

博士論文

カルボニル隣接アジドの性質を利用した
アジド基の位置選択的変換法の開発

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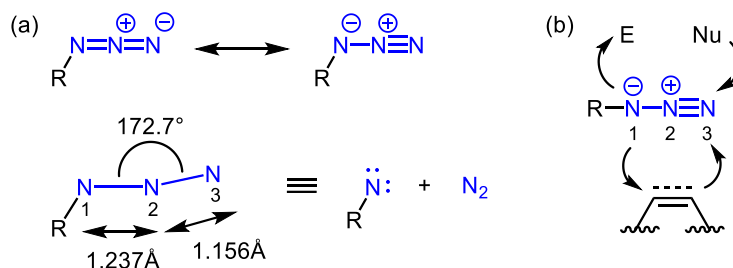
略語表

Ac	acetyl
Ala	alanine
Ar	aryl
Asc	ascorbic acid
Bn	benzyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMF	<i>N,N</i> -dimethylformamide
DMI	<i>N,N</i> -dimethylimidazolidinone
DMSO	dimethylsulfoxide
Et	ethyl
EWG	electron-withdrawing group
Gly	glycine
ⁱ Pr	isopropyl
Lys	lysine
Me	methyl
MOM	methoxymethyl
Ms	methanesulfonyl
ⁿ Bu	normal butyl
Ph	phenyl
Pro	proline
Pyr	pyridine
^t Bu	tertiary butyl
TBAF	tetrabutylammonium fluoride
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMG	<i>N,N,N',N'</i> -tetramethylguanidine
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	<i>para</i> -toluenesulfonyl

第1章 緒言

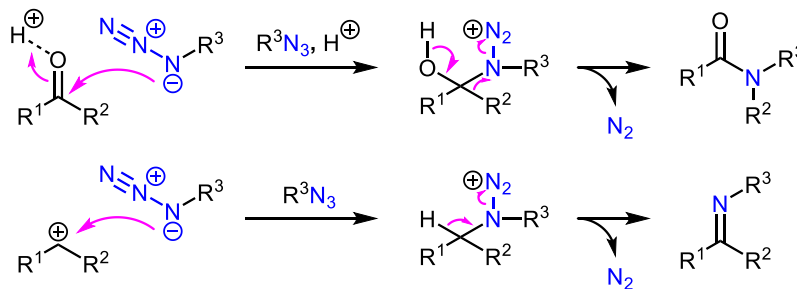
1-1 有機アジドの化学

有機アジドの化学は 1864 年に Griess によって初の有機アジドとなるフェニルアジドの合成報告に始まり¹⁾、1890 年に Curtius によるアジ化水素酸を用いたアシル化合物の転位反応²⁾を機に大きく発展を遂げた。現在では含窒素天然物の合成や創薬研究のみならず、生体分子標識などのケミカルバイオロジー、機能性高分子の合成などの幅広い分野で活用されている³⁾。その多様な反応性はアジドの構造的特徴に起因している。アジドは 3 つの窒素原子が連なった化学的に安定な双極性官能基であるが、その二面角は 172.7° と直線構造ではないことに加えて、それぞれの窒素原子間の結合長は 1.237\AA (N1-N2)、 1.156\AA (N2-N3) と差がある (Scheme 1-1a)^{3d)}。つまり、アジドはナイトレンと脱離基の窒素から構成されていると見なすことができ、潜在的に高い反応性を有している。実際の反応は、反応相手となる基質によって反応部位が変わり、求電子種 (E) とは N1 部での反応に対して、求核種 (Nu) とは N3 部で反応が進行する (Scheme 1-1b)。また、1,3-双極子としても働き、アルケンやアルキン、ニトリルなどの親双極子と [3+2] 環化反応を起こす。



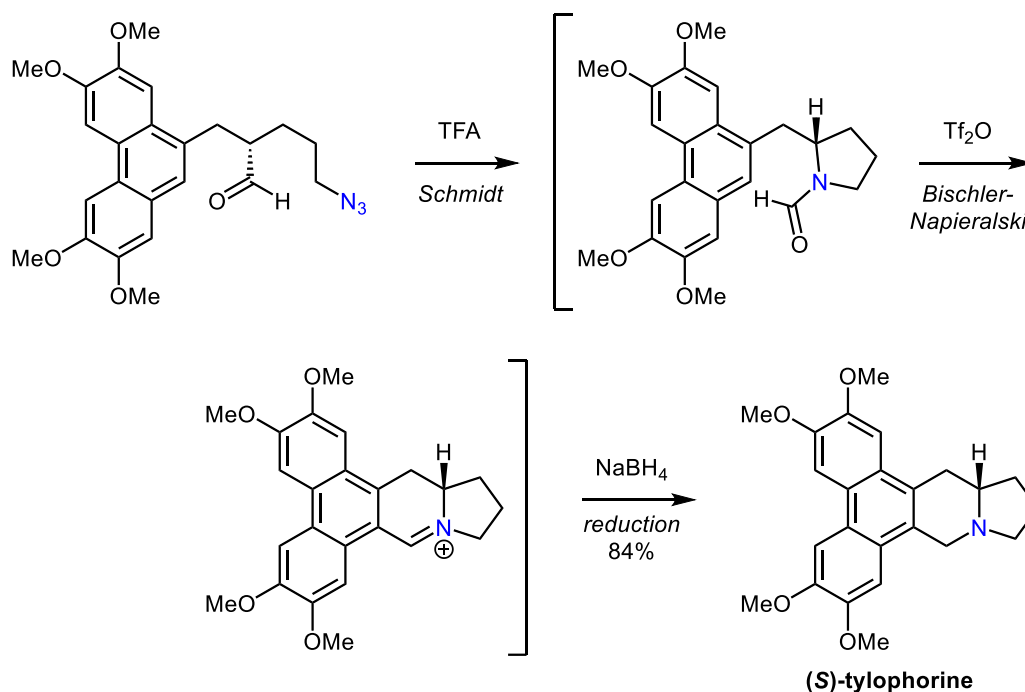
Scheme 1-1. Organic azide

代表的なアジドと求電子種との反応は Schmidt 反応である (Scheme 1-2)^{3d)}。Schmidt 反応は活性化されたカルボニル基やカルボカチオン種などにアジドの N1 部から求核攻撃が起こり、ジアゾニウム中間体を經由して窒素を脱離することで、様々な含窒素化合物を与える。



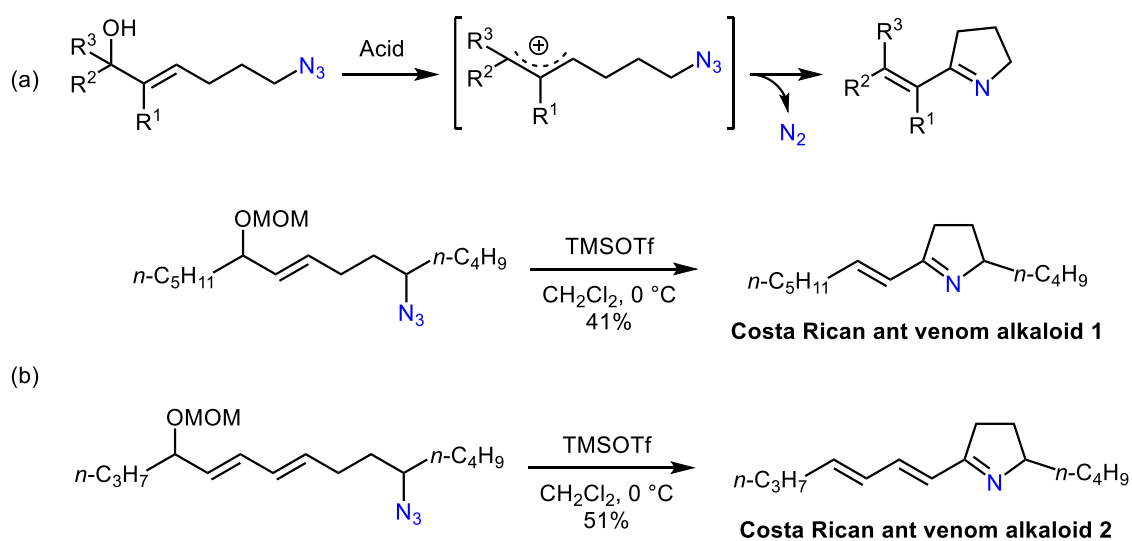
Scheme 1-2. Schmidt reaction

Schmidt 反応は天然物合成にも利用されており、Wang らは Schmidt 反応を利用したホルムアミドの構築と、続く Bischler-Napieralski 反応、還元反応をワンポットで行うことによって、(S)-tylophorine の全合成を達成している (Scheme 1-3)⁴⁾。



