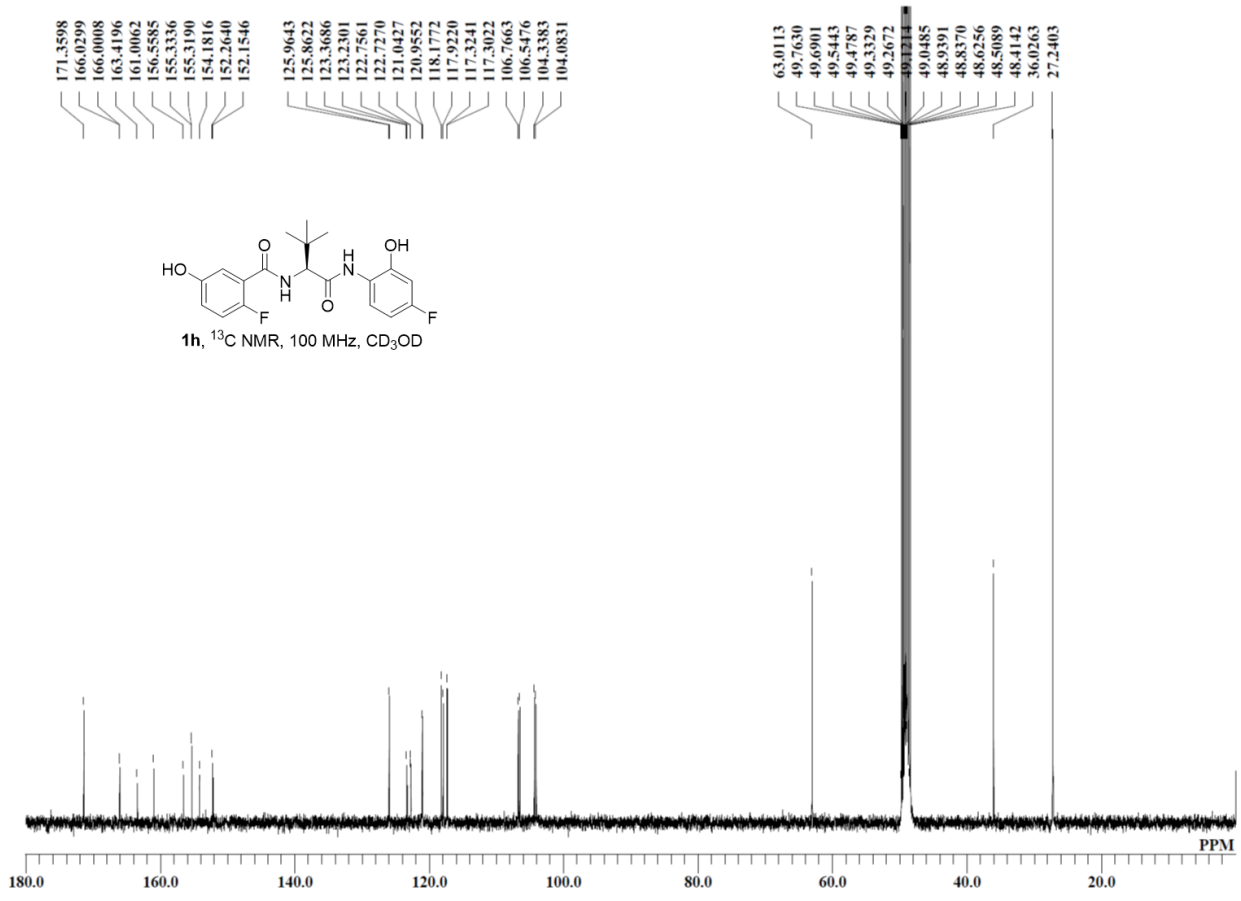
S2h, ^{1}H NMR, 400 MHz, $CDCl_3$



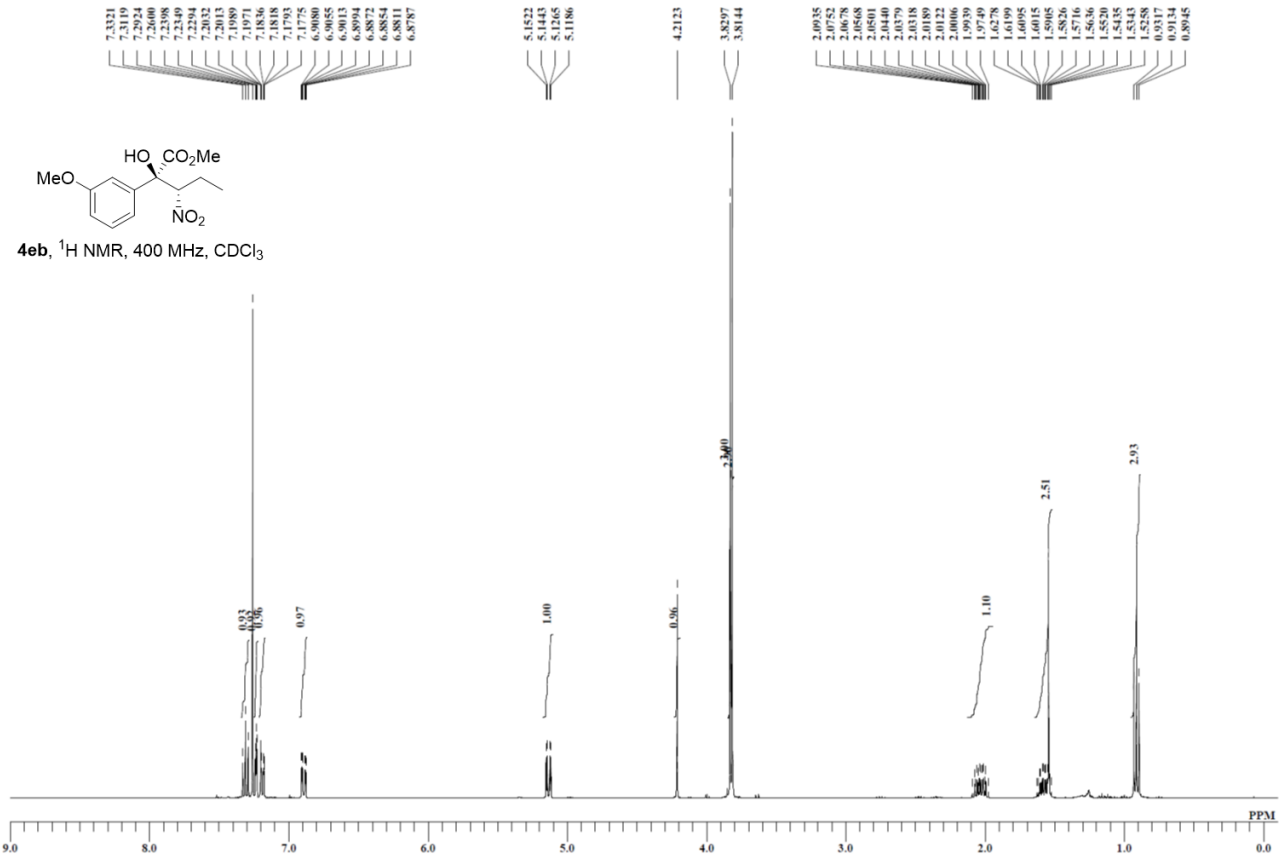
S2h, ^{13}C NMR, 100 MHz, $CDCl_3$



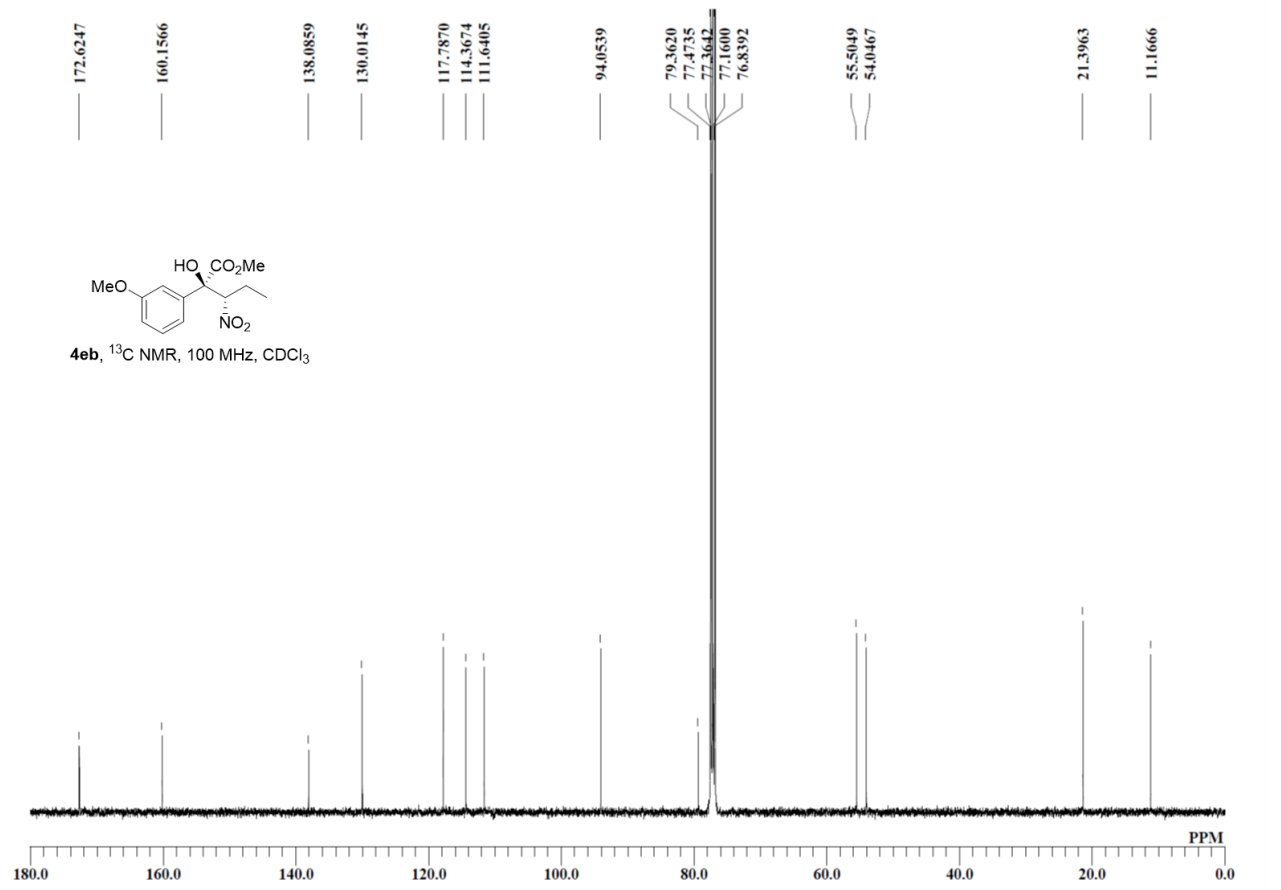
1h, ^{1}H NMR, 400 MHz, CD_3OD



1h, ^{13}C NMR, 100 MHz, CD_3OD



4eb, ^{1}H NMR, 400 MHz, $CDCl_3$



4eb, ^{13}C NMR, 100 MHz, $CDCl_3$

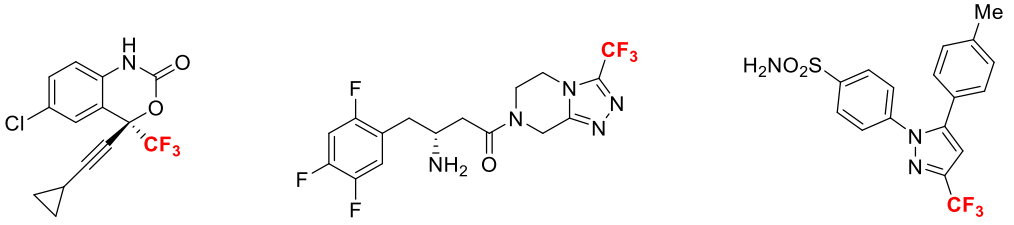
第 4 章

トリフルオロメチルケトンの *anti* 選択的触媒的不斉ニトロアルドール反応

４－１　はじめに

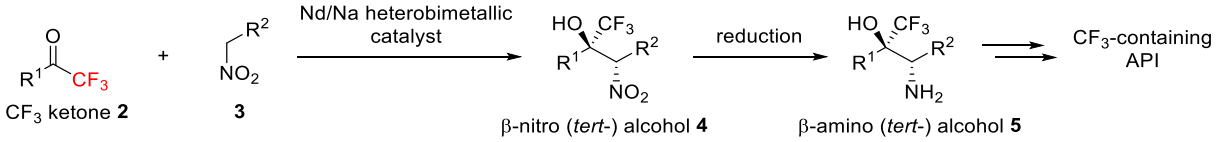
トリフルオロメチル基(CF_3 基)は医薬、農薬、機能性材料など様々な分野で利用されている官能基である。CF_3 基の導入により、1) 疎水性の向上、2) 分子内の電子密度分布の変化、3) 代謝安定性の向上が期待できるため、医薬分野においては、新たな薬理作用の発現や物性の改善、バイオアベイラビリティの向上を目的に CF_3 基含有医薬品の研究が活発に進められている[1]。

Figure 1. APIs containing CF_3 group



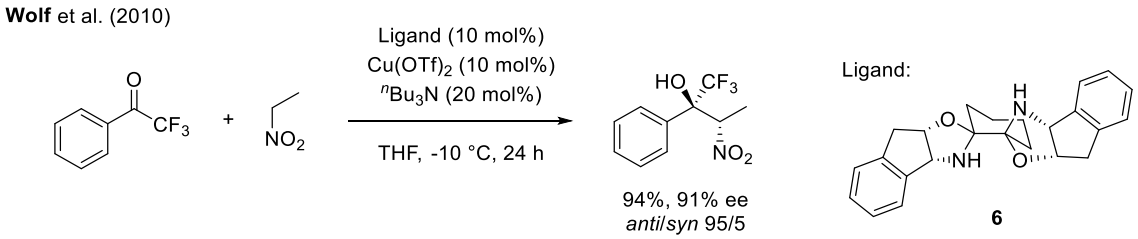
今回私は、医薬品に散見される β-アミノアルコールに CF_3 基を導入した医薬品誘導体の合成に Nd/Na 異種二核金属触媒を用いた不斉ニトロアルドール反応が有効であると考え、CF_3 ケトンの *anti* 選択的触媒的不斉ニトロアルドール反応の開発を目指した。

Scheme 1. Nitroaldol reaction of CF_3 ketone



これまでに CF_3 ケトンとニトロメタンのエナンチオ選択的なニトロアルドール反応は多数報告されていた[2]が、求核剤としてニトロエタンを用いたエナンチオおよびジアステレオ選択的なニトロアルドール反応の報告は 1 例のみであった。Wolf らはビスオキサゾリンリガンド **6** を持つ銅触媒を用いた *anti* 選択的な反応を報告している[3]が、反応例は 4 例に限られていた(Scheme 2)。そこで、Nd/Na 異種二核金属触媒を CF_3 ケトンの不斉ニトロアルドール反応へ適用し、汎用的に β-ニトロ 3 級アルコール合成できる手法の開発を目指した。

Scheme 2. Past examples for enantio- and diastereo-selective nitroaldol reaction of CF_3 ketones

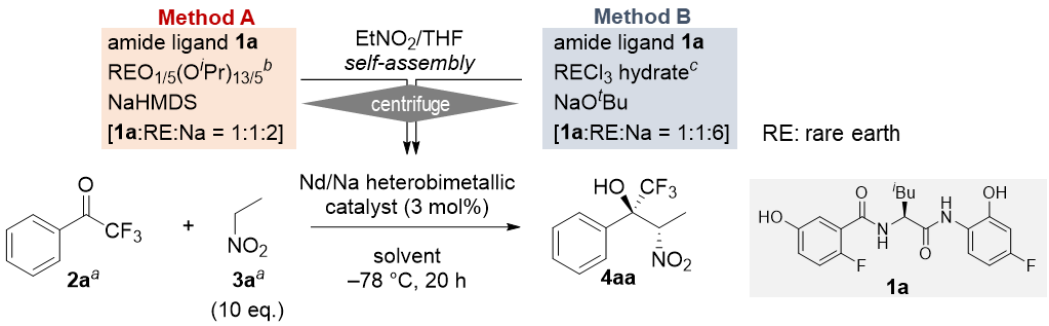


４－２　反応条件の最適化

CF_3ケトンの *anti* 選択的触媒的不斉ニトロアルドール反応の触媒に用いる希土類金属(Rare Earth、以下 RE)を検討した(Table 1)。$RE_{1/5}(O^iPr)_{13/5}$, NaHMDS とアミド型配位子 **1a** を 1:1:2 の比で混合し、異種 2 核金属触媒の調製を試みた(method A)ところ、Nd と Pr からのみ自己組織化が進行し、Nd/Na ならびに Pr/Na 異種 2 核金属錯体が不均一系触媒として形成された。これらの錯体を **2a** と **3a** のニトロアルドール反応に用いたところ、高収率、高立体選択性で目的の付加体 **4aa** が得られた(RE = Nd: 90% yield, 93% ee, *anti*/*syn* = 96/4, RE = Pr: 92% yield, 95% ee, *anti*/*syn* = 97/3)(entry 1, 3)。一方、Nd, Pr 以外の RE からは自己組織化は進行せず、均一系溶液を触媒として用いても反応はほとんど進行しなかった(entry 2, 4-9)。

Nd と Pr に対し、近年報告された安価な $RECl_3$ 水和物と NaO^tBu による触媒調製法(method B)で得た異種二核金属触媒を用いたところ、method A から調製した触媒と同等の結果を与えた(entry 9, 10)。

Table 1. Rare earth screening

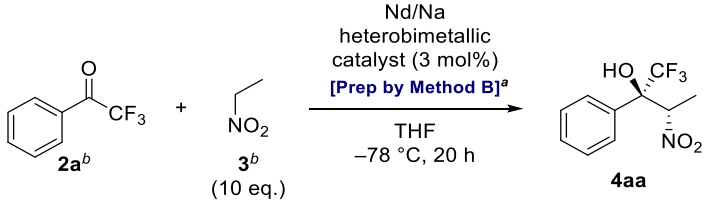


entry	RE	method	self-assembly[d]	yield[e] (%)	*anti*/*syn*[e]	% ee[f] (*anti*)
1	Nd	A	+	90	96/4	93
2	La	A	–	trace	-	-
3	Pr	A	+	92	97/3	95
4	Sm	A	–	12	-	-
5	Gd	A	–	trace	-	-
6	Dy	A	–	trace	-	-
7	Er	A	–	trace	-	-
8	Yb	A	–	trace	-	-
9	Nd	B	+	95	95/5	92
10	Pr	B	+	91	96/4	94

[a] **2a**: 0.12 mmol, **3a**: 1.2 mmol. [b] For Pr, Dy, Er and Yb, $RE(O^iPr)_3$ was used. [c] $NdCl_3{\cdot}6H_2O$ or $PrCl_3{\cdot}7H_2O$. [d] Amount of precipitation by self-assembly; +: high, –: low. [e] Determined by ^1H NMR analysis. [f] Determined by chiral HPLC analysis.

続いて、先の検討で良好な結果を与えた Nd/Na 異種 2 核金属触媒を用い、各種エーテル系溶媒を検討したところ、THF が収率、選択性共に最も良い結果を与えた(95% yield, *anti*/*syn* = 95/5, 93% ee)(entry 1)。一方、α-ケトエステルの反応(2 章参照)で THF を上回る結果を与えた 2-Me-THF は収率、立体選択性共に中程度に留まった(Table 2)。

Table 2. Solvent screening



entry	solvent	yield[c] (%)	*anti* /*syn* [d]	% ee[e] (*anti*)
1	THF	95	95/5	93
2	Et_2O	84	84/16	90
3	DME	trace	-	-
4	CPME	62	92/8	82
5	2-Me-THF	70	92/8	84

[a] Descrived in Table 1. [b] **2a**': 0.12 mmol, **3**: 1.2 mmol. [c] Determined by ^{1}H NMR analysis of the crude mixture with mesitylene as internal standard. [d] Determined by ^{1}H NMR analysis. [e] Determined by HPLC analysis.

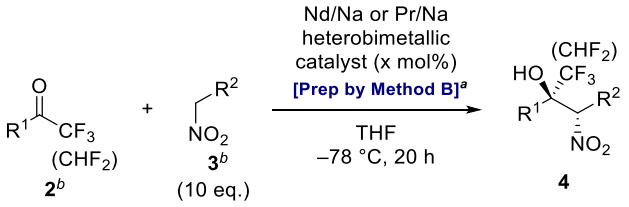
４－３　基質一般性の検討

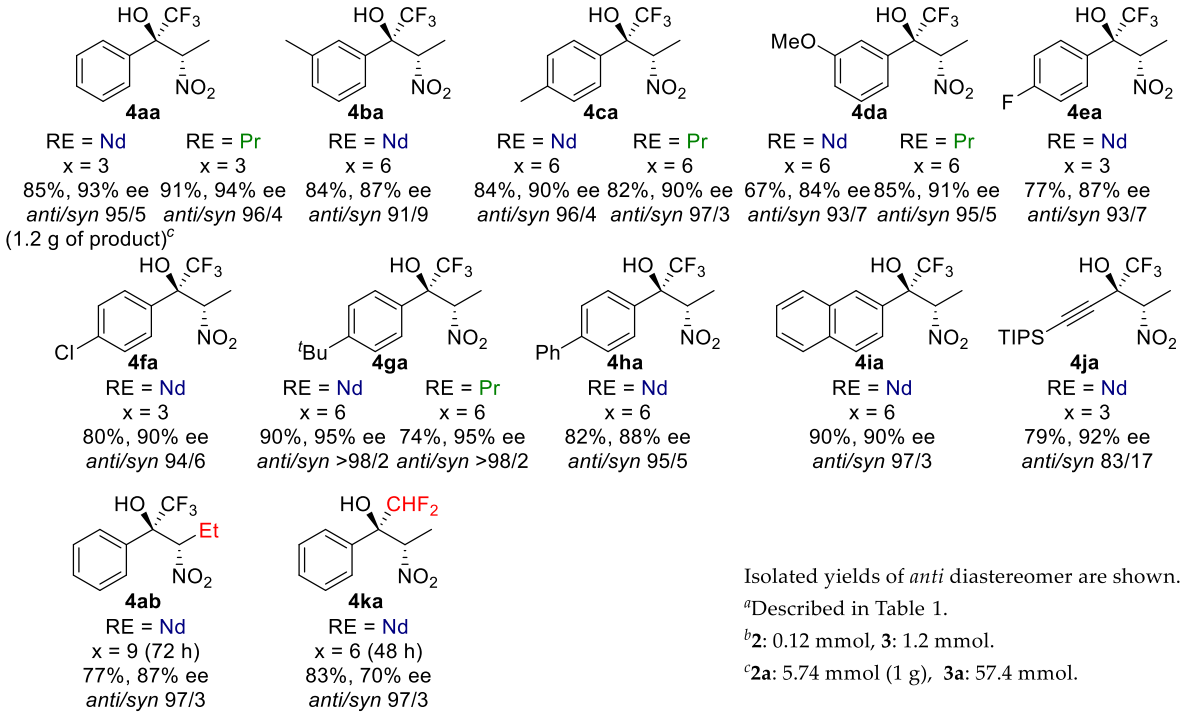
本反応の基質一般性を調べた。まず、トリフルオロメチルフェニルケトンを基質とした場合にはグラムスケールでも良好に反応は進行し、高収率、高立体選択性で **4aa** を与えた(85% yield, *anti*/*syn* = 95/5, 93% ee)。電子供与性の Me 基、OMe 基が置換したフェニルケトンは求電子性が低下し、6 mol%の触媒を要したものの、高い立体選択性で付加体が得られた。電子求引性のハロゲンが置換したフェニルケトンは高い立体選択性で反応が進行した。嵩高い ^{t}Bu が置換したフェニルケトンは最も高い立体選択性を与えた(**4ga,** *anti*/*syn* = >98/2, 95% ee)。アルキニルケトンからも反応は進行し、ジアステレオ選択性は中程度であったものの、良好なエナンチオ選択性であった(**4ja**, *anti*/*syn* = 83/17, 92% ee)。生成物中のアルキニル基は様々な官能基に変換可能であるため、**4ja** は医薬品合成において有用なキラルビルディングブロックであると考えている[4]。ニトロアルカンとして、ニトロプロパンを反応させた場合には 9 mol%の触媒が必要であったものの、高い選択性で **4ab** を与えた(77% yield, *anti*/*syn* = 97/3, 87% ee)。またトリフルオロメチルケトンよりも反応性が低いことが予想されるジフルオロメチルケトンを基質としても反応は進行し、エナンチオ選択性が中程度であったものの **4ka** が得られた(83% yield, *anti*/*syn* = 97/3, 70% ee)。

また、一部の基質において、Pr/Na 異種二核金属触媒が Nd/Na 系より良い結果を与えた(**4aa**, **4da**)。Nd と Pr は類似したルイス酸性度を持つため、触媒構造はほぼ同一であると考えられるが、僅かなイオン半径の違いが立体選択性に影響したと考えている。

以上、本反応は幅広い基質一般性で進行し、対応する α-CF_3-β-ニトロアルコールを高収率、高立体選択性で与えることを明らかにした。

Scheme 3. Reaction scope



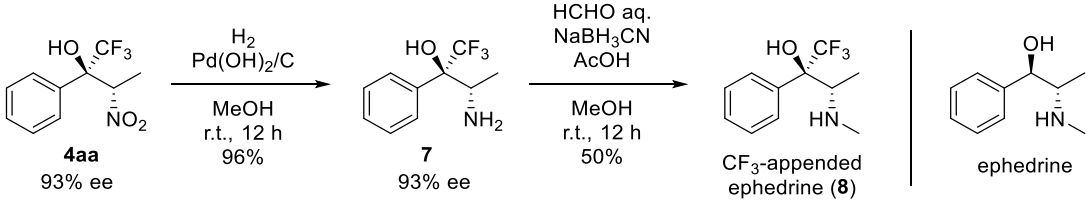


Isolated yields of *anti* diastereomer are shown.
[a]Described in Table 1.
[b]**2**: 0.12 mmol, **3**: 1.2 mmol.
[c]**2a**: 5.74 mmol (1 g), **3a**: 57.4 mmol.

