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Aziridine Opening

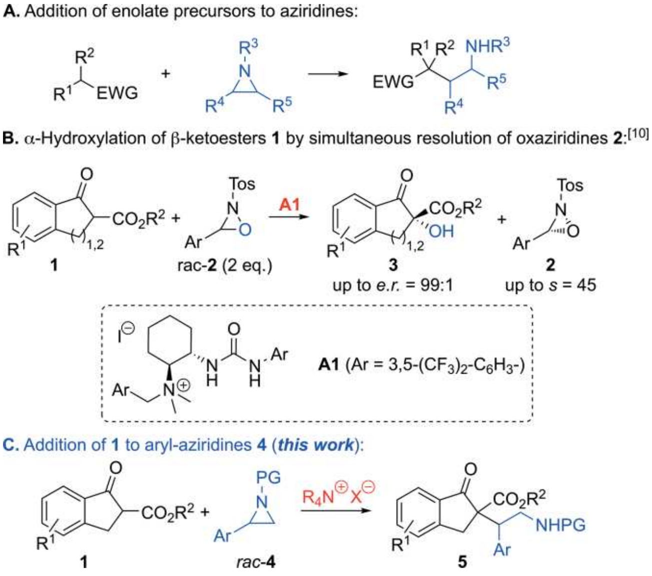
Ammonium Salt-Catalyzed Ring-Opening of Aryl-Aziridines with β-Keto Esters

Victoria Haider,[a] Viktoria Kreuzer,[a] Maximilian Tiffner,[a] Bernhard Spingler,[b] and Mario Waser*[a]

Abstract: We herein report an ammonium salt-catalyzed protocol for the regioselective ring opening of aryl-aziridines with β-keto esters. The reaction gives access to a variety of highly functionalized target molecules with two consecutive stereogenic centers and can be rendered enantioselective (up to *e.r.* = 91:9) by using bifunctional chiral ammonium salt catalysts.

Introduction

Aziridines have been established as interesting building blocks for a variety of (asymmetric) transformations and their synthetic versatility can be attributed to the fact that they easily undergo ring opening reactions with a variety of different nucleophiles.[1] In addition, a broad variety of (chiral) aziridines can be accessed straightforwardly (racemic or enantiopure) by established synthesis strategies starting from simple precursors,[1,2] making approaches relying on aziridine opening reactions very appealing. The reactions of aziridines with C-nucleophiles, i.e. enolate species, can lead to interesting γ-amino-carbonyl targets which are not easily accessible by other strategies. In addition, depending on the aziridine substitution pattern, rather complex structural motives containing two or even three consecutive stereogenic centers can be accessed (Scheme 1A) and the use of a chiral catalyst may allow to control such reactions in a stereoselective manner.[1,3–6]


A. Addition of enolate precursors to aziridines:

B. α-Hydroxylation of β-ketoesters **1** by simultaneous resolution of oxaziridines **2**:[10]

C. Addition of **1** to aryl-aziridines **4** (***this work***):

Scheme 1. General reactivity of aziridines towards nucleophilic attack (A), our recently developed asymmetric α-hydroxylation of β-keto esters **1** with oxaziridines **2** (B), and the herein investigated addition of compounds **1** to aryl-aziridines **4** (C).

Our group has a strong interest in asymmetric ion pairing catalysis[7–10] and we recently reported that bifunctional ammonium salt catalysts[8] containing a (thio)-urea H-bonding motive (i.e. catalysts **A**) can be used for the asymmetric α-hydroxylation of β-keto esters **1** by using racemic oxaziridines **2** as the O-transfer reagents (accompanied by a simultaneous resolution of the oxaziridines **2** as outlined in Scheme 1B).[10] Based on the general interest in aziridine-opening reactions and given our focus on asymmetric ammonium salt catalysis we now wanted to explore if ammonium salt catalysts (like compounds **A**) may also facilitate the addition of pronucleophiles **1** to aryl-aziridines **4**. In general, the asymmetric ring-opening of aziridines with β-keto esters **1** using chiral ammonium salt catalysts has been well-investigated, i.e. by the groups of Dixon and Jørgenson.[4] However, in those cases no aryl-aziridines **4** were used and to the best of our knowledge there are only very few reports in general, where enolate precursors were added to such aziridines in an asymmetric manner.[5] Interestingly, some previous reports describing the addition of malonates to such aziridines in the absence of a chiral catalyst showed that these reagents predominately undergo nucleophile addition to the benzylic position of the aziridine, and that these reactions proceed via a stereospecific ring-opening pathway with inversion of configuration of the benzylic stereogenic center.[6] We thus wondered if we could introduce a protocol

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for the regio- and stereoselective addition of pronucleophiles **1** to (racemic) aziridines **4**, which would result in the formation of the highly functionalized target molecules **5** (Scheme 1C).

Results and Discussion

We started our investigations by carrying out the reaction between the *tert*-butyl ester **1a** and the phenyl aziridine **4a**. The reason why we opted for the *N*-tosyl protected **4a** was because we previously (during the hydroxylation of **1** with oxaziridines **2**) realized that sulfonamide groups provide a very good point of coordination for our bifunctional ammonium salts **A**.[10] Besides our own catalysts **A**[10,11] (on which we put our main focus), we also compared the other classical and well-established ammonium salt catalysts **B**[7,12] and **C**[7,13] and the recently reported bifunctional Cinchona alkaloid derivative **D**.[14]

First experiments without any catalyst (entry 1) and in the presence of a simple achiral ammonium salt (entry 2) clearly proved the beneficial effect of the phase-transfer catalyst and showed that the reaction proceeds via addition to the benzylic carbon of the aziridine (giving **5a**). The relative configuration of the major diastereomer of product **5a** was assigned by single-crystal X-ray analysis[15] and in all further experiments the *unlike* diastereomer was found to be the main product. We then carried out a first base screening with our urea-containing catalyst **A1** (entries 3–6) and found that the targeted product **5a** could be obtained in a reasonable yield of 79 % and with promising enantio- and diastereoselectivities (*d.r.* = 6:1; *e.r.* = 89:11) after 24 h when using two equivalents of solid Cs_2CO_3 (entry 6). The use of aqueous bases on the other hand significantly slowed down the conversion (entry 4) and stronger bases (e.g. NaOH) were found to be not suited at all (results not given in the table), i.e. as the aziridine decomposed significantly under these conditions. Interestingly, while the major diastereomer could be obtained with a good enantiomeric ratio of 89:11, the minor diastereomer was formed in an almost racemic manner (entry 6).

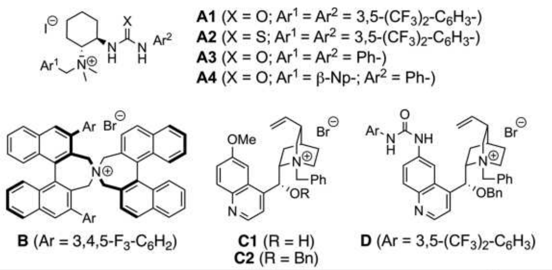
We then tested other derivatives of the bifunctional ammonium salts **A** (entries 7–9 give three representative examples), but neither the use of a thiourea (entry 7), nor using sterically more bulky systems (entry 9) resulted in any improvement. When using the well-established Maruoka catalyst **B** next (entry 10),[7,12] the reaction stalled after around 50 % conversion and the observed diastereoselectivity was rather low (*d.r.* = 1.5:1). In sharp contrast to ammonium salt **A1** however, catalyst **B** allowed for higher enantioselectivities of the minor diastereomer (favoring the same major enantiomers of both diastereomers as **A1**). The classical Cinchona alkaloid ammonium salts **C** were found to be less suited for this reaction (entries 11 and 12), while the bifunctional catalyst **D**[14] gave at least some levels of selectivity (entry 13), although clearly not as promising as compounds **A**.

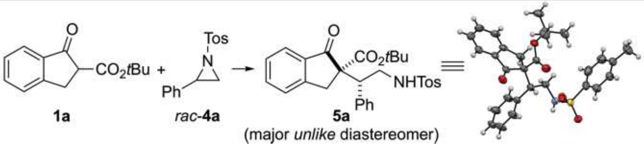
Based on these results, which support a beneficial effect of the bifunctional nature of the catalyst, we then tried to further optimize the reaction conditions using **A1** (entries 14–18). While non-aromatic solvents were found to be less suited (entries 14, 15), the use of a lower amount of base resulted in a slightly increased enantioselectivity of 91:9 (compare entries 16 and 6). However, the yield was noticeable lower, and we found that actually this reaction stalled after around 60 % conversion, requiring addition of more base to proceed to completion. When carrying out the reaction under more concentrated conditions, the yield improved slightly, while the enantioselectivity decreased (entry 17). This result is in line with our recent observations for the α-hydroxylation of compounds **1**, where higher dilution was beneficial for high enantioselectivities as well.[10] Finally, lowering the catalyst loading to 5 mol-% resulted in a slightly lower selectivity but in a noteworthy reduced yield. Again, the reaction stalled after a while and addition of more catalyst was necessary in those cases, while longer reaction times were not beneficial. This phenomenon was generally observed in all the other reactions that did not show a satisfying conversion after 24 h (compare with entries 4, 10, and 16). Lower temperatures were tried as well but the reactions became very slow with unreliable conversions and no benefit in enantioselectivity.

Unfortunately, during these optimization attempts we observed a very strong influence of the starting material quality on the stereoselectivity of the reaction. First, the aziridine **4** has to be rather clean and especially even very minor quantities of iodine residues originating from the synthesis route[16] lead to a significant decrease of the *e.r.* In addition, the used β-keto ester **1** has to be “perfectly clean” as well, as we observed that batches of **1a** that contained very small quantities of unidentified impurities (less than 1 % by ^1H NMR) resulted in reduced enantioselectivities down to *e.r.* = 75:25 under otherwise identical conditions (in addition the yields were a bit higher here, demonstrating the notable influence of these unknown impurities on the reaction performance). Thus, use tests of each batch of the starting materials had to be made during all these optimizations. In sharp contrast to this pronounced sensitivity on the starting material quality observed for the synthesis of **5**, use tests of different keto ester **1a** batches for other reactions catalyzed by catalysts **A** (like the above mentioned α-hydroxylation[10] or analogous α-halogenations[17]) revealed no measurable dependency of selectivity and/or yield therein. Accordingly, this rather unpractical sensitivity, where seemingly small impurities or changes in the reagent's quality affected the outcome significantly, required a tedious purification of the starting materials for all asymmetric experiments. As a consequence, the results given in entries 6 and 16 in Table 1 are the best we could obtain with carefully purified reagents only. On the other hand, it should be noted that with given qualities of a single batch of **1a** and/or **4a** reproducible results were obtained when repeating the experiments several times.

During our **A1**-catalyzed α-hydroxylation of **1** with oxaziridines **2** we also observed a practical simultaneous kinetic resolution of compounds **2** (up to *s* = 45)[10] and we therefore speculated that a resolution may be possible for our herein used aziridine **4a** too. We thus carried out the addition of **1a** to *rac*-**4a** (2 equiv.) under the optimized conditions (entry 16, Table 1) and observed some moderate enantioenrichment of recovered **4a** as well [*e.r.* = 60:40 for (*S*)-**4a** after 25 % conversion; *s* = 4.8]. Giving the significantly lower stereoselectivity in the synthesis of **5a** compared to our previous synthesis of **3**, this lower effi-

Table 1. Catalyst screening and optimization of the asymmetric reaction conditions.[a]





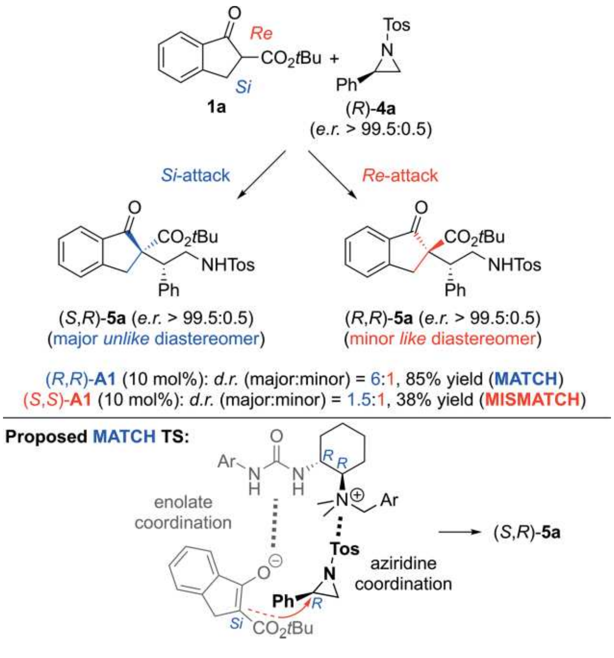
Entry	Catalyst [mol-%]	Solvent	Base	Yield [%][b]	*d.r.*[c]	*e.r.*$_{\text{major}}$[d]
1	–	toluene	K_2CO_3 (2 ×)	< 5	–	–
2	**TBAB**[e] (10 %)	toluene	K_2CO_3 (2 ×)	49	3:1	–
3	**A1** (10 %)	toluene	K_2CO_3 (2 ×)	66	3.5:1	85:15
4	**A1** (10 %)	toluene	K_2CO_3 (50 % aq.; 2 ×)	21[f]	4:1	86:14
5	**A1** (10 %)	toluene	K_2HPO_4 (2 ×)	71	2:1	76:24
6	**A1** (10 %)	toluene	Cs_2CO_3 (2 ×)	79	6:1	89:11 (56:44)[g]
7	**A2** (10 %)	toluene	Cs_2CO_3 (2 ×)	60	2.5:1	63:37
8	**A3** (10 %)	toluene	Cs_2CO_3 (2 ×)	72	1.5:1	81:19
9	**A4** (10 %)	toluene	Cs_2CO_3 (2 ×)	54	2:1	82:18
10	**B** (10 %)	toluene	Cs_2CO_3 (2 ×)	39[f]	1.5:1	70:30 (86:14)[g]
11	**C1** (10 %)	toluene	Cs_2CO_3 (2 ×)	89	2:1	52:48
12	**C2** (10 %)	toluene	Cs_2CO_3 (2 ×)	90	3:1	50:50
13	**D** (10 %)	toluene	Cs_2CO_3 (2 ×)	82	3:1	64:36
14	**A1** (10 %)	MTBE	Cs_2CO_3 (2 ×)	75	4:1	87:13
15	**A1** (10 %)	CH_2Cl_2	Cs_2CO_3 (2 ×)	84	3:1	66:34
16	**A1** (10 %)	toluene	Cs_2CO_3 (1 ×)	56	8:1	91:9
17	**A1** (10 %)	toluene[h]	Cs_2CO_3 (2 ×)	83	5:1	81:19
18	**A1** (5 %)	toluene	Cs_2CO_3 (2 ×)	36[f]	7:1	87:13

[a] All reactions were run at room temperature using 0.1 mmol **1a** and 0.2 mmol *rac*-**4a** for 24 h in the indicated solvent (0.02 M with respect to **1a**) unless otherwise stated. [b] Isolated yields of both diastereomers. [c] Determined by ^{1}H NMR and/or HPLC analysis of the crude product. [d] Determined by HPLC using a chiral stationary phase. [e] Tetrabutylammonium bromide. [f] Less than 50–60 % conversion. [g] *e.r.* of the minor diastereomer. [h] 0.1 M with respect to **1a**.

ciency for the simultaneous resolution of **4a** comes as no surprise, but nevertheless this result supports our initial hypothesis.

To gather further information about this aziridine-opening reaction, we next carried out the addition of **1a** to enantiopure (*R*)-**4a**[18] in the presence of either (*R*,*R*)-**A1** or (*S*,*S*)-**A1** as a catalyst (Scheme 2).

In both cases, the two diastereomers of **5a** were formed with complete enantiospecifity, supporting an S_N2-mechansim for the ring opening, as observed by others as well.[6] The use of the (*R*,*R*)-catalyst enantiomer (which was also used during the screening summarized in Table 1) lead to a reasonable diastereoselectivity of 6:1 in favor of the major *unlike* diastereomer



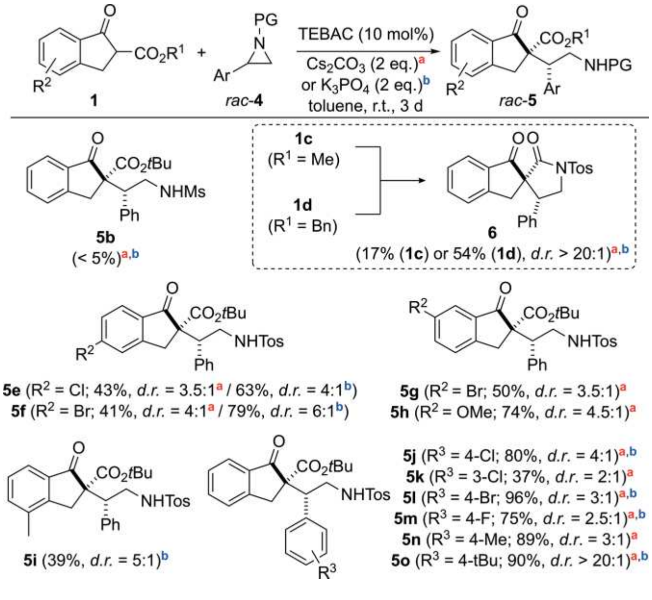
Scheme 2. Match/mismatch scenario in the addition of **1a** to (*R*)-**4a** in the presence of both enantiomers of the catalyst **A1** and the proposed match-transition state.

with high yield (match case). On the other hand, the reaction with the (*S*,*S*)-catalyst proceeded significantly slower and with much lower diastereoselectivity (mismatch case). In our previous investigations on the use of catalysts **A** for reactions of β-keto esters **1** we observed that the (*S*,*S*)-catalyst enantiomers always favor *Re*-face addition of the nucleophile.[10,17] In addition, previous DFT calculations of the **A1**-catalyzed α-hydroxylation of **1a** with **2** support a transition state where the enolate is H-bonded to the urea moiety, while the electrophile is coordinated to the ammonium group.[10,19] Based on these previous observations, the herein observed pronounced match/mismatch behavior in the stereospecific addition to enantiopure aziridine **4a**, and the unambiguously determined relative configuration of **4a**,[15] the (*R*,*R*)-catalyst is supposed to interact with both starting materials **1a** and **4a** in an organized bifunctional manner as illustrated in Scheme 2, rationalizing formation of the observed favored major stereoisomer (*S*,*R*)-**5a**. Based on this model it can also be proposed that the slightly preferred enantiomer of the minor *like* diastereomer is (*S*,*S*)-**5a**.

Summing these investigations up, it was demonstrated that the stereoselective addition of pronucleophile **1a** to aziridine **4a** can be controlled by using the bifunctional ammonium salts **A**. Unfortunately however, because of the unexpected pronounced sensitivity that we observed during all these test reactions, and despite the promising selectivities up to *e.r.* = 91:9, this reaction as such is far from being as robust and practical as other chiral ammonium salt catalyzed reactions that we investigated recently.[9,10,17]

Considering the novelty of the products **5** that are accessible by this strategy in general, but keeping in mind the practical limitations of the asymmetric protocol, i.e. the sensitivity to the starting material qualities, we thus investigated the application scope for the racemic phase transfer-catalyzed addition of various β-keto esters **1** to aryl-aziridines **4** only.

As shown in Scheme 3, a variety of differently functionalized pronucleophiles **1** and acceptors **4** were reacted for three days in the presence of benzyltriethylammonium chloride (TEBAC) using Cs_2CO_3 (a) or K_3PO_4 (b) as the base. Interestingly, mesylated aziridines did not react well (see the result given for product **5b**) and when using *N*-Boc aziridines no reaction was observed at all. On the other hand, the use of methyl or benzyl esters revealed a strong influence of this group on the overall outcome, as both of them resulted in the direct formation of the spirocyclic γ-lactam **6** upon addition to aziridine **4a**. Different substituents on the donor side were tolerated (see products **5e**–**i**), although in some of these cases the use of K_3PO_4 was found to be beneficial over Cs_2CO_3 (in the latter case significant amounts of decomposition products were observed). On the other hand, variations of the acceptor aryl group were generally well accepted in the 4-position, independent of the nature of the base, while the 3-position was lower yielding (see product **55**) and in this case again significant amounts of unidentified decomposition products were formed. Nevertheless, the racemic protocol generally gives access to a variety of differently functionalized products **5** with relatively good yields and reasonable diastereoselectivities under these operationally simple ammonium salt-catalyzed conditions.



Scheme 3. Application scope of the racemic ammonium salt-catalyzed ring-opening of aryl-aziridines **4** with β-keto esters **1**.

Conclusions

Summing these investigations up, we have shown that β-keto esters **1** react with aryl-aziridines **4** under (chiral) ammonium salt catalysis giving access to highly functionalized products **5**. In principle a catalytic and reasonably enantioselective protocol could be developed by using the bifunctional ammonium salt catalysts **A**. Unfortunately, however, this reaction was found to be very sensitive towards the quality of the starting materials. Nevertheless, control experiments showed a pronounced match/mismatch behavior of the bifunctional catalyst and the used aziridine, thus pointing towards a mechanism where the catalyst simultaneously activates both of the reaction partners.

Experimental Section

General experimental and analytical details as well as the characterization data of all the novel compounds can be found in the online supporting information.

Racemic Protocol: A mixture of 0.1 mmol β-keto ester **1** (1 equiv.), 2.2 mg of TEBAC (0.01 mmol, 10 mol-%) and 0.2 mmol base (2 equiv.) was dissolved in 5 mL of toluene (Ar-atmosphere). Then 0.2 mmol of aziridine **4** (2 equiv.) were added in one portion. After a reaction time of three days the mixture was filtered through a plug of Na_2SO_4 and washed with DCM. The crude product, obtained after evaporation of the solvent, was subjected to column chromatography (silica gel, heptanes:EtOAc = 5:1) to isolate products **5** and **6** as mixtures of diastereomers. The diastereomers were in some cases separated using preparative HPLC (Grace Alltima Silica 10 µm 250 × 10 mm, *n*-hexane/EtOAc, 5 mL/min).

Enantioselective Screening Protocol: A mixture of the β-keto ester **1a** (0.1 mmol, 1 equiv.), catalyst **A1** (7.6 mg, 0.01 mmol, 10 mol-%) and 0.2 mmol of the tested base (2 equiv.) were dissolved in 5 mL of the given solvent (argon atmosphere, room temperature). Then 48 mg of 2-phenyltosylaziridine **4a** (0.2 mmol, 2 equiv.) were added in one portion. After a reaction time of one day the mixture was filtered through a plug of Na_2SO_4 and washed with DCM. The crude product, obtained after evaporation of the solvent under reduced pressure, was then subjected to column chromatography purification (silica gel, heptanes:EtOAc = 2:1) to isolate product **5a** as a mixture of two diastereomers (*d.r.* up to 8:1) in yields up to 84 %. The diastereomers were separated using preparative HPLC (Grace Alltima Silica 10 µm 250 × 10 mm, *n*-hexane/EtOAc = 9:1, 5 mL/min, retention times: 39.1 min major, 46.8 min minor). The enantiomeric excess of the minor diastereomer was determined by HPLC using a YMC Amylose SA column (*n*-hexane/*i*PrOH = 3:1, 1 mL/min, 10 °C, retention times: 21.0 and 35.5 min). The enantiomeric excess of the major diastereomer was determined by HPLC using a YMC Cellulose SB column (*n*-hexane/*i*PrOH = 10:1, 1 mL/min, 10 °C, retention times: 22.2 min major, 20.2 min minor).

Analytical Details for Compound 5a: HRMS (ESI): *m/z* calculated for $C_{29}H_{32}NO_5S^+$: 506.2001 [M + H]$^+$, found 506.1992. *Major Diastereomer*: ^{1}H-NMR (700 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.67 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 7.7 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.28 (d, J = 8.2 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 7.11–7.05 (m, 5H), 4.42–4.40 (m, 1H), 3.87 (dd, J_1 = 9.7 Hz, J_2 = 5.7 Hz, 1H), 3.69 (d, J = 17.2 Hz, 1H), 3.65–3.61 (m, 1H), 3.38–3.34 (m, 1H), 3.22 (d, J = 17.2 Hz, 1H), 2.43 (s, 3H), 1.37 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 200.7, 169.0, 153.2, 143.6, 137.2, 136.2, 135.2, 135.0, 129.9, 129.6, 128.7, 127.8, 127.6, 127.3, 126.0, 124.7, 83.1, 65.4, 48.0, 44.4, 33.3, 27.8, 21.6. *Minor Diastereomer:* ^{1}H-NMR (700 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.73 (d, J = 7.5 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.56–7.54 (m, 1H), 7.37–7.34 (m, 2H), 7.22–7.18 (m, 5H), 7.11–7.08 (m, 2H), 4.20–4.18 (m, 1H), 3.90–3.88 (m, 1H), 3.64 (d, J = 16.8 Hz, 1H), 3.40–3.36 (m, 1H), 3.33–3.29 (m, 1H), 3.27 (d, J = 16.8 Hz, 1H), 2.40 (s, 3H), 1.20 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 202.1, 168.5, 153.2, 143.4, 137.9, 137.0, 135.7, 135.4, 129.8, 129.2, 128.8, 127.9, 127.8, 127.2, 126.3, 124.7, 82.8, 65.2, 49.0, 45.5, 34.7, 27.6, 21.6.