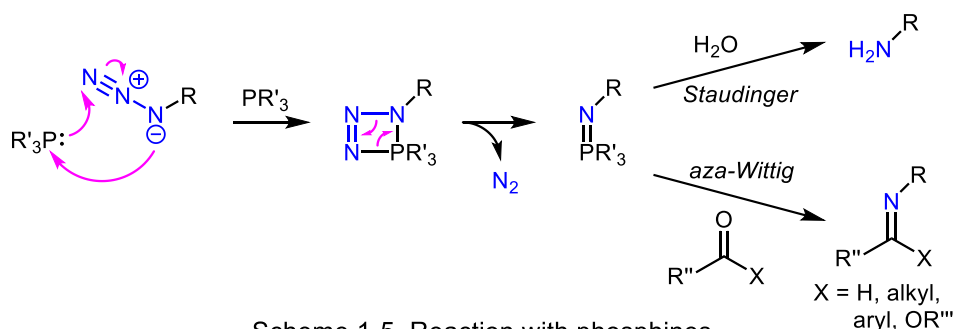
Scheme 1-3. Total synthesis of (S)-tylophorine

当研究室においてもアリルアルコールとアジドの Schmidt 反応による α,β -不飽和イミンの合成法を開発しており (Scheme 1-4a)、この反応を利用することで、不安定な不飽和イミン天然物である蟻毒アルカロイド類の全合成に成功している (Scheme 1-4b)⁵⁾。



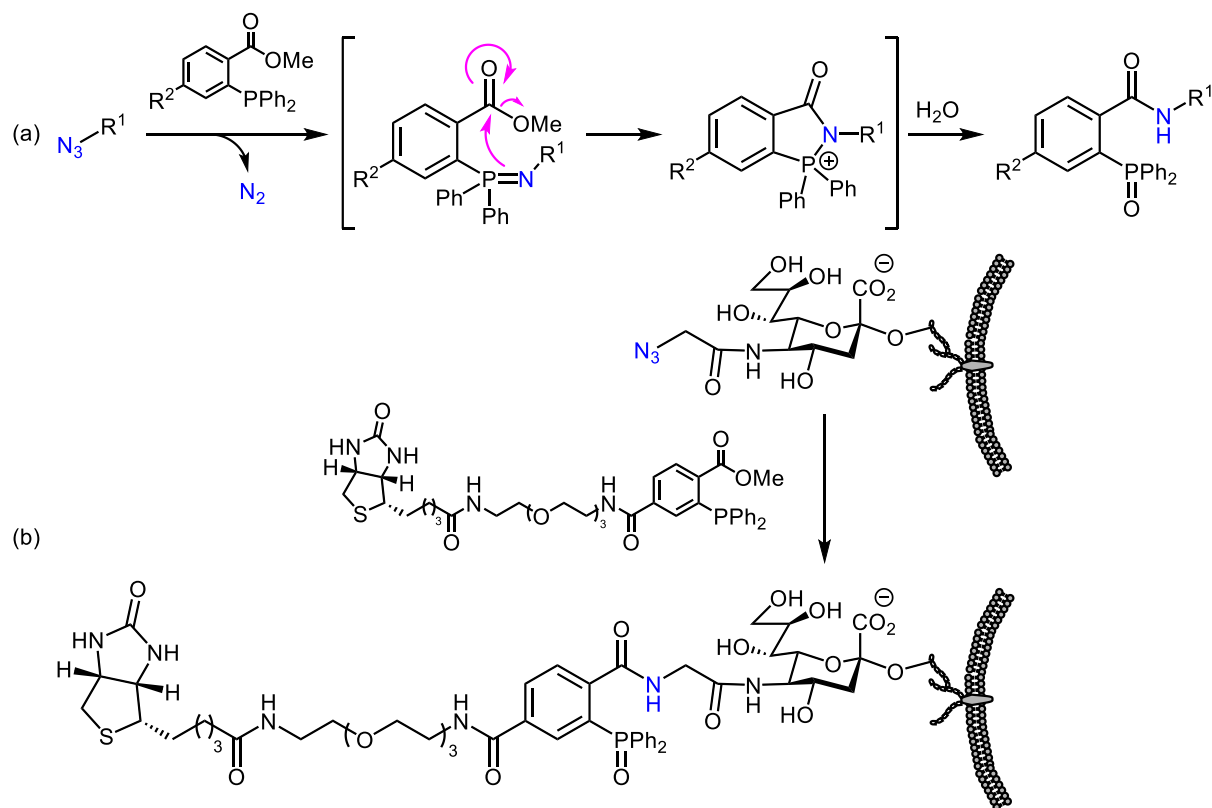
Scheme 1-4. Unsaturated imine synthesis

アジドと求核種との反応はホスフィン試薬による **Staudinger 反応**⁶⁾や、その反応中間体を利用した **aza-Wittig 反応**⁷⁾などが広く知られている(Scheme 1-5)。これらの反応はホスフィンのアジド末端への求核攻撃と続く脱窒素によって形成されるイミノホスホランを鍵中間体とする反応であり、イミノホスホラン中間体に水やカルボニル種を作用させることでアジドが還元された1級アミンやイミンへと導ける。



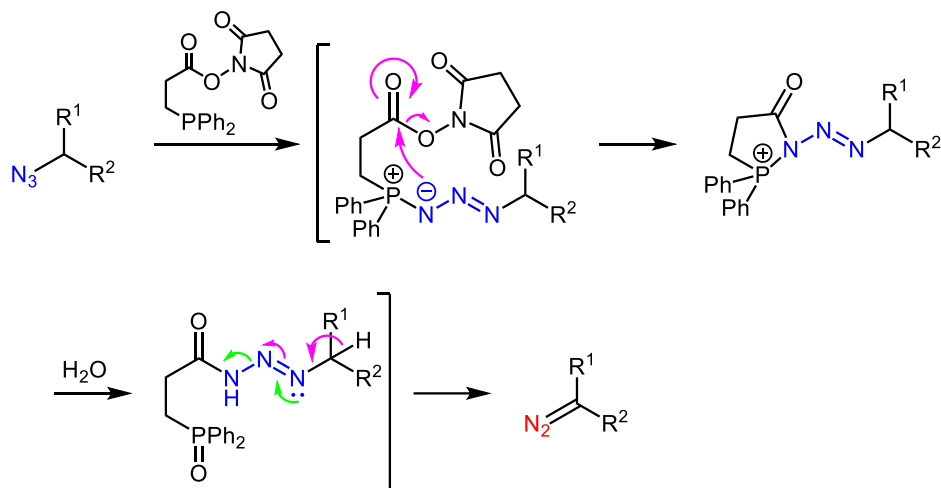
Scheme 1-5. Reaction with phosphines

さらに、**Staudinger 反応**を応用した**ライゲーション反応**が **Bertozzi** らによって報告されており⁸⁾、イミノホスホランを分子内エステルでトラップすることで分子連結を可能にしている(Scheme 1-6a)。この反応を利用して、**Jurkat** 細胞表面に処理したシアル酸誘導体上のアジド基に**ビオチンタグ**を連結することに成功している(Scheme 1-6b)。この反応は高分子合成にも用いられており⁹⁾、外部試薬を必要としない強力な分子連結手法として知られている。