4－4　トリフルオロメチル基含有医薬品誘導体の合成

本反応により得た **4aa** から CF_3 基含有 ephedrine[5] の合成を試みた。まず、**4aa** を Pd/C を用いた接触水素化反応により β-アミノアルコール **7** へ変換した。この際、鏡像異性体過剰率の低下は見られなかった。続いて、還元的アミノ化条件下メチル化し、CF_3 基含有 ephedrine(**8**)の合成に成功した。序論で述べた通り、β-アミノアルコールを含む医薬品は ephedrine のほかにも多数が知られており、β-アミノアルコール部位に CF_3 基を導入した誘導体の合成に本手法は有効である。

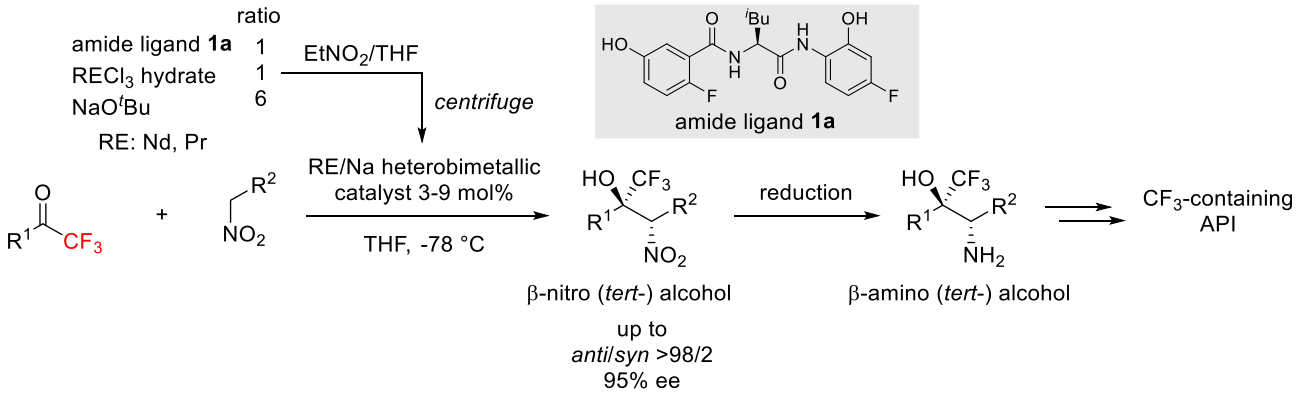
Scheme 4. Stereoselective synthesis of CF_3-appended ephedrine



４－５　まとめ

本章では、CF_3 ケトンの *anti* 選択的触媒的不斉ニトロアルドール反応の開発について述べた [6]。本反応は Nd/Na または Pr/Na 異種二核金属触媒により、広範の基質で進行し、α-CF_3-β-ニトロ 3 級アルコールを高収率、高立体選択性で与えた。生成物中のニトロ基は還元反応により容易にアミノ基へ変換可能であり、β-アミノ 3 級アルコールユニットの迅速不斉合成法を確立した。さらに CF_3 基含有 ephedrine 誘導体の合成を通じて、医薬化学における本反応の有用性を示した。

Scheme 5. Summary of chapter 4



References

1. (a) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications, 2nd ed.*; Wiley-VCH: Weinheim, Germany, 2013. (d) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432. (e) Zhu, W.; Wang, J.; Wanga, S.; Gu, Z.; Acena, J. L.; Izawa, K.; Liu, H.; Soloshonok, V. A. *J. Fluorine Chem.* **2014**, *167*, 37. (f) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315. (g) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Acena, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev.* **2016**, *116*, 422.
2. (a) Tur, F.; Saá, J. M. Org. Lett. **2007**, 9, 5079. (b) Bandini, M.; Sinisi, R.; Umani-Ronchi, A. *Chem. Commun.* **2008**, 4360. (c) Saá, J. M.; Tur, F.; Gonzalez, J. *Chirality* **2009**, *21*, 836. (d) Palacio, C.; Connon, S. J. *Org. Lett.* **2011**, *13*, 1298. (e) Das, A.; Choudhary, M. K.; Kureshy, R. I.; Jana, K.; Verma, S.; Khan, N. H.; Abdi, S. H. R.; Bajaj, H. C.; Ganguly, B. *Tetrahedron* **2015**, *71*, 5229.
3. Xu, H.; Wolf, C. *Chem. Commun.* **2010**, *46*, 8026.
4. Trost, B. M.; Li, C.-J. *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations*; Wiley: Hoboken, NJ, 2014.
5. Abourashed, E. A.; El-Alfy, A. T.; Khan, I. A.; Walker, L. *Phytother. Res.* **2003**, *17*, 703.
6. Karasawa, T.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2018**, *20*, 308.

Experimental Section for chapter 4 entitled

anti-Selective Catalytic Asymmetric Nitroaldol Reaction of α-CF_3 Ketones

Table of Contents:

A. General Methods

A-1. Reactions and purifications

Unless otherwise noted, all reactions were carried out in an oven-dried glassware fitted with a 3-way glass stopcock under an argon atmosphere with magnetically stirred chips. All work-up and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Thin layer chromatography (TLC) was performed on Merck TLC plates (0.25 mm) pre-coated with silica gel 60 F254 and visualized by UV quenching and staining with $KMnO_4$ or ninhydrine. Flash column chromatography was performed on a Biotage Isolera Spektra One with a Redisep column.

A-2. Characterizations

Infrared (IR) spectra were recorded on a HORIBA FT210 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL ECS-400. Chemical shifts (δ) are given in ppm relative to residual solvent peaks.[1] Data for ^{1}H NMR are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet), q (quartet), m (multiplet), br (broad). For ^{19}F NMR, chemical shifts were reported in the scale relative to $PhCF_3$ (δ –62.7680 ppm in $CDCl_3$) as an external reference. High performance liquid chromatography (HPLC) analysis was performed on Jasco analytical instruments with single pump and UV detector. Optical rotation was measured using a 1 mL cell with a 10 cm path length on a JASCO polarimeter P-1030. High-resolution mass spectra were measured on a Thermo Fisher Scientific LTQ Orbitrap XL.

A-3. Solvents and reagents

THF, Et_2O, DME and CPME were purified by passing through a solvent purification system (Glass Contour). Nitroethane (**3a)**, nitropropane (**3b**) and 2-Me-THF was purchased from TCI Co. Ltd. and nitroethane was used after distillation. Amide-based ligand **1a** was prepared by following the reported procedure.[2] $NdCl_3 \bullet 6H_2O$ was purchased from Wako Pure Chemical Co. Ltd. $PrCl_3 \bullet 7H_2O$ was purchased from Kanto Chemical Co. Ltd. All other RE reagents were purchased from Kojundo Chemical Laboratory Co. Ltd. Trifluoromethyl ketone **2a**, **2c**, **2e** and **2f** were purchased from TCI Co. Ltd. Trifluoromethyl ketone **2b**,[3] **2d**,[4] **2g**,[5] **2h**,[6] **2i**,[7] and **2j**[8] were prepared to the known procedure with a slight modification. Difluoromethyl ketone **2k** was purchased from Aldrich. All other materials were used as supplied by commercial vendors.

B. Preparation of catalyst by Method A

To a flame dried test tube (20 mL) was charged with amide-based ligand **1a** (9.1 mg, 0.024 mmol), and dried under vacuum at room temperature at least for 5 min. Ar was backfilled (evacuation/backfill was repeated for 5 times) to the test tube, and THF (400 μL) and 0.2 M $NdO_{1/5}(O\textit{i}\text{-}Pr)_{13/5}$/THF (120 μL, 0.024 mmol) were added successively by well-dried syringes and needles at 0 °C. After stirring the resulting slightly cloudy suspension at room temperature for 30 min, 1.0 M NaHMDS/THF (48 μL, 0.048 mmol) was added dropwise at 0 °C. After stirring the resulting mixture at room temperature for 1 h (white precipitate appeared), nitroethane (172 μL, 2.4 mmol) was added. Self-assembly of Nd/Na catalyst initiated in a few minutes and the resulting mixture was stirred at room temperature for 2 h to give a thick white suspension. The whole suspension was transferred to an Eppendorf tube with THF washing (0.5 mL x2). The tube was centrifuged at ca. 10^4 rpm for 30 sec. The supernatant was decanted and THF (1.6 mL) was added. The tube was agitated using a vortex mixer for 30 sec and centrifuged again, then the supernatant was decanted (washing process). The resulting precipitate was agitated with THF (1.6 mL) and a part of resulting suspension (240 μL, 0.0036 mmol, 3 mol%) was used for *anti*-selective catalytic asymmetric nitroaldol reaction.

C. Preparation of catalyst by Method B

To a flame dried test tube (20 mL) was charged with $NdCl_3 \bullet 6H_2O$ (8.6 mg, 0.024 mmol), and dried under vacuum at room temperature at least for 5 min. Ar was backfilled (evacuation/backfill was repeated for 5 times) to the test tube, and THF (200 μL) and 0.6 M amide based ligand **1a**/THF (200 μL, 0.012 mmol) were added successively by well-dried syringes and needles at room temperature. After stirring the resulting slightly cloudy suspension at 60 °C for 30 min, 2.0 M NaO^{t}Bu/THF (72 μL, 0.144 mmol) was added dropwise at the same temperature. After stirring the resulting mixture at 60 °C for 1 h (white precipitate appeared), the mixture was cooled to room temperature and nitroethane (172 μL, 2.4 mmol) was added. Self-assembly of Nd/Na catalyst initiated in a few minutes and the resulting mixture was stirred at room temperature for 12 h to give a thick white suspension. The whole suspension was transferred to an Eppendorf tube with THF washing (0.5 mL x2). The tube was centrifuged at ca. 10^4 rpm for 30 sec. The supernatant was decanted and THF (1.6 mL) was added. The tube was agitated using a vortex mixer for 30 sec and centrifuged again, then the supernatant was decanted (washing process). This washing process was repeated again. The resulting precipitate was agitated with THF (1.6 mL) and a part of resulting suspension (240 μL, 0.0036 mmol, 3 mol%) was used for *anti*-selective catalytic asymmetric nitroaldol reaction.

D. Representive procedure for anti-selective catalytic asymmetric nitroaldol reaction

To a flame-dried 20 mL test tube was charged with THF (960 μL) and catalyst suspension (240 μL, 0.0036 mmol, 3 mol%). After adding nitroethane (86 μL, 1.2 mmol, 10 eq.) at room temperature, the mixture was cooled to –78 °C and then 0.82 M 2,2,2-trifluoroacetophenone/THF (146 μL, 0.12 mmol) was added dropwise for 1 min. After stirring the reaction mixture at the same temperature for 20 h, 0.2 M AcOH/THF (500 μL) was added slowly and warmed to room temperature. Water (1 mL) was added and the resulting mixture was extracted with EtOAc (2 mL). The organic layer was dried over Na_2SO_4. After removal of volatiles under reduced pressure, the resulting residue was analyzed by ^{1}H NMR to determine yield and diastereomeric ratio of product (mesitylene was used as internal standard). The crude product was purified by silica gel column chromatography (EtOAc/*n*-hexane) to give product. Enantiomeric excess was determined by chiral HPLC analysis.

E. Procedure for anti-selective catalytic asymmetric nitroaldol reaction on gram scale

To a flame dried round-bottom flask (30 mL) were charged with $NdCl_3 \bullet 6H_2O$ (61.7 mg, 0.172 mmol, 3 mol%) and amide-based ligand **1a** (97.7 mg, 0.172 mmol, 3 mol%), and dried under vacuum at room temperature for 5

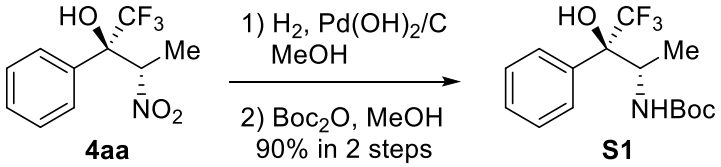
min. Ar was backfilled (evacuation/backfill was repeated for 5 times) to the test tube, and THF (4.3 mL) was added by well-dried syringes and needles at room temperature. After stirring the resulting slightly cloudy suspension at 60 °C for 30 min, 2.0 M NaO^{t}Bu/THF (516 μL, 1.03 mmol, 18 mol%) was added dropwise at the same temperature. After stirring the resulting mixture at 60 °C for 1 h (white precipitate appeared), the mixture was cooled to room temperature and nitroethane (1.23 mL, 17.2 mmol, 3.0 eq.) was added. Self-assembly of Nd/Na catalyst initiated in a few minutes and the resulting mixture was stirred at room temperature for 12 h to give a thick white suspension. The whole suspension was transferred to a conical tube (50 mL) with THF washing (3.5 mL x2). The tube was centrifuged at ca. 4,000 rpm for 1 min. The supernatant was decanted and THF (11 mL) was added. The tube was agitated using a vortex mixer for 1 min and centrifuged again, then the supernatant was decanted (washing process). This washing process was repeated again. The resulting precipitate was agitated with THF (11 mL) and the resulting suspension was transferred to a flame-dried round-bottom flask (200 mL). After adding THF (45 mL) and nitroethane (4.1 mL, 57.4 mmol, 10 eq.), the mixture was cooled to –78 °C and then 0.82 M 2,2,2-trifluoroacetophenone/THF (7.0 mL, 5.74 mmol) was added dropwise for 5 min. After stirring the reaction mixture at the same temperature for 20 h, 0.2 M AcOH/THF (25 mL) was added slowly and warmed to room temperature. Water (50 mL) was added and the resulting mixture was extracted with EtOAc (100 mL). The organic layer was dried over Na_2SO_4. After removal of volatiles under reduced pressure, the resulting residue was analyzed by ^{1}H NMR to determine diastereomeric ratio of product (mesitylene was used as internal standard). The crude product was purified by silica gel column chromatography (*n*-hexane/ EtOAc) to give (2*R*,3*S*)-1,1,1-trifluoro-3-nitro-2-phenylbutan-2-ol (**4aa**, 1.21 g, 85%) as white solid. Enantiomeric excess was determined by chiral HPLC analysis (93% ee).

F. Procedure for synthesis of 7 and 8

To a solution of **4aa** (250 mg, 1.00 mmol, 93% *ee*) in MeOH (10 mL) was added $Pd(OH)_2/C$ (50 mg [10 wt%Pd, 50% wet] and resulting mixture was stirred at room temperature under H_2 atmosphere for 12 h. After filtration through syringe filter, the filtrate was concentrated in *vacuo* to give (2*R*,3*S*)-3-amino-1,1,1-trifluoro-2-phenylbutan-2-ol (**7**, 212.2 mg, 96%) as colorless oil.
To a solution of **7** (87.6 mg, 0.40 mmol) in MeOH (950 μL) was added AcOH (50 μL) and formaldehyde (35wt% in water, 37.8 μL, 0.44 mmol, 1.1 eq.). After stirring at room temperature for 30 min, $NaB(CN)H_3$ (50.4 mg, 0.80 mmol, 2.0 eq.) was added to reaction mixture at 0 °C. After stirring at room temperature for 12 h, reaction mixture was concentrated in *vacuo* and $CHCl_3$ (2 mL) and sat. $NaHCO_3$ aq. (2 mL) was added to the residue. After separation, the aqueous layer was extracted with $CHCl_3$ (2 mL). The combined organic layers were washed with brine (2 mL) and dried over Na_2SO_4. After concentration in *vacuo*, the resulting residue was purified by silica gel chromatography (EtOAc/*n*-hexane) to give (2*R*,3*S*)-1,1,1-trifluoro-3-(methylamino)-2-phenylbutan-2-ol (**8**, 46.7 mg, 0.20 mmol, 50%) as colorless oil.

G. Procedure for synthesis of S1.

Enantiomeric purity after reduction of nitro group of **4aa** was determined after converting to Boc-protected **S1**.



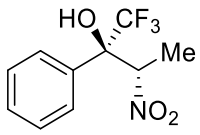
4aa **S1**

To a solution of **4aa** (100 mg, 0.40 mmol, 93% *ee*) in MeOH (3 mL) was added $Pd(OH)_2/C$ (20 mg [10 wt% Pd, 50% wet] and resulting mixture was stirred at room temperature under H2 atmosphere for 12 h. After purging with Ar, Boc_2O (175 mg, 0.80 mmol, 2.0 eq.) was added to the mother liquid and stirred at room temperature for 12 h. After filtration through disk filter, filtrate was concentrated in *vacuo*. The resulting residue was purified

by silica gel chromatography (EtOAc/*n*-hexane) to give **S1** (116 mg, 0.36 mmol, 90% in 2 steps) as white solid. Enantiomeric excess was determined by chiral HPLC analysis (93% ee).

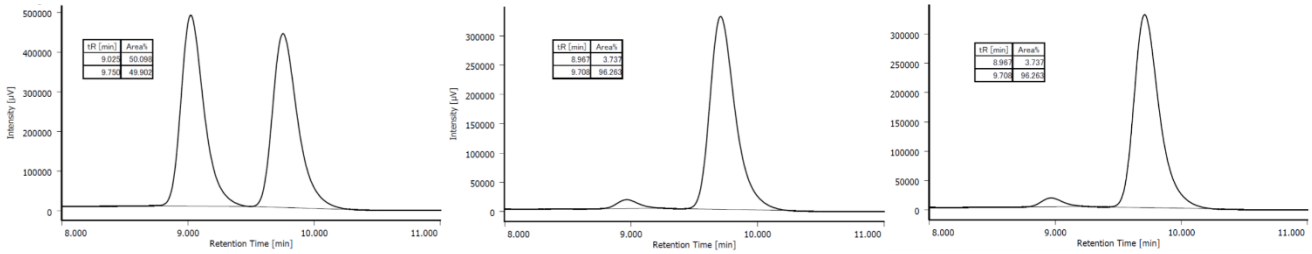
H. Characterizations.