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Keywords: Organocatalysis · Bifunctional ammonium salt · Aziridine opening · Alkylation · Regioselectivity

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Supporting Information

Ammonium Salt-Catalyzed Ring-Opening of Aryl-Aziridines with β-Keto Esters

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1. General Information

1.1. General Methods

Solvents and reagents were purchased from commercial suppliers and were used without further purification unless otherwise mentioned. Anhydrous solvents were dried using a molecular sieve drying plant. All reactions were performed under an argon atmosphere. TLC analysis were carried out using Macherey-Nagel pre-coated TLC sheets Alugram ® Xtra SIL G/UV with detection at 254 nm. For column chromatography Davisil LC 60A 70-200 MICRON silica gel was used. HPLC was performed using a Dionex Summit HPLC system with a YMC Chiral Art Cellulose - SB (250 x 4.6 mm, 5 µm) and a YMC Chiral Art Amylose SA (250 x 4.6 mm, 5 µm) chiral stationary phase. Preparative HPLC was carried out using a Thermo Scientific Dionex Ultimate 3000 system with variable wavelength detection and a Grace Alltima Silica 10µm 250x10 mm column. ^{1}H- and ^{13}C-NMR spectra were recorded using a Bruker Avance III 300 MHz spectrometer with a broad band observe probe and a sample changer for 16 samples, a Bruker Avance DRX 500 MHz spectrometer, and a Bruker Avance III 700 MHz spectrometer with an Ascend magnet and TCI cryoprobe of the Austro-Czech NMR-Research Center. High resolution mass spectra were obtained using a Thermo Fisher Scientific LTQ Orbitrap XL with an Ion Max API Source.

Chiral catalysts **A**[1], starting β-ketoesters **1**[2], and racemic[3] and enantiopure[4] aziridines **4** were synthesized as described previously.

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1.2. Single-Crystal Analysis

Crystallographic data were collected at 160.0(1) K on a Rigaku-Oxford Diffraction XtaLAB Synergy-S dual source diffractometer. This is a kappa-axis four-circle goniometer with a Dectris Pilatus3 R 200K HPC (Hybrid Photon Counting) detector and Cu and Mo PhotonJet microfocus X-ray sources. A suitable crystal was covered with oil (Infineum V8512, formerly known as Paratone N), placed on a nylon loop that is mounted on a CrystalCap Magnetic™ pin (Hampton Research) and immediately transferred to the diffractometer. The program suite *CrysAlis^{Pro}* was used for data collection, numerical and multi-scan absorption correction as well as data reduction.[5] The structure was solved with the dual-space algorithm using *SHELXT*[6] and was refined by full-matrix least-squares methods on F^2 with *SHELXL-2018*[7] using the *Olex2* GUI.[8] Compound **5a** crystallized in the chiral space group *C*2 with a Flack parameter of 0.011(6) (*S* configuration at C1 and *R* configuration at C15). The sulfonylamide methylene unit was disordered in a ratio 78:22. The graphical output was produced with the help of the program *Mercury*.[9][5] CCDC 2012449 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/structures.

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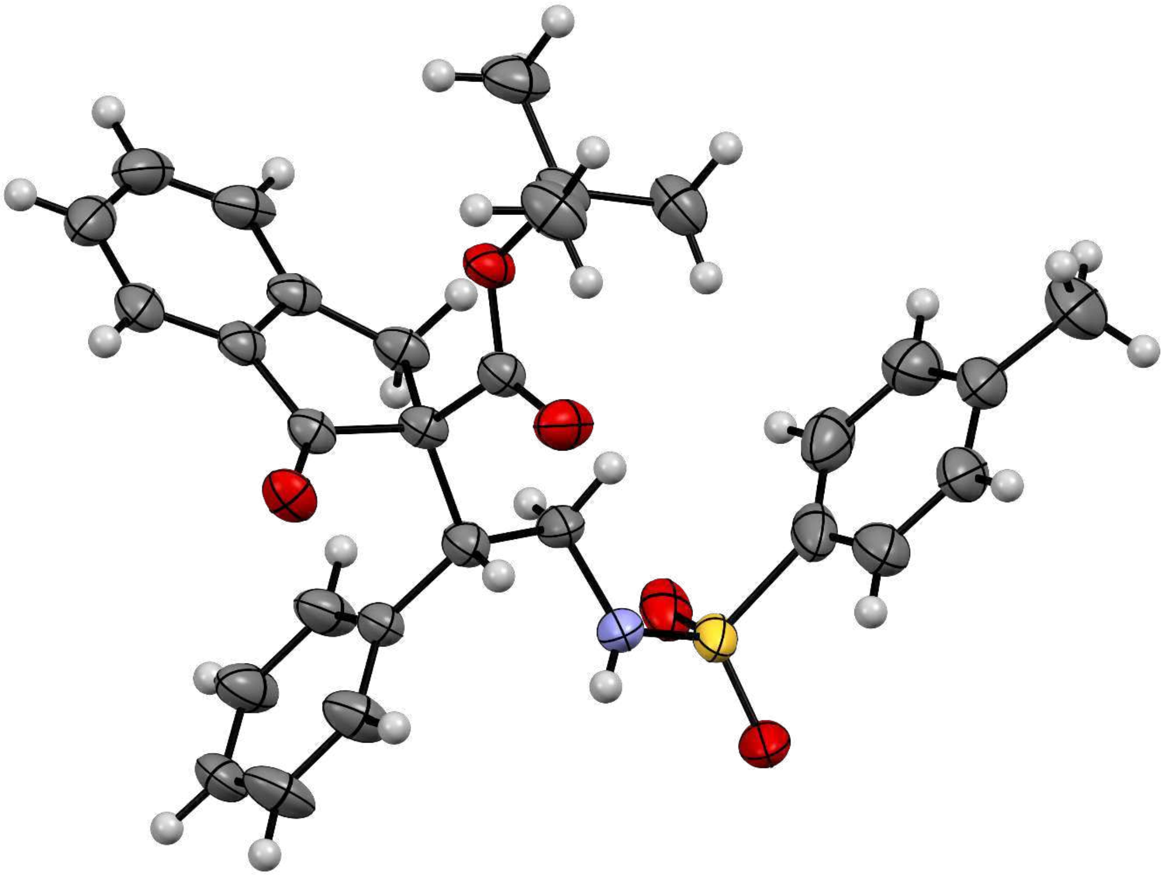


Fig. S1: Displacement ellipsoid representation of compound **5a** at 50% probability. Disordered parts are omitted for clarity.

Table S1. Crystal data and structure refinement for **5a**.

Empirical formula	$C_{29}H_{31}NO_5S$
Formula weight	505.61
Crystal system	Monoclinic
Space group	C2
a [Å]	20.65539(16)
b [Å]	5.88663(4)
c [Å]	22.57135(19)
α [°]	90
β [°]	103.4741(9)
γ [°]	90
Volume [Å^3]	2668.92(4)
Z	4
Density (calculated) [Mg/m^3]	1.258
Temperature [K]	160.01(10)
Wavelength [Å]	1.54184
Absorption coefficient [mm^{-1}]	1.392
F(000)	1072
Crystal size [mm^3]	0.594 x 0.122 x 0.101
Crystal description	colourless needle
Theta range for data collection [°]	4.028 to 79.558
Index ranges	-21<=h<=26, -7<=k<=7, -27<=l<=28
Reflections collected	31300
Independent reflections	5436 [R(int) = 0.0260]
Reflections observed	5380
Criterion for observation	$I > 2\sigma(I)$
Completeness to theta	94.4 % to 67.684°
Absorption correction	Gaussian
Max. and min. transmission	1.000 and 0.344
Data / restraints / parameters	5436 / 98 / 375
Goodness-of-fit on F^2	1.057
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0359, wR2 = 0.0973
R indices (all data)	R1 = 0.0365, wR2 = 0.0997
Absolute structure parameter	0.011(6)
Largest diff. peak and hole [e.Å^{-3}]	0.249 and -0.200

Table S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **5a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	8205(1)	2033(3)	6408(1)	47(1)
S(1B)	8032(2)	1079(8)	6507(2)	35(1)
O(1)	7625(1)	8928(3)	8714(1)	41(1)
O(2)	6758(1)	8461(3)	7220(1)	50(1)
O(3)	6062(1)	6663(3)	7694(1)	42(1)
O(4)	8702(1)	2763(6)	6099(1)	59(1)
O(4B)	8568(6)	2419(15)	6344(5)	40(2)
O(5)	8269(2)	-115(7)	6715(1)	56(1)
O(5B)	8137(6)	-1327(19)	6624(4)	44(2)
N(1)	8190(1)	4008(6)	6910(1)	46(1)
N(1B)	7887(4)	2274(17)	7123(4)	39(2)
C(1)	7199(1)	5772(4)	8029(1)	33(1)
C(2)	7325(1)	7146(4)	8630(1)	32(1)
C(3)	7005(1)	5926(4)	9056(1)	34(1)
C(4)	6922(1)	6627(5)	9621(1)	44(1)
C(5)	6588(1)	5176(6)	9934(1)	55(1)
C(6)	6346(1)	3104(6)	9681(1)	57(1)
C(7)	6430(1)	2420(5)	9123(1)	48(1)
C(8)	6764(1)	3858(4)	8803(1)	37(1)
C(9)	6933(1)	3458(4)	8199(1)	37(1)
C(10)	6655(1)	7126(4)	7592(1)	35(1)
C(11)	5430(1)	7480(4)	7291(1)	41(1)
C(12)	4920(1)	6420(6)	7596(2)	58(1)
C(13)	5377(2)	6555(5)	6660(1)	55(1)
C(14)	5390(2)	10036(5)	7306(2)	56(1)
C(15)	7830(1)	5691(4)	7766(1)	38(1)
C(16)	8482(1)	5315(4)	8225(1)	36(1)
C(17)	8643(1)	3348(5)	8560(1)	51(1)
C(18)	9247(1)	3114(6)	8979(2)	59(1)
C(19)	9705(1)	4849(5)	9072(1)	54(1)
C(20)	9560(1)	6788(5)	8729(2)	61(1)
C(21)	8959(1)	7018(5)	8315(1)	53(1)
C(22)	7686(2)	3834(7)	7272(2)	42(1)
C(22B)	7805(6)	4770(20)	7083(6)	38(2)

C(23)	7408(1)	1936(6)	5885(1)	55(1)
C(24)	7269(1)	3756(6)	5487(1)	58(1)
C(25)	6678(1)	3796(6)	5053(1)	56(1)
C(26)	6219(1)	2023(6)	4991(1)	55(1)
C(27)	6366(2)	242(7)	5402(2)	63(1)
C(28)	6954(2)	198(7)	5853(1)	64(1)
C(29)	5604(2)	2049(9)	4486(2)	82(1)

Table S3. Bond lengths [Å] and angles [°] for **5a**.

S(1)-O(4)	1.435(3)
S(1)-O(5)	1.433(4)
S(1)-N(1)	1.629(3)
S(1)-C(23)	1.789(3)
S(1B)-O(4B)	1.475(10)
S(1B)-O(5B)	1.448(10)
S(1B)-N(1B)	1.647(10)
S(1B)-C(23)	1.744(4)
O(1)-C(2)	1.211(3)
O(2)-C(10)	1.206(3)
O(3)-C(10)	1.326(3)
O(3)-C(11)	1.486(3)
N(1)-C(22)	1.468(4)
N(1B)-C(22B)	1.480(17)
C(1)-C(2)	1.548(3)
C(1)-C(9)	1.549(3)
C(1)-C(10)	1.534(3)
C(1)-C(15)	1.554(3)
C(2)-C(3)	1.472(3)
C(3)-C(4)	1.390(3)
C(3)-C(8)	1.387(3)
C(4)-C(5)	1.390(4)
C(5)-C(6)	1.391(5)
C(6)-C(7)	1.371(4)
C(7)-C(8)	1.396(3)
C(8)-C(9)	1.502(3)
C(11)-C(12)	1.520(4)
C(11)-C(13)	1.506(4)
C(11)-C(14)	1.507(4)
C(15)-C(16)	1.513(3)
C(15)-C(22)	1.541(4)
C(15)-C(22B)	1.625(12)
C(16)-C(17)	1.380(3)
C(16)-C(21)	1.386(3)
C(17)-C(18)	1.386(4)
C(18)-C(19)	1.375(4)
C(19)-C(20)	1.372(4)

C(20)-C(21)	1.376(4)
C(23)-C(24)	1.384(5)
C(23)-C(28)	1.378(5)
C(24)-C(25)	1.377(4)
C(25)-C(26)	1.396(5)
C(26)-C(27)	1.386(5)
C(26)-C(29)	1.496(4)
C(27)-C(28)	1.391(5)

O(4)-S(1)-N(1)	104.9(2)
O(4)-S(1)-C(23)	110.01(16)
O(5)-S(1)-O(4)	120.24(19)
O(5)-S(1)-N(1)	107.9(2)
O(5)-S(1)-C(23)	104.9(2)
N(1)-S(1)-C(23)	108.46(14)
O(4B)-S(1B)-N(1B)	106.1(6)
O(4B)-S(1B)-C(23)	95.8(4)
O(5B)-S(1B)-O(4B)	118.6(6)
O(5B)-S(1B)-N(1B)	108.2(6)
O(5B)-S(1B)-C(23)	118.7(5)
N(1B)-S(1B)-C(23)	108.1(4)
C(10)-O(3)-C(11)	122.85(17)
C(22)-N(1)-S(1)	118.0(3)
C(22B)-N(1B)-S(1B)	114.3(8)
C(2)-C(1)-C(9)	103.85(17)
C(2)-C(1)-C(15)	111.51(17)
C(9)-C(1)-C(15)	116.38(17)
C(10)-C(1)-C(2)	103.90(16)
C(10)-C(1)-C(9)	111.54(18)
C(10)-C(1)-C(15)	108.89(18)
O(1)-C(2)-C(1)	124.37(19)
O(1)-C(2)-C(3)	127.7(2)
C(3)-C(2)-C(1)	107.89(18)
C(4)-C(3)-C(2)	128.6(2)
C(8)-C(3)-C(2)	109.42(19)
C(8)-C(3)-C(4)	122.0(2)
C(5)-C(4)-C(3)	117.8(3)
C(4)-C(5)-C(6)	120.3(3)
C(7)-C(6)-C(5)	121.7(2)

C(6)-C(7)-C(8)	118.8(3)
C(3)-C(8)-C(7)	119.5(2)
C(3)-C(8)-C(9)	111.93(18)
C(7)-C(8)-C(9)	128.5(2)
C(8)-C(9)-C(1)	104.91(18)
O(2)-C(10)-O(3)	125.1(2)
O(2)-C(10)-C(1)	124.4(2)
O(3)-C(10)-C(1)	110.44(17)
O(3)-C(11)-C(12)	101.17(19)
O(3)-C(11)-C(13)	108.80(19)
O(3)-C(11)-C(14)	110.8(2)
C(13)-C(11)-C(12)	112.0(2)
C(13)-C(11)-C(14)	112.9(2)
C(14)-C(11)-C(12)	110.6(2)
C(1)-C(15)-C(22B)	122.0(5)
C(16)-C(15)-C(1)	115.84(19)
C(16)-C(15)-C(22)	112.5(2)
C(16)-C(15)-C(22B)	115.3(4)
C(22)-C(15)-C(1)	105.2(2)
C(17)-C(16)-C(15)	124.0(2)
C(17)-C(16)-C(21)	117.0(2)
C(21)-C(16)-C(15)	118.9(2)
C(16)-C(17)-C(18)	121.3(2)
C(19)-C(18)-C(17)	120.6(3)
C(20)-C(19)-C(18)	118.7(3)
C(19)-C(20)-C(21)	120.5(3)
C(20)-C(21)-C(16)	121.8(3)
N(1)-C(22)-C(15)	108.2(3)
N(1B)-C(22B)-C(15)	107.1(9)
C(24)-C(23)-S(1)	115.0(3)
C(24)-C(23)-S(1B)	138.4(3)
C(28)-C(23)-S(1)	124.7(3)
C(28)-C(23)-S(1B)	101.2(3)
C(28)-C(23)-C(24)	120.3(3)
C(25)-C(24)-C(23)	119.4(3)
C(24)-C(25)-C(26)	121.8(3)
C(25)-C(26)-C(29)	120.3(3)
C(27)-C(26)-C(25)	117.5(3)
C(27)-C(26)-C(29)	122.2(3)

C(26)-C(27)-C(28)	121.4(3)
C(23)-C(28)-C(27)	119.5(3)

Symmetry transformations used to generate equivalent atoms:

Table S4. Anisotropic displacement parameters ($Å^2 x 10^3$) for **5a**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	30(1)	80(1)	31(1)	-6(1)	5(1)	9(1)
S(1B)	31(2)	45(2)	31(2)	2(1)	12(1)	1(2)
O(1)	44(1)	30(1)	47(1)	0(1)	3(1)	-4(1)
O(2)	39(1)	58(1)	54(1)	22(1)	10(1)	4(1)
O(3)	26(1)	52(1)	43(1)	13(1)	1(1)	2(1)
O(4)	33(1)	106(2)	41(2)	-9(2)	13(1)	4(1)
O(4B)	28(5)	55(5)	41(6)	10(4)	17(4)	-10(4)
O(5)	43(2)	77(2)	44(2)	-2(2)	0(1)	27(2)
O(5B)	60(6)	40(5)	36(4)	0(4)	20(4)	10(4)
N(1)	31(1)	73(2)	34(1)	-7(1)	10(1)	-4(1)
N(1B)	35(4)	50(4)	32(3)	8(3)	10(3)	0(3)
C(1)	28(1)	31(1)	38(1)	1(1)	4(1)	0(1)
C(2)	28(1)	29(1)	37(1)	5(1)	1(1)	4(1)
C(3)	24(1)	39(1)	37(1)	8(1)	1(1)	5(1)
C(4)	32(1)	57(1)	39(1)	4(1)	1(1)	7(1)
C(5)	36(1)	88(2)	42(1)	15(1)	10(1)	10(1)
C(6)	34(1)	80(2)	57(2)	27(1)	10(1)	-3(1)
C(7)	29(1)	49(1)	64(2)	21(1)	4(1)	-3(1)
C(8)	24(1)	38(1)	47(1)	12(1)	1(1)	3(1)
C(9)	31(1)	29(1)	49(1)	1(1)	4(1)	-1(1)
C(10)	30(1)	36(1)	36(1)	2(1)	3(1)	-1(1)
C(11)	27(1)	43(1)	46(1)	3(1)	-5(1)	2(1)
C(12)	30(1)	65(2)	74(2)	14(1)	6(1)	2(1)
C(13)	46(1)	58(2)	54(2)	-8(1)	-5(1)	2(1)
C(14)	47(2)	42(1)	70(2)	-2(1)	-3(1)	4(1)
C(15)	30(1)	45(1)	37(1)	-2(1)	5(1)	1(1)
C(16)	28(1)	41(1)	36(1)	-3(1)	5(1)	-3(1)
C(17)	32(1)	54(1)	62(2)	14(1)	-1(1)	-10(1)
C(18)	36(1)	73(2)	63(2)	29(2)	-1(1)	-6(1)
C(19)	29(1)	77(2)	48(1)	4(1)	-5(1)	-8(1)
C(20)	34(1)	55(2)	85(2)	2(2)	-6(2)	-13(1)
C(21)	36(1)	43(1)	73(2)	8(1)	-1(1)	-6(1)
C(22)	29(1)	60(2)	38(2)	-9(2)	12(1)	-2(1)
C(22B)	29(4)	53(5)	34(4)	5(4)	9(4)	-2(4)

C(23)	43(1)	88(2)	32(1)	-7(1)	7(1)	18(1)
C(24)	39(1)	80(2)	52(2)	-3(1)	5(1)	3(1)
C(25)	42(1)	81(2)	42(1)	16(1)	4(1)	6(1)
C(26)	38(1)	86(2)	41(1)	7(1)	5(1)	5(1)
C(27)	48(2)	80(2)	59(2)	11(2)	10(2)	-1(2)
C(28)	59(2)	88(2)	44(2)	19(2)	13(2)	21(2)
C(29)	48(2)	125(3)	62(2)	11(2)	-5(2)	4(2)

Table S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10 ^{3}) for **5a**.

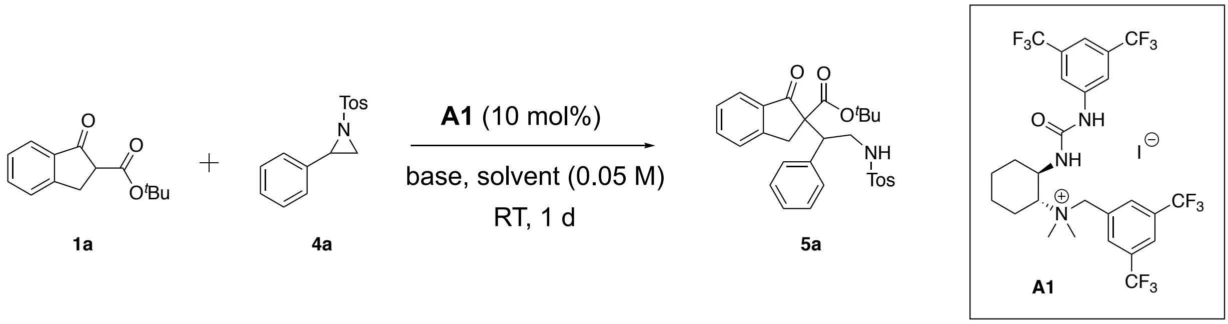
	x	y	z	U(eq)
H(1)	8474	5144	6963	55
H(1B)	7860	1493	7449	47
H(4)	7088	8052	9788	52
H(5)	6526	5602	10323	66
H(6)	6115	2138	9900	69
H(7)	6264	993	8958	58
H(9A)	6534	2990	7888	45
H(9B)	7278	2264	8234	45
H(12A)	4966	4763	7597	86
H(12B)	4471	6842	7370	86
H(12C)	4993	6972	8016	86
H(13A)	5714	7276	6480	83
H(13B)	4933	6879	6407	83
H(13C)	5450	4909	6681	83
H(14A)	5487	10556	7730	84
H(14B)	4942	10525	7096	84
H(14C)	5716	10687	7100	84
H(15)	7861	7175	7559	45
H(15A)	7875	7353	7693	45
H(17)	8333	2129	8502	62
H(18)	9345	1744	9204	71
H(19)	10114	4708	9367	64
H(20)	9878	7980	8777	74
H(21)	8868	8381	8086	63
H(22A)	7707	2314	7464	50
H(22B)	7236	4045	7007	50
H(22C)	7374	5169	6805	46
H(22D)	8167	5464	6924	46
H(24)	7579	4965	5514	69
H(25)	6580	5067	4787	67
H(27)	6058	-974	5376	75
H(28)	7042	-1021	6136	76
H(29A)	5302	3239	4563	122

H(29B)	5382	570	4464	122
H(29C)	5725	2354	4099	122

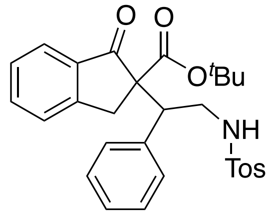
2. Experimental procedures

2.1. General procedures for the ring-opening reactions of aryl-aziridines 4 with β-ketoesters 1

2.1.1. General procedure for the enantioselective screening and optimization reactions



A mixture of the β-ketoester **1a** (0.1 mmol, 1 equiv.), catalyst **A1** (7.6 mg 0.01 mmol, 10 mol%) and 0.2 mmol of the tested base (2 equiv.) was dissolved in 5 mL of the given solvent under an argon atmosphere (room temperature). Then 48 mg of 2-phenyltosylaziridine **4a** (0.2 mmol, 2 equiv.) were added in one portion. After a reaction time of one day the mixture was filtrated through a plug of Na_2SO_4 and washed with DCM. The crude product, obtained after evaporation of the solvent under reduced pressure, was then subjected to column chromatography purification (silica gel, heptanes:EtOAc = 2:1) to isolate product **5a** as a mixture of two diastereomers (d.r. up to 8:1) in yields up to 84%. The diastereomers were separated using preparative HPLC (Grace Alltima Silica 10 µm 250x10 mm, n-hexane:EtOAc = 9:1, 5 mL/min, retention times: 39.1 min major, 46.8 min minor). The enantiomeric excess of the minor diastereomer was determined by HPLC using a YMC Amylose SA column (n-hexane:i-PrOH = 3:1, 1 mL/min, 10 °C, retention times: 21.0 and 35.5 min). The enantiomeric excess of the major diastereomer was determined by HPLC using a YMC Cellulose SB column (n-hexane:i-PrOH = 10:1, 1 mL/min, 10 °C, retention times: 22.2 min major, 20.2 min minor).