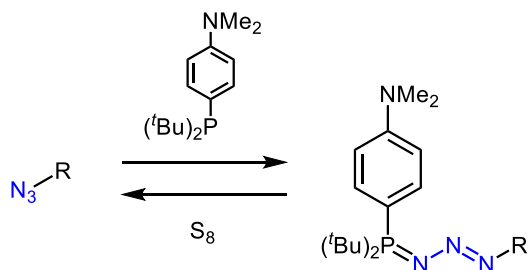
Scheme 1-6. Staudinger ligation reaction

アジドとホスフィンによる反応は上記で述べたような脱窒素を伴ったイミノホスホランの形成に限定されたものではない。例えば Raines らは、エステル部の反応性を高めることでホスファジド中間体をトラップし、続く加水分解によってアシルトリアゼンへと導くことで、アジドからジアゾへの変換に成功している (Scheme 1-7)¹⁰。



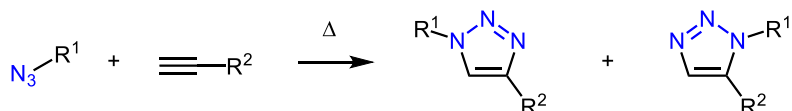
Scheme 1-7. Conversion of azido to diazo groups

一方細谷らは、立体障害が大きく、尚且つ電子豊富なホスフィンを利用することで安定なホスファジドを構築している (Scheme 1-8)¹¹。このホスファジドは分子硫黄によって元のアジドへと再生が可能である。



Scheme 1-8. Transient protection of azides

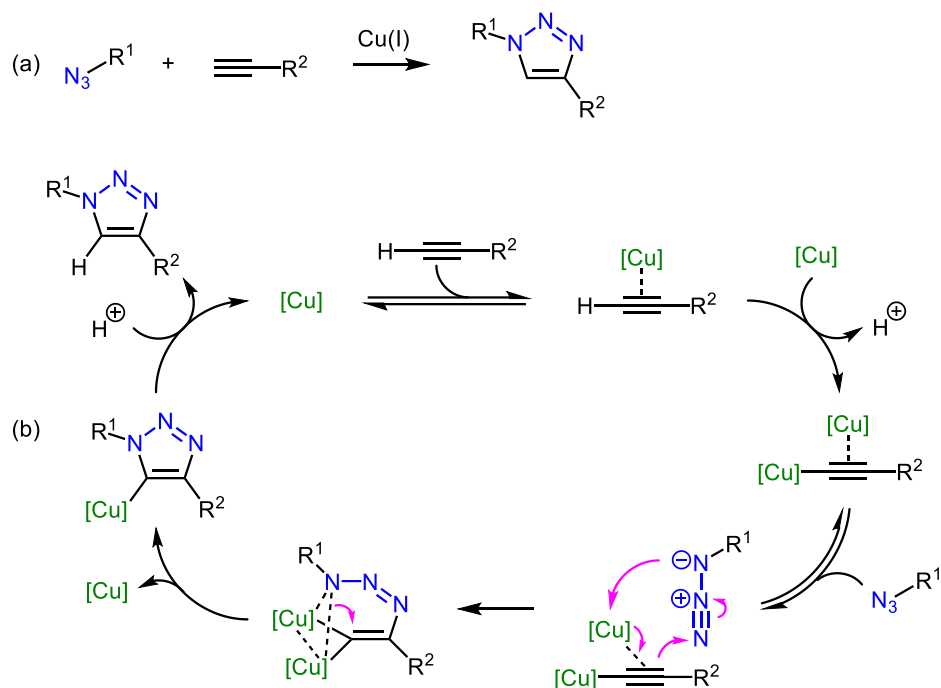
一方、アジドを 1,3-双極子とするアルキンとの環化反応は Huisgen 反応と呼ばれ、高温条件下、長時間攪拌することで反応が進行し、位置異性体の混合物を与える (Scheme 1-9)¹²。



Scheme 1-9. Azide-alkyne cycloaddition reaction (Huisgen reaction)

これに対して Sharpless、および Meldal らは 1 価の銅触媒を用いることで、室温下、水存在中でも反応が進行し、高収率かつ 1,4 位置換トリアゾールが高選択的に得られることを同時期に見出している (Scheme 1-10a)¹³。この高い位置選択性は、2 つの銅が関与した銅アセチリドによって環化反応が進行

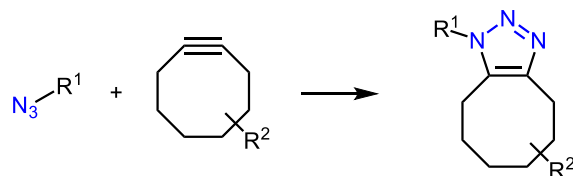
することで発現している(Scheme 1-10b)¹⁴⁾。



Scheme 1-10. Copper catalyzed azide-alkyne cycloaddition reactions (CuAAC)

また、ルテニウム触媒を用いた場合、銅による環化、すなわち CuAAC (Copper catalyzed Azide-Alkyne Cycloaddition)とは逆の環化位置選択性にて 1,5 位置換トリアゾールが得られる¹⁵⁾ほか、銅触媒では反応性の低いアリアルアジドも適用可能となる¹⁶⁾など、金属触媒を介したアジドとアルキンの環化反応は柔軟性の高い反応である。そのため近年では、クリックケミストリーの代表的な反応として、創薬探索や高分子合成で盛んに利用されている^{3f, 17)}。

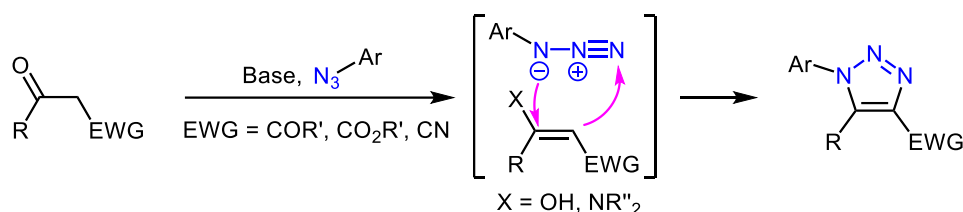
しかし、これらの反応は生体細胞に毒性のある銅などの金属試薬が必要であることから、細胞実験などへの応用は好ましくない。そこで Bertozziらは、歪んだ環状アルキンが触媒を必要とせず、アジドと温和な条件下で環化反応が進行することを見出した(Scheme 1-11)¹⁸⁾。SPAAC(Strain-Promoted Azide-Alkyne Cycloaddition)と呼ばれるこの手法は生体直交反応として知られ、*in vivo*でのイメージングを可能にしている¹⁹⁾。



Scheme 1-11. Strain-promoted azide-alkyne cycloaddition reactions (SPAAC)

歪みアルキンを利用する手法以外にも金属試薬を用いない[3+2]環化反応は多数報告されており²⁰⁾、酸や塩基による活性種を利用した例も知られている。例えば、 β -ケトエステルなどを塩基性条件下に付すことで生成するエノ