(2*R*,3*S*)-1,1,1-Trifluoro-3-nitro-2-phenylbutan-2-ol (**4aa**):

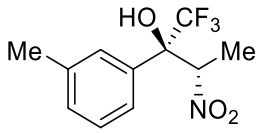


White solid; 1.21 g (85%, RE = Nd), 25.2 mg (84%, RE = Pr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.58 (m, 2H), 7.48–7.43 (m, 3H), 5.31 (q, *J* = 6.8 Hz, 1H), 4.71 (s, 1H), 1.37 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.9, 129.8, 129.1, 125.8, 124.4 (q, *J* = 285.8 Hz), 83.9, 77.9 (q, *J* = 29.2 Hz), 15.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.9; IR (thin film) *ν* 3497, 1559, 1450, 1230, 1278, 1201, 1187, 1170, 702, 628 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_{10}F_3NO_3Na$ *m*/*z* 272.0505 [M+Na]$^+$, found 272.0501; $[\alpha]_D^{25}$ 5.9 (*c* 0.95, $CHCl_3$, 94% ee); HPLC analysis: Daicel CHIRALPAK IA, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t_R = 9.7 min (major), 9.0 min (minor):

Racemic Sample | Reaction Sample (RE = Nd) | Reaction Sample (RE = Pr)

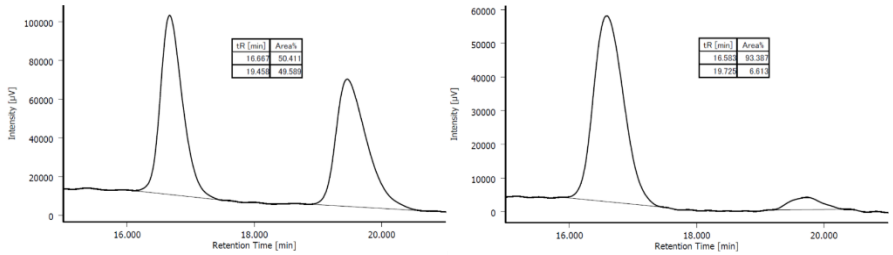


(2*R*,3*S*)-1,1,1-Trifluoro-3-nitro-2-(*m*-tolyl)butan-2-ol (**4ba**):

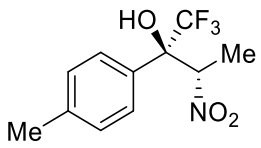


White solid; 26.6 mg (84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.36–7.31 (m, 2H), 7.24 (d, *J* = 6.6 Hz, 1H), 5.29 (q, *J* = 6.8 Hz, 1H), 4.68 (s, 1H), 2.40 (s, 3H), 1.37 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 132.8, 130.5, 129.0, 126.4, 124.4 (q, *J* = 285.8 Hz), 122.8, 83.9, 77.6 (q, *J* = 29.2 Hz), 21.8, 15.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.8; IR (thin film) *ν* 3509, 1559, 1357, 1270, 1200, 1121, 1161, 1002, 969, 723 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}O_3NF_3Na$ *m*/*z* 286.0661 [M+Na]$^+$, found 286.0664; $[\alpha]_D^{25}$ 4.6 (*c* 0.97, $CHCl_3$, 87% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 99.9/0.1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t_R = 16.6 min (major), 19.7 min (minor):

Racemic Sample | Reaction Sample

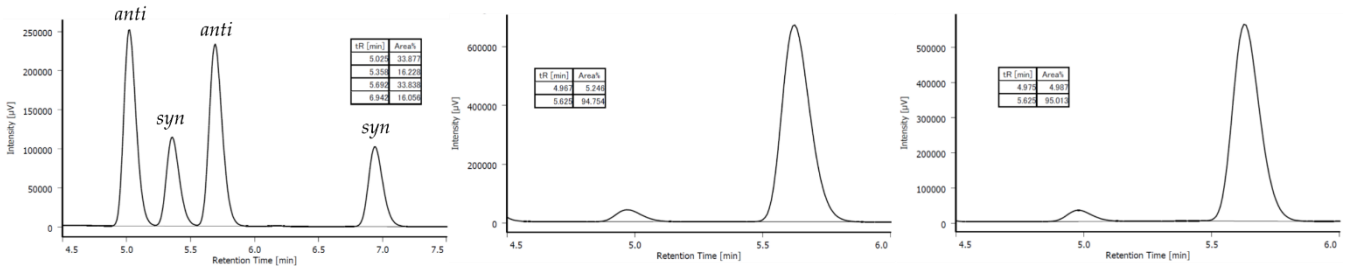


(2*R*,3*S*)-1,1,1-Trifluoro-3-nitro-2-(*p*-tolyl)butan-2-ol (**4ca**):



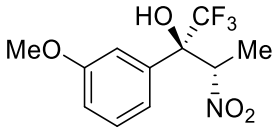
White solid; 26.6 mg (84%, RE = Nd), 25.9 mg (82%, RE = Pr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 5.28 (q, *J* = 6.8 Hz, 1H), 4.66 (s, 1H), 2.38 (s, 3H), 1.37 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 129.9, 129.8, 125.7, 124.5 (q, *J* = 285.8 Hz), 83.9, 77.6 (q, *J* = 29.1 Hz), 21.2, 15.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.0; IR (thin film) *ν* 3504, 1554, 1299, 1272, 1201, 1190, 1169, 1002, 920, 813 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}O_3NF_3Na$ *m*/*z* 286.0661 [M+Na]$^+$, found 286.0657; $[\alpha]_D^{25}$ 5.0 (*c* 0.51, $CHCl_3$,

90% ee); HPLC analysis: Daicel CHIRALPAK ID, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t_R = 5.6 min (major), 4.9 min (minor):



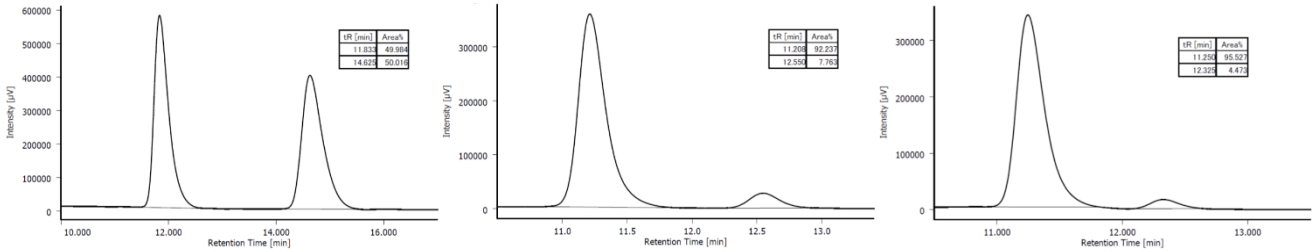
Racemic Sample | Reaction Sample (RE = Nd) | Reaction Sample (RE = Pr)

(2*R*,3*S*)-1,1,1-Trifluoro-2-(3-methoxyphenyl)-3-nitrobutan-2-ol (**4da**):

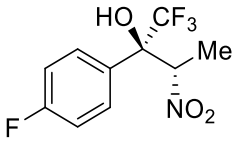


White solid; 22.4 mg (67%, RE = Nd), 26.9 mg (85%, RE = Pr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.1, 7.8 Hz, 1H), 7.19 (s, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 6.96 (dd, *J* = 8.1, 2.7 Hz, 1H), 5.27 (q, *J* = 6.8 Hz, 1H), 4.71 (s, 1H), 3.85 (s, 3H), 1.37 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 134.4, 130.2, 124.4 (q, *J* = 285.8 Hz), 117.7, 115.0, 112.2, 83.9, 77.8 (q, *J* = 29.2 Hz), 55.5, 15.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.8; IR (thin film) *ν* 3503, 2359, 1558, 1494, 1456, 1357, 1268, 1200, 1163, 724 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{12}O_3NF_3Na$ *m*/*z* 302.0611 [M+Na]$^+$, found 302.0606; $[\alpha]_D^{25}$ 2.9 (*c* 1.13, $CHCl_3$, 91% ee); HPLC analysis: Daicel CHIRALPAK IA, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t_R = 11.2 min (major), 12.6 min (minor):

Racemic Sample | Reaction Sample (RE = Nd) | Reaction Sample (RE = Pr)

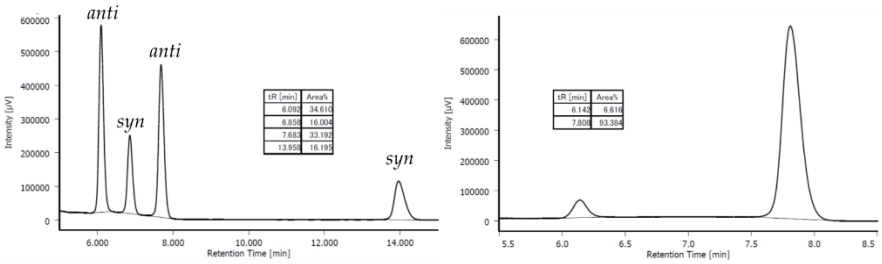


(2*R*,3*S*)-1,1,1-Trifluoro-2-(4-fluorophenyl)-3-nitrobutan-2-ol (**4ea**):

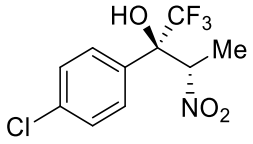


White solid; 24.7 mg (77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 5.1, 3.7 Hz, 2H), 7.15 (m, 2H), 5.27 (q, *J* = 6.8 Hz), 4.76 (s, 1H), 1.37 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (d, J = 248.6 Hz), 128.7 (d, *J* = 3.7 Hz), 127.9 (d, *J* = 8.0 Hz), 124.3 (q, *J* = 286.5 Hz), 116.2 (d, *J* = 29.1 Hz), 83.7, 77.5 (q, *J* = 29.2 Hz), 15.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.1, −111.3; IR (thin film) *ν* 3504, 1560, 1514, 1392, 1357, 1274, 1241, 1201, 1164, 837 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_8O_3NF_4$ *m*/*z* 266.0446 [M-H]$^-$, found 266.0437; $[\alpha]_D^{25}$ 5.6 (*c* 0.76, $CHCl_3$, 87% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t_R = 7.8 min (major), 6.1 min (minor):

Racemic Sample | Reaction Sample

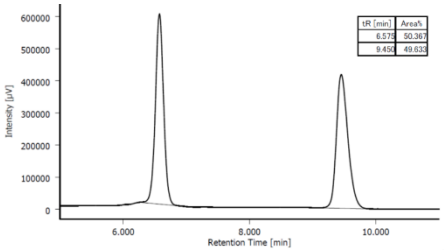


(2*R*,3*S*)-2-(4-Chlorophenyl)-1,1,1-trifluoro-3-nitrobutan-2-ol (**4fa**):

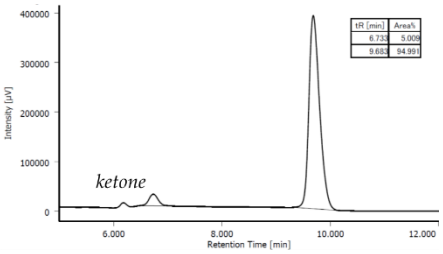


White solid; 27.2 mg (80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 5.25 (q, *J* = 6.9 Hz, 1H), 4.76 (s, 1H), 1.37 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.4, 132.0, 127.6, 124.4, 124.1 (q, *J* = 285.8 Hz), 83.5, 77.7 (q, *J* = 29.2 Hz), 15.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.0; IR (thin film) *ν* 3503, 1559, 1496, 1357, 1271, 1202, 1166, 1096, 920, 824 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_8O_3NClF_3$ *m*/*z* 282.0150 [M-H]$^-$, found 282.0148; $[\alpha]_D^{25}$ 10.4 (*c* 1.06, $CHCl_3$, 90% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t_R = 9.7 min (major), 6.7 min (minor):

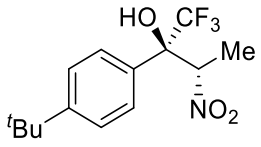
Racemic Sample



Reaction Sample

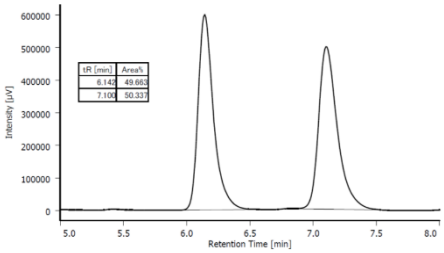


(2*R*,3*S*)-2-(4-(*tert*-Butyl)phenyl)-1,1,1-trifluoro-3-nitrobutan-2-ol (**4ga**):

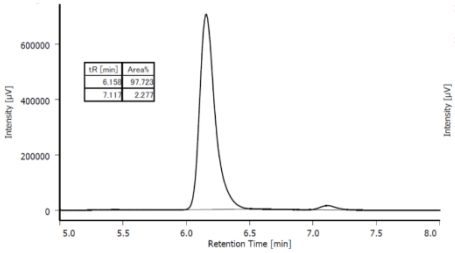


White solid; 32.8 mg (90%, RE = Nd), 27.3 mg (74%, RE = Pr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 5.29 (q, *J* = 6.8 Hz, 1H), 4.65 (s, 1H), 1.37 (d, *J* = 6.8 Hz, 3 H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 129.8, 126.3, 125.5, 124.5 (q, *J* = 285.8 Hz), 83.9, 77.9 (q, *J* = 29.2 Hz), 34.8, 31.3, 15.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.0; IR (thin film) *ν* 3510, 2964, 1559, 1355, 1273, 1198, 1164, 1122, 1109, 706 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{17}O_3NF_3$ *m*/*z* 304.1166 [M-H]$^-$, found 304.1153; $[\alpha]_D^{25}$ 6.7 (*c* 0.81, $CHCl_3$, 95% ee); HPLC analysis: Daicel CHIRALPAK IA, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t_R = 6.2 min (major), 7.1 min (minor):

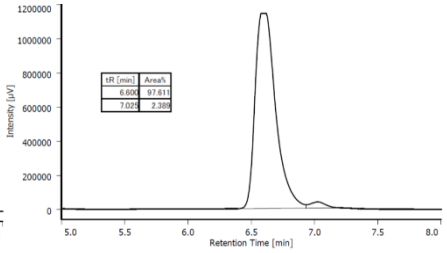
Racemic Sample



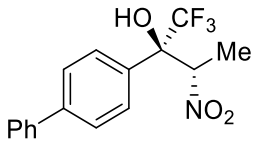
Reaction Sample (RE = Nd)



Reaction Sample (RE = Pr)

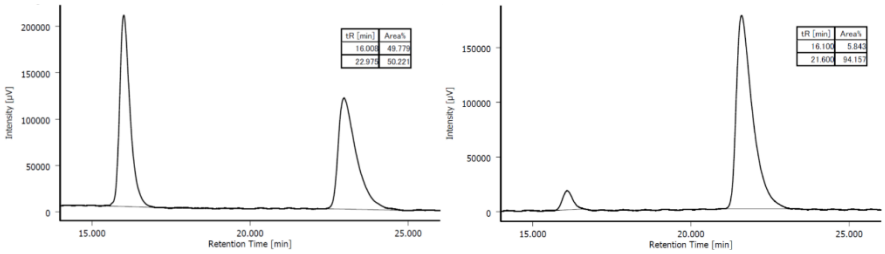


(2*R*,3*S*)-2-([1,1'-Biphenyl]-4-yl)-1,1,1-trifluoro-3-nitrobutan-2-ol (**4ha**):

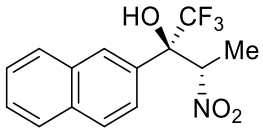


White solid; 32.1 mg (82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69−7.59 (m, 6H), 7.49−7.37 (m, 3H), 5.34 (q, *J* = 6.8 Hz, 1H), 4.74 (s, 1H), 1.42 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 139.3, 131.1, 128.5, 127.5, 127.1, 126.7, 125.7, 123.8 (q, *J* = 286.6 Hz), 83.2, 77.3 (q, *J* = 29.2 Hz), 14.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.9; IR (thin film) *ν* 3500, 1557, 1300, 1271, 1199, 1170, 1002, 835, 765, 732 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{14}O_3NF_3Na$ *m*/*z* 348.0818 [M+Na]$^+$, found 348.0815; $[\alpha]_D^{25}$ 9.4 (*c* 1.23, $CHCl_3$, 88% ee); HPLC analysis: Daicel CHIRALPAK IA, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t_R = 21.6 min (major), 16.1 min (minor):

Racemic Sample Reaction Sample

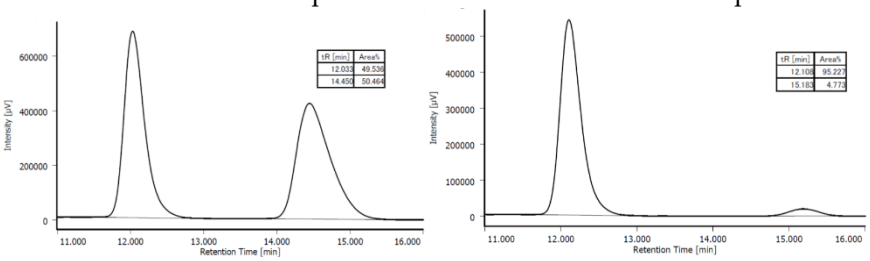


(2*R*,3*S*)-1,1,1-Trifluoro-2-(naphthalen-2-yl)-3-nitrobutan-2-ol (**4ia**):

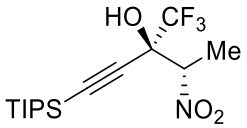


White solid; 32.4 mg (90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.94–7.87 (m, 3H), 7.60-7.56 (m, 3H), 5.44 (q, *J* = 6.9 Hz, 1H), 4.84 (s, 1H), 1.39 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.6, 133.1, 130.1, 129.1, 128.8, 127.8, 127.5, 127.1, 126.4, 124.5 (q, *J* = 285.8 Hz), 122.1, 83.8, 78.1 (q, *J* =29.2 Hz), 15.0, 14.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.5; IR (thin film) *ν* 3487, 1555, 1354, 1311, 1272, 1253, 1191, 1162, 822, 752 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{13}O_3NF_3$ *m*/*z* 300.0842 $[M+H]^+$, found 300.0843; $[\alpha]_D^{25}$ 1.0 (*c* 0.76, $CHCl_3$, 90% ee); HPLC analysis: Daicel CHIRALPAK IA, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t_R = 12.1 min (major), 15.1 min (minor):

Racemic Sample Reaction Sample

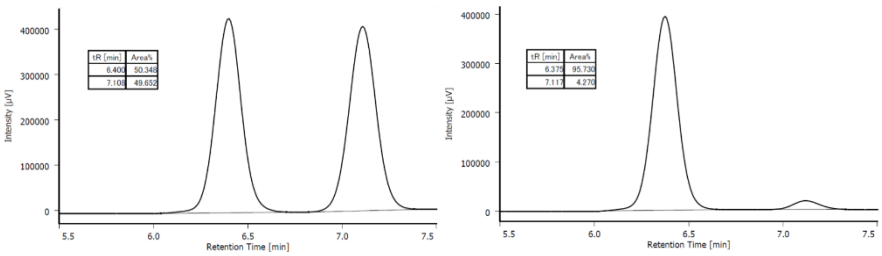


(3*R*,4*S*)-4-Nitro-3-(trifluoromethyl)-1-(triisopropylsilyl)pent-1-yn-3-ol (**4ja**):

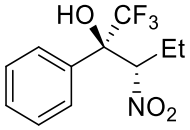


Colorless oil, 33.5 mg (79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (q, *J* = 6.8 Hz, 1H), 3.77 (s, 1H), 1.81 (d, *J* = 6.8 Hz, 3H), 1.14–1.08 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.7 (q, *J* = 284.3 Hz), 96.1, 94.5, 83.9, 73.2 (q, *J* = 32.1 Hz), 18.5, 15.9, 11.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ −78.2; IR (thin film) *ν* 3491, 2947, 2869, 1567, 1357, 1264, 1204, 1062, 882, 666 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{26}O_3NF_3NaSi$ *m*/*z* 376.1526 $[M+Na]^+$, found 376.1526; $[\alpha]_D^{25}$ −43.3 (*c* 1.34, $CHCl_3$, 92% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 99/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t_R = 6.4 min (major), 7.1 min (minor):

Racemic Sample Reaction Sample

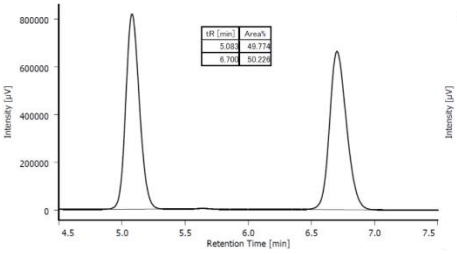


(2*R*,3*S*)-1,1,1-Trifluoro-3-nitro-2-phenylpentan-2-ol (**4ab**):

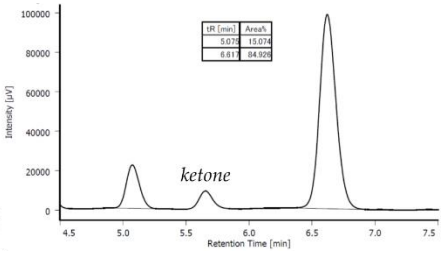


White solid; 26.0 mg (83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.57 (m, 2H), 7.48–7.41 (m, 3H), 5.07(dd, *J* = 3.2, 11.8 Hz, 1H), 4.73 (s, 1H), 2.05 (ddq, *J* = 3.2, 7.4, 11.8 Hz, 1H), 1.41 (ddq, *J* = 3.2, 4.4, 7.4 Hz, 1H), 0.85 (dd, *J* = 7.4, 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2, 129.7, 129.1, 125.7, 124.3 (q, *J* = 285.8 Hz), 90.7, 77.9 (q, *J* = 29.2 Hz), 22.2, 10.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.0; IR (thin film) *ν* 3504, 1559, 1454, 1374, 1306, 1265, 1200, 1164, 723, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{13}O_3NF_3$ *m*/*z* 264.0842 $[M+H]^+$, found 264.0838; $[\alpha]_D^{25}$ 15.6 (*c* 0.56, $CHCl_3$, 70% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t_R = 6.6 min (major), 5.1 min (minor):

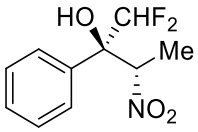
Racemic Sample



Reaction Sample

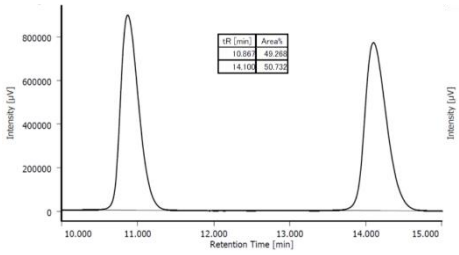


(2*R*,3*S*)-1,1-Difluoro-3-nitro-2-phenylbutan-2-ol (**4ka**):

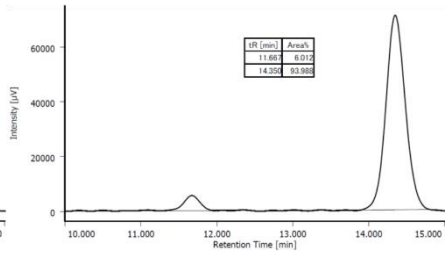


White solid; 21.4 mg (77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.1 Hz, 2H), 7.47-7.40 (m, 3H), 5.80 (t, *J* = 184.8 Hz, 1H), 5.24 (q, *J* = 6.8 Hz, 1H), 4.24 (s, 1H), 1.37 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 129.4, 129.1, 125.9, 115.8 (t, *J* = 251.6 Hz), 83.8, 77.0 (t = 43.0 Hz), 14.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.7 (dd, *J* = 55.3, 293.5 Hz), -129.5 (dd, *J* = 55.7, 283.0 Hz); IR (thin film) *ν* 3525, 1556, 1451, 1390, 1356, 1195, 1126, 1075, 916, 701 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_{10}O_3NF_2$ *m*/*z* 230.0634 $[M-H]^-$, found 230.0627; $[\alpha]_D^{25}$ −2.1 (*c* 0.36, $CHCl_3$, 87% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, t_R = 14.4 min (major), 11.7 min (minor):

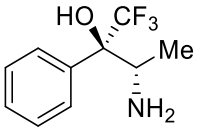
Racemic Sample



Reaction Sample

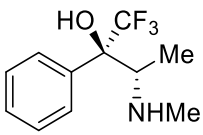


(2*R*,3*S*)-3-Amino-1,1,1-trifluoro-2-phenylbutan-2-ol (**7**)



Colorless oil; 212.2 mg (96%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.56–7.54 (m, 2H), 7.40–7.31 (m, 3H), 3.67 (q, *J* = 6.6 Hz, 1H), 0.77 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 139.4, 130.1, 130.1, 128.6 (q, *J* = 285.5 Hz), 128.0, 80.4 (q, *J* = 25.5 Hz), 52.4, 18.4; ^{19}F NMR (376 MHz, CD_3OD) δ −75.2; IR (thin film) *ν* 3416, 3352, 1452, 1385, 1269, 1153, 1075, 984, 913, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{10}H_{13}ONF_3$ *m*/*z* 220.0944 $[M+H]^+$, found 220.0941; $[\alpha]_D^{25}$ −39.5 (*c* 0.61, MeOH, 93% ee)

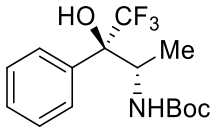
(2*R*,3*S*)-1,1,1-Trifluoro-3-(methylamino)-2-phenylbutan-2-ol (**8**)



Colorless oil; 46.7 mg (50%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.59–7.57 (m, 2H), 7.42–7.36 (m, 3H), 3.27 (q, *J* = 6.6 Hz, 1H), 2.46 (s, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 139.7, 132.8, 130.0, 130.0, 128.5 (q, *J* = 285.1 Hz), 128.2, 80.4 (q, *J* = 25.5 Hz), 60.9, 35.5, 16.0; ^{19}F NMR (376 MHz, CD_3OD) δ −74.8; IR (thin film) *ν* 2867, 1451, 1380, 1266, 1155, 1075, 1002,

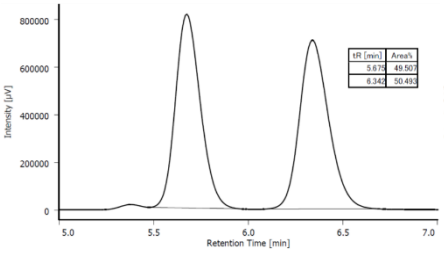
910, 761, 704 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{15}ONF_3$ *m*/*z* 234.1100 $[M+H]^+$, found 234.1092; $[\alpha]_D^{25}$ −25.8 (*c* 0.33, $CHCl_3$, 93% ee)

***tert*-Butyl ((2S,3R)-4,4,4-trifluoro-3-hydroxy-3-phenylbutan-2-yl)carbamate (S1)**

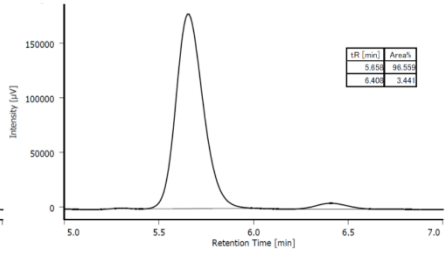


White solid; 116 mg (90%); ^1H NMR (400 MHz, CD_3OD) δ 7.60 (d, *J* = 7.6 Hz, 2H), 7.45−7.36 (m, 3H), 4.41 (q, *J* = 6.8 Hz, 1H), 1.50 (s, 9H), 0.88 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 136.8, 128.6, 128.5, 126.1, 125.8 (q, *J* = 286.5 Hz), 81.3, 77.2 (q, *J* = 33.5 Hz), 52.6, 28.4, 14.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.7; IR (thin film) *ν* 3383, 2981, 1671, 1520, 1369, 1269, 1161, 1119, 1063, 702 cm^{-1}; HRMS (ESI) calcd. for $C_{15}H_{21}O_3NF_3$ *m*/*z* 320.1468 [M+H]+, found 320.1464; $[\alpha]_D^{25}$ −22.1 (*c* 0.96, $CHCl_3$, 93% ee); HPLC analysis: Daicel CHIRALPAK IF, φ 0.46 cm x 25 cm, *n*-hexane/*i*-PrOH = 20/1, flow rate = 1.0 mL/min, detection at 210 nm flow rate = 1.0 mL/min, tR = 5.7 min (major), 6.4 min (minor):

Racemic Sample



Reaction Sample



I. Determination of Absolute Configuration

The absolute configuration of nitroaldol product **4aa** was determined by X-ray crystallographic analysis. Single crystals of **4aa** were obtained from a solution of *n*-hexane. A suitable crystal was selected and the sample was measured on a Rigaku R-AXIS RAPID diffractometer using graphite monochromated Cu-Ka radiation. The data were collected at 93 K. Refined structure and crystallographic parameters are summarized in Figure S1 and Table S1. The ORTEP diagram was drawn by Mercury 3.8. CCDC 1587722 contains the supplementary crystallographic data for **4aa**.