5a

Analytical data for compound **5a** (e.r., d.r., and yield depending on the conditions are given in the main manuscript).

HRMS (ESI): m/z calculated for $C_{29}H_{32}NO_5S^+$: 506.2001 [M+H]$^+$; found: 506.1992

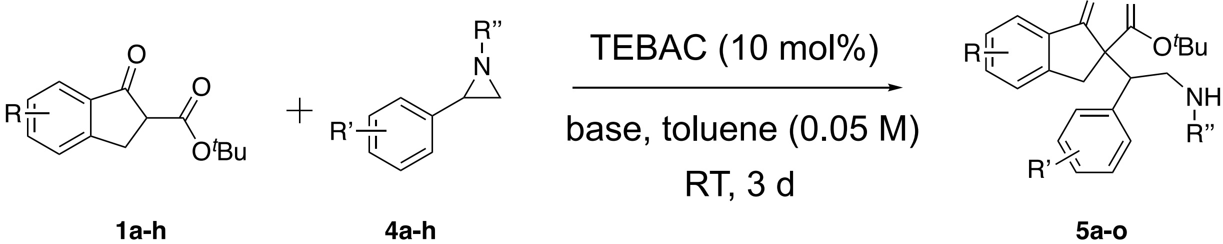
Major diastereomer:

^{1}H-NMR (700 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.67 (d, J = 8.2 Hz, 2H), 7.49 (d, J = 7.7 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.28 (d, J = 8.2 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 7.11-7.05 (m, 5H), 4.42-4.40 (m, 1H), 3.87 (dd, J_1 = 9.7 Hz, J_2 = 5.7 Hz, 1H), 3.69 (d, J = 17.2 Hz, 1H), 3.65-3.61 (m, 1H), 3.38-3.34 (m, 1H), 3.22 (d, J = 17.2 Hz, 1H), 2.43 (s, 3H), 1.37 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 200.7, 169.0, 153.2, 143.6, 137.2, 136.2, 135.2, 135.0, 129.9, 129.6, 128.7, 127.8, 127.6, 127.3, 126.0, 124.7, 83.1, 65.4, 48.0, 44.4, 33.3, 27.8, 21.6.

Minor diastereomer:

^{1}H-NMR (700 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.73 (d, J = 7.5 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.56-7.54 (m, 1H), 7.37-7.34 (m, 2H), 7.22-7.18 (m, 5H), 7.11-7.08 (m, 2H), 4.20-4.18 (m, 1H), 3.90-3.88 (m, 1H), 3.64 (d, J = 16.8 Hz, 1H), 3.40-3.36 (m, 1H), 3.33-3.29 (m, 1H), 3.27 (d, J = 16.8 Hz, 1H), 2.40 (s, 3H), 1.20 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 202.1, 168.5, 153.2, 143.4, 137.9, 137.0, 135.7, 135.4, 129.8, 129.2, 128.8, 127.9, 127.8, 127.2, 126.3, 124.7, 82.8, 65.2, 49.0, 45.5, 34.7, 27.6, 21.6.

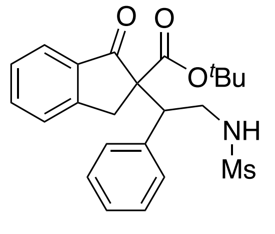
2.1.2. General procedure for the racemic application scope



1a-h **4a-h** **5a-o**

A mixture of 0.1 mmol β-ketoester **1a-h** (1 equiv.), 2.2 mg TEBAC (0.01 mmol, 10 mol%) and 0.2 mmol base (2 equiv.) was dissolved in 5 mL toluene (Ar-atmosphere). Then 0.2 mmol of aziridine **4a-h** (2 equiv.) were added in one portion. After a reaction time of three days the mixture was filtrated through a plug of Na_2SO_4 and washed with DCM. The crude product, obtained after evaporation of the solvent, was subjected to column chromatography (silica gel, heptanes:EtOAc = 5:1) to isolate products **5a-o** and **6** as mixtures of two diastereomers.

The diastereomers were in some cases separated using preparative HPLC (Grace Alltima Silica 10 µm 250x10 mm, n-hexane:EtOAc, 5 mL/min) but otherwise the mixture of diastereomers was analysed and in some cases the signals for the minor diastereomer were hardly detectable (i.e. in the 13C NMR) and mainly assigned with HSQC and HMBC methods.

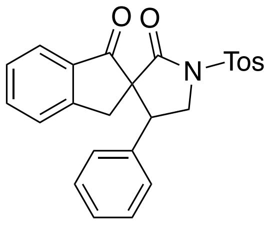


5b

Compound **5b** was prepared according to the general procedure described in 2.1.2 using Cs_2CO_3 as base and was obtained as a white residue in a yield of 4%. Only one diastereomer was detected.

HRMS (ESI): m/z calculated for $C_{23}H_{31}N_2O_5S^+$: 447.1954 $[M+NH_4]^+$; found: 447.1946

^{1}H-NMR (700 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.72 (d, J = 7.6 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.41-7.29 (m, 10H), 5.70 (d, J = 7.6 Hz, 1H), 4.70-4.67 (m, 1H), 3.77 (d, J = 7.5 Hz, 1H), 3.27 (d, J = 17.2 Hz, 1H), 2.94 (dd, J_1 = 10.9 Hz, J_2 = 15.0 Hz, 1H), 2.45 (s, 3H), 1.84 (dd, J_1 = 5.3 Hz, J_2 = 15.0 Hz, 1H), 1.39 (s, 9H).

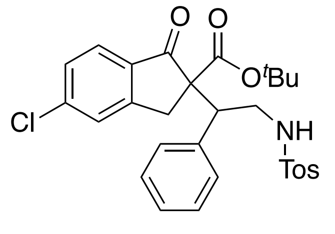


6

Compound **6** was prepared by the general procedure described in 2.1.2 starting from **1c** or **1d** using Cs_2CO_3 or K_3PO_4 (54% yield from **1d** and 17% from **1c**). Only one diastereomer was formed.

HRMS (ESI): m/z calculated for $C_{25}H_{25}N_2O_4S^+$: 449.1535 $[M+NH_4]^+$; found: 449.1528

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 8.02 (d, J = 8.3 Hz, 1H), 7.47-7.42 (m, 1H), 7.36 (d, J = 4.1 Hz, 2H), 7.37-7.32 (m, 2H), 7.20-7.13 (m, 6H), 4.68 (dd, J_1 = 11.4 Hz, J_2 = 9.4 Hz, 1H), 4.33 (dd, J_1 = 9.4 Hz, J_2 = 7.8 Hz, 1H), 3.80-3.73 (m, 1H), 3.73 (d, J = 17.5 Hz, 1H), 3.12 (d, J = 17.5 Hz, 1H), 2.45 (s, 3H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 201.1, 171.0, 153.0, 145.5, 135.7, 135.0, 134.9, 133.5, 129.8, 128.8, 128.5, 128.5, 128.4, 127.9, 126.1, 124.5, 64.9, 49.3, 48.7, 34.8, 21.9.



5e

Compound **5e** was prepared by the general procedure described in 2.1.2 using K_3PO_4 as base and was obtained as a colourless residue in a yield of 63% and with a d.r. of 1:4.

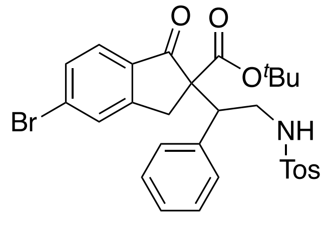
HRMS (ESI): m/z calculated for $C_{29}H_{34}ClN_2O_5S^+$: 557.1877 $[M+NH_4]^+$; found: 557.1870

Major diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.67 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.2 Hz, 1H), 7.32-7.27 (m, 3H), 7.20-7.17 (m, 1H), 7.12-7.09 (m, 3H), 7.04-7.01 (m, 2H), 4.39-4.37 (m, 1H), 3.93-3.89 (m, 1H), 3.68 (d, J = 17.3 Hz, 1H), 3.64-3.55 (m, 1H), 3.36-3.28 (m, 1H), 3.20 (d, J = 17.3 Hz, 1H), 2.43 (s, 3H), 1.38 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 199.4, 168.9, 154.7, 144.1, 143.7, 135.7, 133.4, 129.9, 129.5, 128.8, 128.5, 128.0, 127.3, 126.3, 125.7, 109.4, 83.5, 65.5, 47.8, 44.1, 32.7, 27.8, 21.7.

Minor diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.67 (d, J = 8.3 Hz, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.36-7.20 (m, 8H), 7.10-7.07 (m, 1H), 4.15-4.12 (m, 1H), 3.94-3.88 (m, 1H), 3.64 (d, J = 17.1 Hz, 1H), 3.36-3.26 (m, 1H), 3.27 (d, J = 22.2 Hz, 1H), 2.41 (s, 3H), 1.38 (s, 9H).



5f

Compound **5f** was prepared by the general procedure described in 2.1.2 using K_3PO_4 as base and was obtained as a white residue in a yield of 79% and with a d.r. of 1:6.

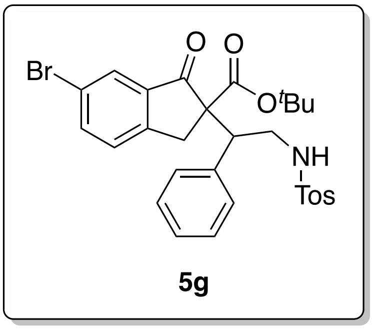
HRMS (ESI): m/z calculated for $C_{29}H_{34}BrN_2O_5S^+$: 601.1372 $[M+NH_4]^+$; found: 601.1363

Major diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.66 (d, J = 4.2 Hz, 2H), 7.51 (s, 1H), 7.34-7.27 (m, 4H), 7.11-7.08 (m, 3H), 7.03-7.00 (m, 2H), 4.37 (dd, J_1 = 8.5 Hz, J_2 = 3.7 Hz, 1H), 3.90 (dd, J_1 = 9.8 Hz, J_2 = 5.7 Hz, 1H), 3.68 (d, J = 17.5 Hz, 1H), 3.64-3.54 (m, 1H), 3.36-3.28 (m, 1H), 3.20 (d, J = 17.5 Hz, 1H), 2.43 (s, 3H), 1.38 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 200.5, 168.5, 154.8, 143.8, 143.7, 136.9, 135.7, 133.7, 131.3, 130.8, 129.9, 129.5, 129.3, 128.8, 128.0, 127.3, 125.8, 83.5, 65.5, 47.9, 44.1, 32.7, 27.8, 21.7.

Minor diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.59 (d, J = 8.2 Hz, 1H), 7.55-7.49 (m, 4H), 7.23-7.20 (m, 5H), 7.10-7.07 (m, 2H), 4.15-4.12 (m, 1H), 3.91 (t, J = 8.1 Hz, 1H), 3.64 (d, J = 17.0 Hz, 1H), 3.37-3.32 (m, 1H), 3.29-3.24 (m, 1H), 3.26 (d, J = 17.0 Hz, 1H), 2.41 (s, 3H), 1.18 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 200.9, 168.0, 154.8, 143.6, 137.8, 136.7, 134.2, 131.5, 131.0, 129.8, 129.6, 129.1, 128.9, 128.0, 127.1, 125.8, 83.1, 65.4, 48.7, 45.7, 29.8, 27.5, 21.7.



5g

Compound **5g** was prepared by the general procedure described in 2.1.2 using Cs_2CO_3 as base and was obtained as a white solid in a yield of 50% and with a d.r. of 1:3.5.

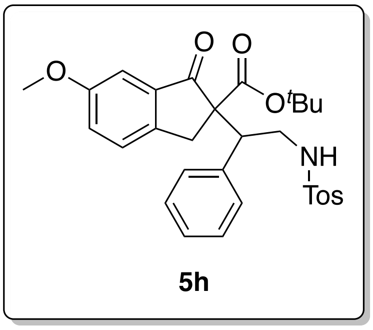
HRMS (ESI): m/z calculated for $C_{29}H_{34}BrN_2O_5S^+$: 601.1372 $[M+NH_4]^+$; found: 601.1368

Major diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.67 (d, J = 8.3 Hz, 2H), 7.60-7.55 (m, 2H), 7.30-7.21 (m, 3H), 7.12-7.09 (m, 3H), 7.04-7.01 (m, 2H), 4.40-4.36 (m, 1H), 3.94-3.88 (m, 1H), 3.65-3.54 (m, 1H), 3.60 (d, J = 17.2 Hz, 1H), 3.36-3.28 (m, 1H), 3.15 (d, J = 17.2 Hz, 1H), 2.43 (s, 3H), 1.37 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 199.3, 168.5, 151.8, 143.7, 138.0, 136.9, 136.7, 135.7, 129.9, 129.5, 128.8, 128.0, 127.5, 127.4, 127.2, 121.7, 83.5, 65.8, 47.7, 44.2, 32.7, 27.8, 21.7.

Minor diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.85-7.53 (m, 3H), 7.28-7.20 (m, 8H), 7.10-7.07 (m, 1H), 4.17-4.11 (m, 1H), 3.93-3.82 (m, 1H), 3.61 (d, J = 17.0 Hz, 1H), 3.39-3.23 (m, 1H), 3.25 (d, J = 17.0 Hz, 1H), 2.41 (s, 3H), 1.18 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 200.8, 168.0, 151.8, 144.1, 143.6, 138.2, 137.2, 136.7, 129.8, 129.1, 128.9, 128.0, 127.8, 127.5, 127.2, 121.9, 83.1, 65.7, 48.9, 31.7, 27.6, 22.8, 14.3.



5h

Compound **5h** was prepared by the general procedure described in 2.1.2 using Cs_2CO_3 as base and was obtained as a white solid in a yield of 74% and with a d.r. of 1:4.5.

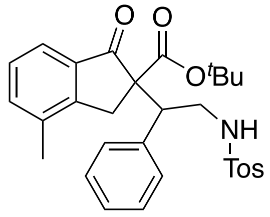
HRMS (ESI): m/z calculated for $C_{30}H_{37}N_2O_6S^+$: 553.2372 $[M+NH_4]^+$; found: 553.2364

Major diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.67 (d, J = 8.3 Hz, 2H), 7.30-7.20 (m, 3H), 7.11-7.04 (m, 6H), 6.92-6.91 (m, 1H), 4.42-4.38 (m, 1H), 3.92-3.87 (m, 1H), 3.73 (s, 3H), 3.65-3.56 (m, 1H), 3.60 (d, J = 17.1 Hz, 1H), 3.37-3.28 (m, 1H), 3.15 (d, J = 17.1 Hz, 1H), 2.43 (s, 3H), 1.37 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 200.6, 169.0, 159.5, 146.1, 143.5, 137.1, 136.2, 136.1, 129.8, 129.6, 128.7, 127.8, 127.3, 126.7, 124.7, 105.7, 83.1, 66.1, 55.6, 48.0, 44.4, 32.7, 27.8, 21.6.

Minor diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.60-7.55 (m, 3H), 7.24-7.14 (m, 9H), 4.22-4.17 (m, 1H), 3.92-3.84 (m, 1H), 3.83 (s, 3H), 3.74 (d, J = 17.7 Hz, 1H), 3.55 (d, J = 16.9 Hz, 1H), 3.38-3.30 (m, 1H), 3.17 (d, J = 16.9 Hz, 1H), 2.41 (s, 3H), 1.21 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 201.9, 168.5, 159.7, 146.1, 143.3, 137.8, 137.0, 136.8, 129.7, 129.2, 128.8, 127.8, 127.2, 126.9, 124.8, 105.8, 82.7, 65.8, 55.7, 49.0, 45.4, 34.0, 27.6, 21.6.



5i

Compound **5i** was prepared by the general procedure described in 2.1.2 using K_3PO_4 as base and was obtained as a colourless residue in a yield of 39% and with a d.r. of 1:5.

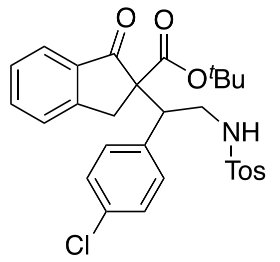
HRMS (ESI): m/z calculated for $C_{30}H_{37}N_2O_5S^+$: 537.2423 $[M+NH_4]^+$; found: 537.2415

Major diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.68 (d, J = 8.3 Hz, 2H), 7.34-7.30 (m, 4H), 7.13 (d, J = 7.5 Hz, 1H), 7.09-7.04 (m, 5H), 4.42-4.38 (m, 1H), 3.92-3.87 (m, 1H), 3.66-3.57 (m, 1H), 3.56 (d, J = 17.4 Hz, 1H), 3.43-3.34 (m, 1H), 3.04 (d, J = 17.4 Hz, 1H), 2.43 (s, 3H), 2.28 (s, 3H), 1.37 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 200.8, 168.9, 152.0, 143.5, 137.2, 136.1, 135.6, 135.1, 134.7, 129.8, 129.5, 128.6, 127.8, 127.7, 127.3, 122.0, 83.1, 65.4, 48.1, 44.2, 32.1, 27.8, 21.6, 17.8

Minor diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.61-7.53 (m, 3H), 7.39-7.30 (m, 2H), 7.22-7.20 (m, 5H), 7.13-7.10 (m, 2H), 4.20-4.14 (m, 1H), 3.93 (t, J = 8.3 Hz, 1H), 3.59 (d, J = 17.1 Hz, 1H), 3.34-3.27 (m, 1H), 3.11 (d, J = 17.1 Hz, 1H), 2.41 (s, 3H), 2.30 (s, 3H), 1.19 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 202.1, 168.4, 152.2, 143.3, 138.0, 137.0, 135.9, 135.5, 135.3, 129.7, 129.1, 128.7, 127.9, 127.8, 127.2, 122.0, 82.7, 65.3, 48.9, 45.6, 33.2, 27.6, 21.6, 17.8



5j

Compound **5j** was prepared by the general procedure described in 2.3.2 using Cs_2CO_3 as base and was obtained as a white residue in a yield of 80% and with a d.r. of 1:4.

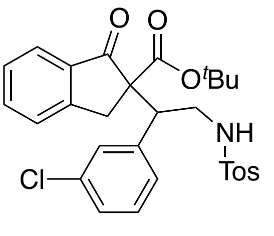
HRMS (ESI): m/z calculated for $C_{29}H_{34}ClN_2O_5S^+$: 557.1877 $[M+NH_4]^+$; found: 557.1883

Major diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.65 (d, J = 8.3 Hz, 2H), 7.52-7.48 (m, 2H), 7.36-7.22 (m, 4H), 7.07-6.98 (m, 4H), 4.41-4.37 (m, 1H), 3.90-3.85 (m, 1H), 3.69 (d, J = 17.2 Hz, 1H), 3.62-3.53 (m, 1H), 3.35-3.26 (m, 1H), 3.18 (d, J = 17.2 Hz, 1H), 2.43 (s, 3H), 1.35 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 200.6, 168.8, 153.0, 143.7, 136.9, 135.5, 134.8, 133.8, 130.9, 129.9, 128.8, 127.8, 127.2, 126.0, 125.0, 124.8, 83.3, 65.1, 47.3, 44.4, 33.2, 27.8, 21.7

Minor diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.73 (d, J = 7.3 Hz, 1H), 7.58 (d, J = 9.2 Hz, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 7.1 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 4.23-4.19 (m, 1H), 3.88-3.83 (m, 1H), 3.60 (d, J = 16.7 Hz, 1H), 3.35-3.27 (m, 2H), 3.20 (d, J = 16.7 Hz, 1H), 2.40 (s, 3H), 1.21 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 201.8, 168.4, 153.0, 143.5, 136.7, 136.4, 135.6, 133.7, 130.5, 129.8, 129.8, 128.9, 127.9, 127.3, 127.1, 126.3, 124.7, 83.0, 64.9, 48.5, 45.4, 34.6, 27.5, 21.7



5k

Compound **5k** was prepared by the general procedure described in 2.1.2 using Cs_2CO_3 as the base and was obtained as a white residue in a yield of 37% and with a d.r. of 2:1.

HRMS (ESI): m/z calculated for $C_{29}H_{34}ClN_2O_5S^+$: 557.1877 $[M+NH_4]^+$; found: 557.1869

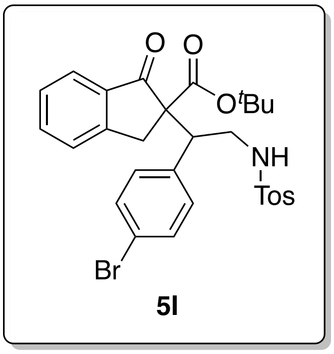
Major diastereomer:

^{1}H-NMR (700 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.66 (d, J = 8.2 Hz, 2H), 7.53-7.49 (m, 2H), 7.36 (d, J = 7.6 Hz, 1H), 7.28-7.23 (m, 3H), 7.07-7.03 (m, 2H), 6.99-6.97 (m, 2H), 4.45-4.43 (m, 1H), 3.81 (dd, J_1 = 9.5 Hz, J_2 = 5.7 Hz, 1H), 3.69 (d, J = 17.2 Hz, 1H), 3.65-3.62 (m, 1H), 3.35-3.31 (m, 1H), 3.18 (d, J = 17.2 Hz, 1H), 2.43 (s, 3H), 1.37 (s, 9H); ^{13}C-NMR (176 MHz,

$CDCl_3$, 298.0 K): δ /ppm = 200.4, 168.8, 152.9, 143.7, 138.6, 137.1, 135.4, 134.9, 134.5, 129.9, 129.5, 128.0, 127.9, 127.2, 126.0, 124.7, 83.3, 65.0, 47.9, 44.4, 33.7, 27.8, 21.6.

Minor diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.75 (d, J = 8.0 Hz, 1H), 7.61-7.54 (m, 3H), 7.41-7.37 (m, 2H), 7.22-7.14 (m, 5H), 7.02-7.00 (m, 2H), 4.23-4.19 (m, 1H), 3.89-3.84 (m, 1H), 3.66 (d, J = 16.8 Hz, 1H), 3.37-3.26 (m, 2H), 3.23 (d, J = 16.8 Hz, 1H), 2.41 (s, 3H), 1.21 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 201.2, 168.0, 143.5, 140.1, 135.6, 135.4, 130.0, 129.8, 129.8, 129.7, 128.0, 127.9, 127.3, 127.2, 127.1, 127.0, 126.3, 124.7, 83.0, 65.1, 48.6, 45.3, 34.3, 27.5, 21.6.



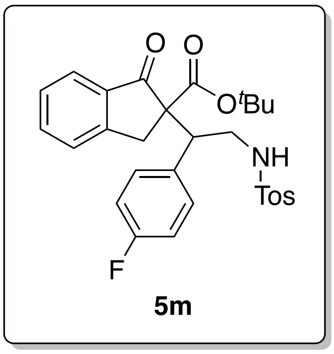
5l

Compound **5l** was prepared by the general procedure described in 2.1.2 using Cs_2CO_3 as base and was obtained as a white residue in a yield of 96% and with a d.r. of 1:3.

HRMS (ESI): m/z calculated for $C_{29}H_{34}BrN_2O_5S^+$: 601.1372 $[M+NH_4]^+$; found: 601.1360

Major diastereomer:

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.64 (d, J = 8.2 Hz, 2H), 7.53-7.48 (m, 2H), 7.40-7.28 (m, 4H), 7.21 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 4.41-4.37 (m, 1H), 3.89-3.84 (m, 1H), 3.69 (d, J = 17.3 Hz, 1H), 3.57-3.52 (m, 1H), 3.34-3.29 (m, 1H), 3.17 (d, J = 17.3 Hz, 1H), 2.43 (s, 3H), 1.35 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 200.7, 168.8, 143.7, 136.9, 135.3, 134.8, 131.8, 131.2, 129.9, 127.8, 127.2, 126.4, 126.0, 124.8, 121.9, 83.3, 65.1, 47.4, 44.4, 33.3, 27.8, 21.7.



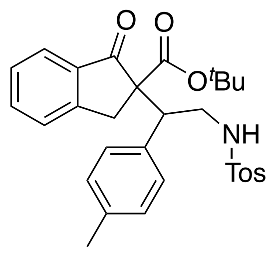
5m

Compound **5m** was prepared by the general procedure described in 2.1.2 using K_3PO_4 as base and was obtained as a white residue in a yield of 75% and with a d.r. of 1:2.5.