ールやエナミンは、アリールアジドと効率よく反応することが知られている (Scheme 1-12)^{20a, 20c}。

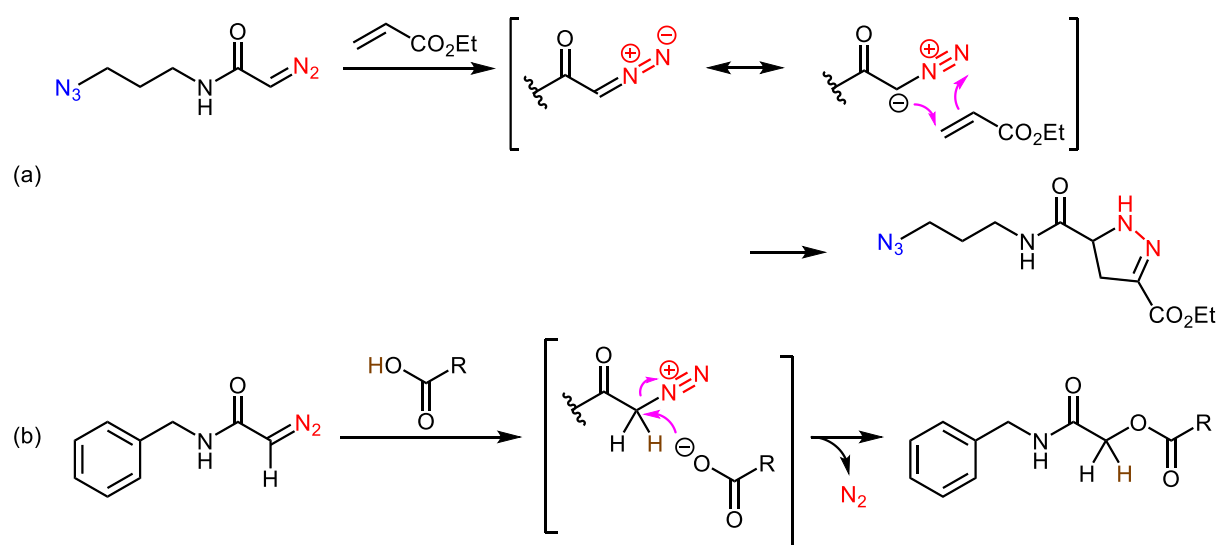


Scheme 1-12. Base-mediated cycloaddition of aryl azides with enolates or enamines

1-2 クリック官能基の種類と反応性

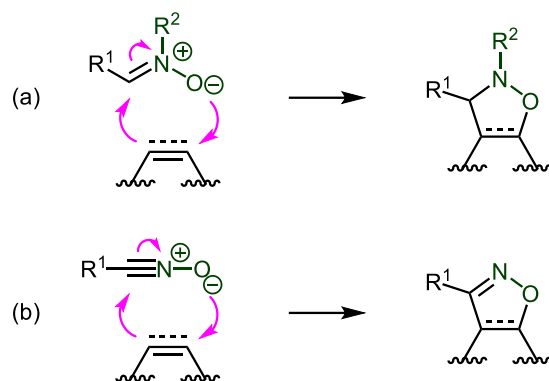
1-1 で述べたように、アジドは様々な含窒素化合物の合成に効果的であるだけでなく、環化反応によって2つの分子を簡便に連結するためのツールとして重要である。また、その導入容易性からも頻繁に用いられる有用官能基となっている。一方、簡便な分子連結を可能とする含ヘテロ官能基はアジド以外にも多数報告されている²¹⁻²⁶。例えば、ジアゾ、ニトロソ、1,2,4,5-テトラジンなどである。これらはアジドと同様に環状アルキンと環化反応を起こすことが可能である他、アジドとは異なる反応性も有している。

例えばジアゾは、アジドでは反応が進行しないアクリルエステルなどの電子不足オレフィンと[3+2]環化反応を起こしてピラゾリン骨格を形成することや(Scheme 1-13a)、カルボン酸によって活性化された後、カルボキシレートとの反応によって窒素が脱離してエステルを形成することで分子接続を可能とする(Scheme 1-13b)²¹。



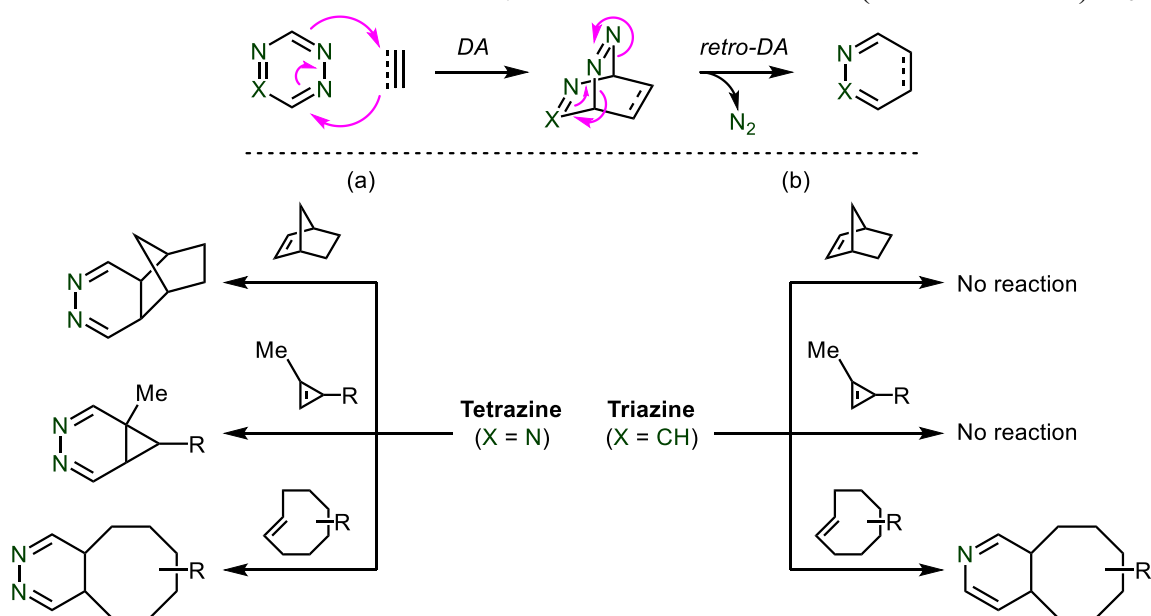
Scheme 1-13. Conjugation of diazo groups with acrylates and carboxylic acids

また、ニトロンも 1,3-双極子として働くことでアルケンやアルキンと環化反応を起こし(Scheme 1-14a)²²⁾、環状アルキンとの環化速度は安定なアジドやジアゾエステルと比べて速い²³⁾。ニトロンとよく似たニトリルオキシドはオキシムから調製でき、ニトロンと同様にアルケンやアルキンと環化反応が進行する(Scheme 1-14b)²²⁾。ニトリルオキシドはニトロンよりも高い反応性を持つため、二量化やポリマー化などの副反応が起こる。



Scheme 1-14. Cycloaddition reaction of nitrones and nitrile oxides

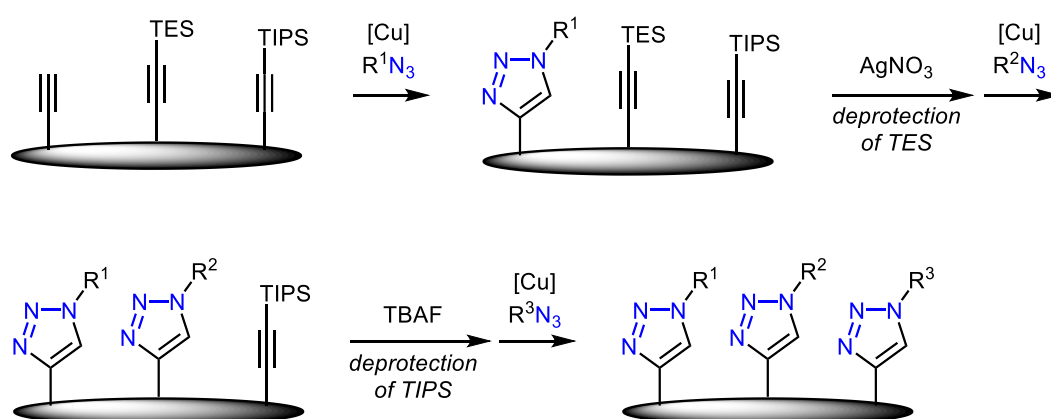
1,2,4,5-テトラジンも同様に、アルケンやアルキンとの逆電子要請型 Diels-Alder(DA)反応と続く retro-DA 反応による脱窒素を伴うことで 2 分子連結が可能である²⁴⁾。特に *trans*-シクロアルケンやシクロプロペンと迅速に環化反応が進行する(Scheme 1-15a)²⁵⁾。また、テトラジンの窒素原子が 1 つ減少した 1,2,4-トリアジンはテトラジンよりも窒素原子が少ないことで求電子性が減少するため反応性が低く、テトラジンでは環化反応が進行する *cis*-シクロアルケンやシクロプロペンとは反応せず、*trans*-シクロアルケンのみ DA/retro-DA 反応が進行する高い化学種選択性を有する(Scheme 1-15b)²⁶⁾。