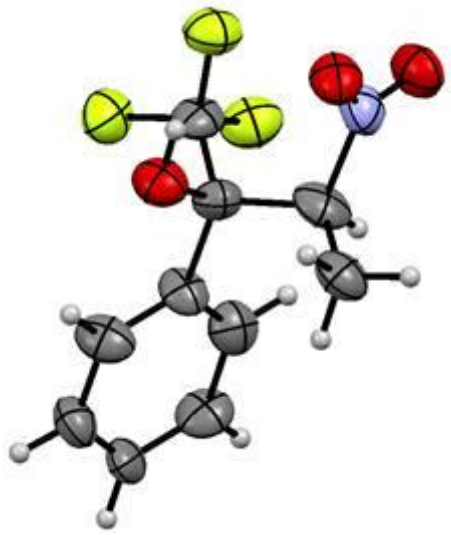


Figure S1. ORTEP diagram of **4aa**. Color code; grey: C, white: H, blue: N, red: O, yellow: F

Table S1. Selected crystal data of **4aa**

Empirical Formula	$C_{20}H_{20}F_6N_2O_6$
Formula Weight	498.38
Crystal Color, Habit	colorless, needle
Crystal Dimensions	0.200 x 0.010 x 0.010 mm
Crystal System	monoclinic
Lattice Parameters	
a	19.267(2) Å
b	5.6798(7) Å
c	13.3285(17) Å
β	132.830(9)°
V	1069.7(3) $Å^3$
Space Group	C2 (#5)
Z value	2
D_{calc}	1.547 g/cm^3
R1	0.0856
Flack parameter[9]	–0.3(6)
F_{000}	512

J. References for Exprimental Section of Chapter 4

1 Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176.

2 Nitabaru, T.; Nojiri, A.; Kobayashi, M.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 13860.

3 Schenck, H. A.; Lenkowski, P. W.; Choudhury-Mukherjee, I.; Ko, S. H.; Stables, J. P.; Patel, M. K.; Brown, M. L. *Bioorg. Med. Chem.* **2004**, *12*, 979.

4 Mayer, T.; Maier, M. E. *Eur. J. Org. Chem.* **2007**, 4711.

5 Konno, T.; Takehana, T.; Mishima, M.; Ishihara, T. *J. Org. Chem.* **2006**, *71*, 3545.

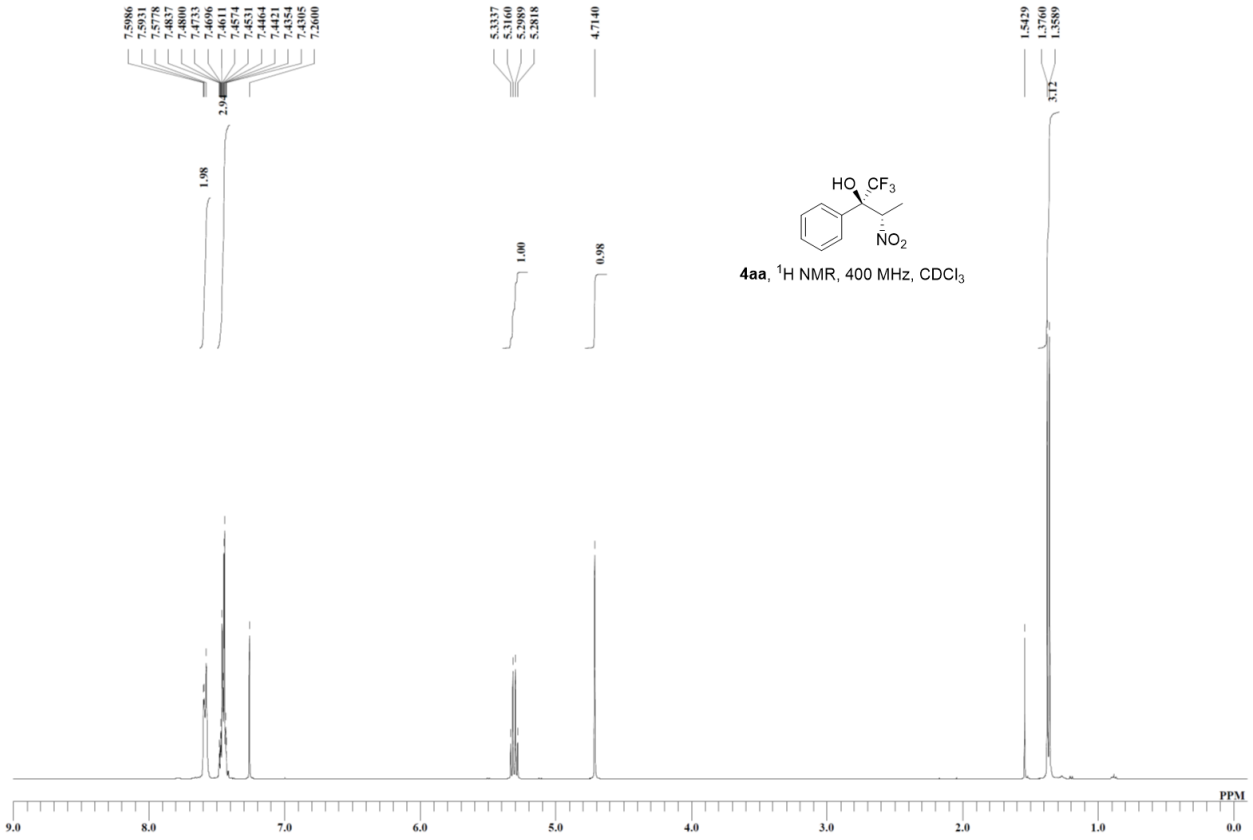
6 Emer, E.; Twilton, J.; Tredwell, M.; Calderwood, S.; Collier, T. L.; Liégault, B.; Taillefer, M.; Gouverneur, V. *Org. Lett.* **2014**, *16*, 6004.

7 Kasztelan, A.; Biedrzycki, M.; Kwiatkowski, P. *Adv. Synth. Catal.* **2016**, *358*, 2962.

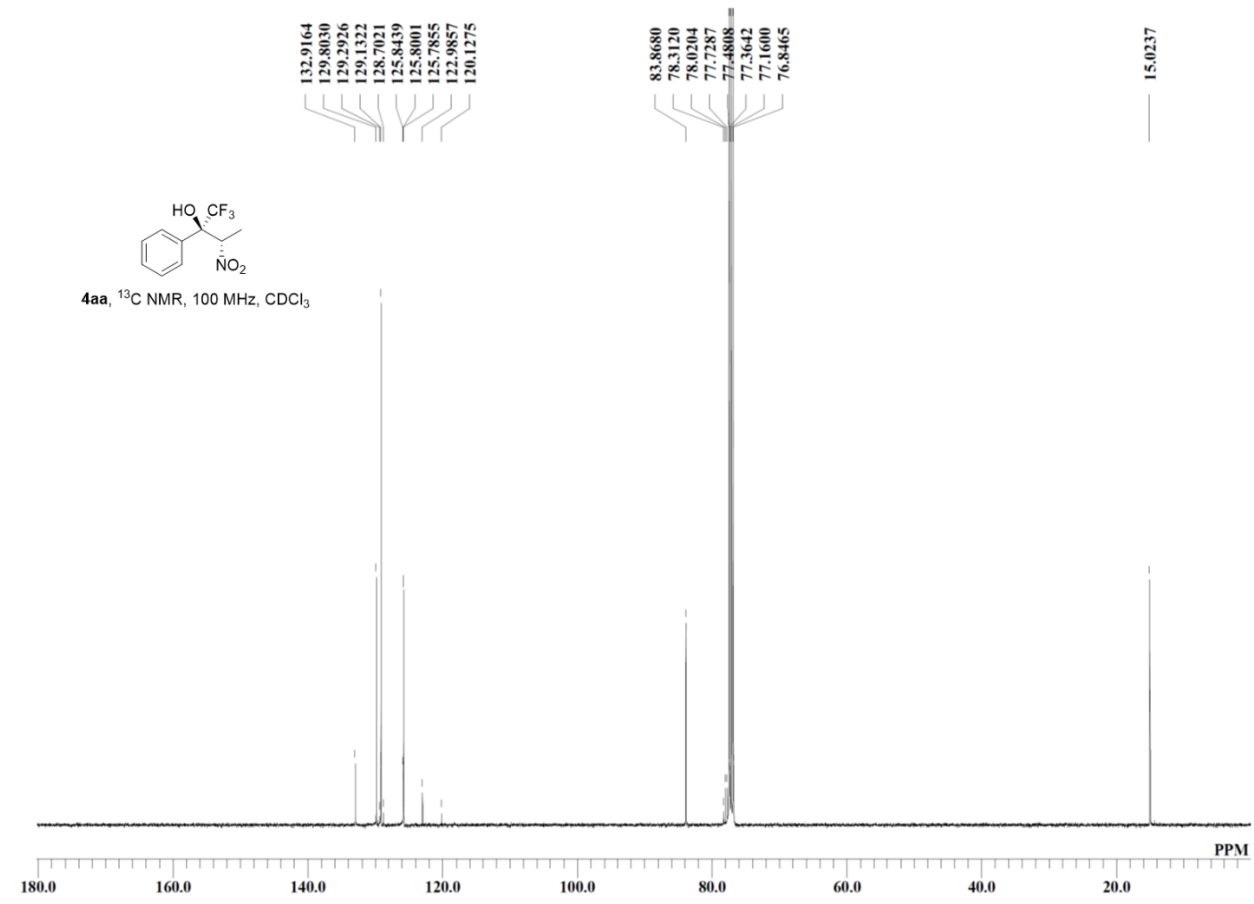
8 Maraval,V.; Leroyer, L.; Harano, A.; Barthes, C.; Saquet, A.; Duhayon, C.; Shinmyozu, T.; Chauvin, R. *Chem. Eur. J.* **2011**, *17*, 5086.

9 Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876.

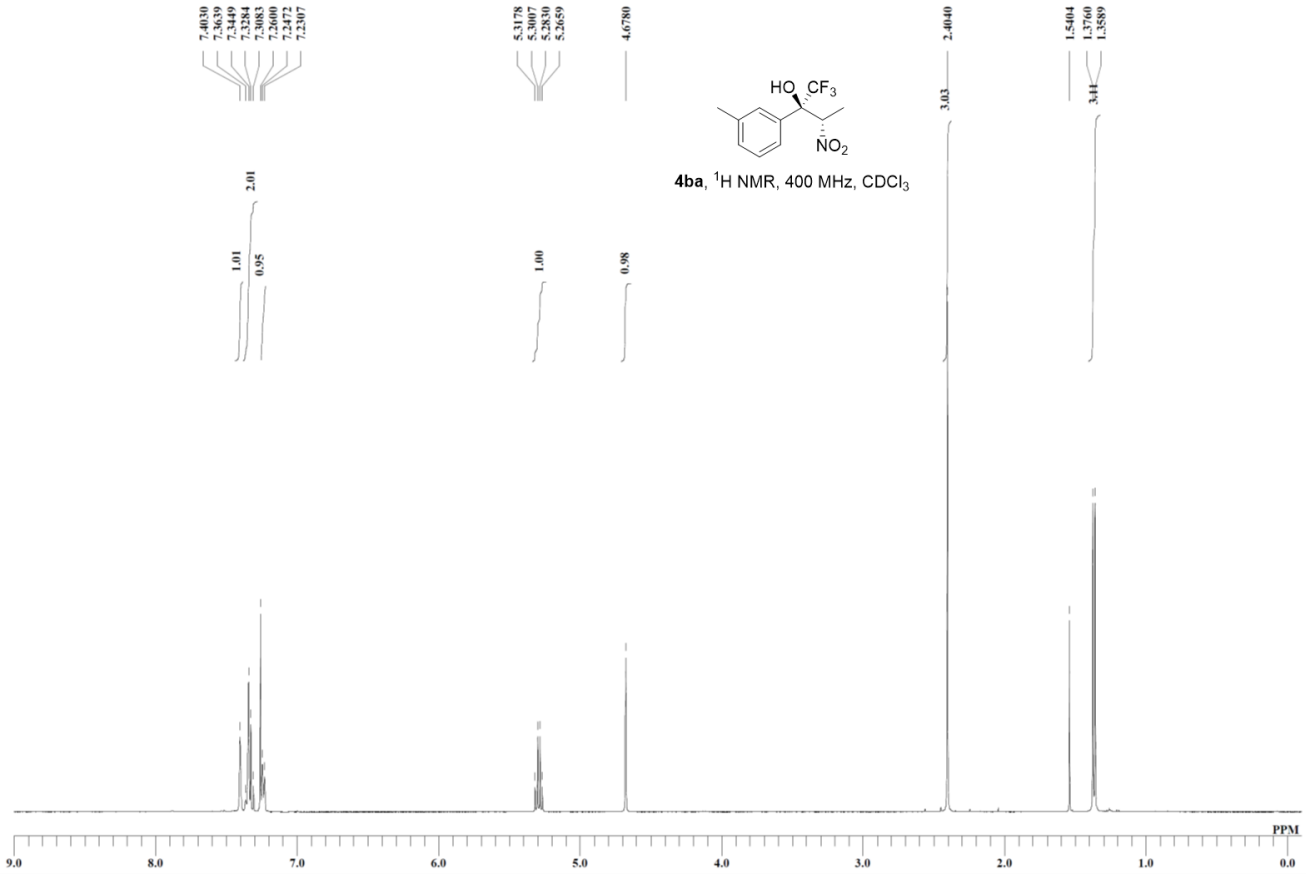
K. ^{1}H and ^{13}C NMR Spectra.



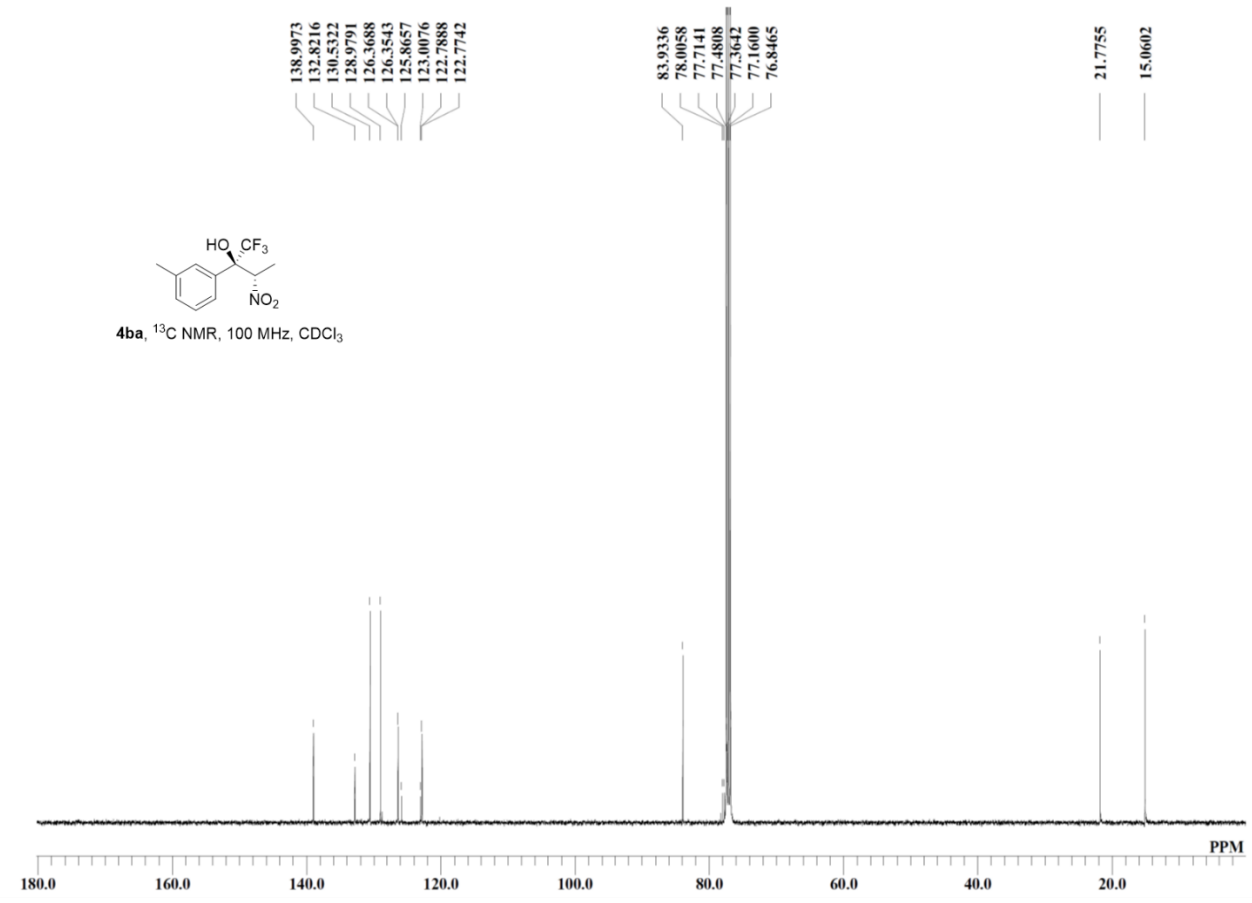
4aa, ^{1}H NMR, 400 MHz, $CDCl_3$



4aa, ^{13}C NMR, 100 MHz, $CDCl_3$



4ba, ^{1}H NMR, 400 MHz, $CDCl_3$



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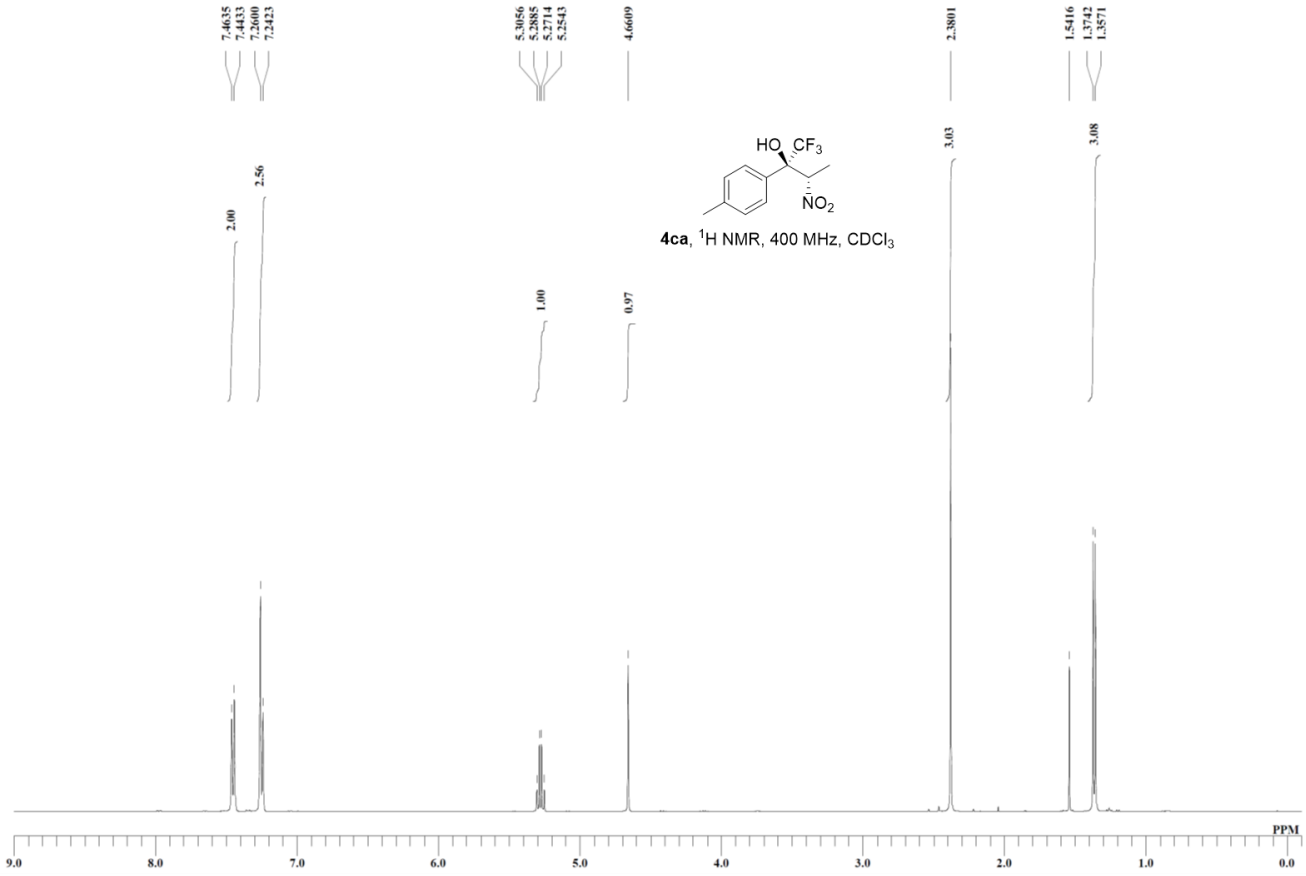
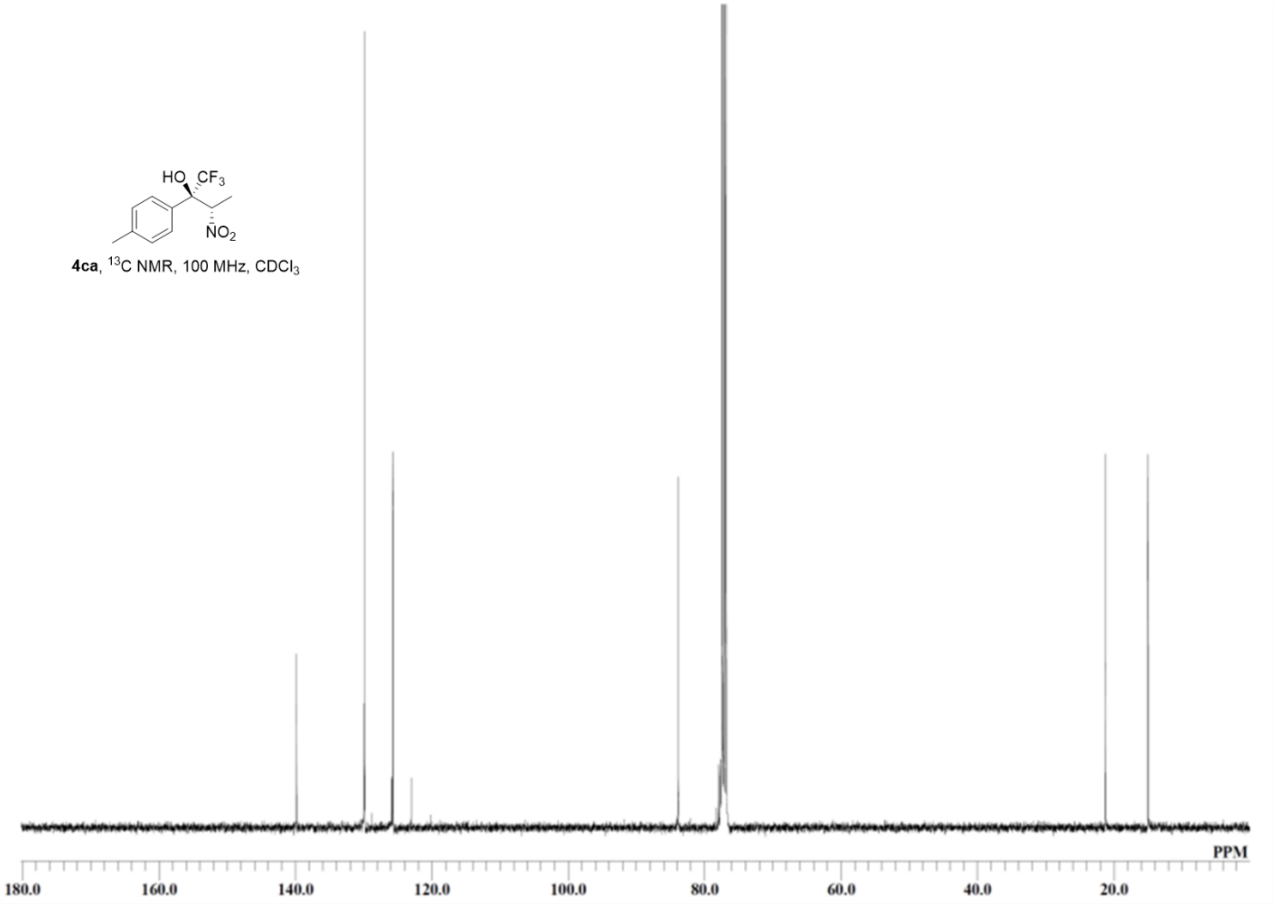