HRMS (ESI): m/z calculated for $C_{29}H_{34}FN_2O_5S^+$: 541.2172 $[M+NH_4]^+$; found: 541.2162

Major diastereomer:

^{1}H-NMR (300 MHz, CDCl$_3$, 298.0 K): δ /ppm = 7.67 (d, J = 8.3 Hz, 2H), 7.52-7.47 (m, 2H), 7.36-7.21 (m, 4H), 7.06-7.01 (m, 2H), 6.83-6.75 (m, 2H), 4.41-4.37 (m, 1H), 3.93-3.88 (m, 1H), 3.70 (d, J = 17.3 Hz, 1H), 3.62-3.51 (m, 1H), 3.35-3.26 (m, 1H), 3.19 (d, J = 17.3 Hz, 1H), 2.43 (s, 3H), 1.36 (s, 9H); ^{13}C-NMR (176 MHz, CDCl$_3$, 298.0 K): δ /ppm = 201.2, 168.9, 144.0, 143.6, 137.1, 135.3, 132.0, 131.2, 131.1, 129.8, 129.5, 127.7, 127.2, 126.7, 126.0, 124.7, 115.6, 83.2, 65.2, 47.3, 44.5, 33.3, 28.0, 21.6.



5n

Compound **5n** was prepared by the general procedure described in 2.1.2 using Cs$_2$CO$_3$ as base and was obtained as a colourless residue in a yield of 89% and with a d.r. of 1:3.

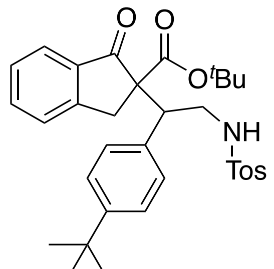
HRMS (ESI): m/z calculated for $C_{30}H_{37}N_2O_5S^+$: 537.2423 $[M+NH_4]^+$; found: 537.2419

Major diastereomer:

^{1}H-NMR (300 MHz, CDCl$_3$, 298.0 K): δ /ppm = 7.67 (d, J = 8.3 Hz, 2H), 7.52-7.45 (m, 2H), 7.35-7.19 (m, 4H), 6.95-6.88 (m, 4H), 4.39-4.36 (m, 1H), 3.89-3.84 (m, 1H), 3.68 (d, J = 17.3 Hz, 1H), 3.64-3.54 (m, 1H), 3.35-3.26 (m, 1H), 3.21 (d, J = 17.3 Hz, 1H), 2.43 (s, 3H), 2.18 (s, 3H), 1.37 (s, 9H); ^{13}C-NMR (176 MHz, CDCl$_3$, 298.0 K): δ /ppm = 200.6, 168.9, 153.2, 143.5, 137.5, 137.2, 135.1, 135.0, 132.9, 129.8, 129.4, 129.4, 127.5, 127.3, 126.0, 124.6, 83.0, 65.5, 47.5, 44.3, 33.2, 27.8, 21.0, 14.2.

Minor diastereomer:

^{1}H-NMR (300 MHz, CDCl$_3$, 298.0 K): δ /ppm = 7.74-7.65 (m, 2H), 7.59-7.45 (m, 3H), 7.36 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 7.9 Hz, 2H), 6.97 (d, J = 4.1 Hz, 2H), 6.91 (d, J = 3.8 Hz, 2H), 4.39-4.35 (m, 1H), 3.88-3.80 (m, 1H), 3.64 (t, J = 17.8 Hz, 1H), 3.36-3.18 (m, 3H), 2.41 (d, J = 7.8 Hz, 3H), 2.21 (d, J = 24.5 Hz, 3H), 1.28 (d, J = 45.1 Hz, 9H).



5o

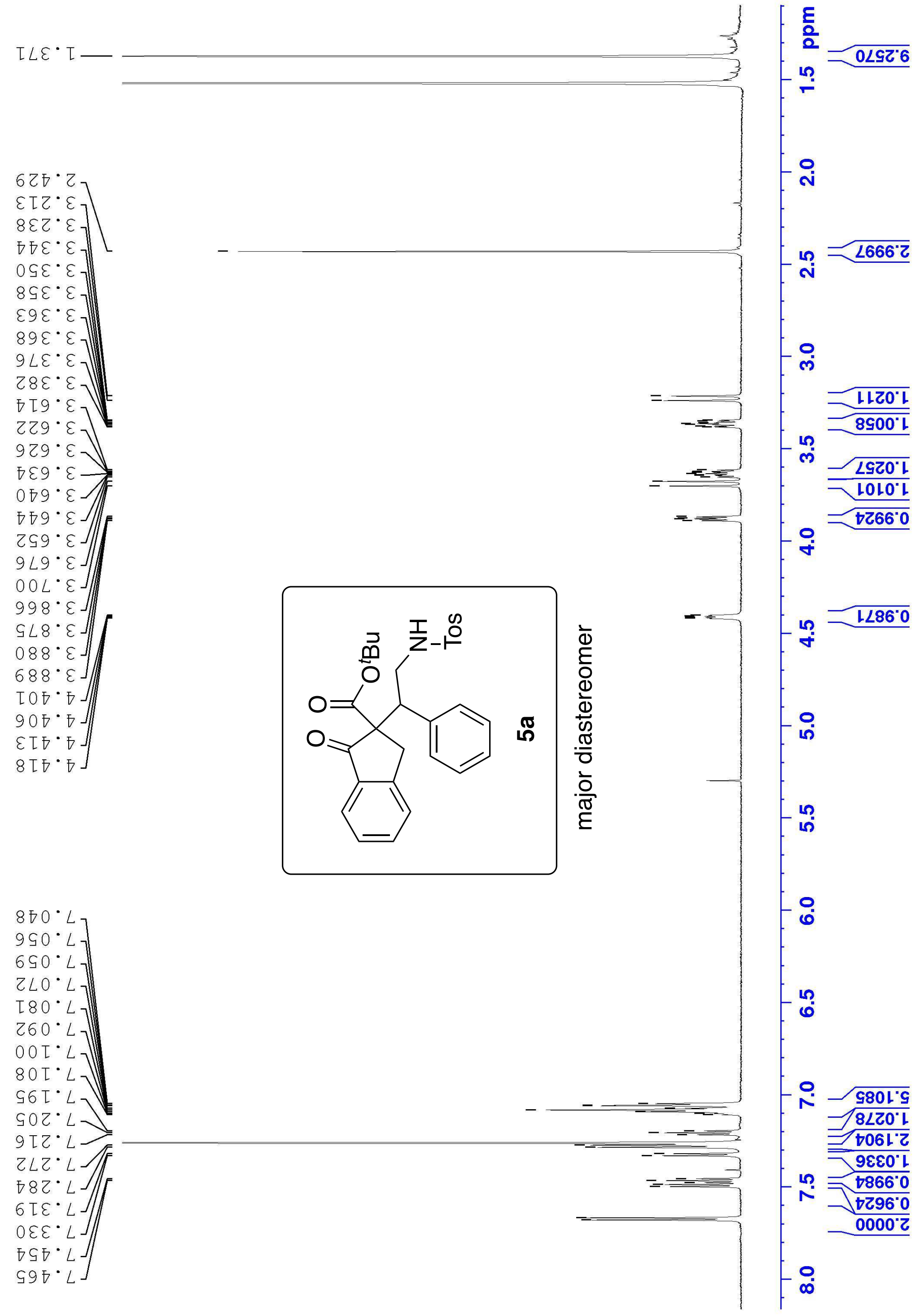
Compound **5o** was prepared by the general procedure described in 2.3.2 using K_3PO_4 as base and was obtained as a white residue in a yield of 90%. Only one diastereomer was formed.

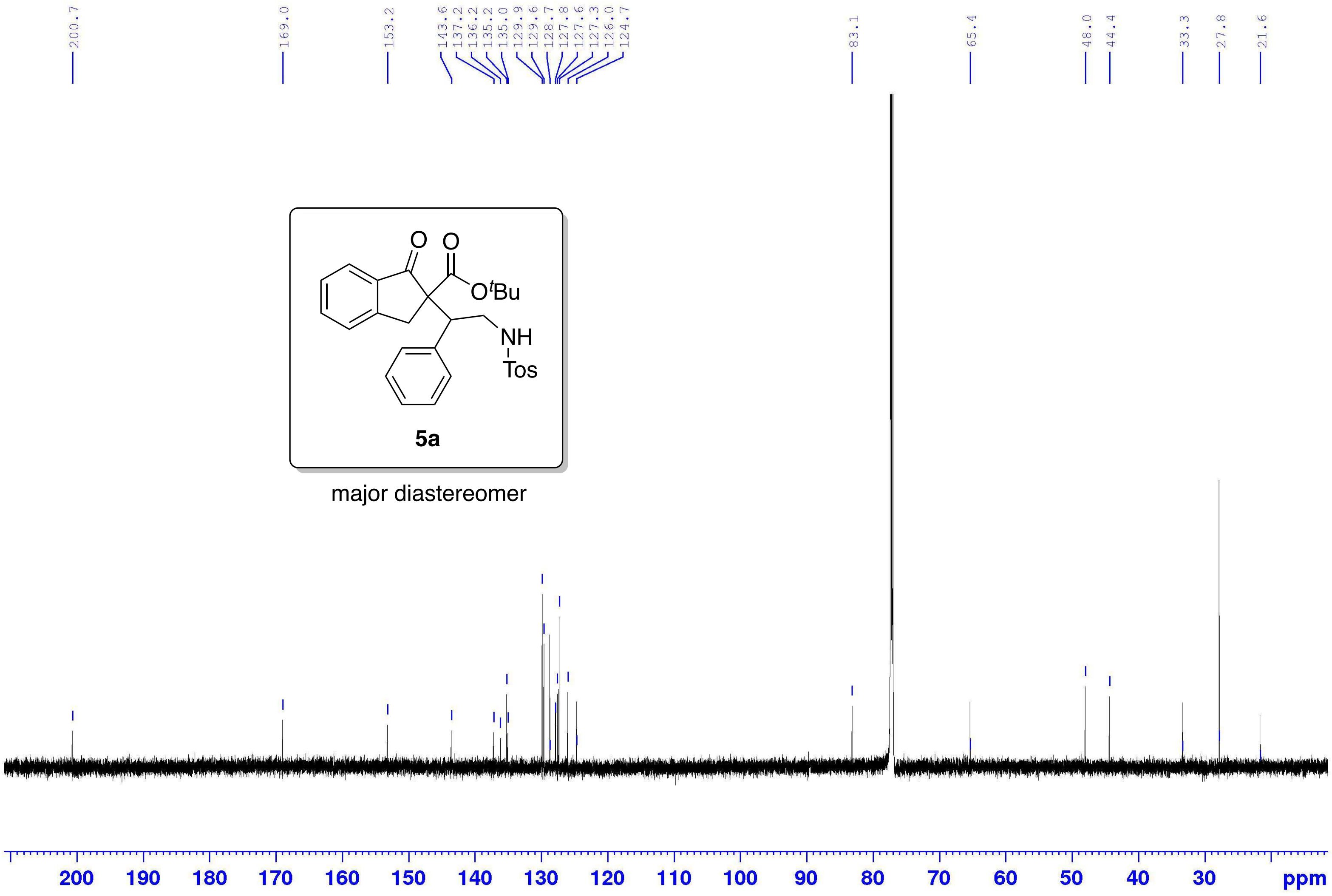
HRMS (ESI): m/z calculated for $C_{33}H_{43}N_2O_5S^+$: 579.2893 $[M+NH_4]^+$; found: 579.2887

^{1}H-NMR (300 MHz, $CDCl_3$, 298.0 K): δ /ppm = 7.67 (d, J = 8.2 Hz, 2H), 7.49-7.43 (m, 2H), 7.33-7.16 (m, 4H), 7.08 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 4.41-4.37 (m, 1H), 3.85-3.80 (m, 1H), 3.67 (d, J = 17.5 Hz, 1H), 3.62-3.55 (m, 1H), 3.37-3.28 (m, 1H), 3.20 (d, J = 17.5 Hz, 1H), 2.42 (s, 3H), 1.36 (s, 9H), 1.17 (s, 9H); ^{13}C-NMR (176 MHz, $CDCl_3$, 298.0 K): δ /ppm = 200.7, 169.0, 153.2, 150.7, 143.5, 137.2, 135.0, 132.8, 129.8, 129.2, 127.9, 127.4, 127.3, 125.9, 125.5, 124.6, 83.0, 65.5, 47.6, 44.3, 34.4, 31.4, 31.2, 27.8, 21.6.

3. Illustrative NMR Spectra of New Compounds

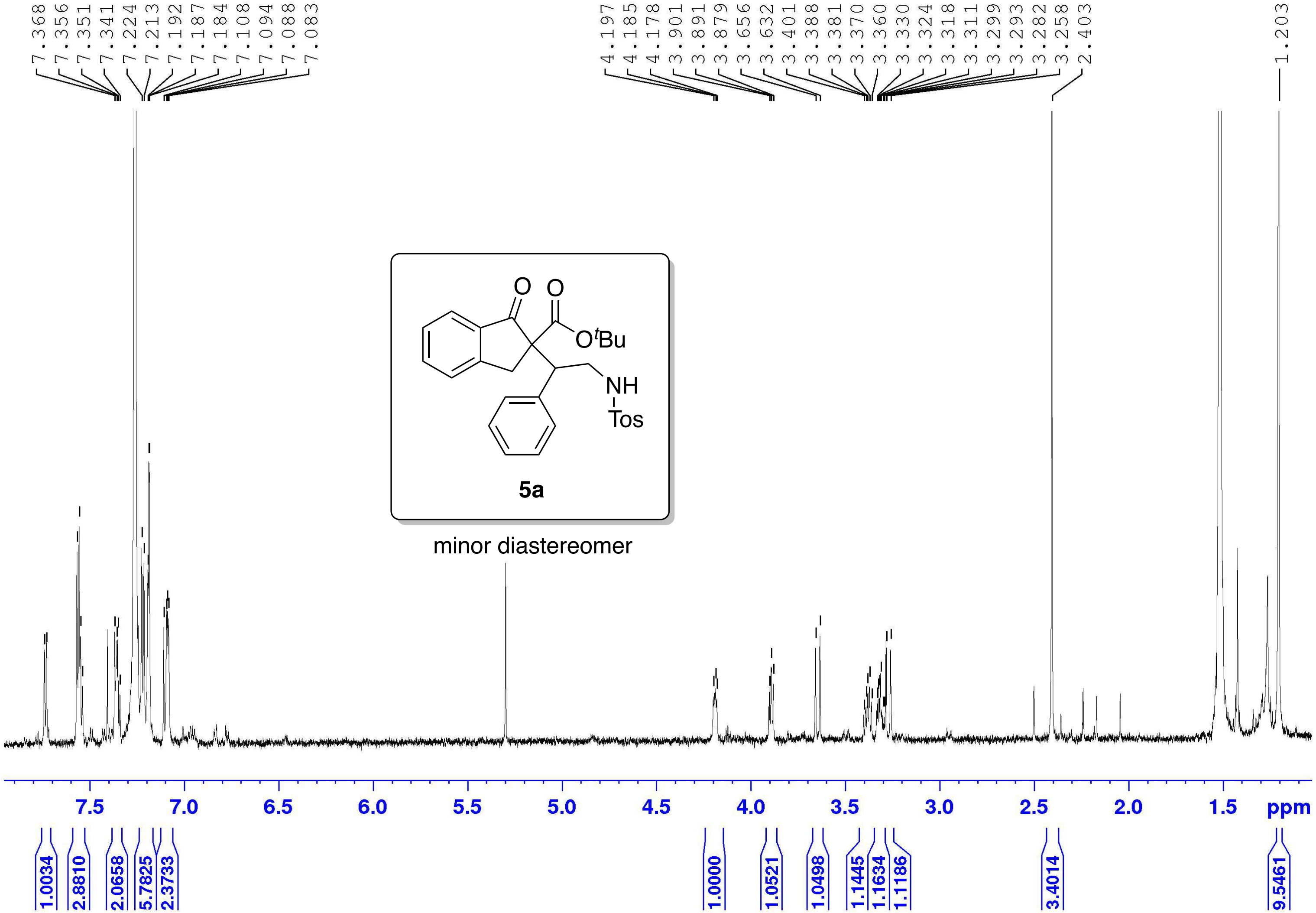
NOTE: Diastereomers had to be separated by semiprep. HPLC and the minor diastereomers could only be obtained in rather small and diluted amounts (if possible at all) sometimes containing detectable amounts of the major diastereomer.





5a

major diastereomer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7.341
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7.213
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7.187
7.184
7.108
7.094
7.088
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4.197
4.185
4.178
3.901
3.891
3.879
3.656
3.632
3.401
3.388
3.381
3.370
3.360
3.330
3.324
3.318
3.311
3.299
3.293
3.282
3.258
2.403
1.203
O
O
O^{t}Bu
NH
Tos
5a
minor diastereomer
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.0034
2.8810
2.0658
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1.0000
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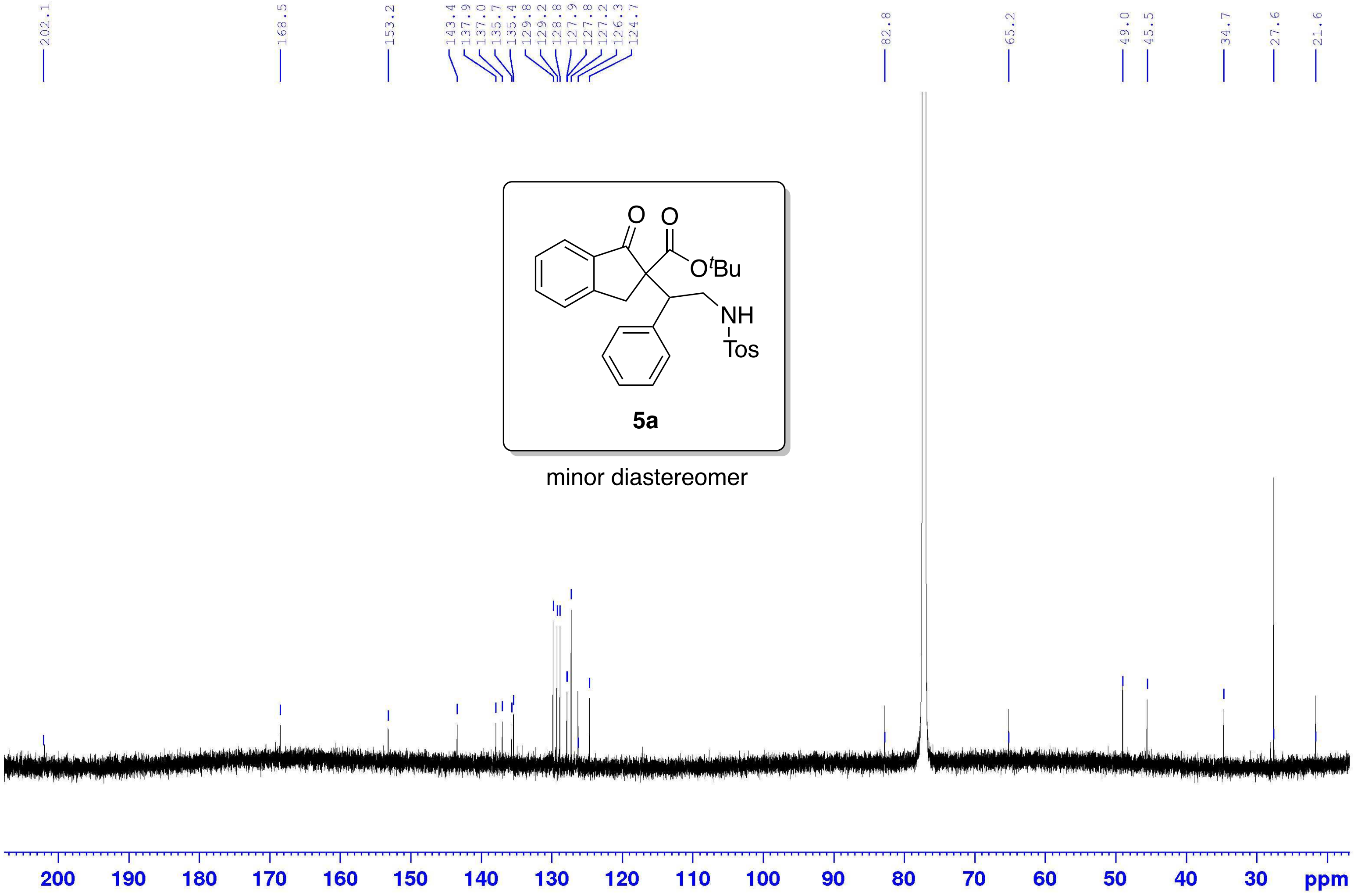
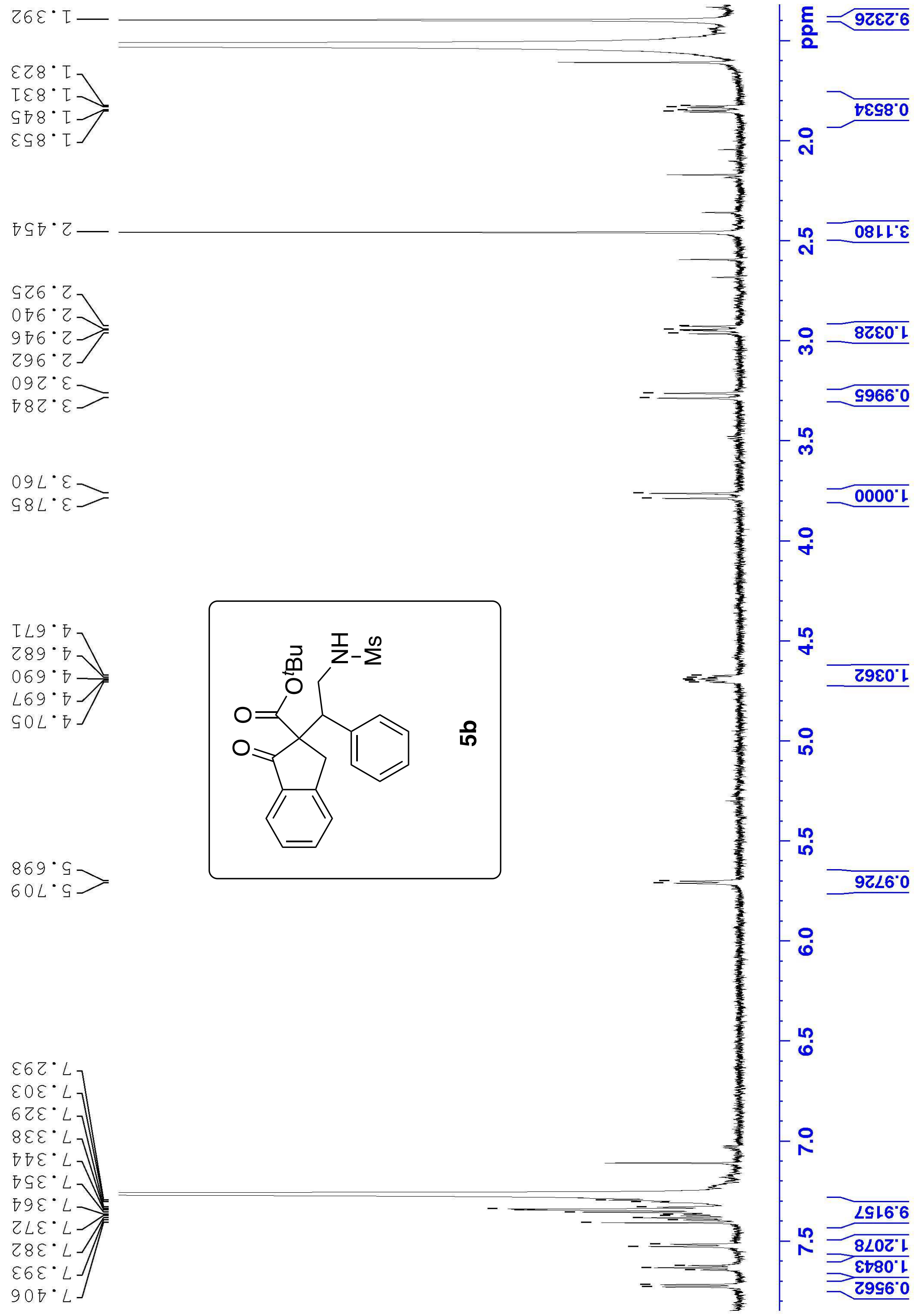
9.5461