Scheme 1-15. Diels-Alder (DA)/retro-DA reactions of tetrazines and triazines

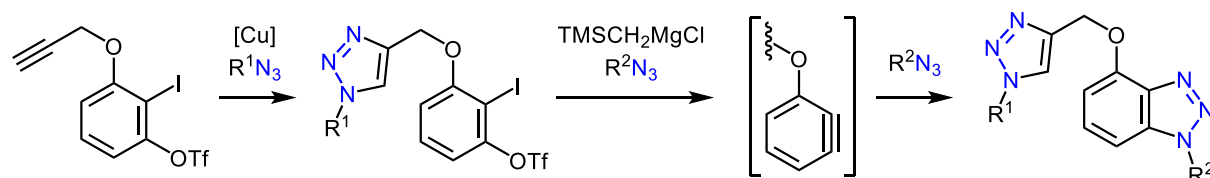
上述したような環化反応による手法以外にも、アルデヒドのオキシム化に代表されるカルボニルライゲーションや、チオール-エン反応、ボロネート形成によるライゲーション²⁷⁾などケミカルバイオロジーだけでなく、高分子合成にも応用可能な生体直交型の優れた連結反応は多様に存在する²⁸⁾。

これまでは2種の成分を連結することに注力されてきたが、最近ではより複雑な多機能性化合物を簡便に合成するため、多数の機能性分子を1つのプラットフォーム分子に集積する手法に注目が集まっている。そこで開発されているのがアルキンを区別して利用する手法である。例えば、シリル基で保護されたアルキンの脱保護とCuAACを繰り返す手法がある(Scheme 1-16)²⁹⁾。



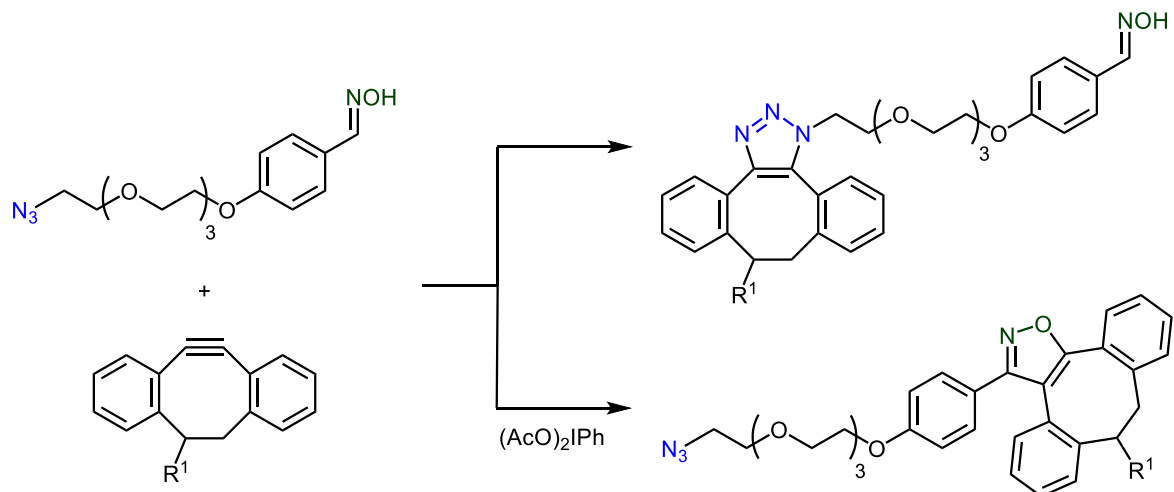
Scheme 1-16. Sequential introduction of three components via deprotection and CuAAC

また、アルキンおよびアライン前駆体を組み合わせることで、アルキン部のCuAAC、およびアラインの発生とその利用によって、同様に位置選択的な分子連結が行える(Scheme 1-17)³⁰⁾。



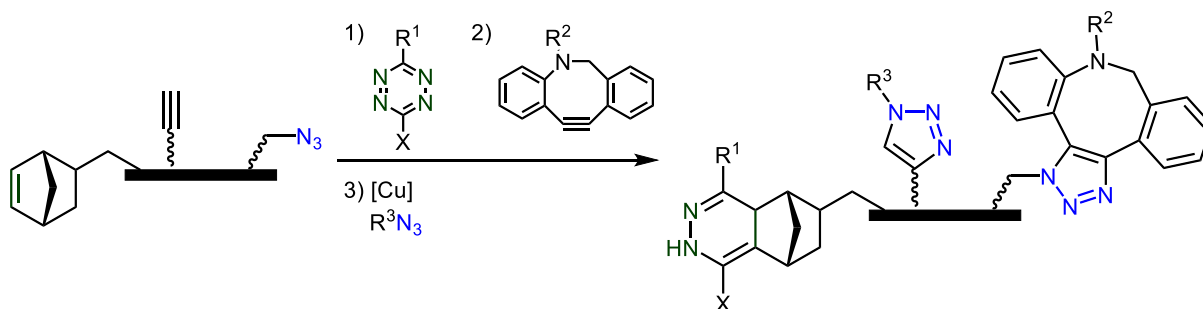
Scheme 1-17. Sequential introduction of two components via CuAAC and azide-aryne cycloaddition

近年になって不斉CuAAC反応や区別可能なアルキンの組み合わせなど、アルキンの保護脱保護を必要としない位置選択的連結手法が開発されているが、未だプラットフォーム分子への利用には至っていない³¹⁾。一方で、それぞれが特異的に反応する反応種が存在することや、反応速度に明確な差が存在することから、2種以上のクリック官能基を組み合わせる手法に期待が集まっている^{23a, 32)}。前述したジアゾとアジドを組み合わせる手法(Scheme 1-13a)やオキシムとアジドを組み合わせ、酸化剤の有無で反応位置を選択する手法などがこれに該当する(Scheme 1-18)。



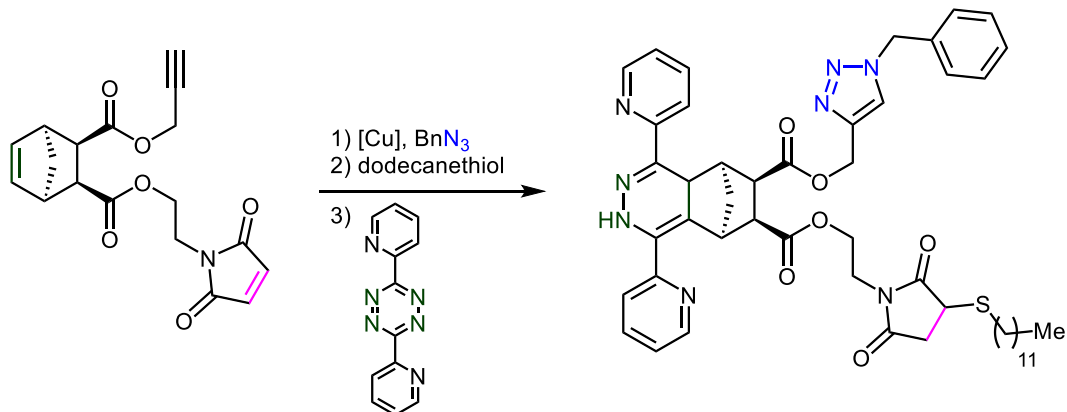
Scheme 1-18. Chemoselective cycloaddition