4ca, ^{1}H NMR, 400 MHz, $CDCl_3$



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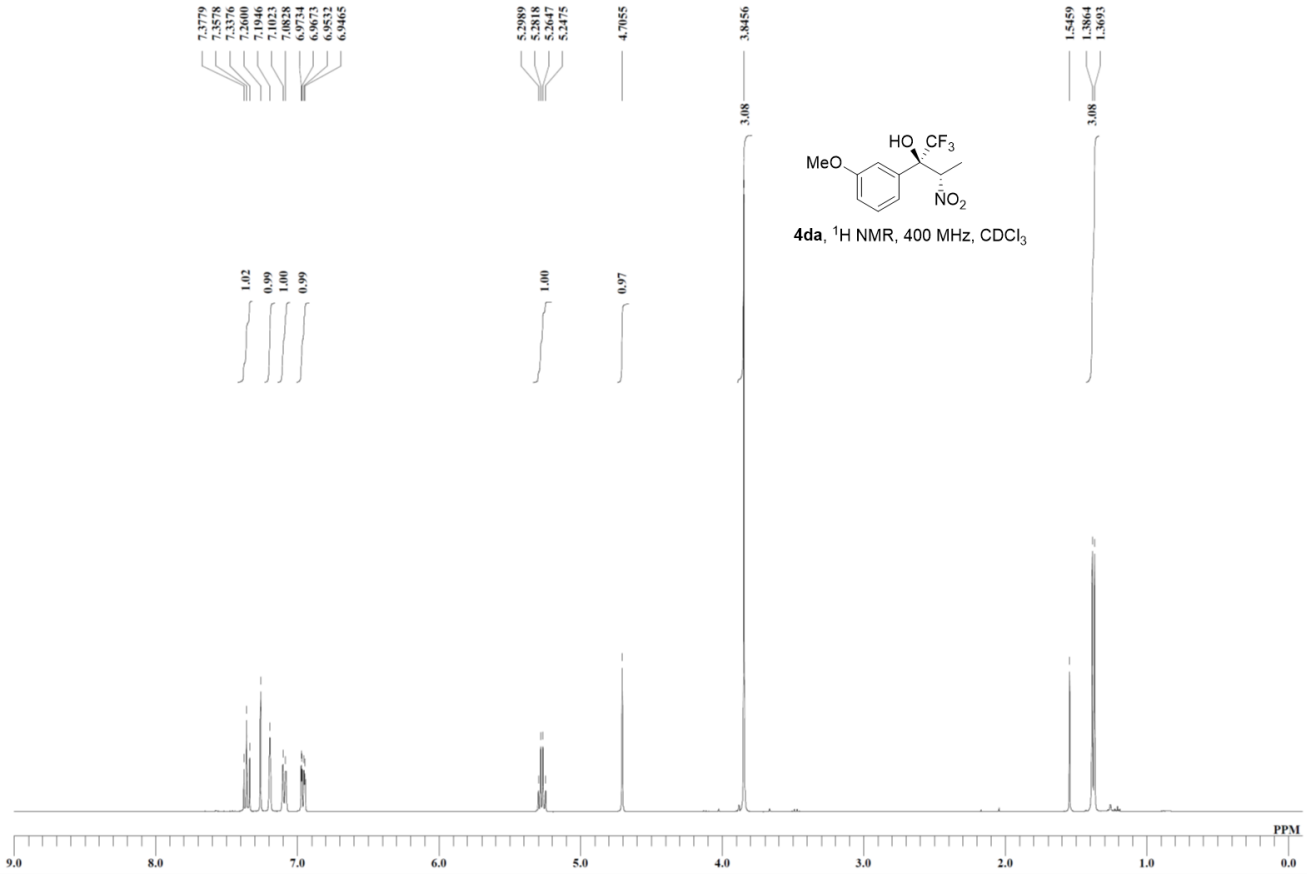
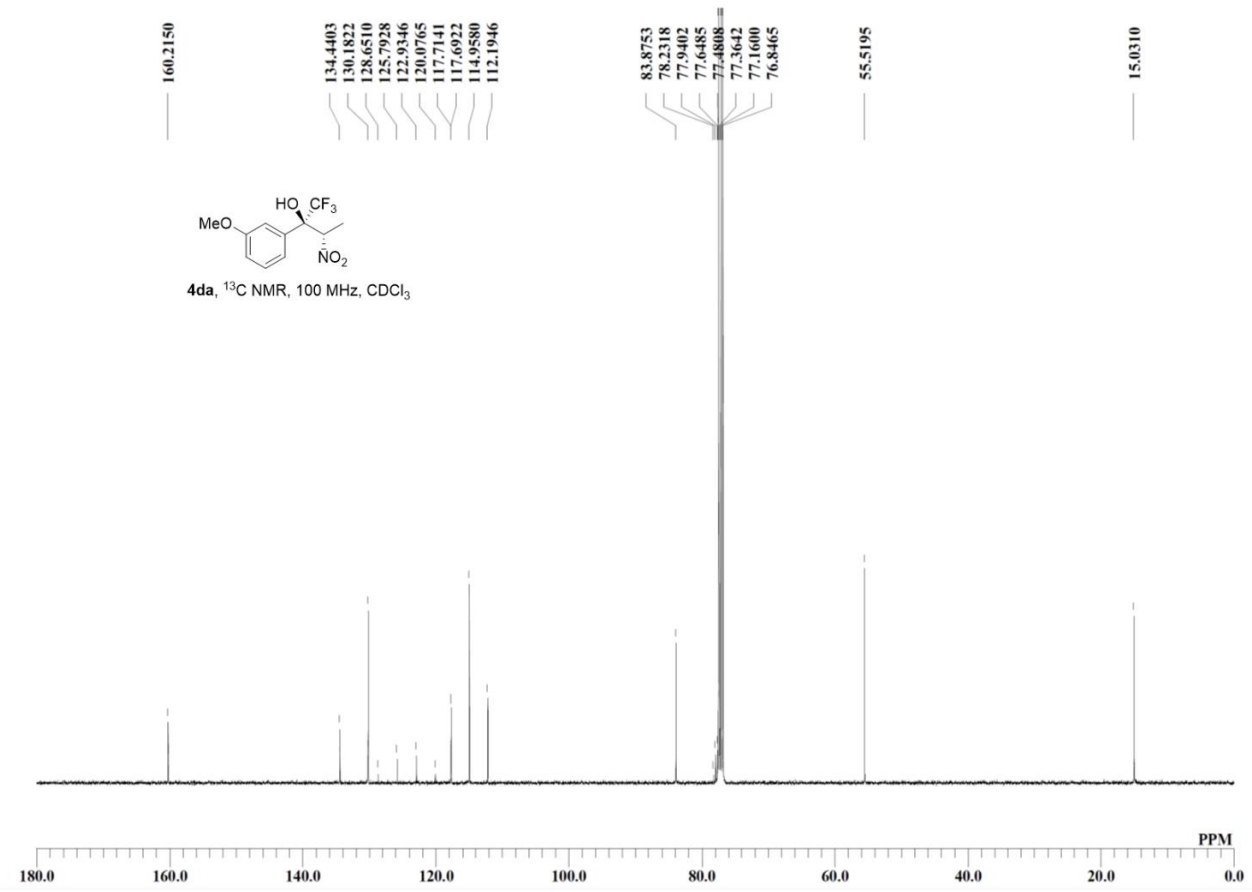


4da, ^{1}H NMR, 400 MHz, $CDCl_3$



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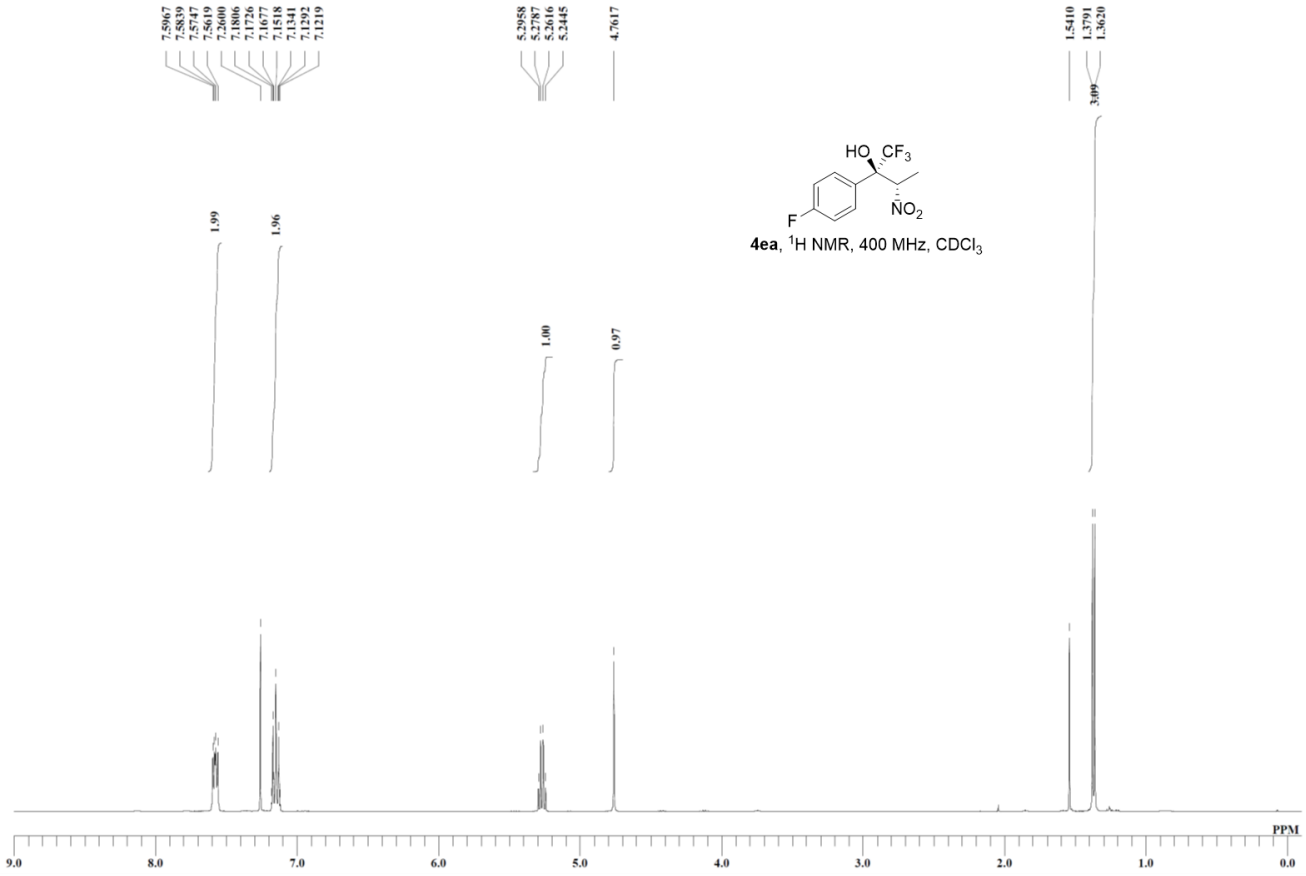

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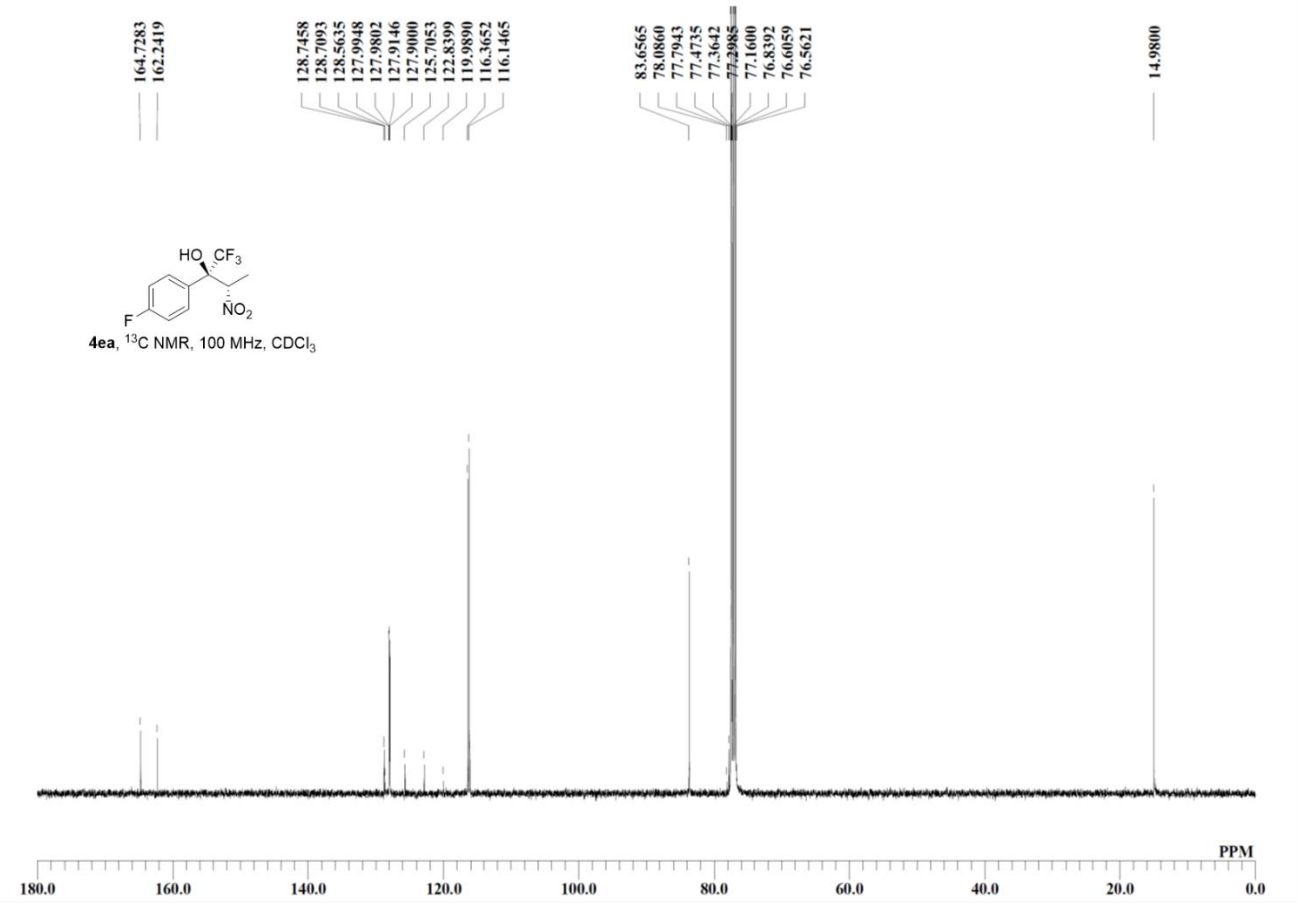