5a

minor diastereomer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1.831
1.845
1.853
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2.925
2.940
2.946
2.962
3.260
3.284
3.760
3.785
4.671
4.682
4.690
4.697
4.705
5.698
5.709
7.293
7.303
7.329
7.338
7.344
7.354
7.364
7.372
7.382
7.393
7.406
O
O
O^{t}Bu
NH
Ms
5b
ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
9.2326
0.8534
3.1180
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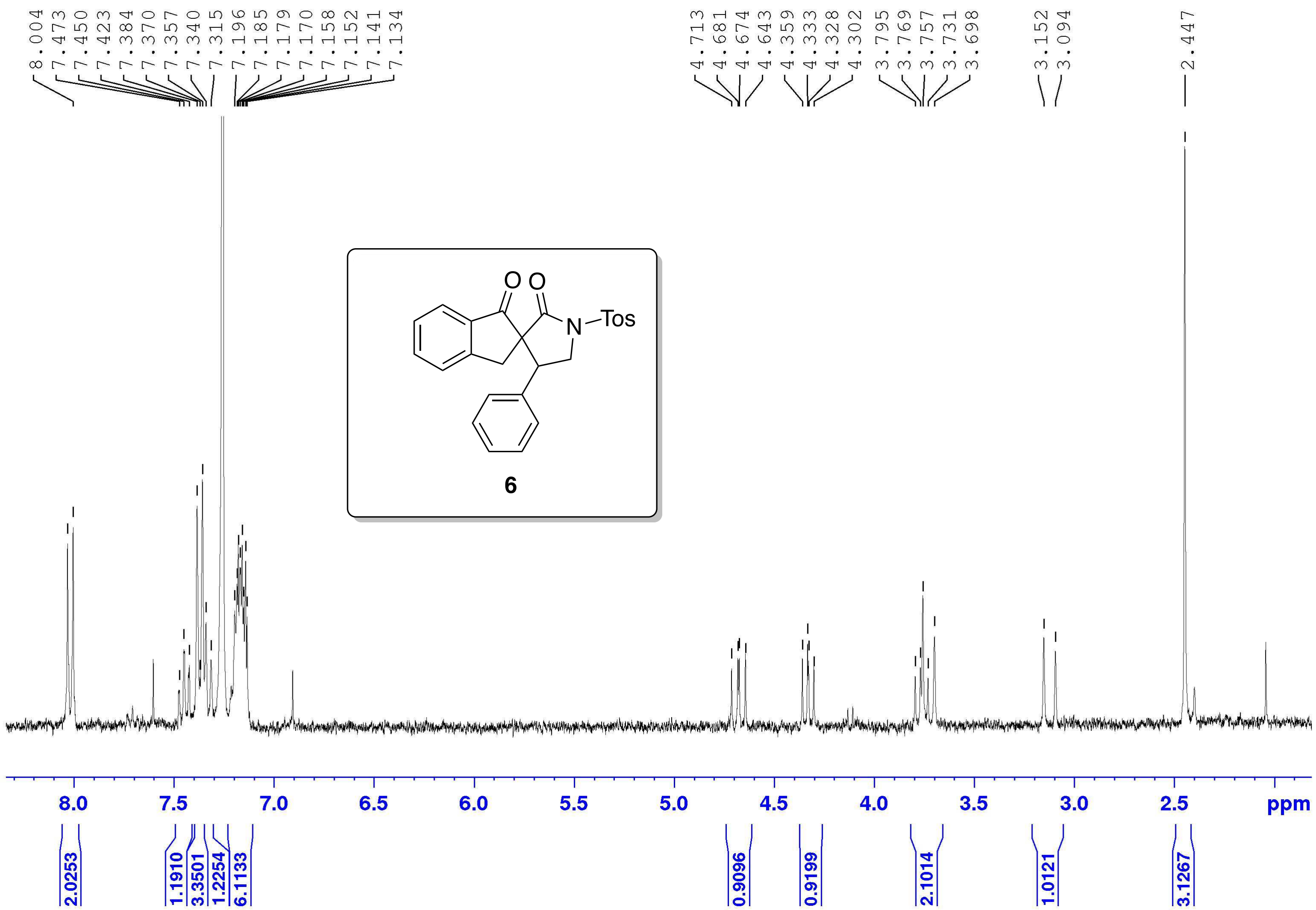
0.9965
1.0000
1.0362
0.9726
9.9157
1.2078
1.0843
0.9562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7.384
7.370
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7.340
7.315
7.196
7.185
7.179
7.170
7.158
7.152
7.141
7.134
4.713
4.681
4.674
4.643
4.359
4.333
4.328
4.302
3.795
3.769
3.757
3.731
3.698
3.152
3.094
2.447
O
O
N
Tos
6
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm
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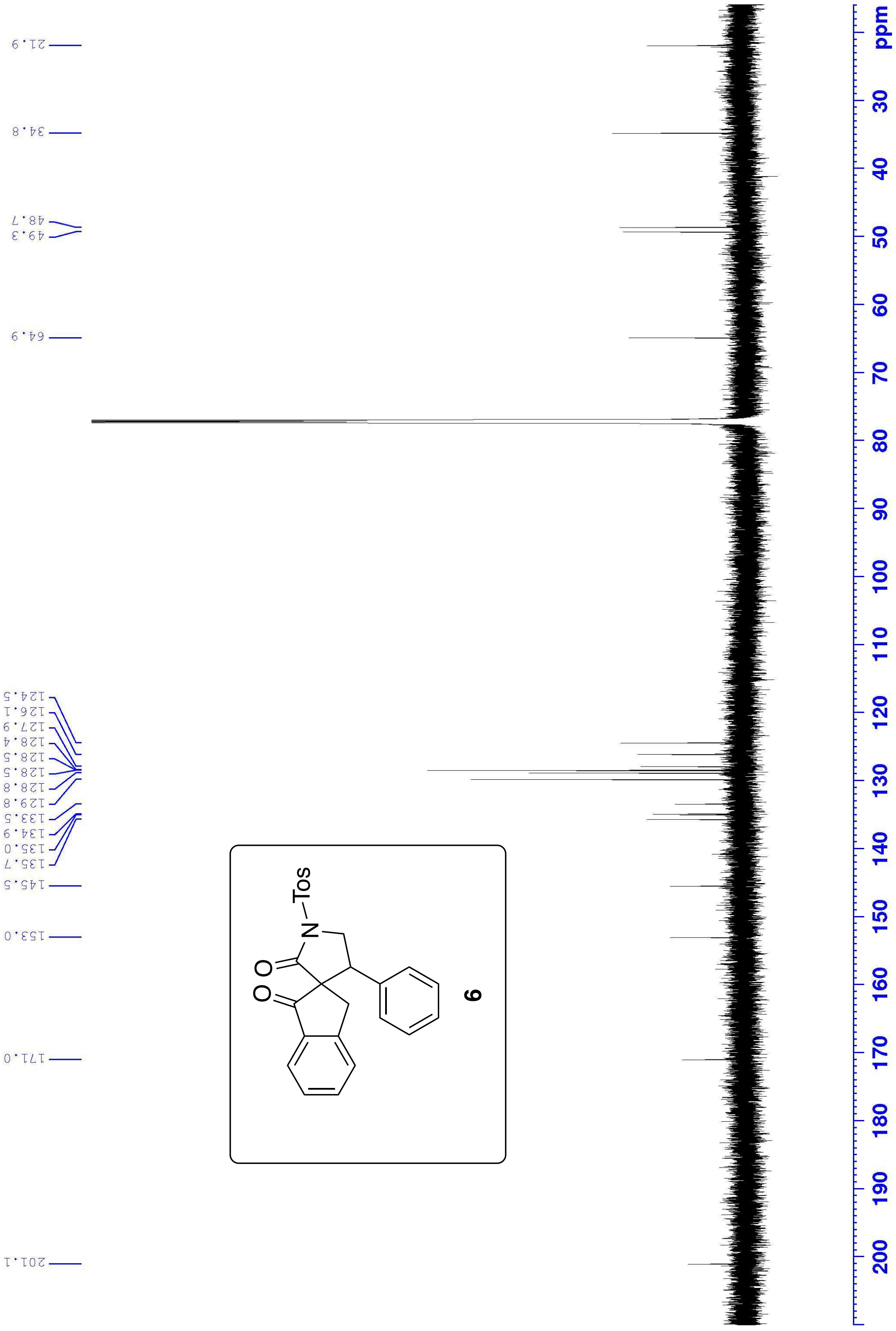
3.3501
1.2254
6.1133
0.9096
0.9199
2.1014
1.0121
3.1267


21.9
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48.7
49.3
64.9
124.5
126.1
127.9
128.4
128.5
128.5
128.8
129.8
133.5
134.9
135.0
135.7
145.5
153.0
171.0
201.1
O
O
N
Tos
6
ppm
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50
60
70
80
90
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170
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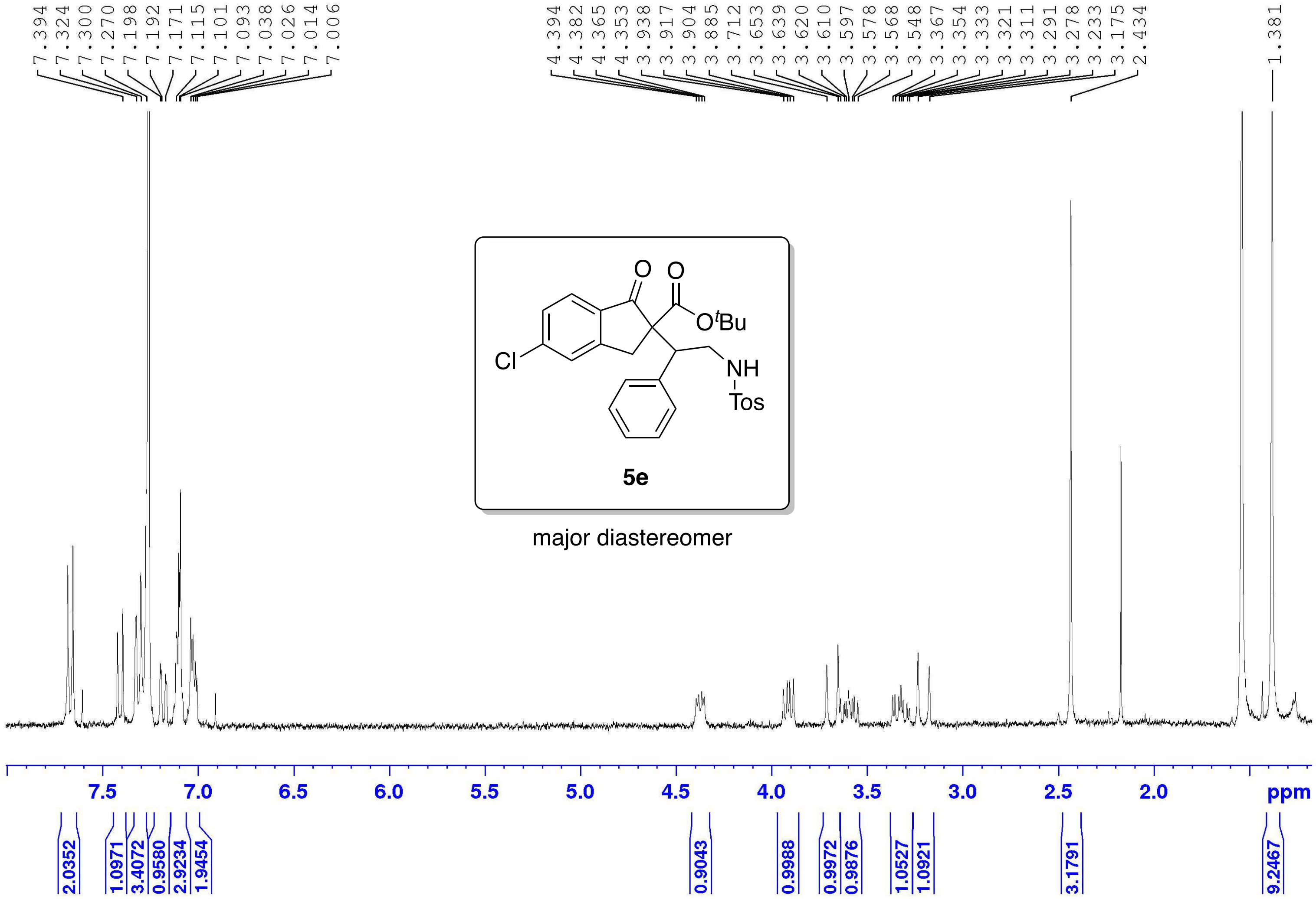
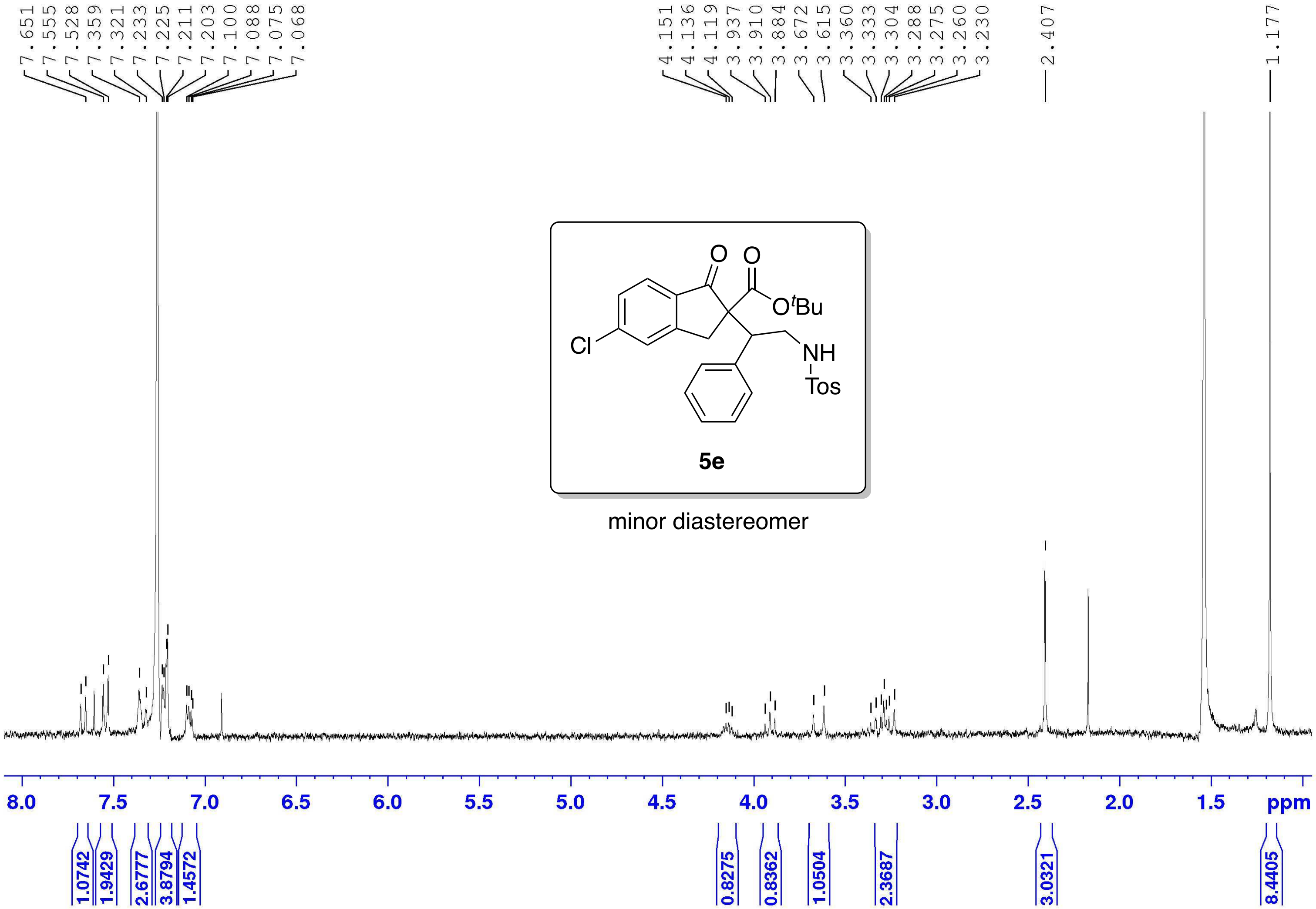
200