また、3種以上のクリック官能基を組み合わせたワンポットでのマルチライゲーション反応によって、多成分連結を達成した報告例もある³³⁾。例えばJaschkeらは、アジドとアルキンおよびノルボルネンを有するDNAもしくはRNAに対して、DA/retro-DA、SPAAC、CuAACの順で反応を行うことで、位置選択的な分子修飾に成功している(Scheme 1-19)^{33c)}。



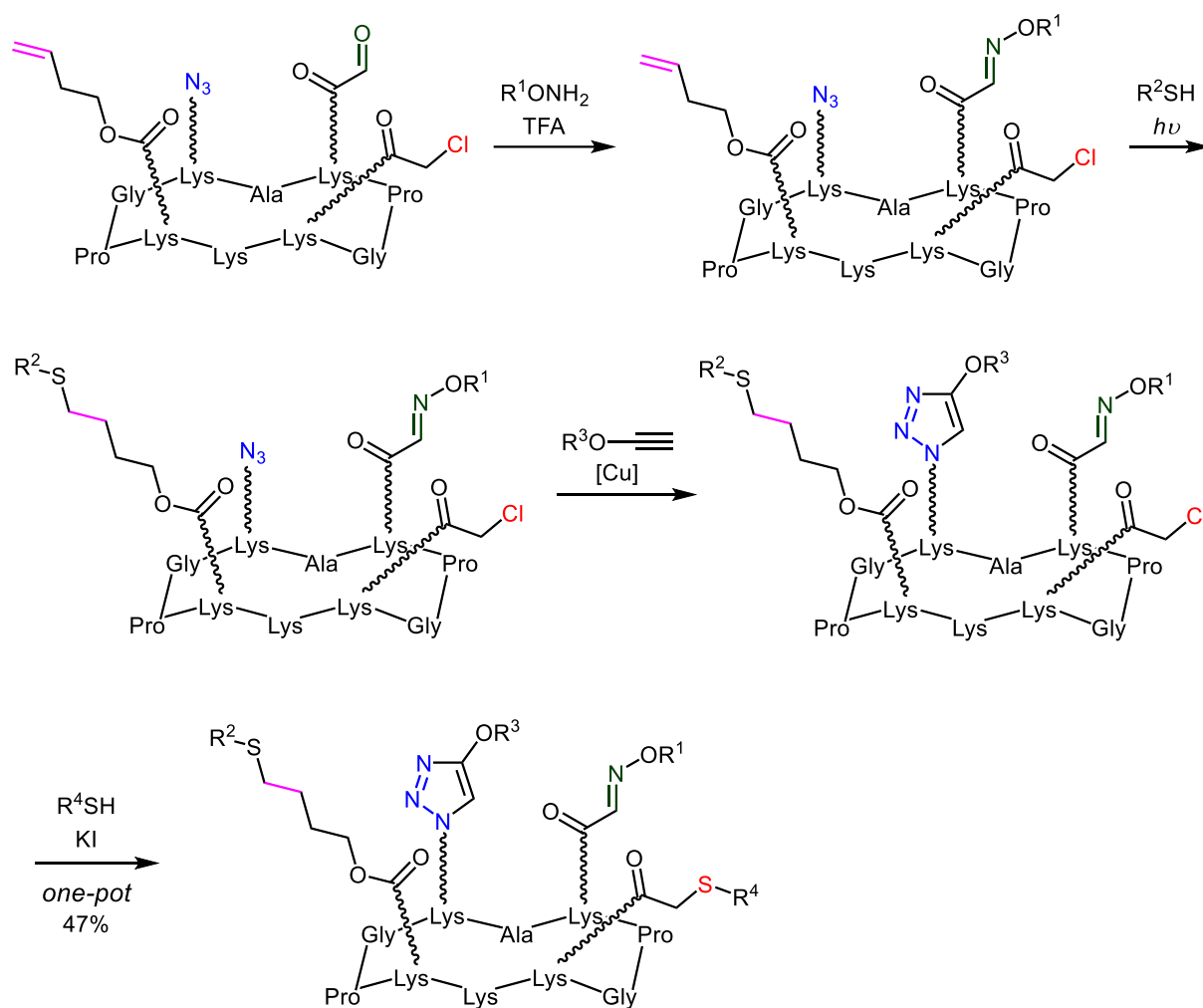
Scheme 1-19. One-pot triple click labeling for DNA and RNA

一方、Knallらはアルケン、アルキンおよびノルボルネンを有するプラットフォーム分子を用い、CuAAC、チオール-エン反応、DA/retro-DAの順で反応を行うことで位置選択的な多成分集積化を達成している(Scheme 1-20)^{33b)}。



Scheme 1-20. One-pot triple click ligation

中でも、Renaudet らは 4 種のクリック官能基を有するプラットフォーム分子へと 4 成分を位置選択的に連結することに成功している (Scheme 1-21)^{33a)}。これは、固相合成法によって調製したペプチドから数段階を経て合成したグリオキシアルデヒド、アルケン、アジドおよびクロロアセチル部から成るプラットフォーム分子に対して、オキシムライゲーション、チオール-エンカップリング、CuAAC、チオール-クロロアセチルカップリングを順に行うことで達成している。

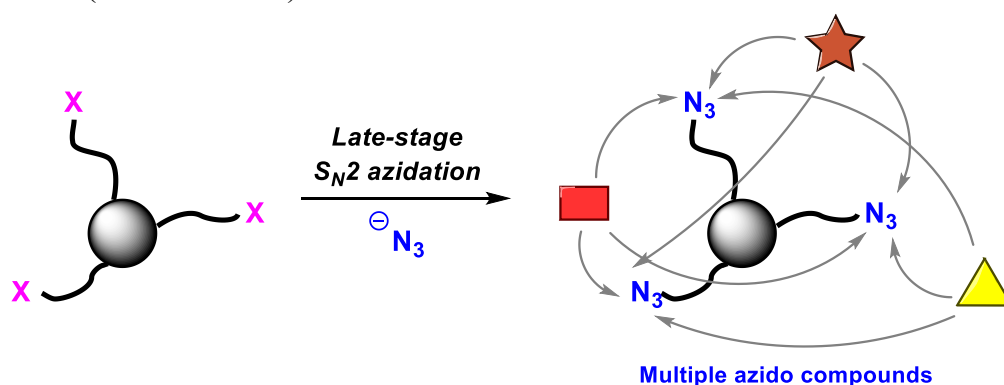


Scheme 1-21. One-pot quadruple click ligation using cyclopeptide scaffold

これらの報告から、クリック官能基を組み合わせたマルチクリックプラットフォーム分子は、多成分集積化を行う上で非常に有効であることがわかる。しかし、マルチクリックプラットフォーム分子の合成はいずれも多大な労力を必要とするため、より簡便な合成手法が望まれている。