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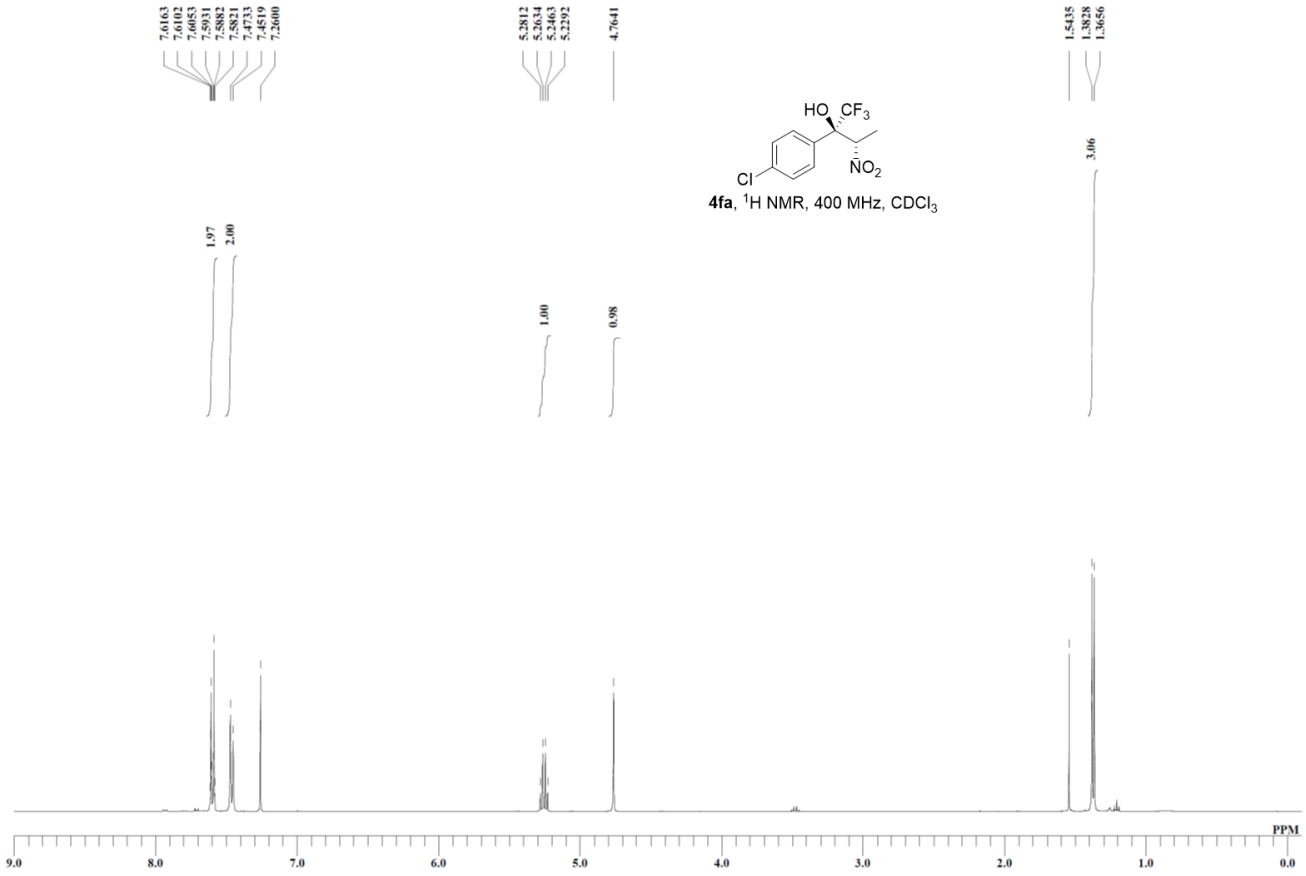
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5.2463
5.2292
4.7641
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CF3
Cl
NO2
4fa, 1H NMR, 400 MHz, CDCl3
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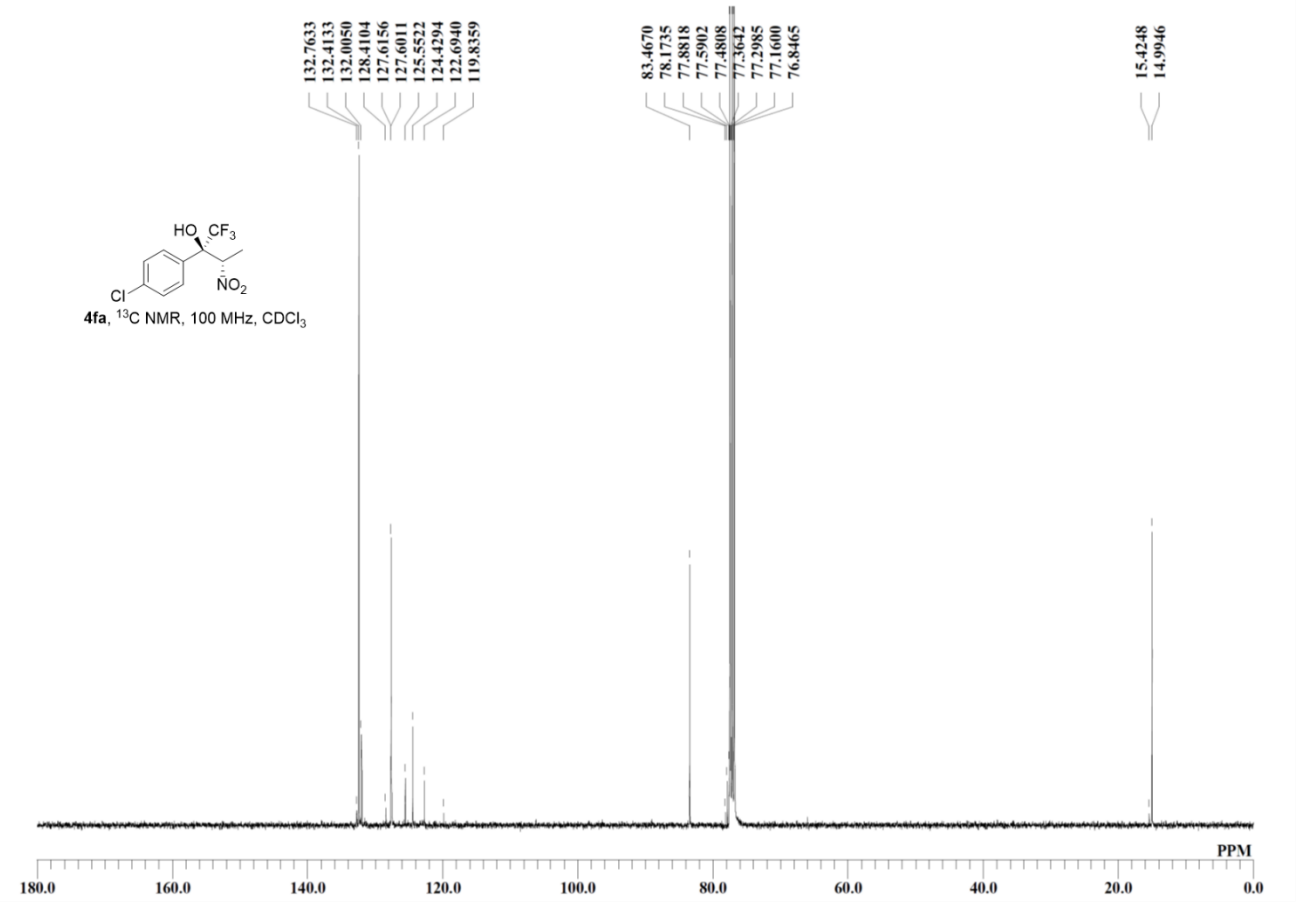
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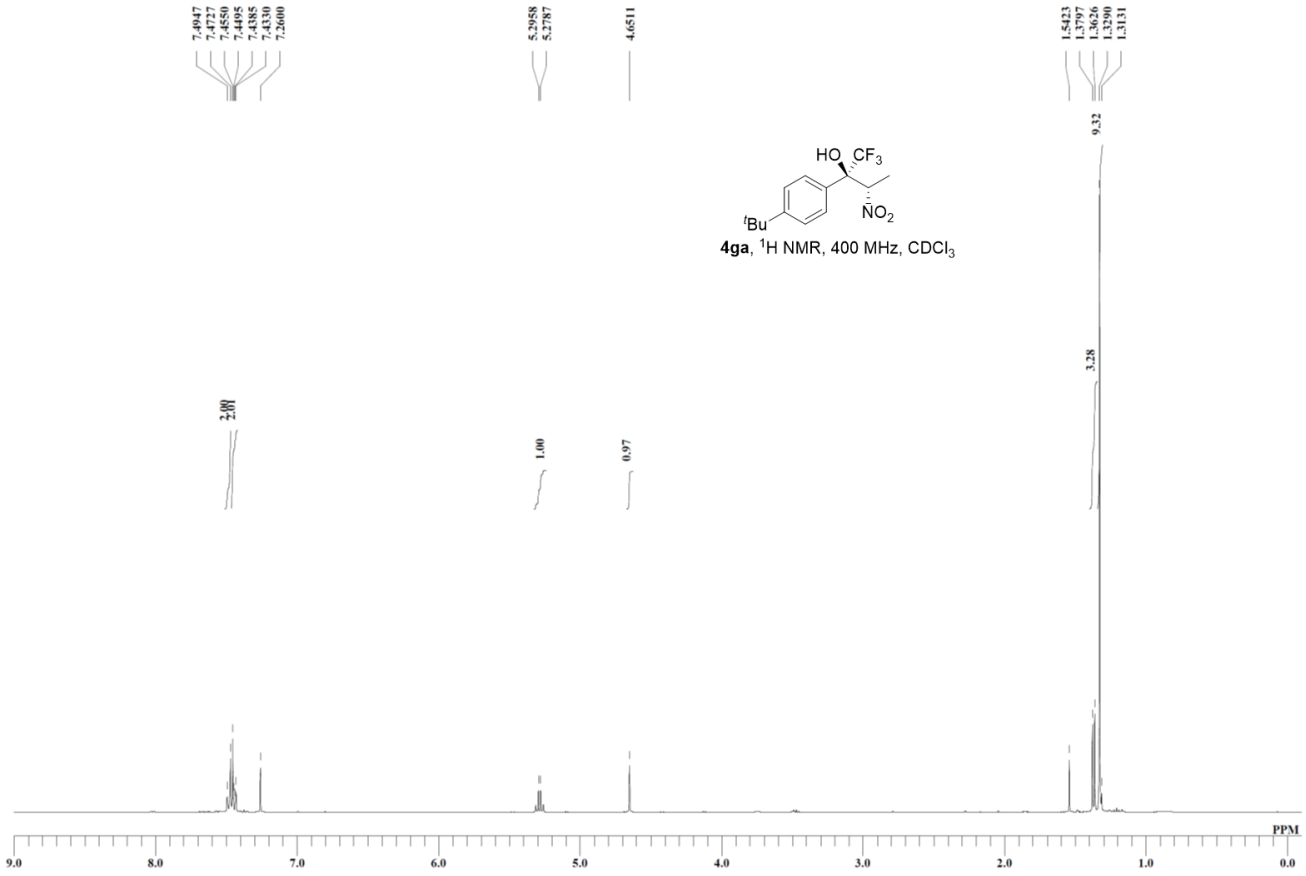
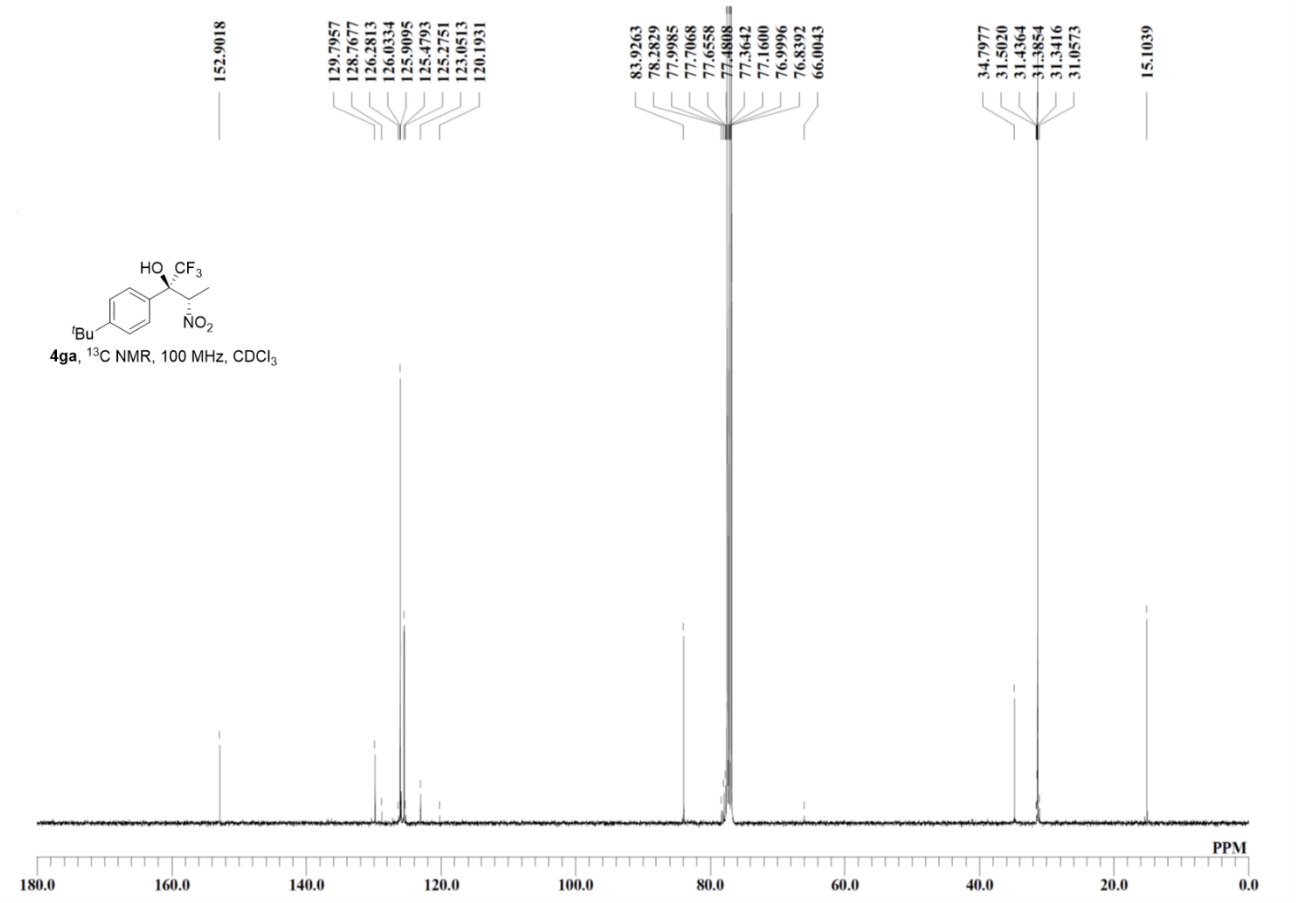
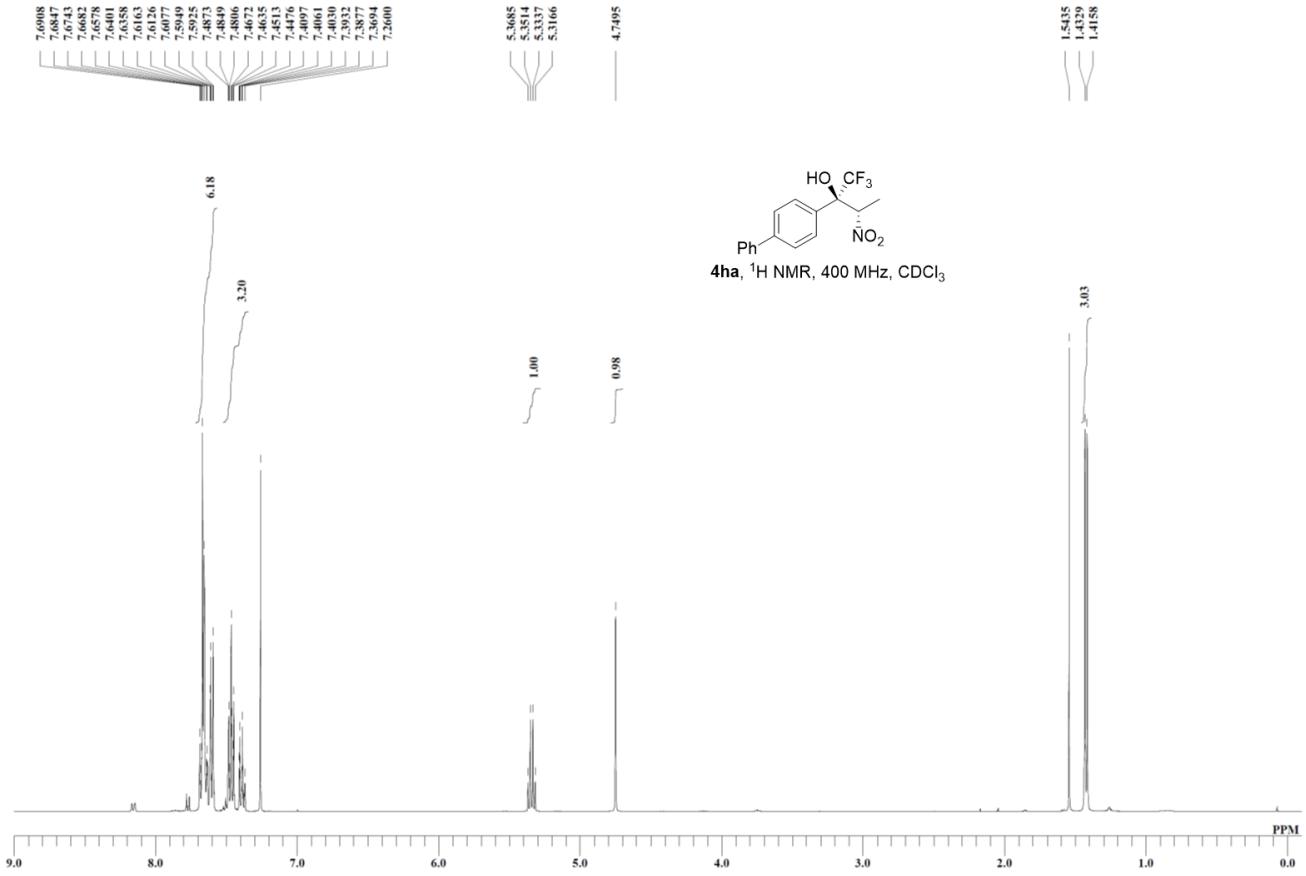


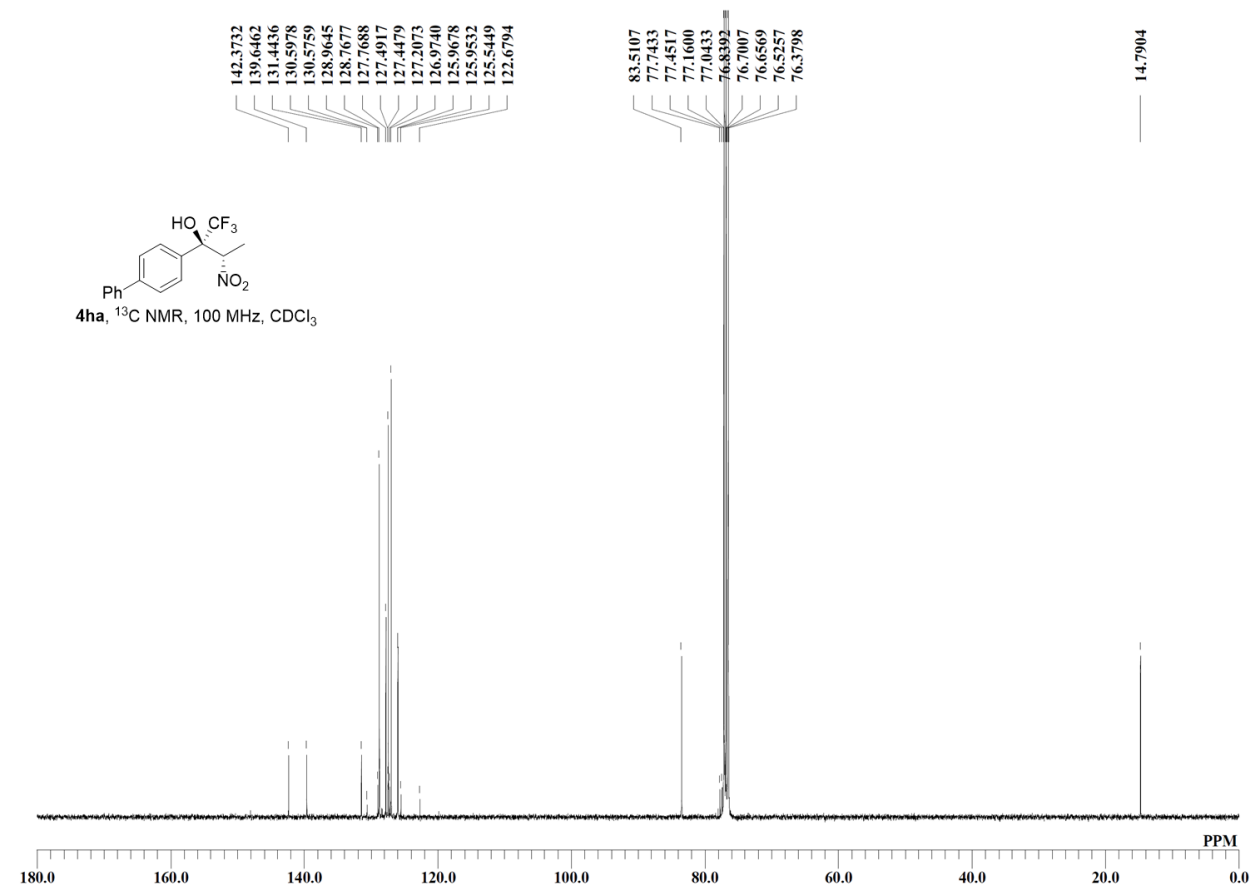
4ga, ^{1}H NMR, 400 MHz, $CDCl_3$



4ga, ^{13}C NMR, 100 MHz, $CDCl_3$



4ha, ^{1}H NMR, 400 MHz, $CDCl_3$



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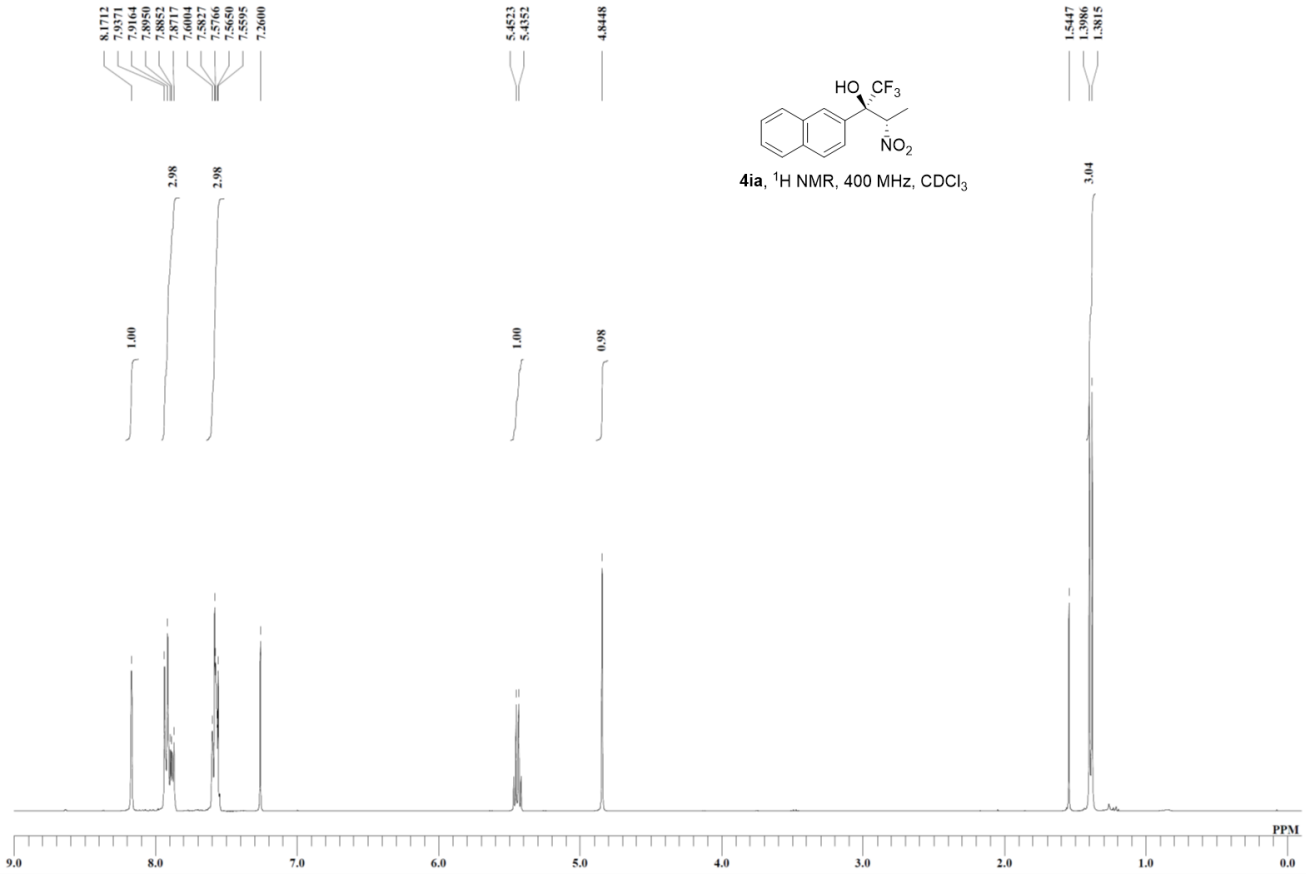
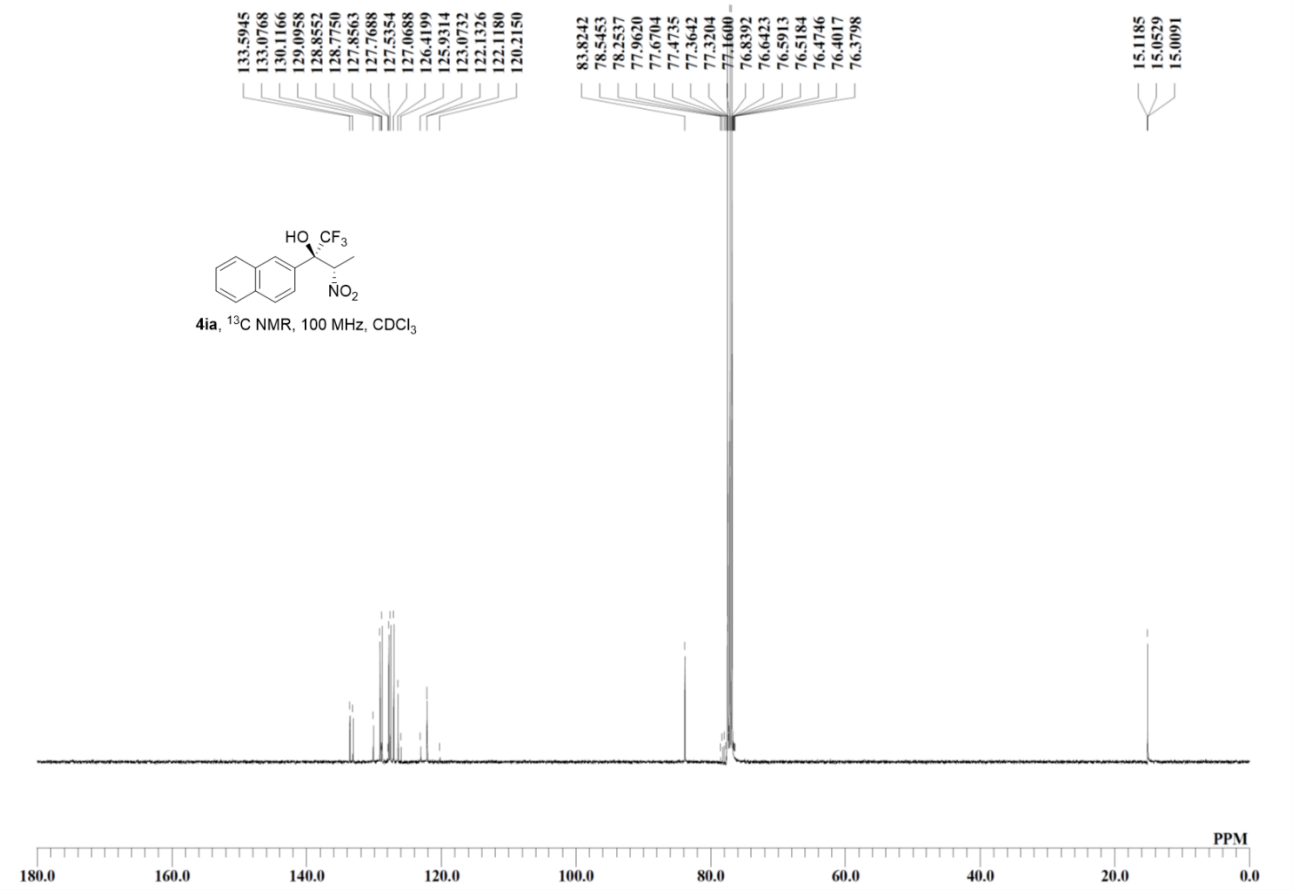