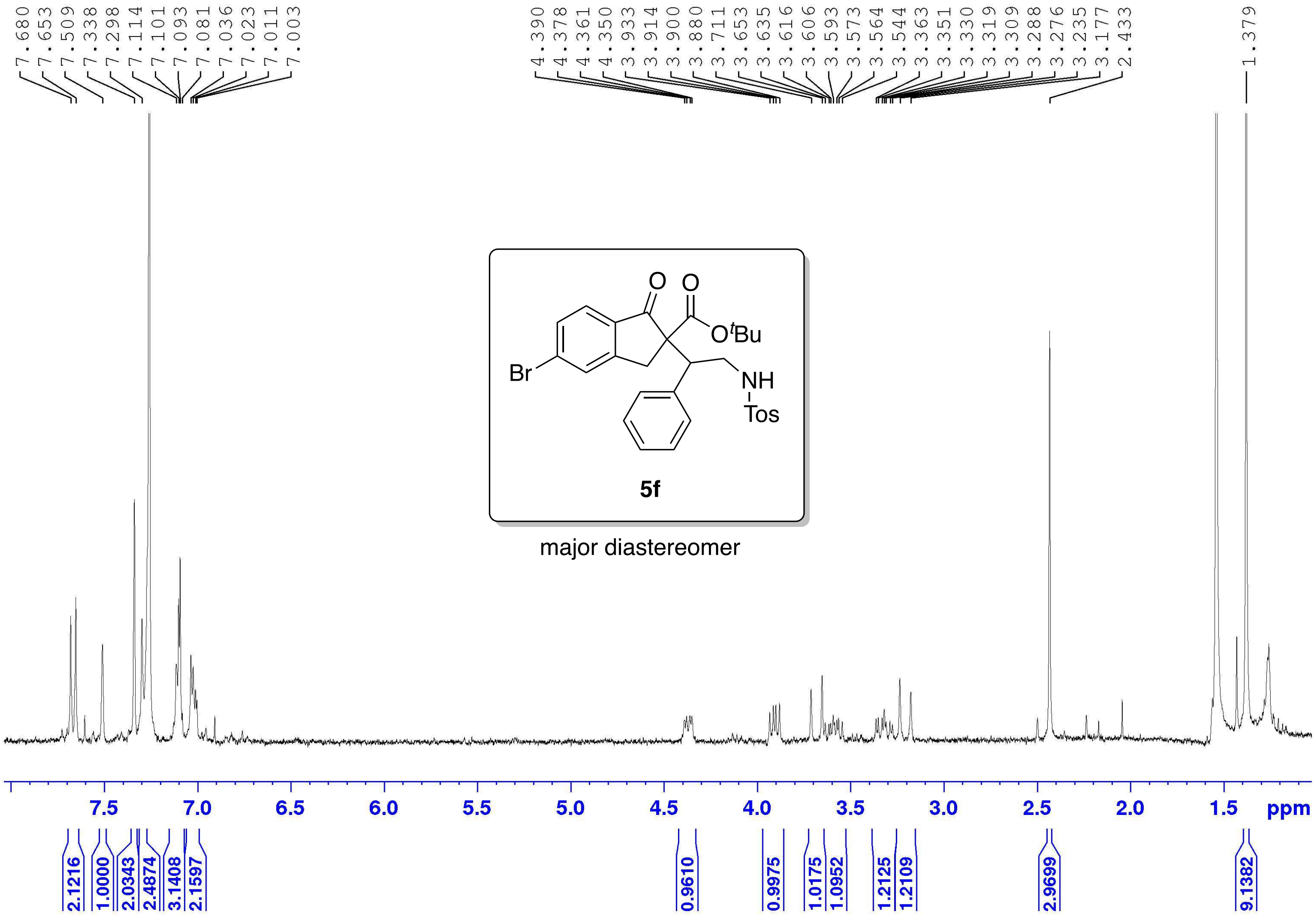
5e

major diastereomer



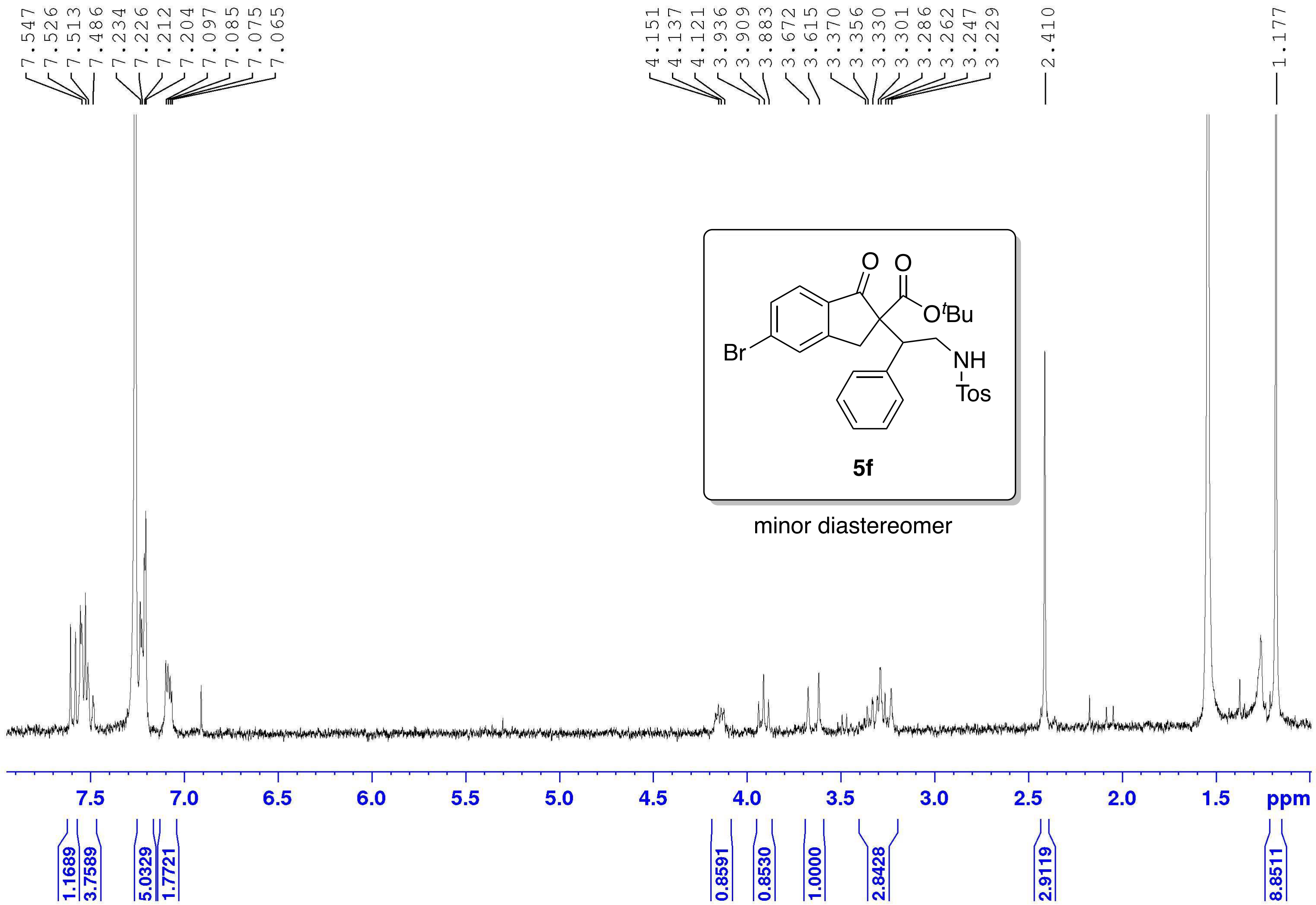
5e

minor diastereomer



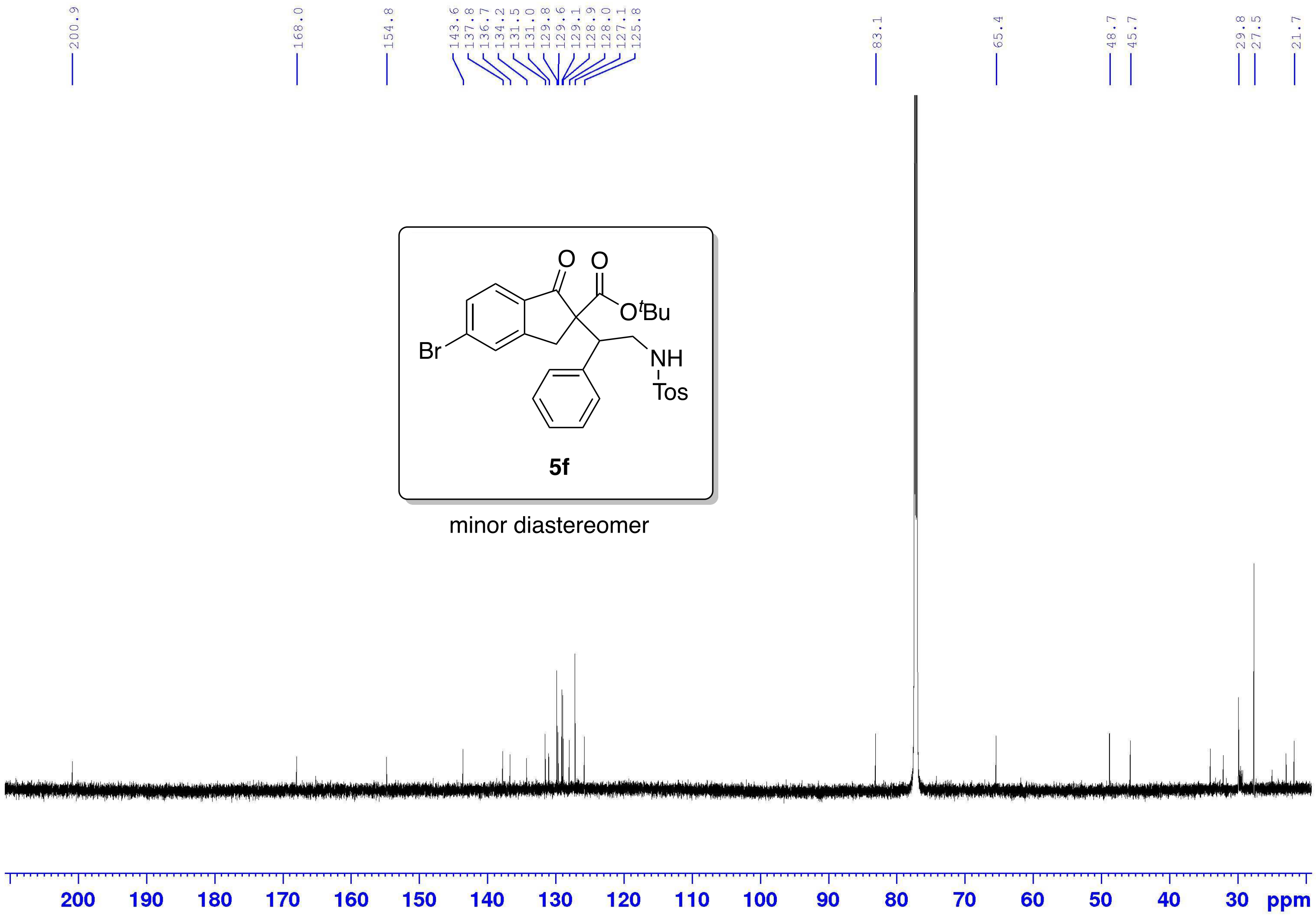
5f

major diastereomer



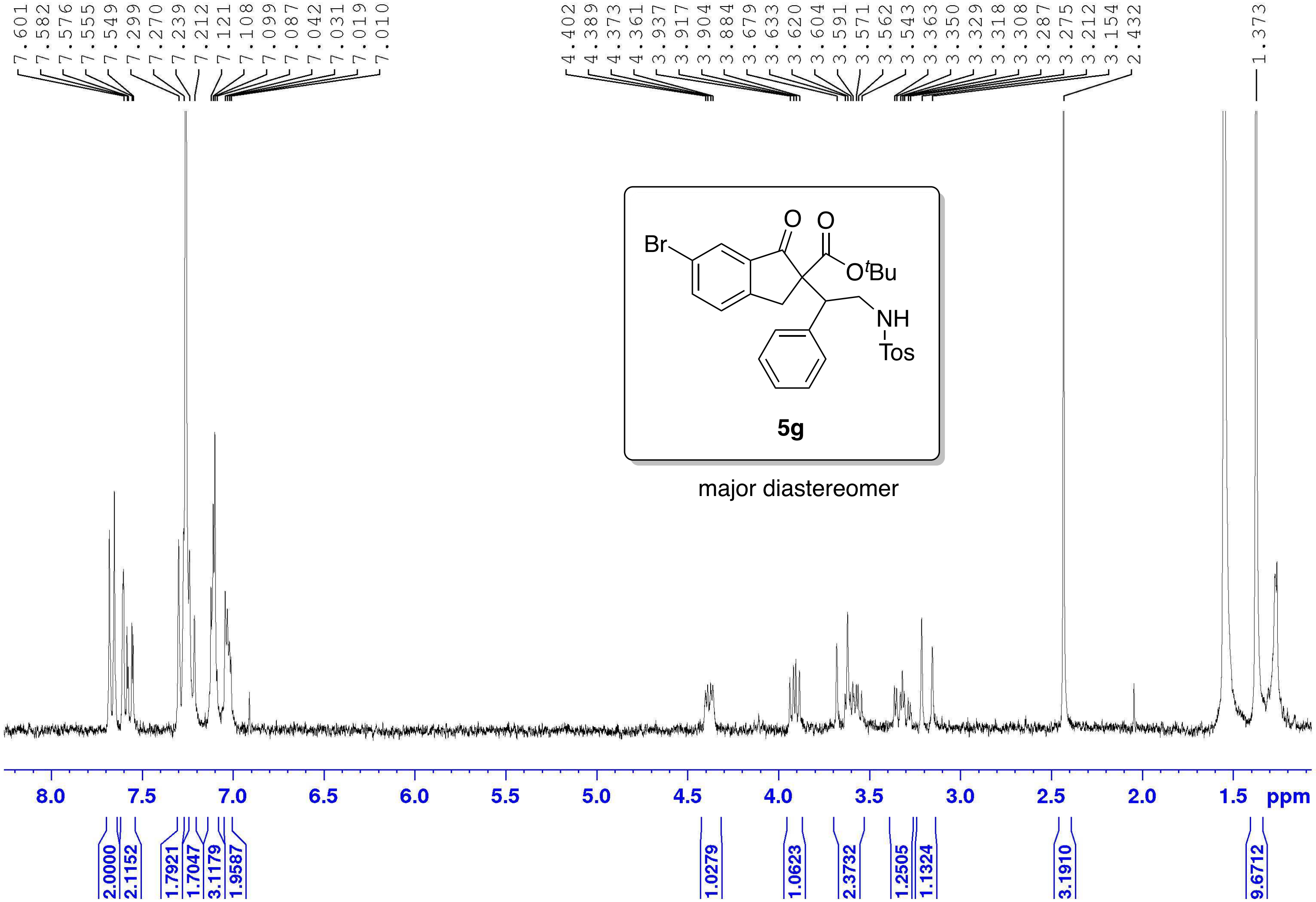
5f

minor diastereomer



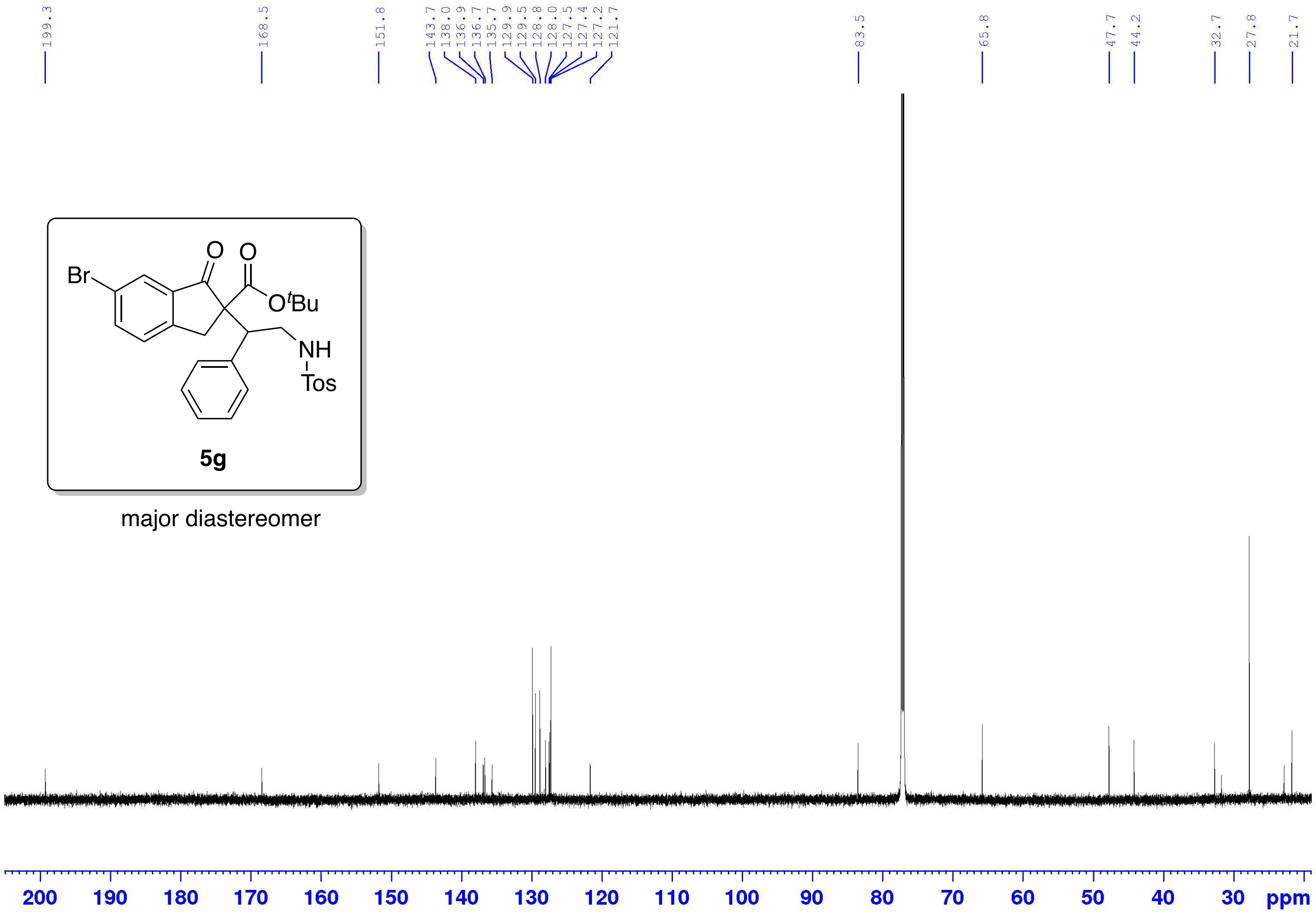
5f

minor diastereomer



5g

major diastereomer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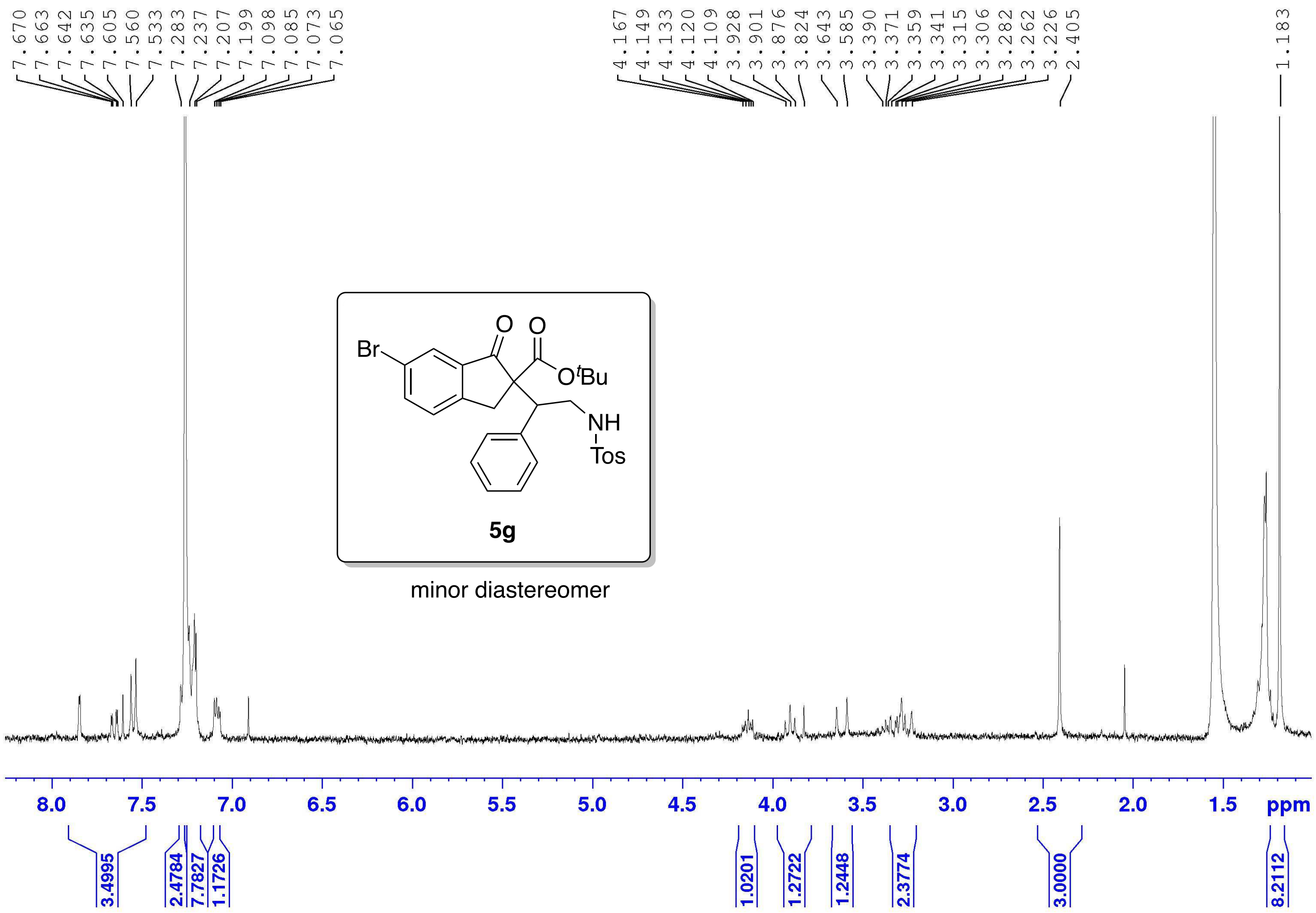
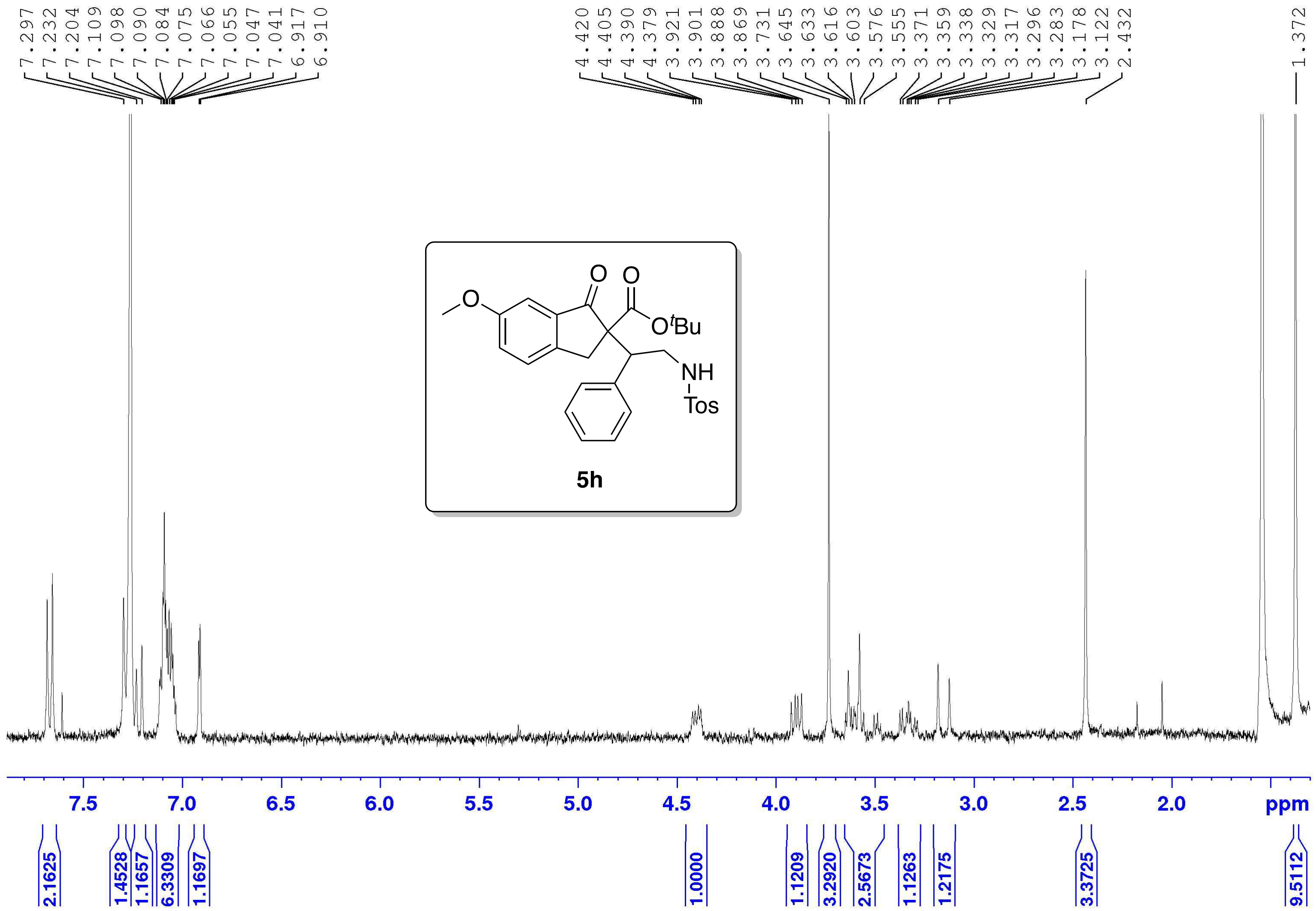
168.5
151.8
143.7
138.0
136.9
136.7
135.7
129.9
129.5
128.8
128.0
127.5
127.4
127.2
121.7
83.5
65.8
47.7
44.2
32.7
27.8
21.7
Br
O
O
O^tBu
NH
Tos
5g
major diastereomer
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm



5g

minor diastereomer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7.098
7.090
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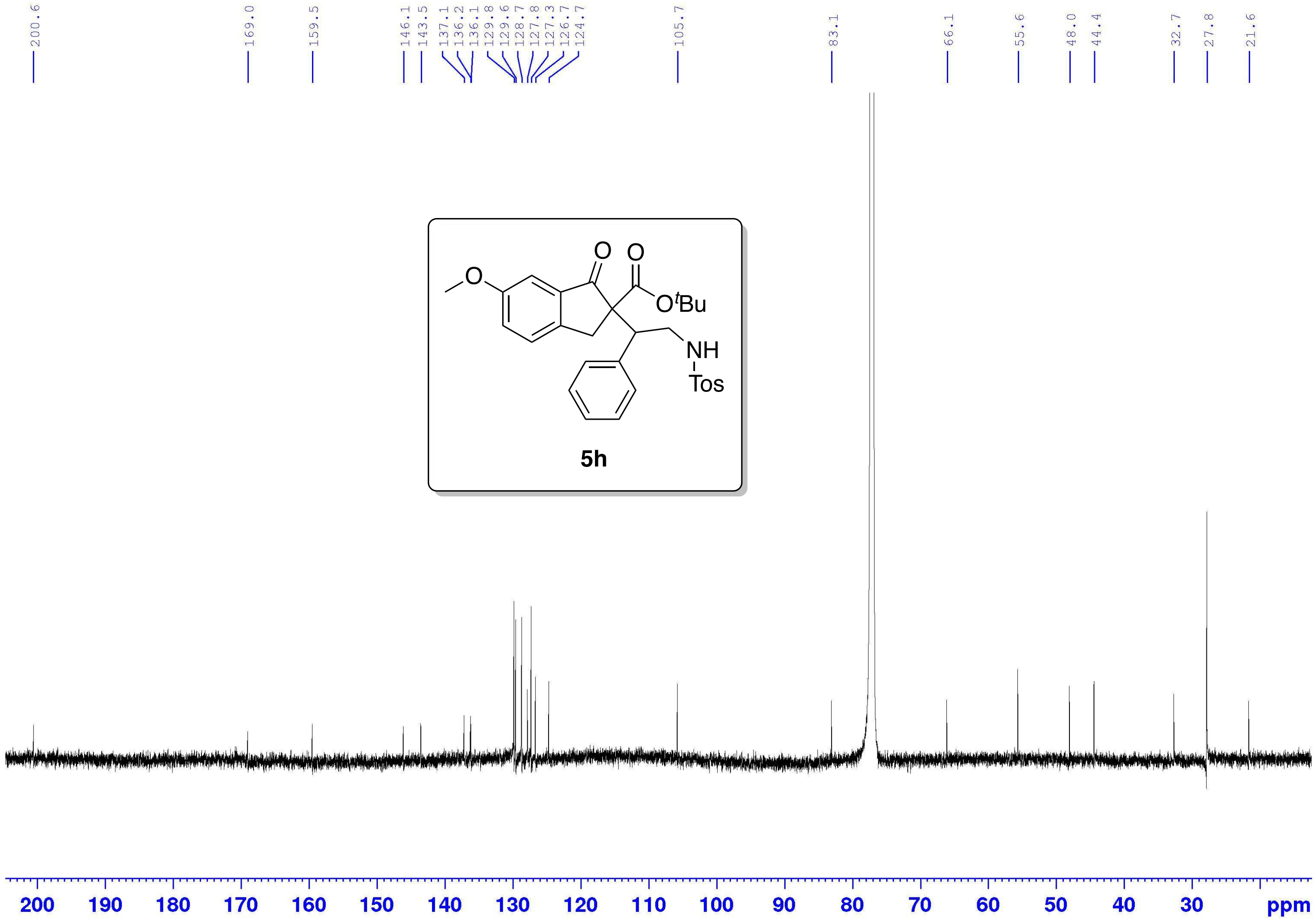
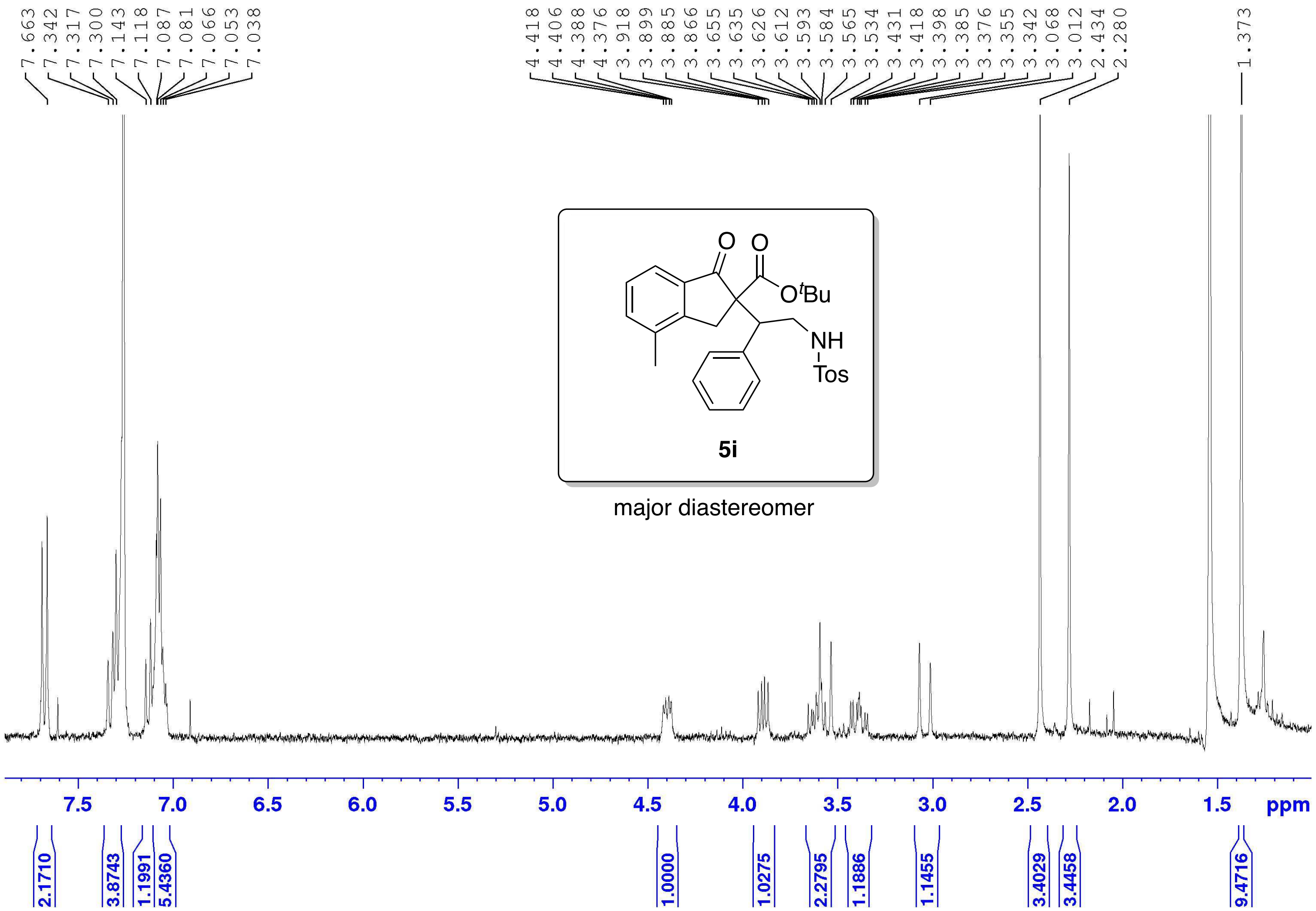
7.075
7.066
7.055
7.047
7.041
6.917
6.910
4.420
4.405
4.390
4.379
3.921
3.901
3.888
3.869
3.731
3.645
3.633
3.616
3.603
3.576
3.555
3.371
3.359
3.338
3.329
3.317
3.296
3.283
3.178
3.122
2.432
1.372
O
O
O
O^{t}Bu
NH
Tos
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
2.1625
1.4528
1.1657
6.3309
1.1697
1.0000
1.1209
3.2920
2.5673
1.1263
1.2175
3.3725
9.5112