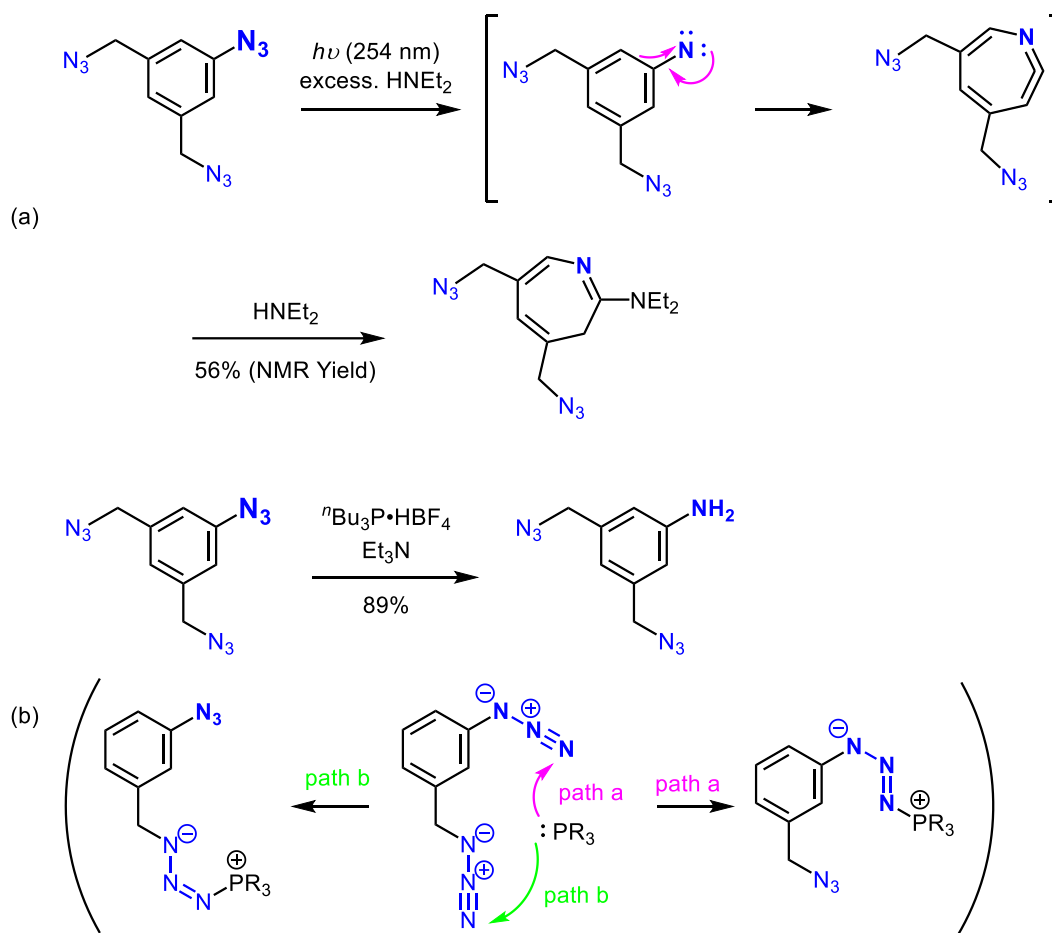
1-3 アジド基の位置選択的反応

プラットフォーム分子の有用性に反して、実用性を考慮した合成容易かつ利用可能なプラットフォーム分子は未だ発展途上であると言える。そこで近年では、導入が容易なクリック官能基であるアジドに再び注目が集まっている。すなわち、アジド基を一挙に導入することで複数有するマルチアジド化合物を簡便に合成し、その位置選択的な変換反応の開発によって、合成容易性および利用性を兼ね備えたプラットフォーム分子を創成する試みである。しかし、アジドは高い反応性を有するため、反応位置を区別して利用することは難しい(Scheme 1-22)。



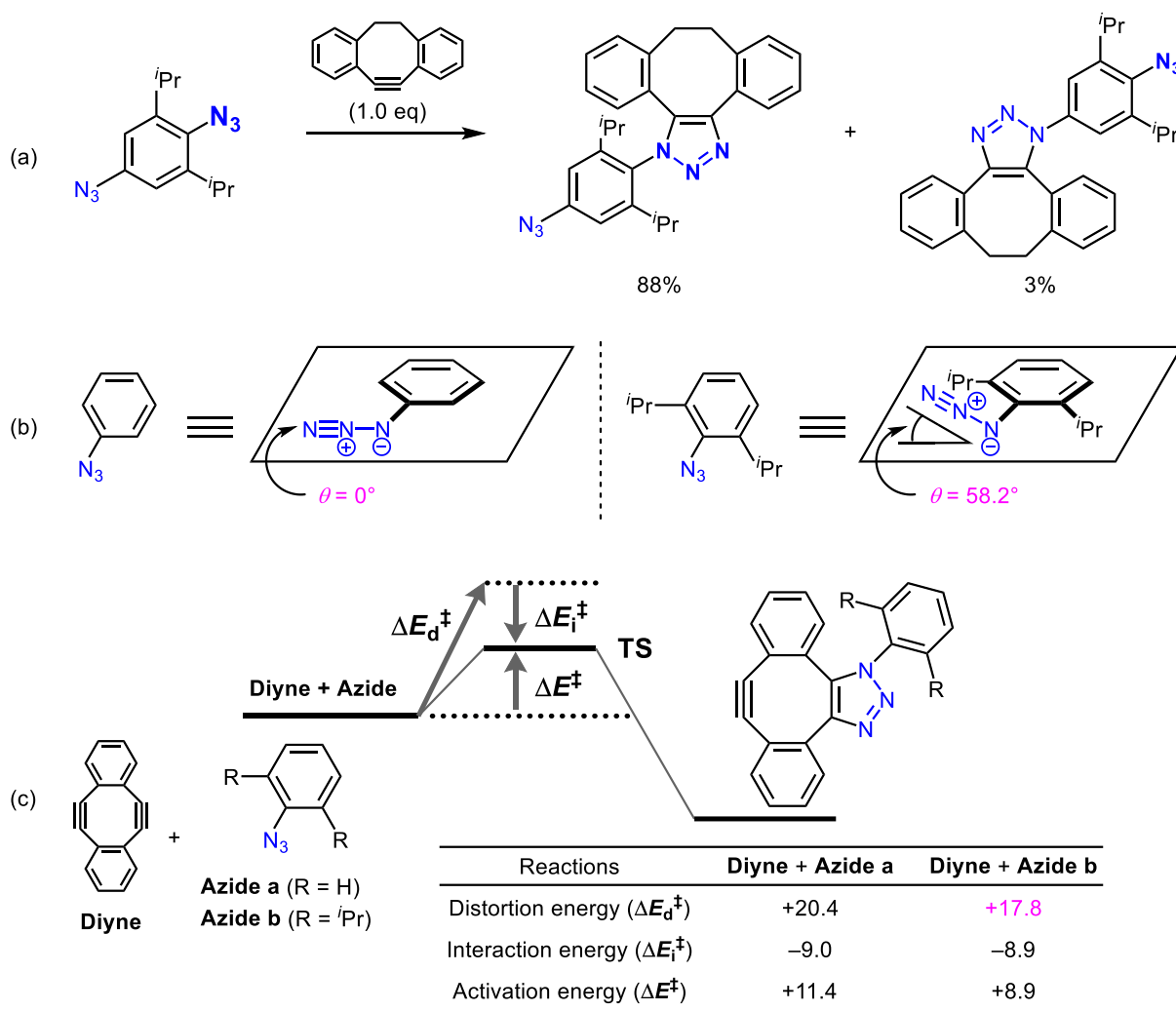
Scheme 1-22. Easily accessible multiple azido compounds

そのような中で、アリールアジドはアジドと芳香環での共鳴効果によってアルキルアジドとは異なる反応性を有しているため、アジドの位置選択的変換反応の開発が進んでいる。例えば、位置選択的な脱窒素を伴うナイトレンへの変換によるアゼパン骨格の構築(Scheme 1-23a)³⁴⁾や、Staudinger 反応によるアミンへの還元(Scheme 1-23b)³⁵⁾が報告されている。光照射による位置選択的な脱窒素反応では、アジドと芳香環との共鳴効果によってアリールアジドの光応答性が向上しているため、アリールアジドが優先的に脱窒素を起こしてナイトレンを生成する。生成したナイトレンは活性アゼピン中間体へと誘導されるため、過剰の求核剤でトラップすることでアゼパン骨格を構築できる。ホスフィン試薬による位置選択的 Staudinger 反応では、ホスフィン試薬の求核攻撃が path a で進行したトリアゼニド中間体の方が、path b で反応が進行した中間体よりも芳香環との共鳴効果によって安定化するため、アリールアジドへの反応が優先する。