4ia, ^{1}H NMR, 400 MHz, $CDCl_3$



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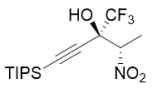

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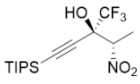
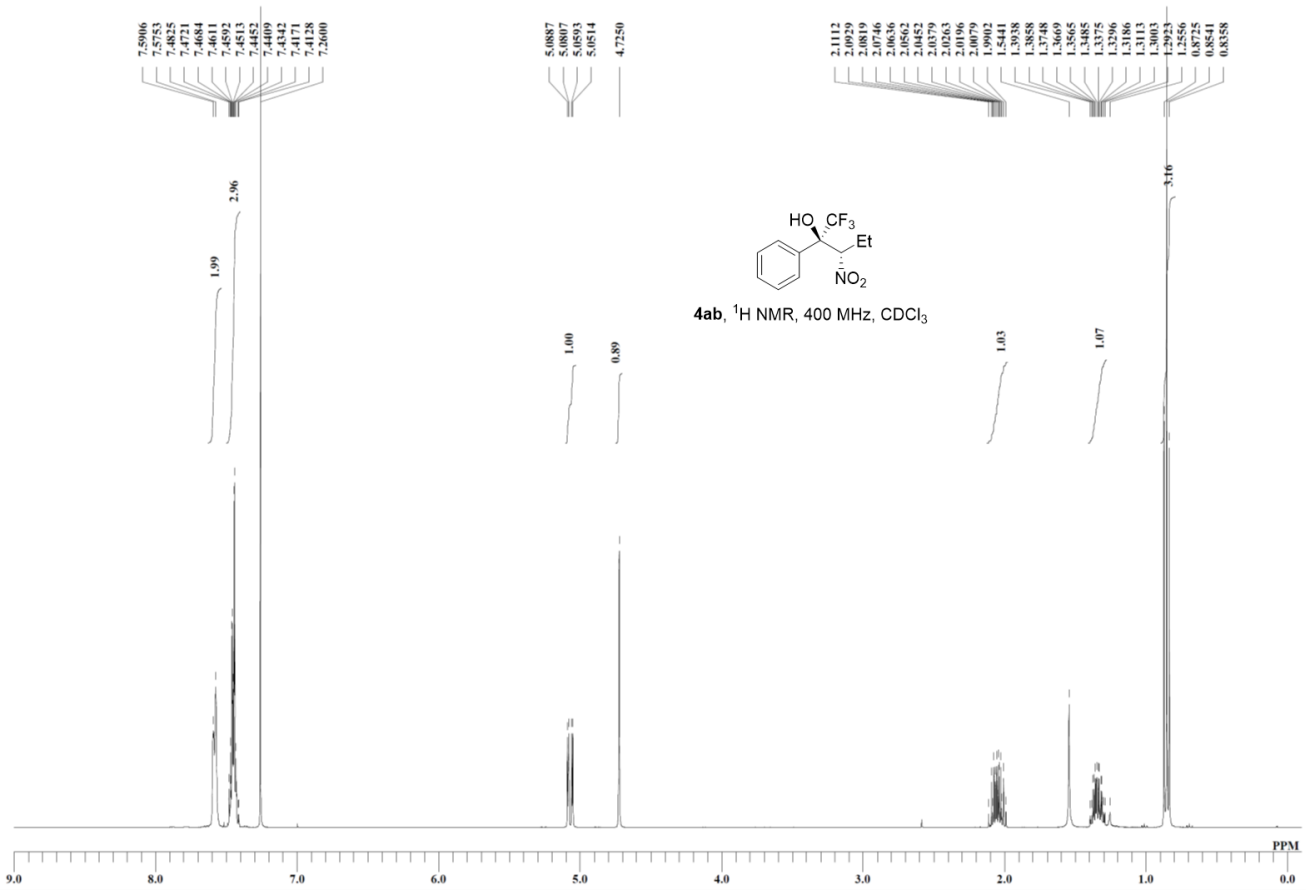
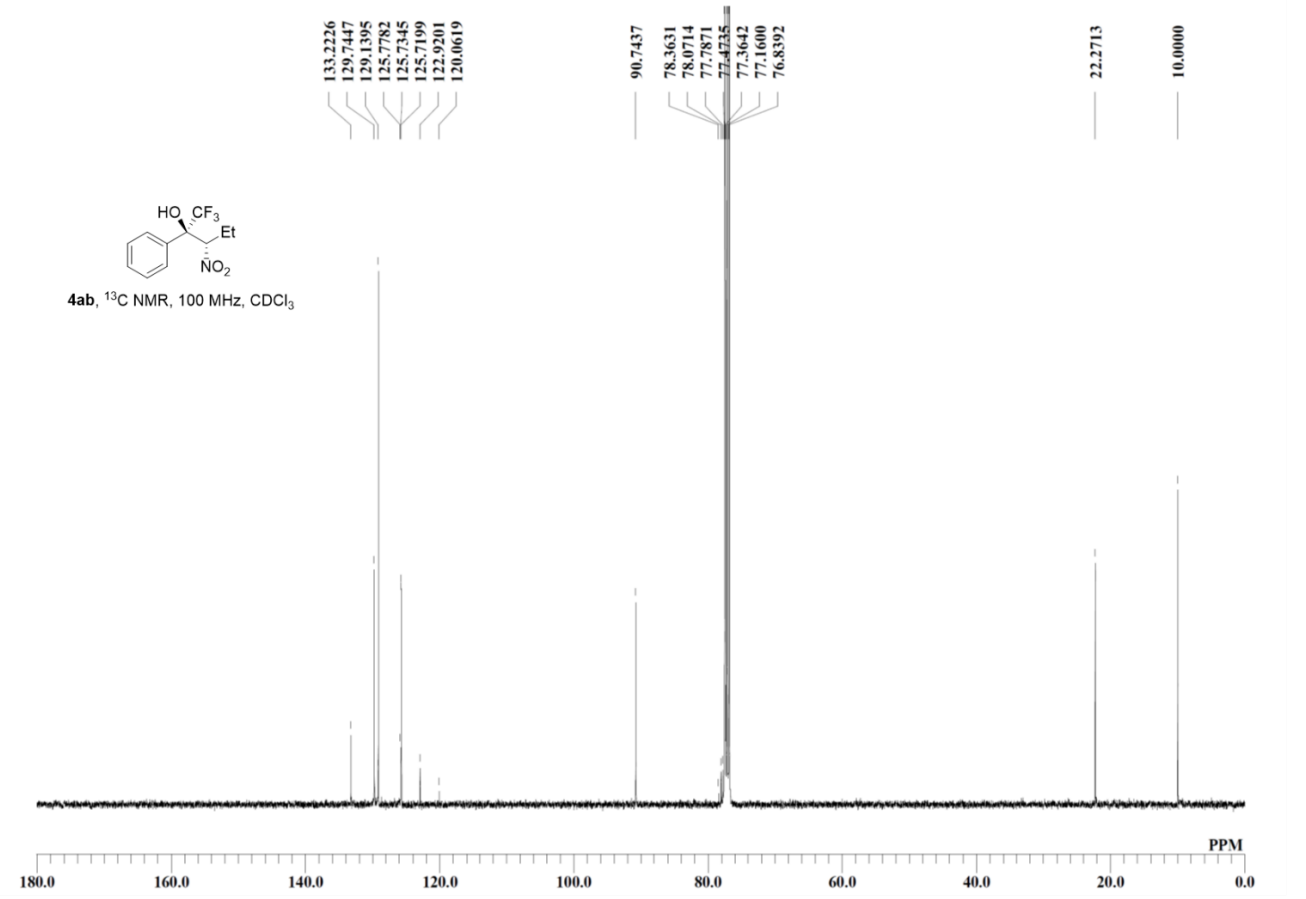