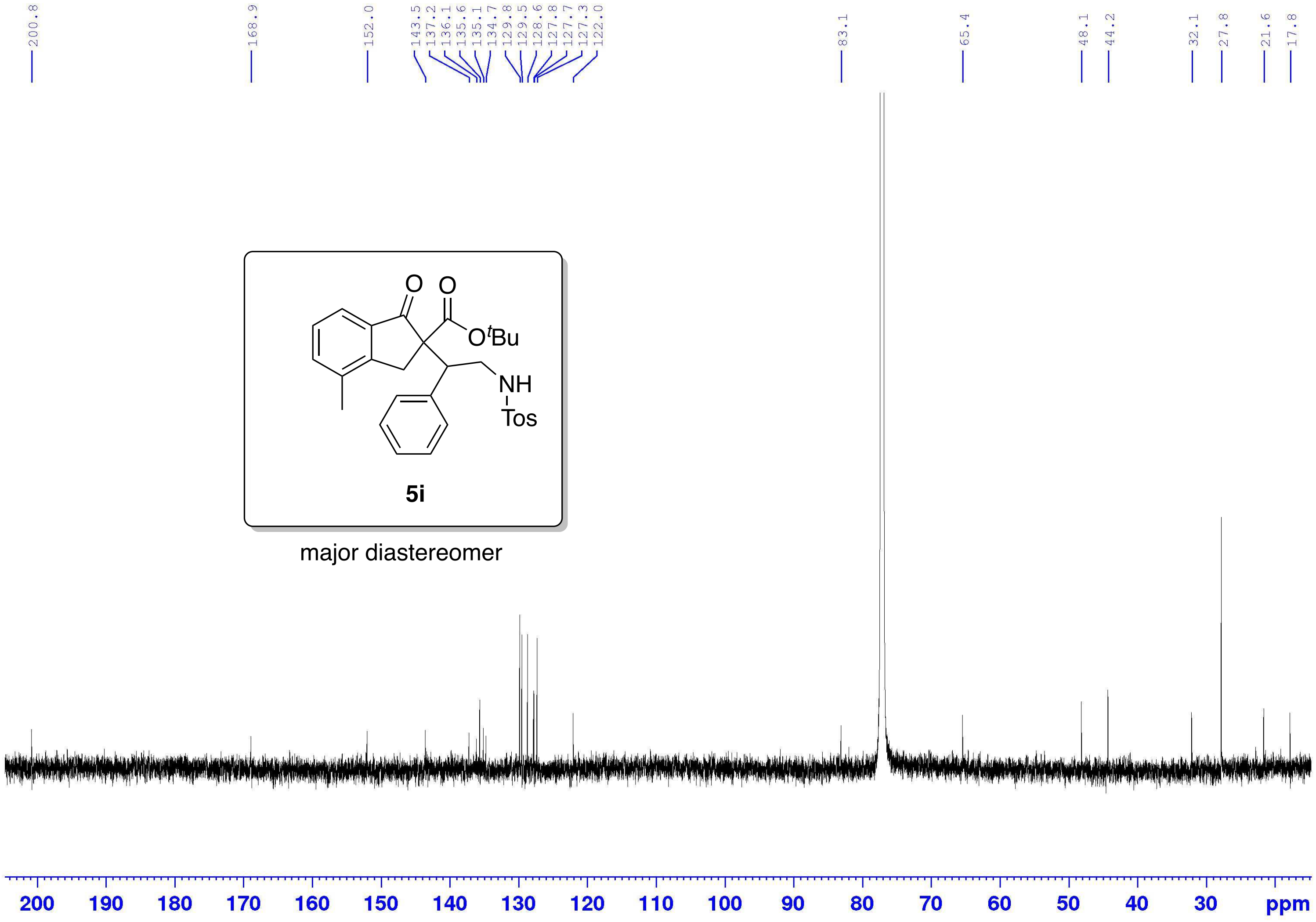
5h


200.6
169.0
159.5
146.1
143.5
137.1
136.2
136.1
129.8
129.6
128.7
127.8
127.3
126.7
124.7
105.7
83.1
66.1
55.6
48.0
44.4
32.7
27.8
21.6
O
O
O
O^tBu
NH
Tos
5h
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm



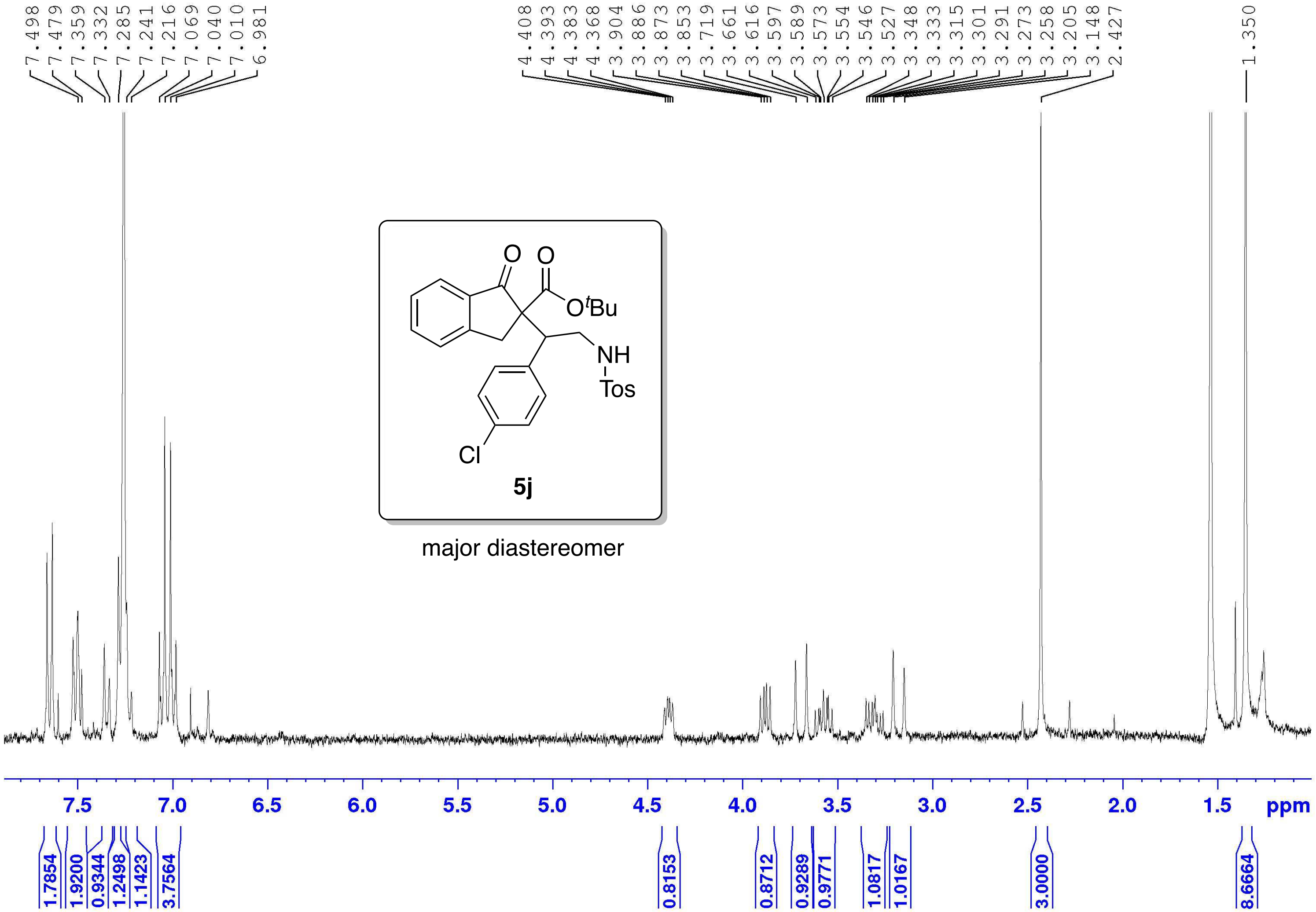
5i

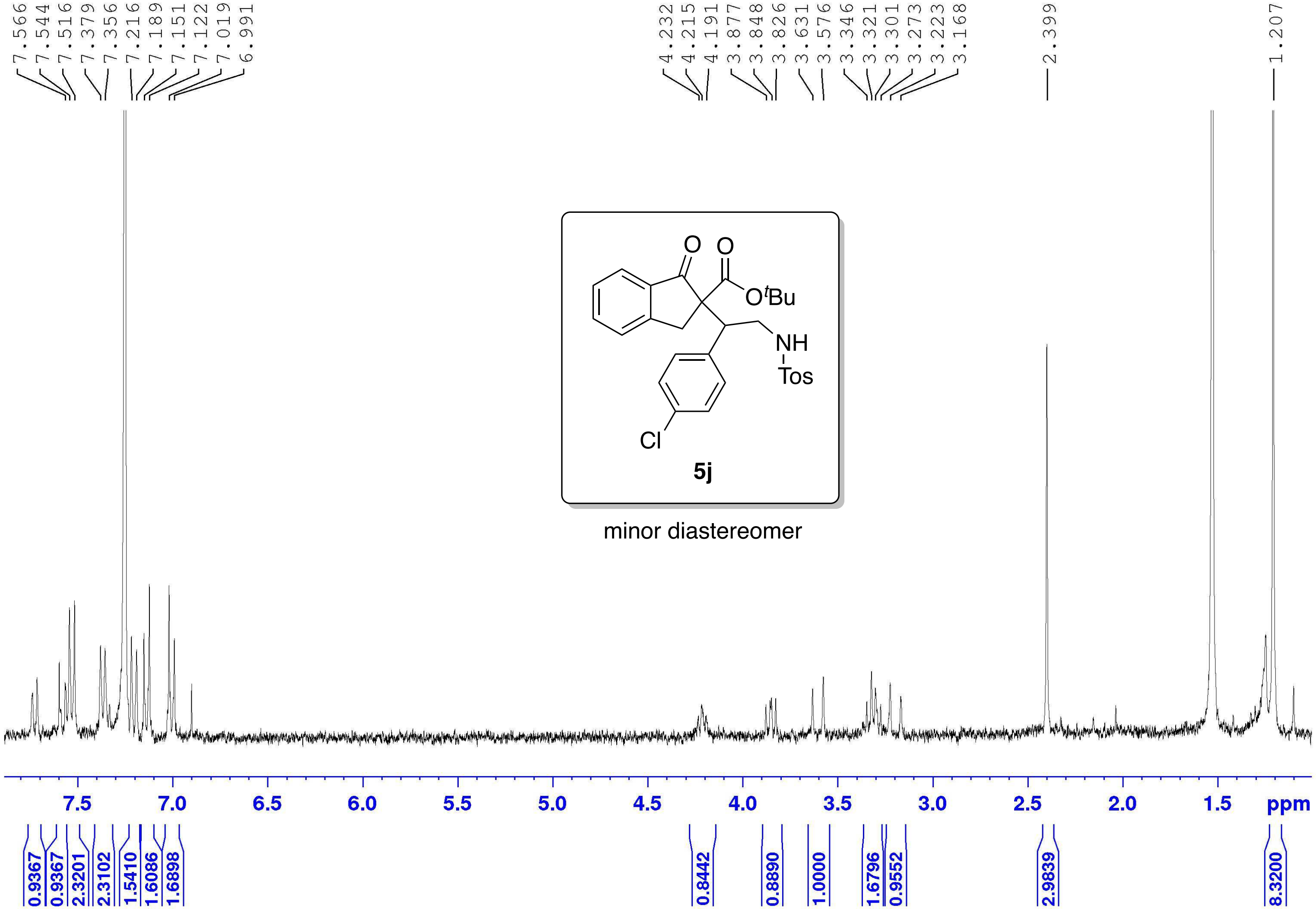
major diastereomer

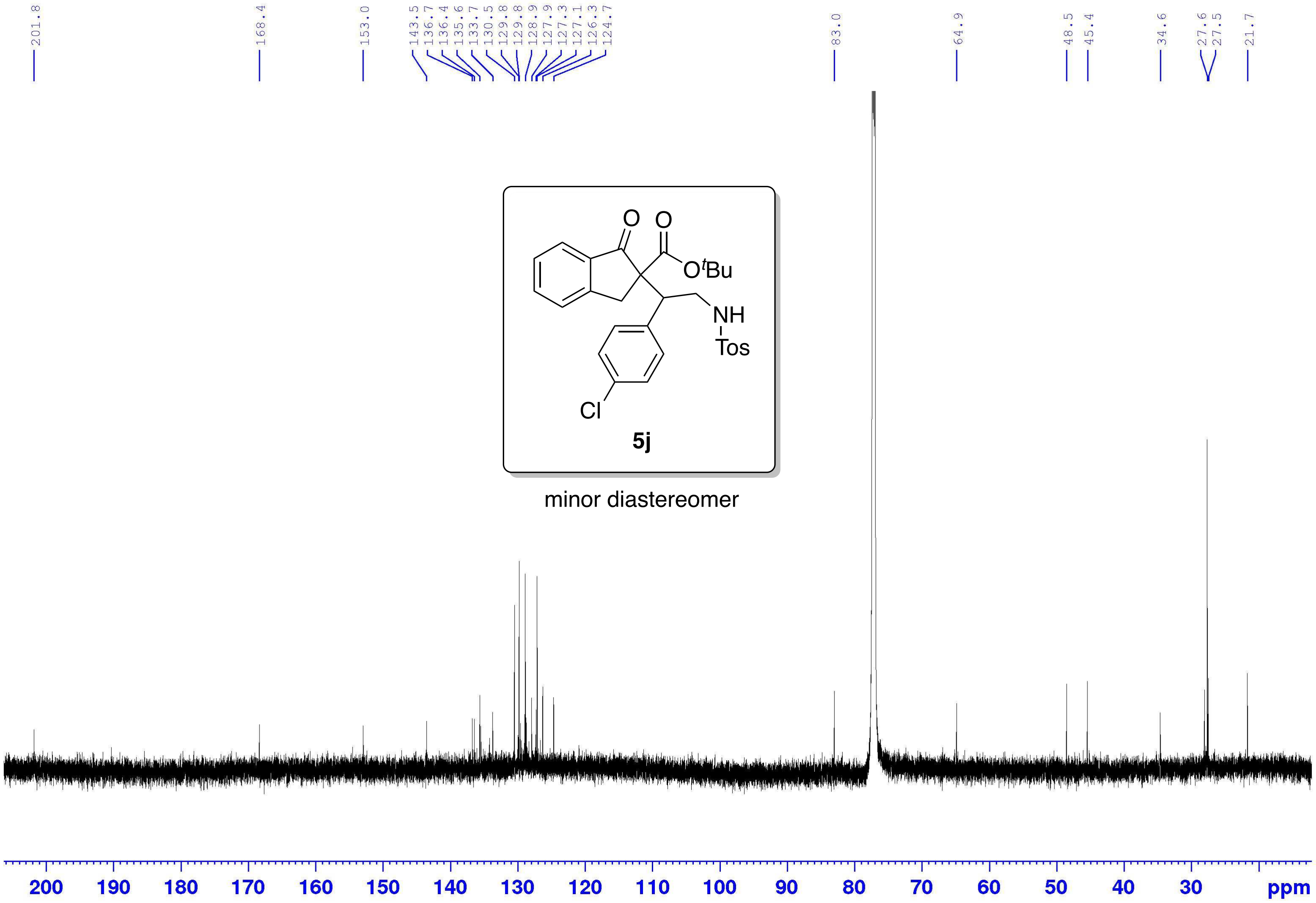


5i

major diastereomer

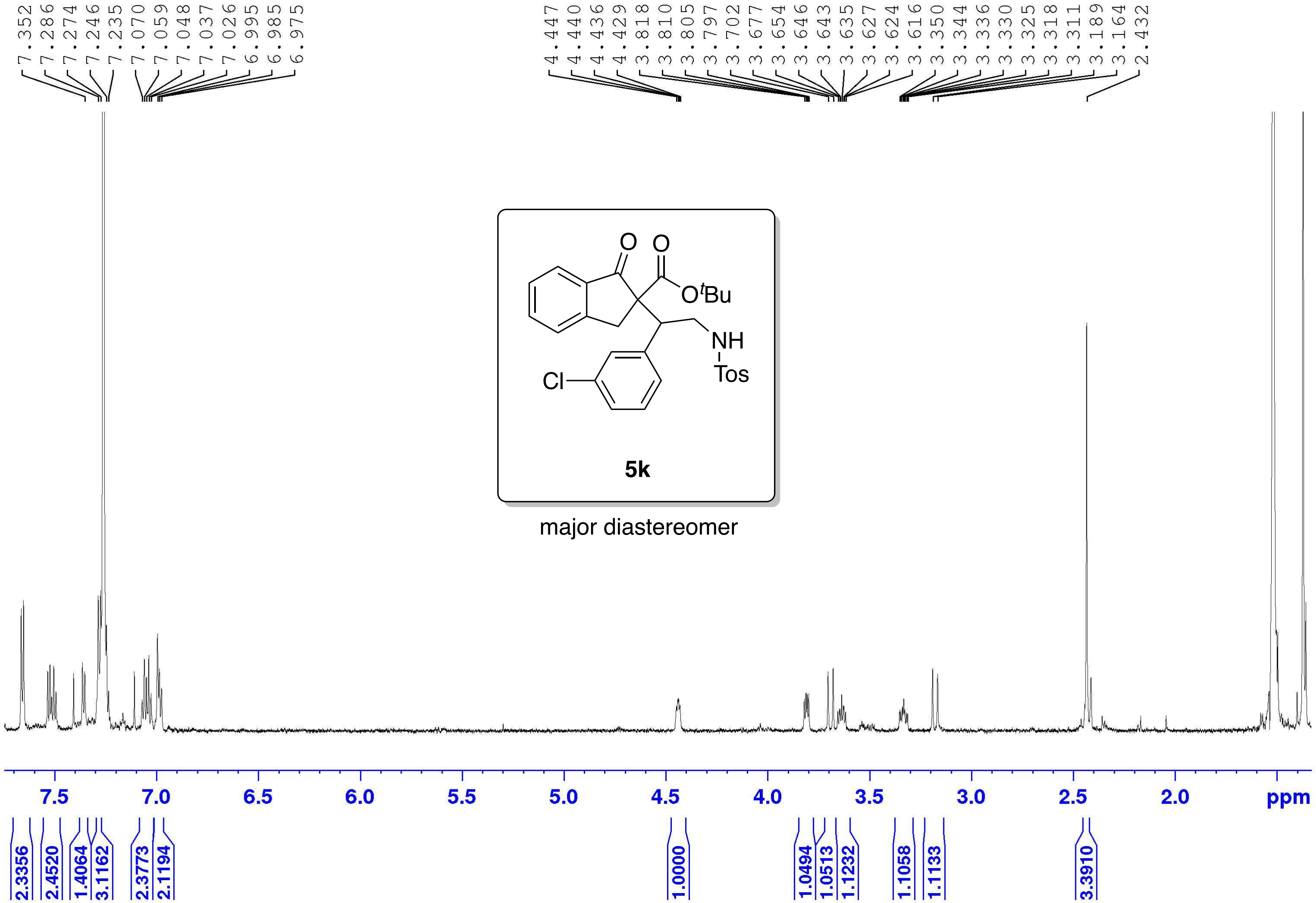

7.498
7.479
7.359
7.332
7.285
7.241
7.216
7.069
7.040
7.010
6.981
4.408
4.393
4.383
4.368
3.904
3.886
3.873
3.853
3.719
3.661
3.616
3.597
3.589
3.573
3.554
3.546
3.527
3.348
3.333
3.315
3.301
3.291
3.273
3.258
3.205
3.148
2.427
1.350
O
O
O^tBu
NH
Tos
Cl
5j
major diastereomer
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.7854
1.9200
0.9344
1.2498
1.1423
3.7564
0.8153
0.8712
0.9289
0.9771
1.0817
1.0167
3.0000
8.6664


7.566
7.544
7.516
7.379
7.356
7.216
7.189
7.151
7.122
7.019
6.991
4.232
4.215
4.191
3.877
3.848
3.826
3.631
3.576
3.346
3.321
3.301
3.273
3.223
3.168
2.399
1.207
O
O
O^tBu
NH
Tos
Cl
5j
minor diastereomer
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.9367
0.9367
2.3201
2.3102
1.5410
1.6086
1.6898
0.8442
0.8890
1.0000
1.6796
0.9552
2.9839
8.3200