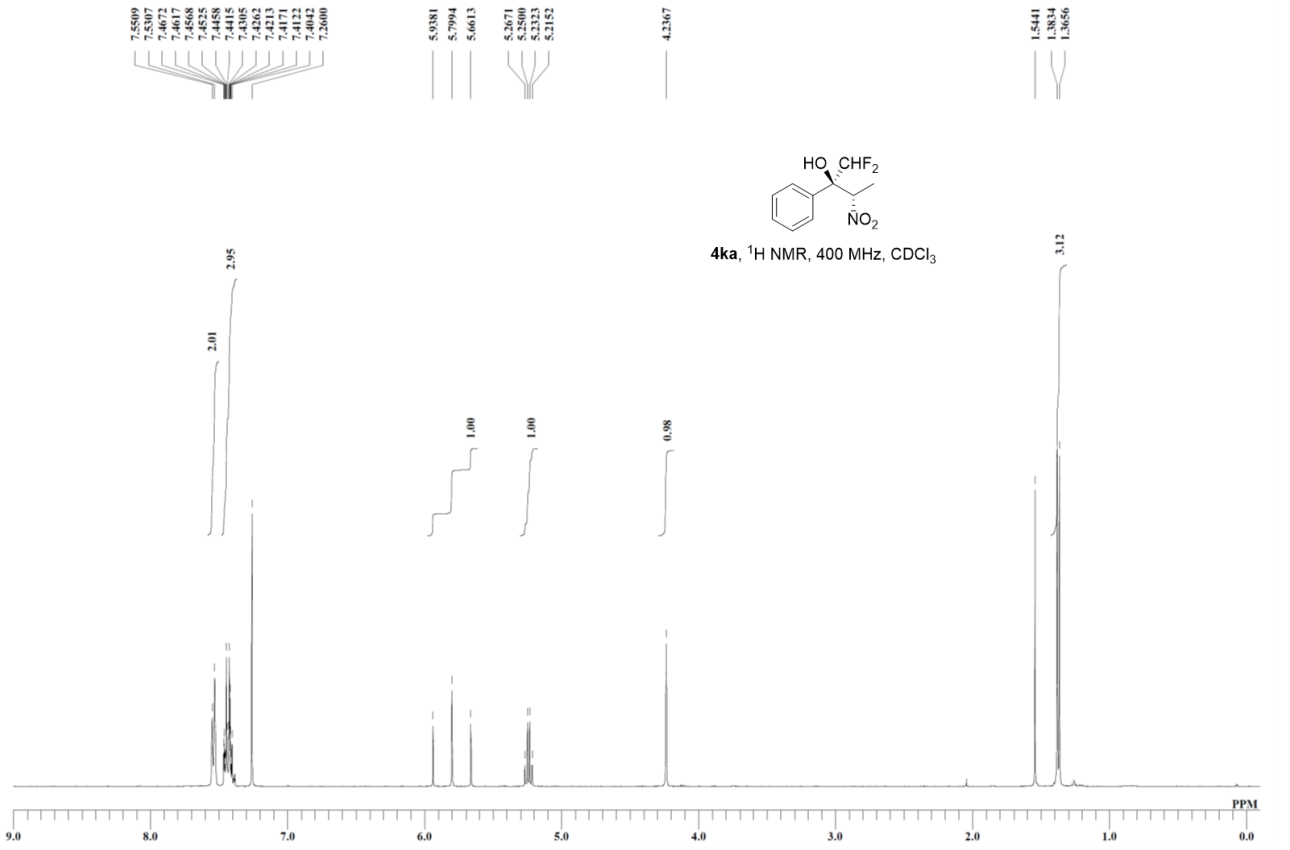
4ja, ^{13}C NMR, 100 MHz, $CDCl_3$



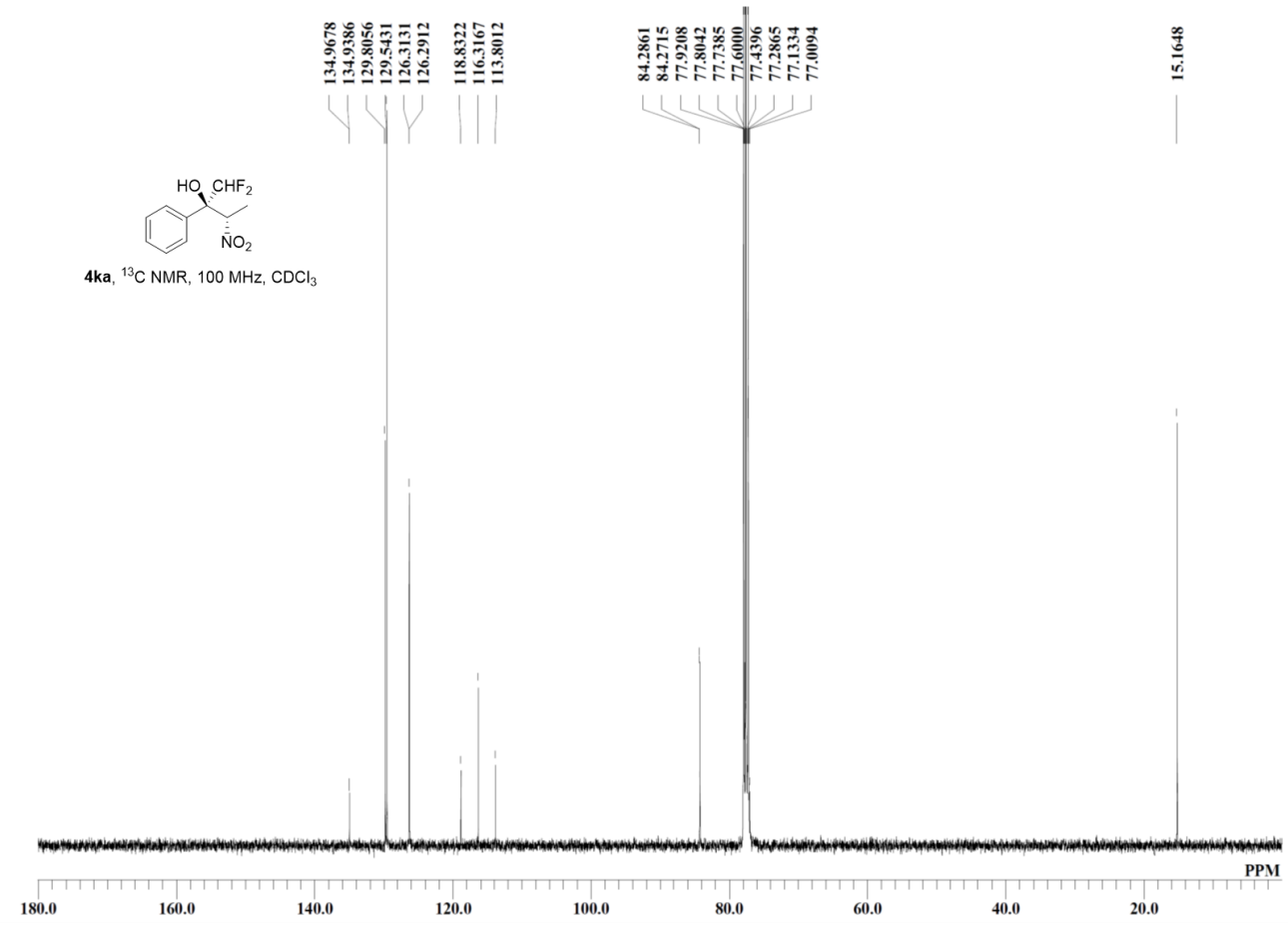
4ab, ^{1}H NMR, 400 MHz, $CDCl_3$



4ab, ^{13}C NMR, 100 MHz, $CDCl_3$



4ka, ^{1}H NMR, 400 MHz, $CDCl_3$



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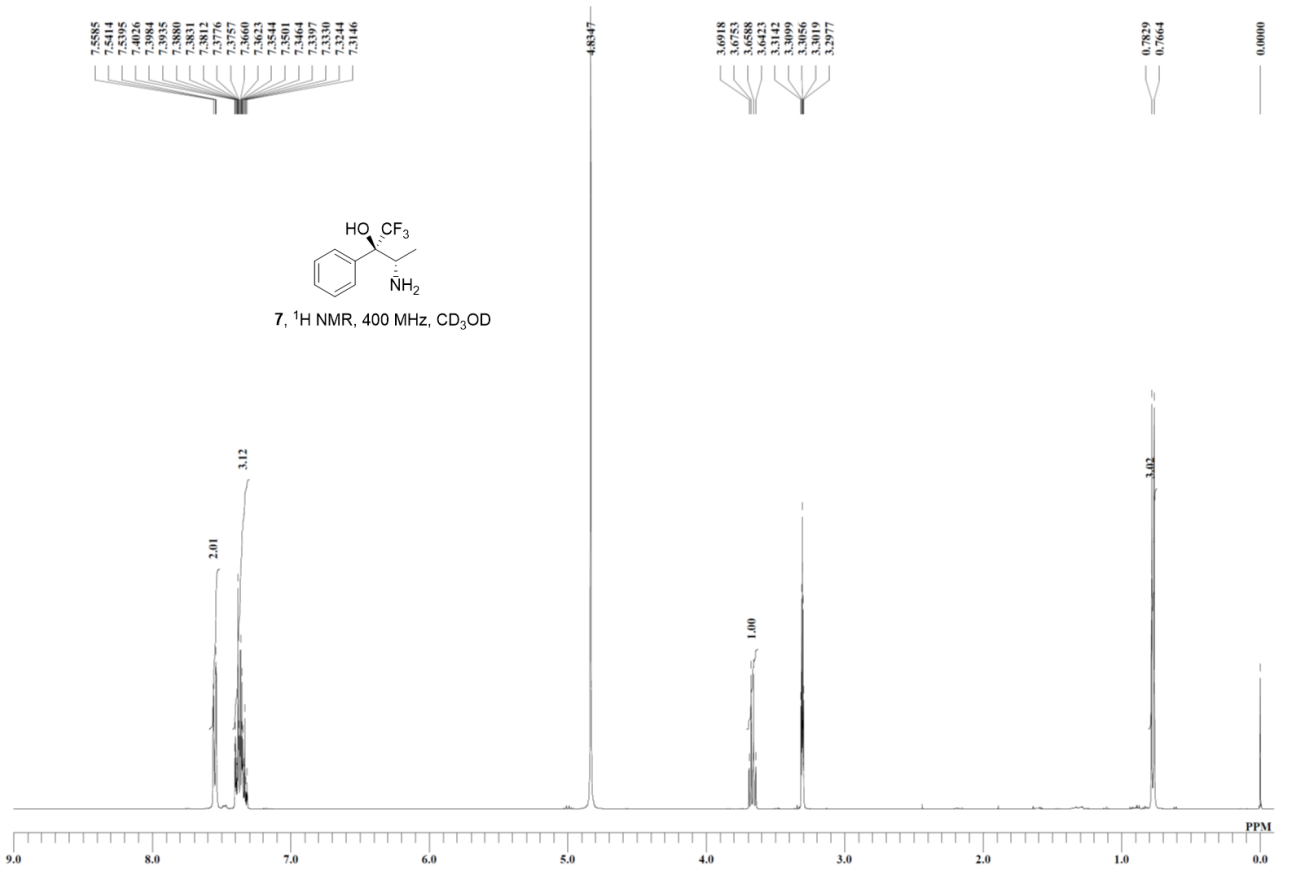
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7, 1H NMR, 400 MHz, CD3OD
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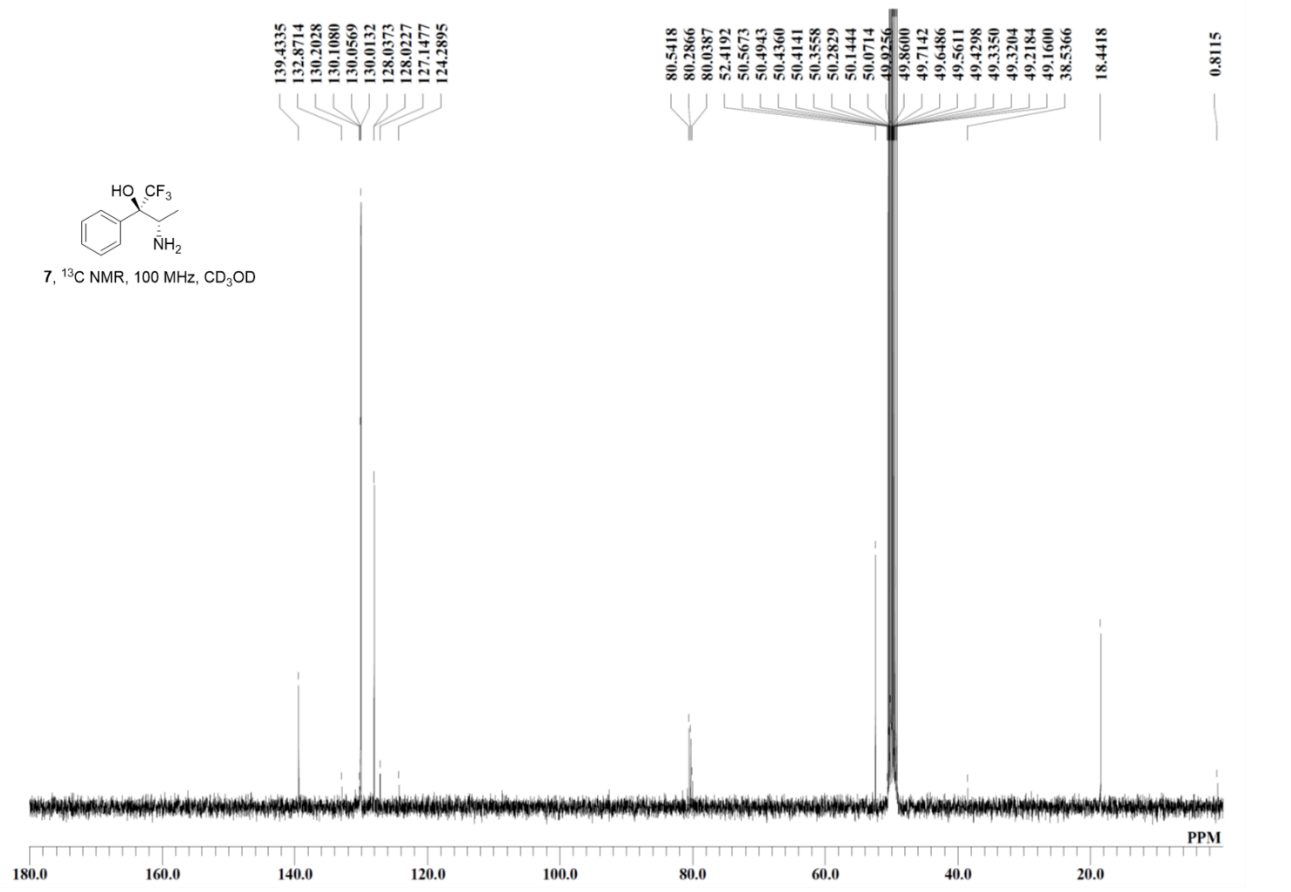
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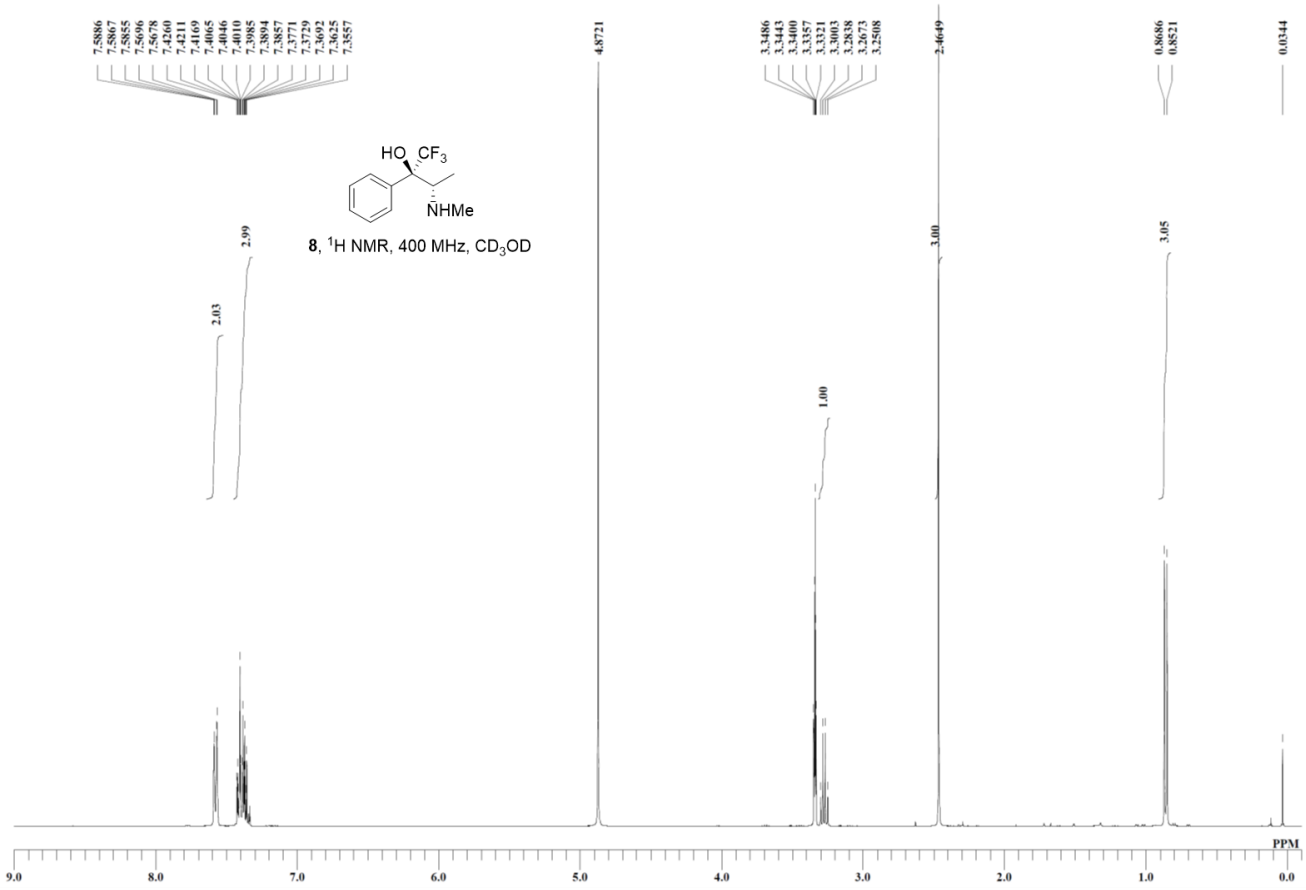
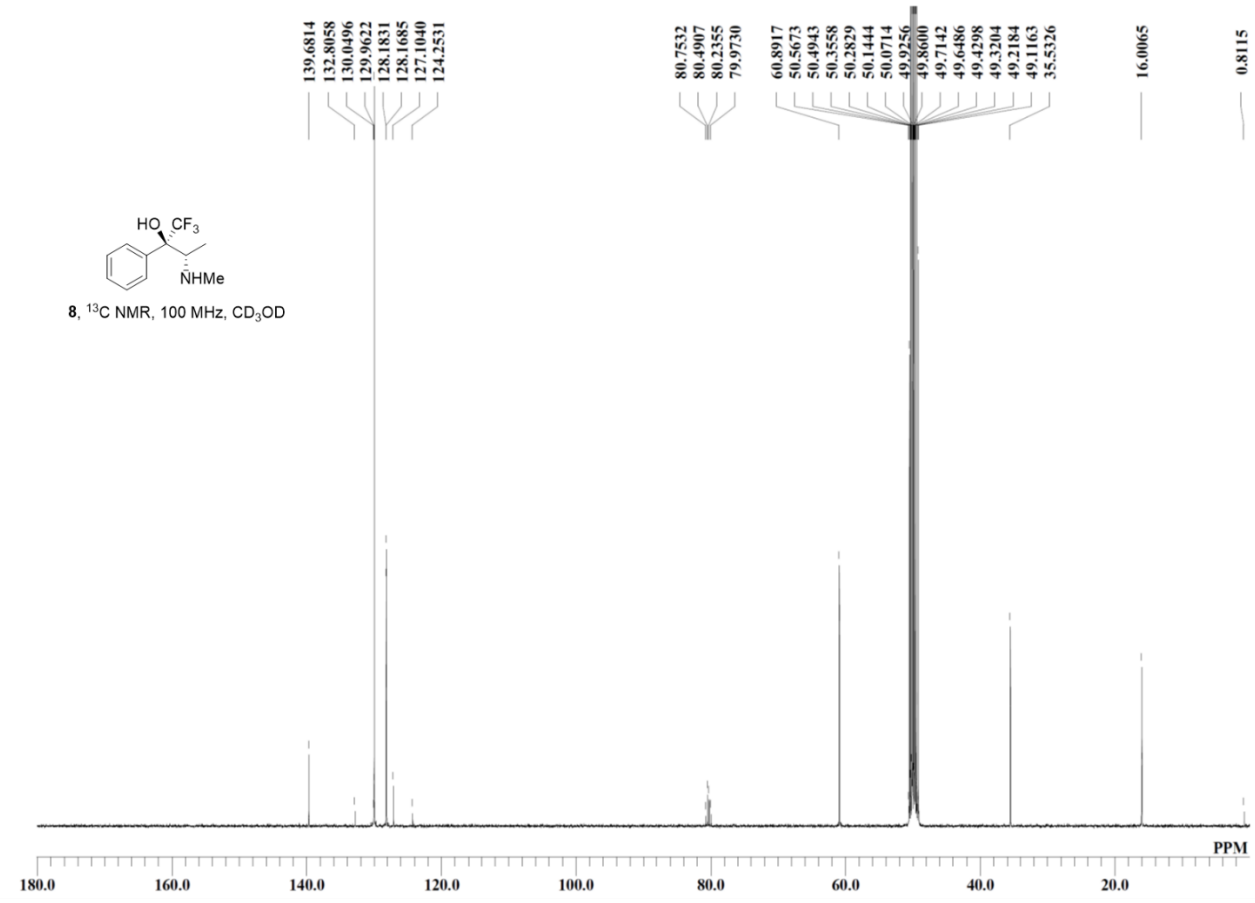
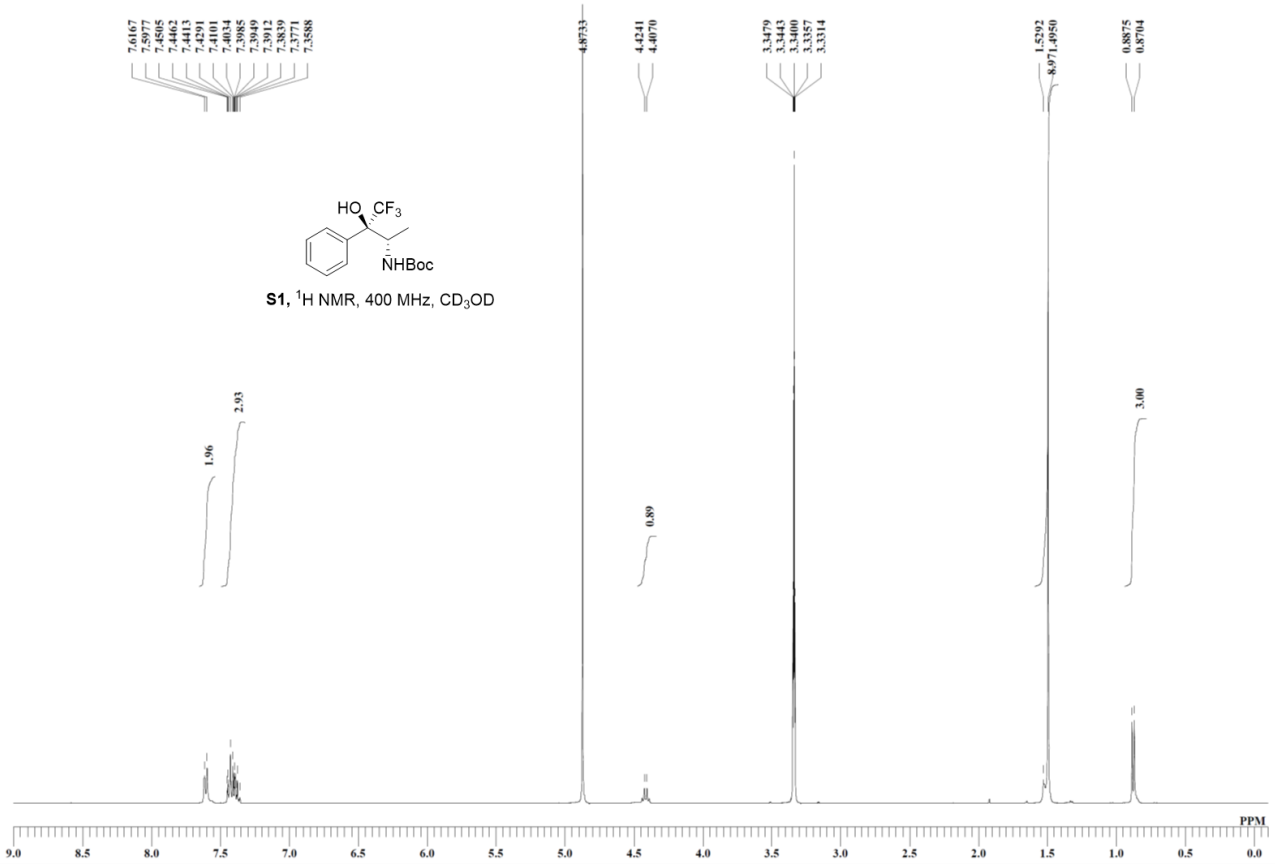


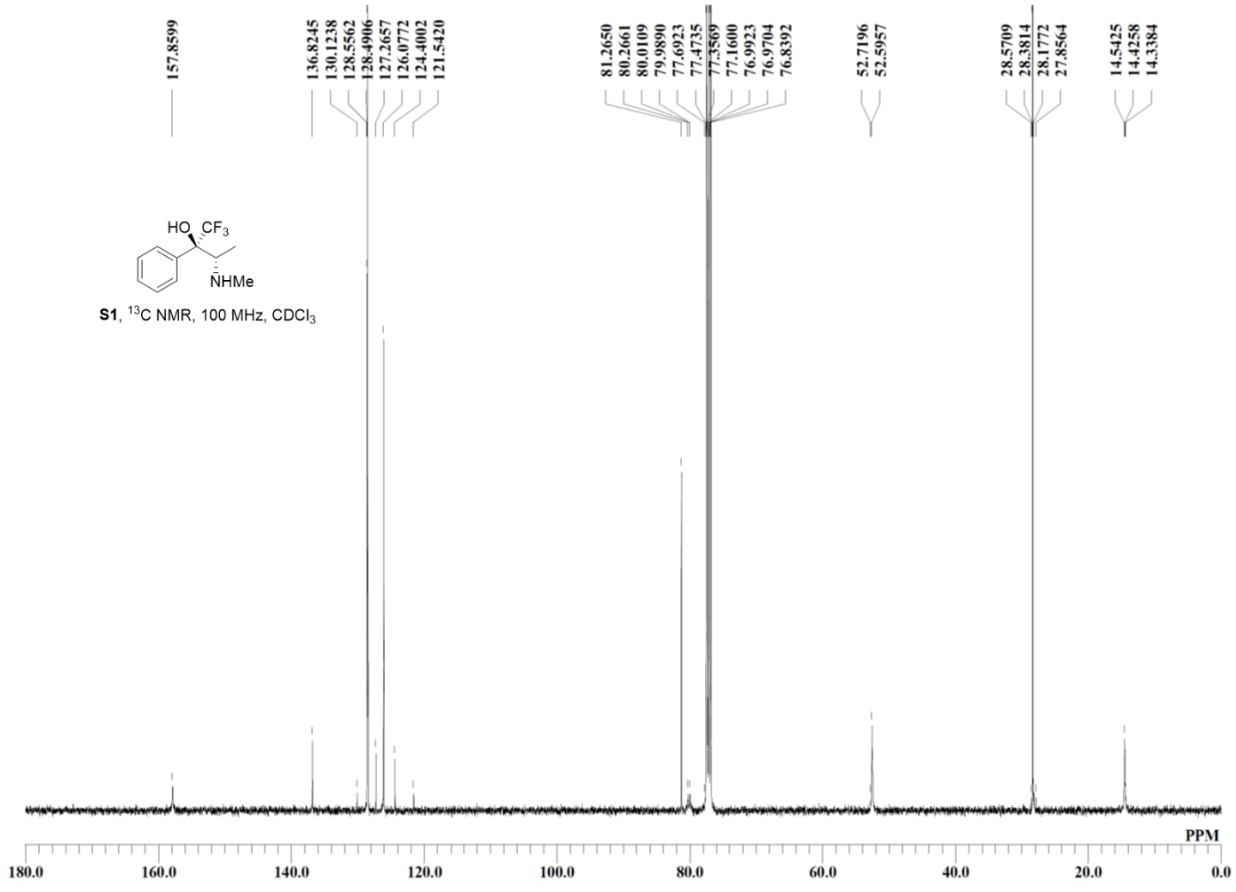
8, ^{1}H NMR, 400 MHz, CD_3OD



8, ^{13}C NMR, 100 MHz, CD_3OD



S1, ^{1}H NMR, 400 MHz, CD_3OD



S1, ^{13}C NMR, 100 MHz, $CDCl_3$

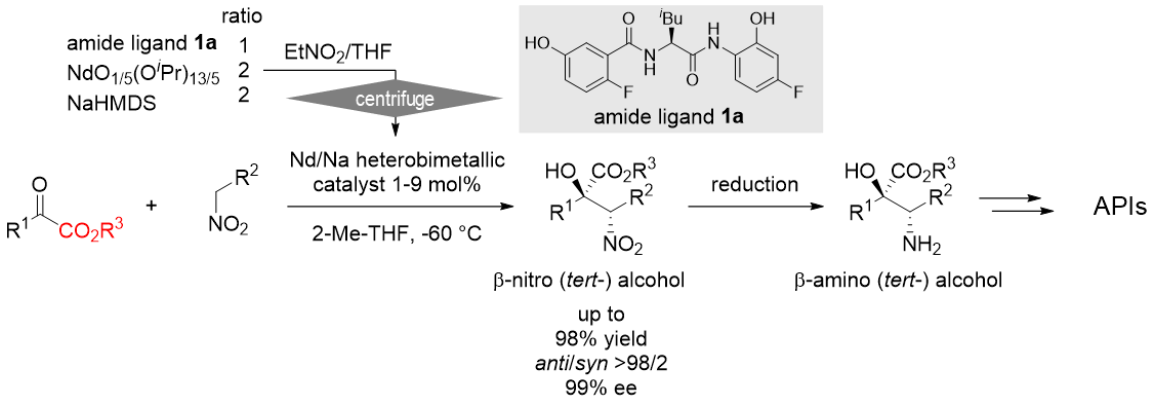
第 5 章

結論

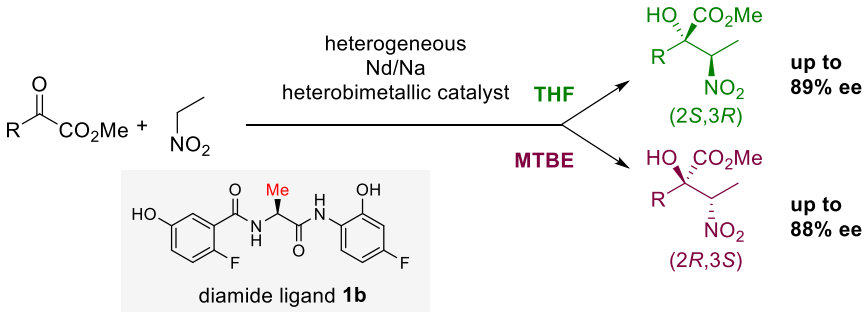
本論文では、希土類/Na 異種 2 核金属触媒を用いた *anti* 選択的触媒的不斉ニトロアルドール反応を α-ケトエステルならびにトリフルオロメチルケトンに適用し、医薬品や天然物に広く見られる β-アミノ 3 級アルコールの迅速合成法を確立した結果について述べた。

第 1 章「序論」では、触媒的不斉ニトロアルドール反応の歴史と柴崎研究室による Nd/Na 異種 2 核金属触媒を用いた *anti* 選択的触媒的不斉ニトロアルドール反応の実用化に向けたこれまでの開発の流れと課題について述べ、本研究の意義を明らかにした。

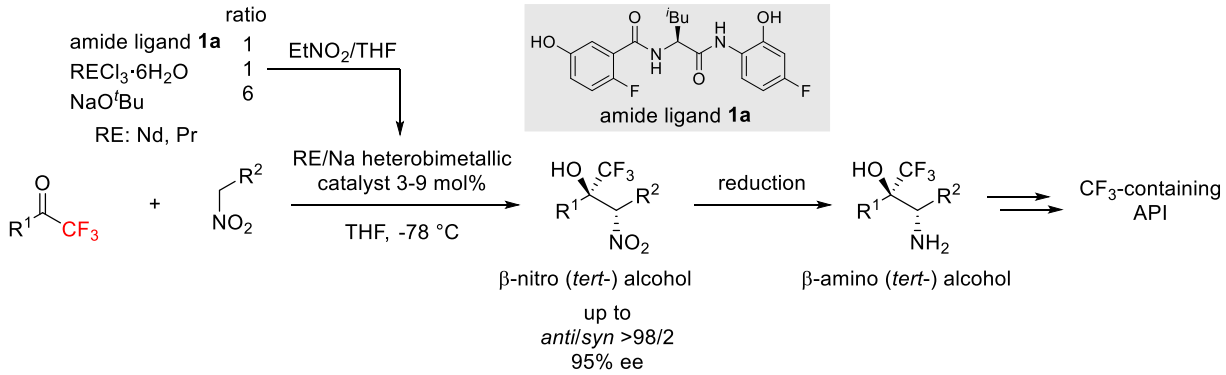
第 2 章「α-ケトエステルの *anti* 選択的触媒的不斉ニトロアルドール反応」では、Nd/Na 異種 2 核金属触媒による *anti* 選択的触媒的不斉ニトロアルドール反応を α-ケトエステルに適用した結果について述べた。各種反応条件を検討した結果、2-Me-THF 中で反応した場合に広範な基質で高収率、高立体選択性で *anti* 付加体が得られることを見出した。続いて、2-Me-THF がキラル分子であることに着目し、光学活性な溶媒が不斉反応に与える影響について精査した。その結果、1) 異種 2 核金属触媒は配位性のエーテル系溶媒を取り込むことによって触媒周辺の不斉環境が変化すること、2) (*R*)-2-Me-THF と触媒の相互作用によって生み出される反応場が高い反応性と立体選択性を達成する上で重要であることを明らかにした。さらに抗菌剤である efinaconazole と albaconazole の不斉合成や MWNT 固定型触媒を用いた連続フロー反応を通じて本反応の有用性を実証した。



第 3 章「溶媒依存性エナンチオ選択的不斉ニトロアルドール反応」では、Nd/Na 異種 2 核金属触媒による α-ケトエステルの不斉ニトロアルドール反応において、特定のジアミド型配位子から調製した Nd/Na 異種二核金属触媒が溶媒の種類によって異なる正負が異なるエナンチオ選択性を与える興味深い現象を見出した。触媒の置換基のサイズや溶媒がエナンチオ選択性に与える影響を精査した結果、立体選択性の逆転はコンパクトなメチル基を側鎖として持つ L-アラニンから誘導したジアミド型配位子からのみ誘導され、同じエーテル系の溶媒である THF と MTBE 中で異なるエナンチオ選択性を与えることが明らかになった。本結果は、1) 本触媒反応の不斉が配位子の不斉中心のみを単純に認識している訳ではなく、触媒の高次構造により構築される不斉を認識して誘起されていること、2) コンパクトな側鎖を持つジアミド型配位子から調製される触媒は配位性の THF を取り込むと、その高次構造が逆のエナンチオマーを与える配座に変化することを示唆している。今後も本現象の理解を深めるために、触媒構造や不斉発現メカニズムの解明に向けた研究を継続する。



第 4 章「トリフルオロメチルケトンの *anti* 選択的触媒的不斉ニトロアルドール反応」ではトリフルオロメチルケトンの anti 選択的触媒的不斉ニトロアルドール反応の開発について述べた。本反応はジアミド型配位子 **1a** を持つ Nd/Na または Pr/Na 異種 2 核金属触媒により、広範の基質で進行し、α-CF_3-β-ニトロ 3 級アルコールを高収率、高立体選択性で与えた。生成物中のニトロ基は還元反応により容易にアミノ基へ変換可能であり、β-アミノ 3 級アルコールユニットの迅速合成法を確立した。さらに CF_3 基含有 ephedrine 誘導体の合成を通じて、医薬化学における本反応の有用性を示した。



以上、本論文では希土類/Na 異種二核金属触媒を用いた α-ケトエステルとトリフルオロメチルケトンの *anti* 選択的触媒的不斉ニトロアルドール反応とその特異な溶媒効果、医薬品合成や連続フロー合成への応用について述べた。本論文で確立した *anti* 選択的触媒的不斉ニトロアルドール反応が多くの医薬品や機能性分子の合成に貢献することを期待すると同時に、本研究が触媒反応に関する研究、ひいては有機合成化学の発展に少しでも寄与できれば望外の喜びである。

謝辞

本研究を遂行するにあたり、終始熱意あふれるご指導ご鞭撻を賜りました微生物化学研究所　柴﨑正勝所長に謹んで感謝申し上げます。

本論文の審査にあたり、多大なご助力、ご指導を賜りました東京大学大学院薬学系研究科　金井求教授に感謝申し上げます。

研究方針から日々の実験の指導まで常に多大なご助言を下さいました微生物化学研究所　熊谷直哉主席研究員に感謝申し上げます。

微生物化学研究所での研究を通じて、研究に対する広い見識を得る機会を与えて頂いた大日本住友製薬株式会社技術研究本部　高橋和彦本部長、プロセス研究所　佐々木幹雄所長に感謝申し上げます。

微生物化学研究所での研究をサポートして頂いた大日本住友製薬株式会社プロセス研究所　安藤丈也グループマネージャー、鬼頭真博士(現在は有機合成薬品工業株式会社)に感謝申し上げます。

研究を遂行するにあたり、Nd/Na 異種 2 核金属触媒の調製法や実験機器の使い方を直接ご指導頂き、また第 3 章の基質一般性の検討の一部でお力添え頂いた柴﨑研究室　齋藤誠博士に感謝申し上げます。

第 2 章の医薬品合成への応用研究は柴﨑研究室　Raphaël Oriez 博士と共同で実施いたしました。感謝申し上げます。

研究を遂行するにあたり、機器分析、特に NMR や質量分析、X 線結晶構造解析で多大なご協力を頂いた微生物化学研究所　澤竜一博士、飯島希昌子博士、木村智之博士、久保田由美子様に感謝申し上げます。

最後に、私の微生物化学研究所での研究の機会を一緒に受け入れ、出産直後にもかかわらず、不慣れな東京で生活を支えてくれた妻　友紀子と長女　結月、またそれをサポートしてくれた両親に心から感謝いたします。

令和元年十月

柄澤　智哉