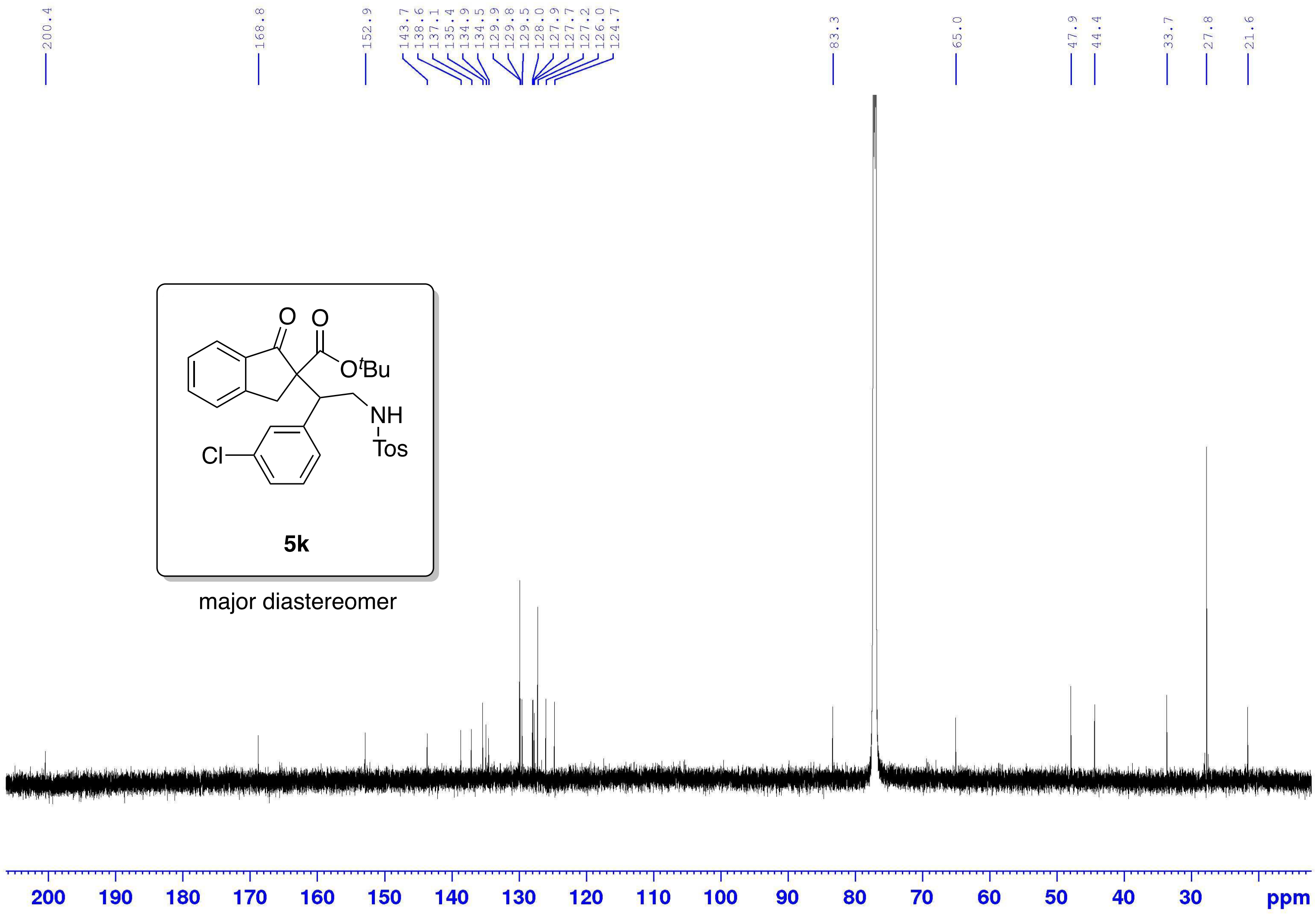
5j

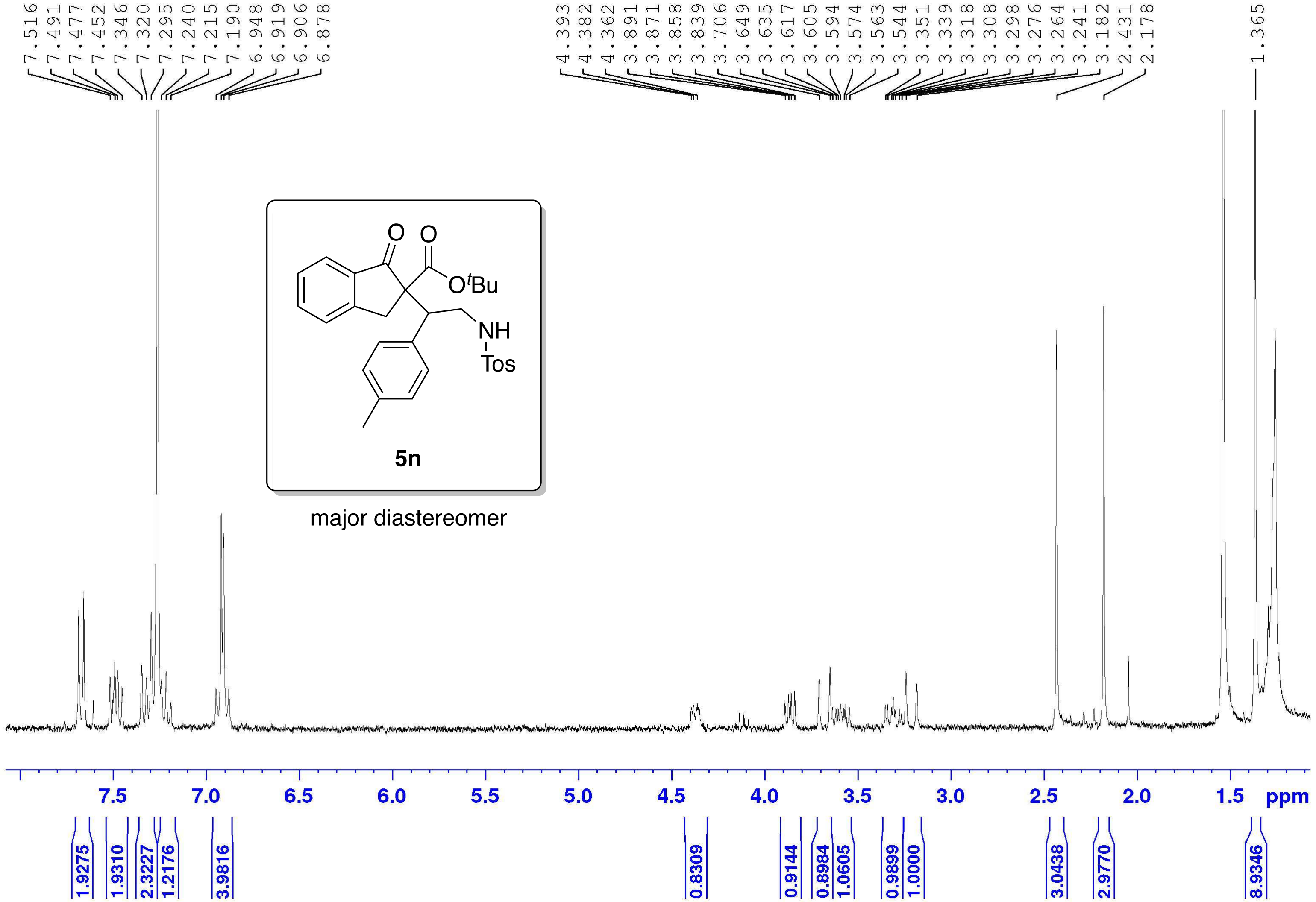
minor diastereomer

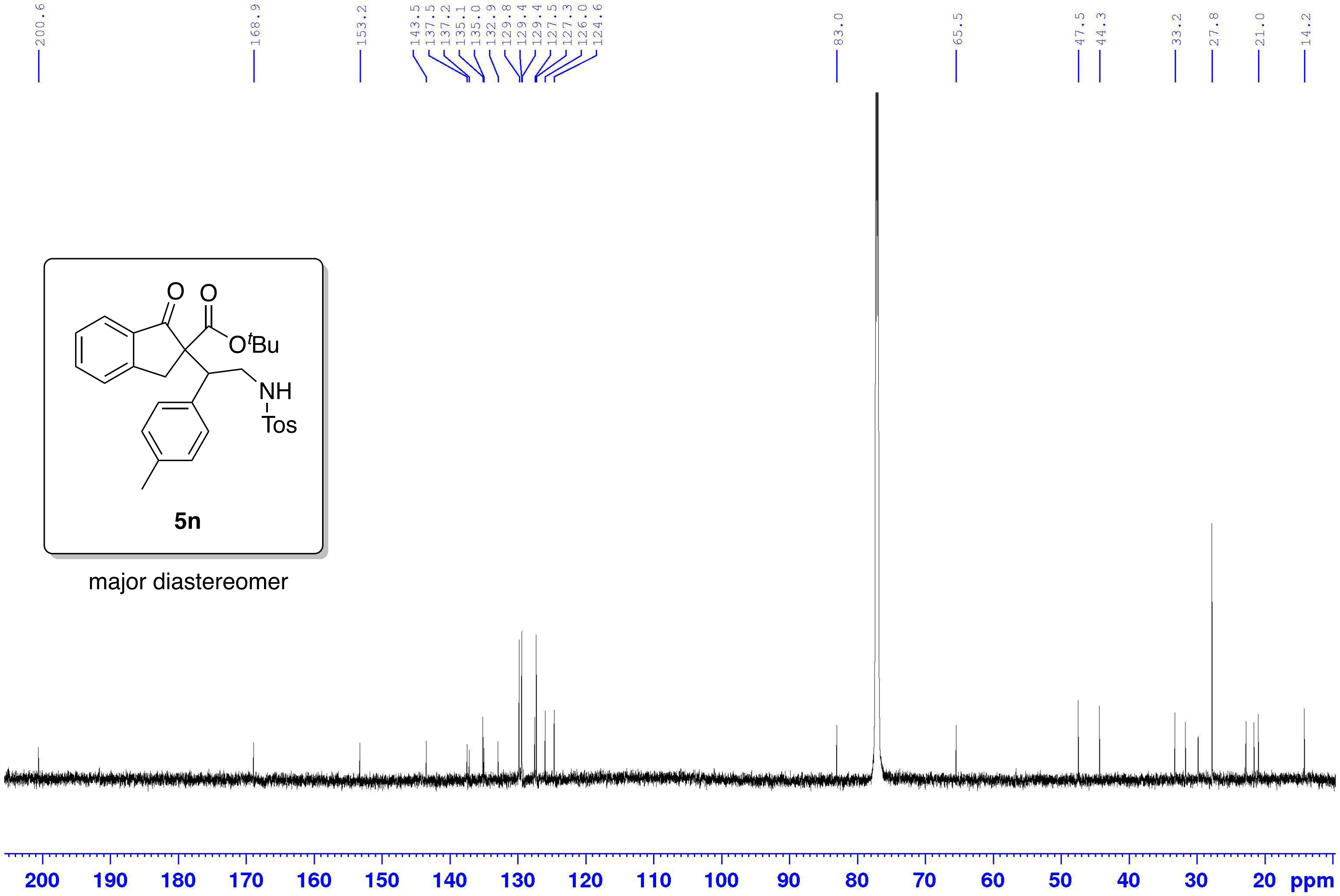


5k

major diastereomer

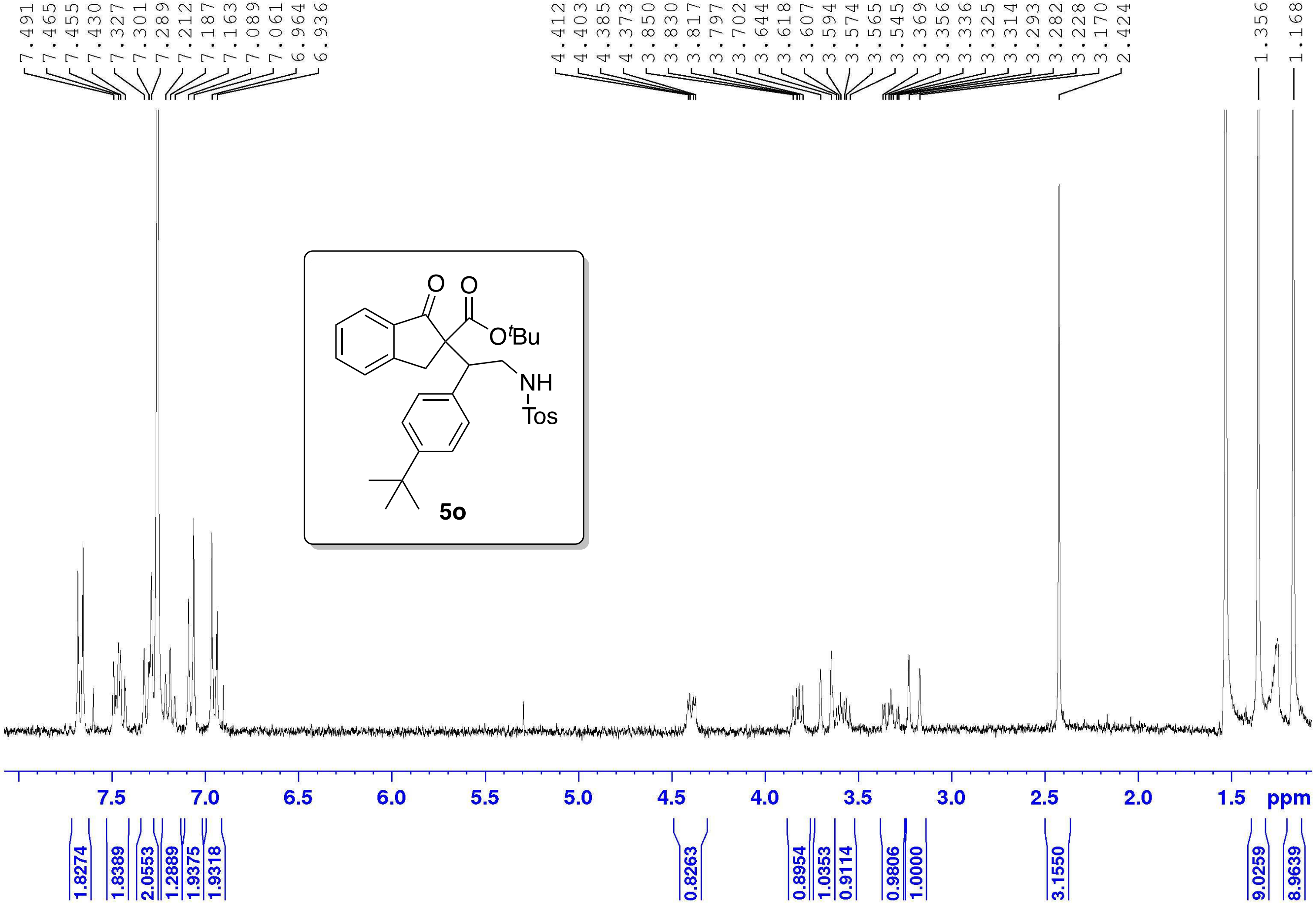

200.4
168.8
152.9
143.7
138.6
137.1
135.4
134.9
134.5
129.9
129.8
129.5
128.0
127.9
127.7
127.2
126.0
124.7
83.3
65.0
47.9
44.4
33.7
27.8
21.6
O
O
O^{t}Bu
NH
Tos
Cl
5k
major diastereomer
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

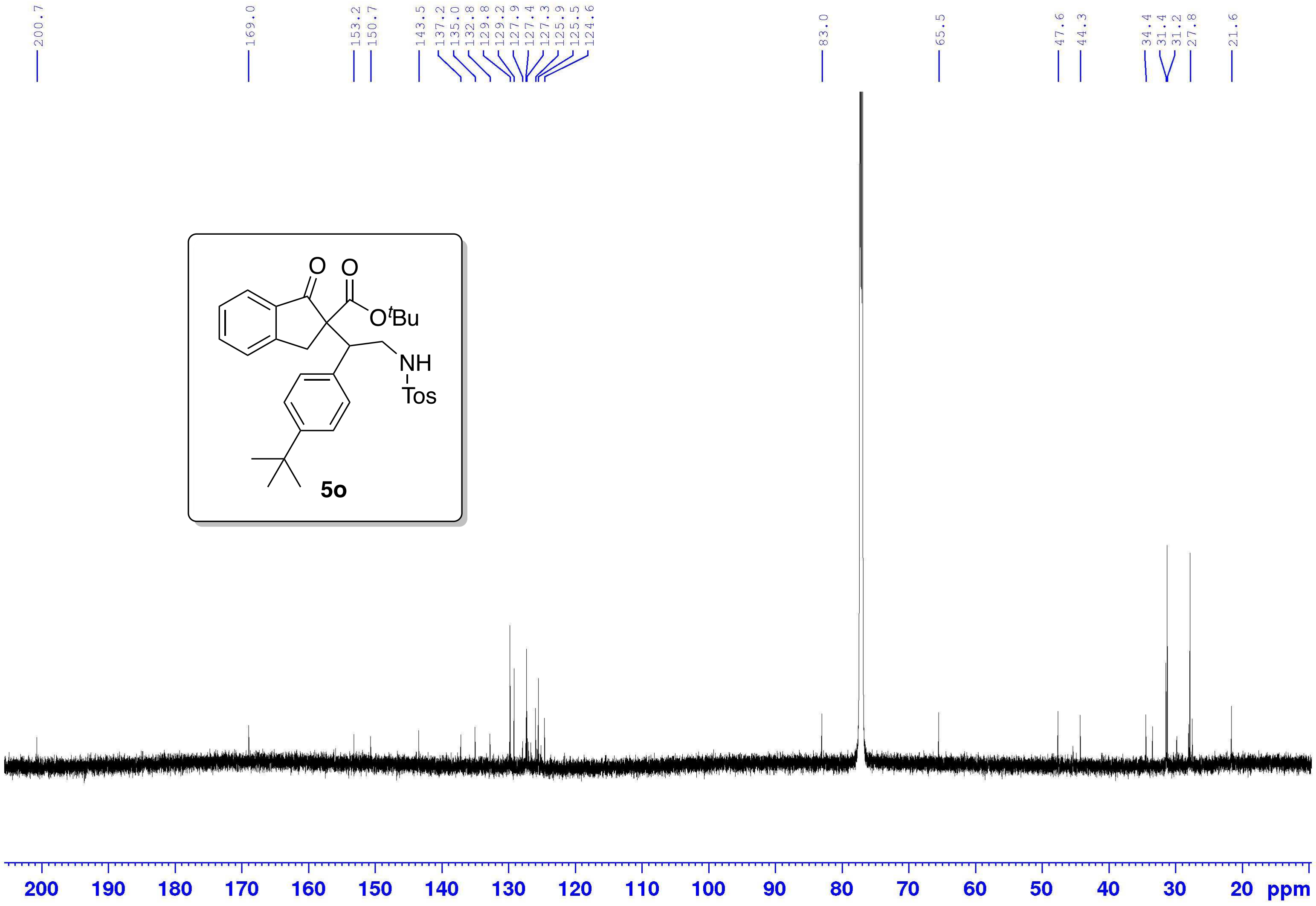

7.516
7.491
7.477
7.452
7.346
7.320
7.295
7.240
7.215
7.190
6.948
6.919
6.906
6.878
4.393
4.382
4.362
3.891
3.871
3.858
3.839
3.706
3.649
3.635
3.617
3.605
3.594
3.574
3.563
3.544
3.351
3.339
3.318
3.308
3.298
3.276
3.264
3.241
3.182
2.431
2.178
1.365
O
O
O^{t}Bu
NH
Tos
5n
major diastereomer
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.9275
1.9310
2.3227
1.2176
3.9816
0.8309
0.9144
0.8984
1.0605
0.9899
1.0000
3.0438
2.9770
8.9346



5n

major diastereomer


7.491
7.465
7.455
7.430
7.327
7.301
7.289
7.212
7.187
7.163
7.089
7.061
6.964
6.936
4.412
4.403
4.385
4.373
3.850
3.830
3.817
3.797
3.702
3.644
3.618
3.607
3.594
3.574
3.565
3.545
3.369
3.356
3.336
3.325
3.314
3.293
3.282
3.228
3.170
2.424
1.356
1.168
O
O
O^tBu
NH
Tos
5o
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.8274
1.8389
2.0553
1.2889
1.9375
1.9318
0.8263
0.8954
1.0353
0.9114
0.9806
1.0000
3.1550
9.0259
8.9639


200.7
169.0
153.2
150.7
143.5
137.2
135.0
132.8
129.8
129.2
127.9
127.4
127.3
125.9
125.5
124.6
83.0
65.5
47.6
44.3
34.4
31.4
31.2
27.8
21.6
O
O
O^{t}Bu
NH
Tos
5o
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

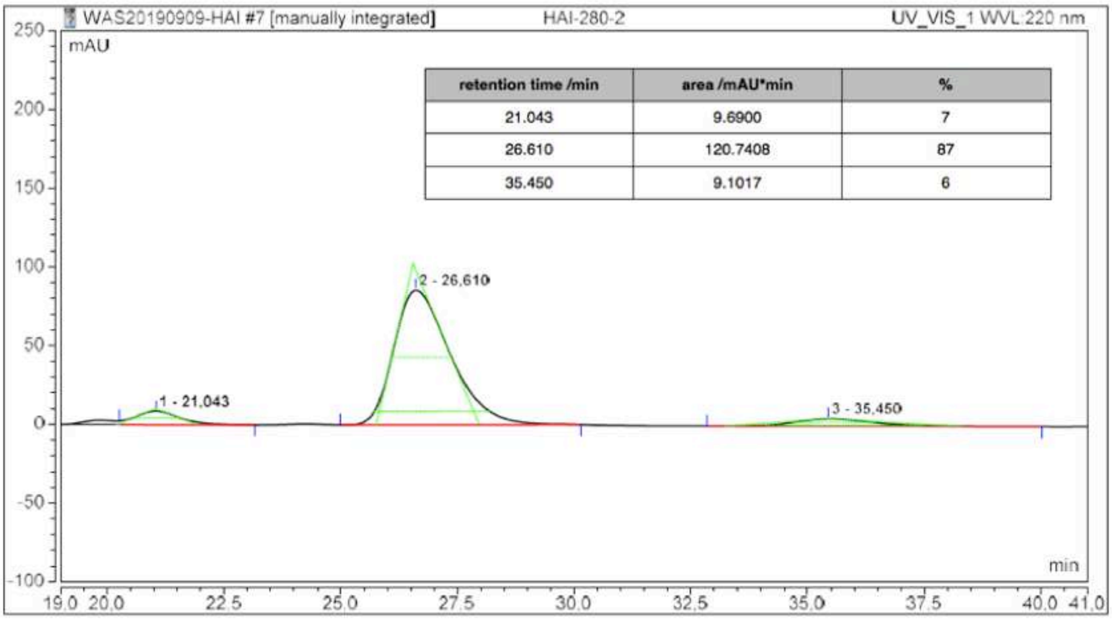
4. HPLC Traces

Determination of the diastereomeric ratio of racemic **5a** by HPLC (YMC-SA)

21.04 min: minor diastereomer, first enantiomer

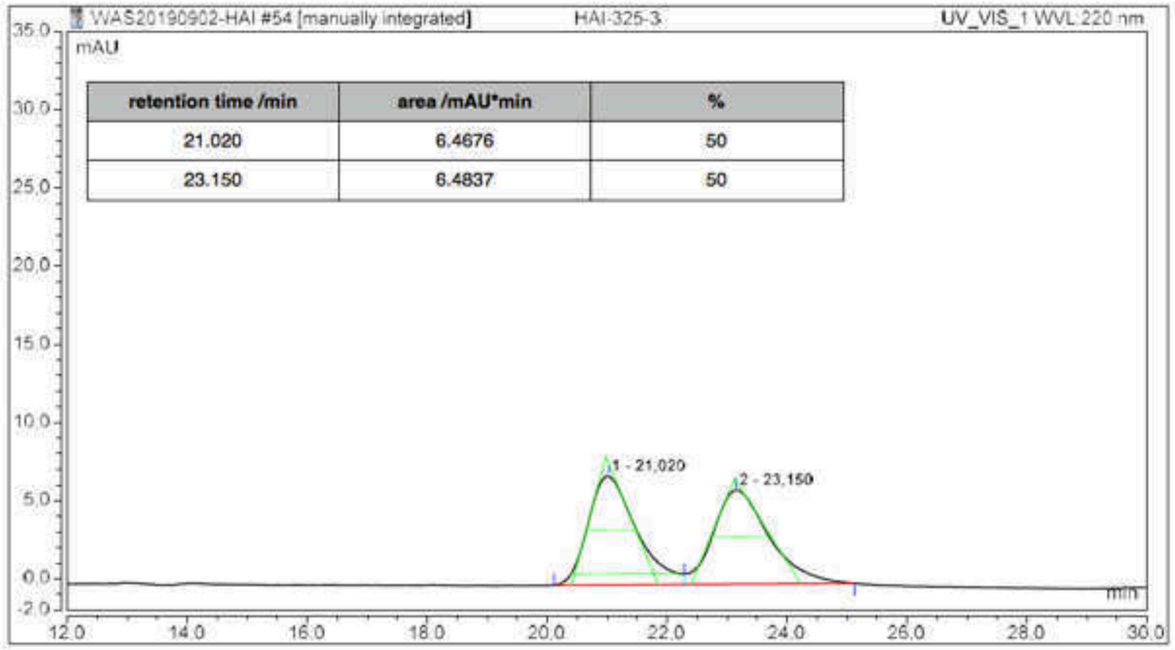
26.61 min: major diastereomer, both enantiomers

35.45 min: minor diastereomer, second enantiomer



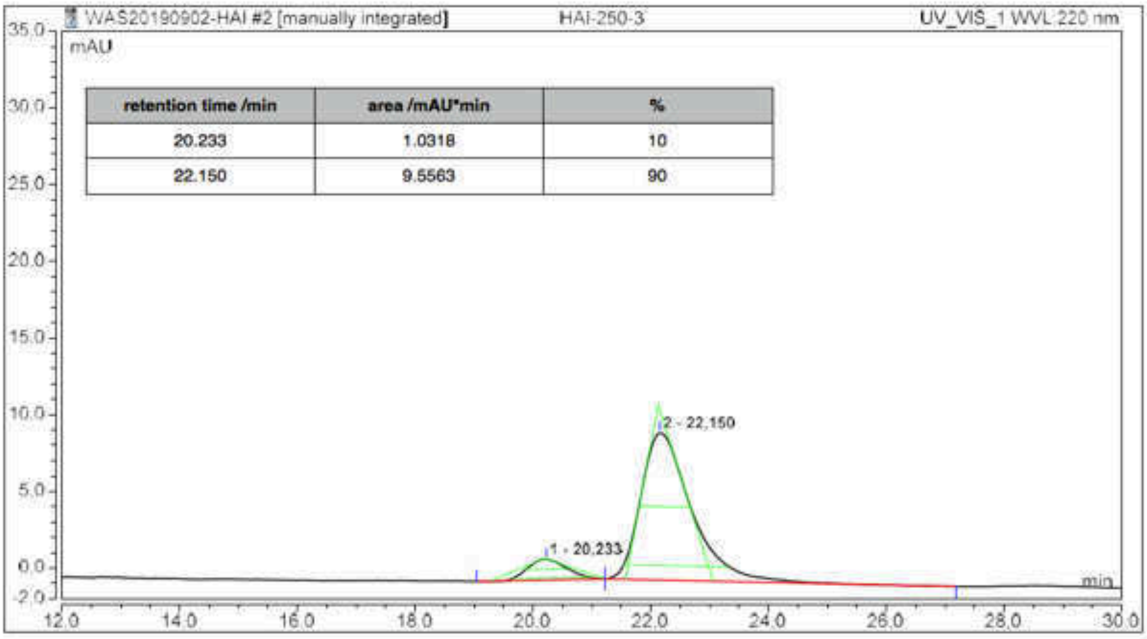
retention time /min	area /mAU*min	%
21.043	9.6900	7
26.610	120.7408	87
35.450	9.1017	6

Product **5a** major diastereomer (racemic mixture)



retention time /min	area /mAU*min	%
21.020	6.4676	50
23.150	6.4837	50

Product **5a** major diastereomer (enantiomer-enriched mixture)



retention time /min	area /mAU*min	%
20.233	1.0318	10
22.150	9.5563	90