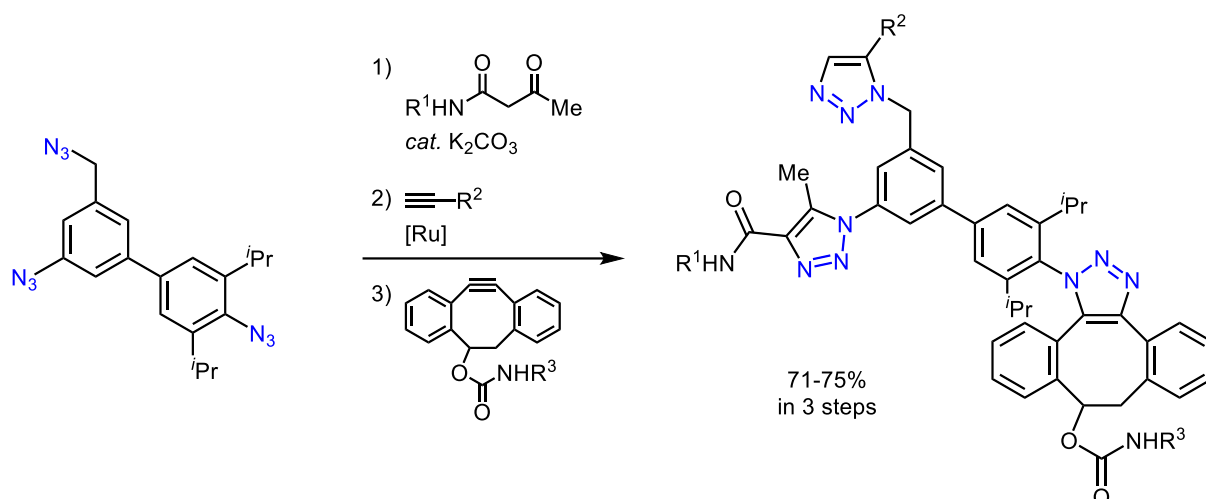
Scheme 1-23. Aryl azide-selective activation and reduction

また、アリールアジドの中でも、アジド基がイソプロピル基のようなかさ高い置換基に囲まれたアジドは反応性が向上することが報告されている (Scheme 1-24a)³⁶⁾。これは、置換基の立体障害によって芳香環との同一平面上にアジドが存在できなくなり、芳香環とアジド間の共役効果が失われると同時に、アジド自体にも歪みが生じることに起因する (Scheme 1-24b)。特に、アジドとアルキンの環化反応に必要な活性化エネルギー (ΔE^\ddagger) は遷移状態 (TS) に至る際のアジドとアルキンに生じる歪みエネルギー (ΔE_d^\ddagger) と相互作用エネルギー (ΔE_i^\ddagger) の和とされ、立体的に混んだアリールアジド (**Azide b**) はアジド自体に歪みが存在するために ΔE_d^\ddagger が通常のアリールアジド (**Azide a**) よりも有利となり、優先して環化反応が進行する (Scheme 1-24c)。



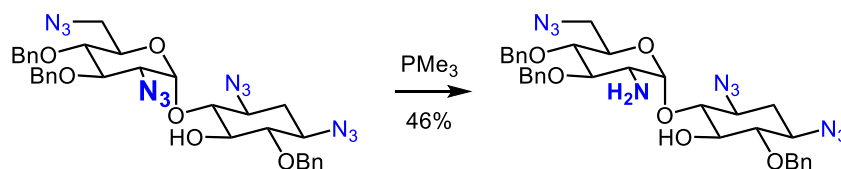
Scheme 1-24. Reactivity and twisted conformation of 2,6-diisopropylphenyl azide

細谷らはアルキルアジドとアリールアジドの反応性の違いや Scheme 1-24 に示した反応性を巧みに利用することで、3種のアジド基を有するトリアジドをプラットフォーム分子として利用することに成功しており (Scheme 1-25)³⁷⁾、エノレートによるアリールアジド選択的環化、ルテニウム触媒によるアルキルアジドへの AAC および歪みアジドへの SPAAC を段階的に行うことで3成分の位置選択的な集積化を達成している。このように、アリールアジドとアルキルアジドで構成されたマルチアジドの位置選択的な反応の開発は徐々に可能になりつつある。



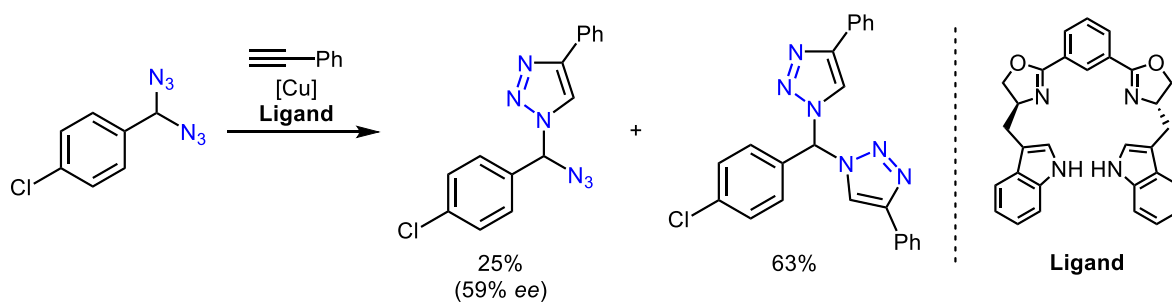
Scheme 1-25. Sequential azido-type selective cycloaddition

一方、アルキルアジド間の位置選択的な変換反応も検討されているが、その報告例は少ない。例えば、マルチアジド糖の位置選択的還元反応はアミノグリコシド系抗生物質合成への有用性から盛んに研究されている³⁸⁾。Wongらはマルチアジド糖の Staudinger 反応において、アジド置換炭素の sp^2 性向上により電子不足となるアジドが存在し、そのアジドが優先して還元されることを発見しており (Scheme 1-26)^{38a)}、その選択性はアジド置換炭素上の水素ピークが低磁場シフトしているかで判別できることを報告している。しかし、その選択性は高くなく、単純な還元反応においても位置選択性を発現することは困難であることがわかる。



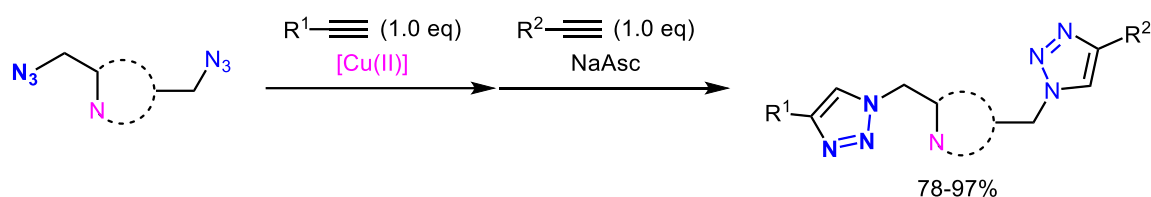
Scheme 1-26. Electron-deficient azide-selective reduction of tetraazide sugar

また、FinnらはCuAAC反応における非対称化反応において、*gem*-ジアジドに対してアルキンを作用させた場合、環化反応のコントロールは困難であり、過剰に反応が進行した生成物が主生成物となることを報告している (Scheme 1-27)³⁹⁾。



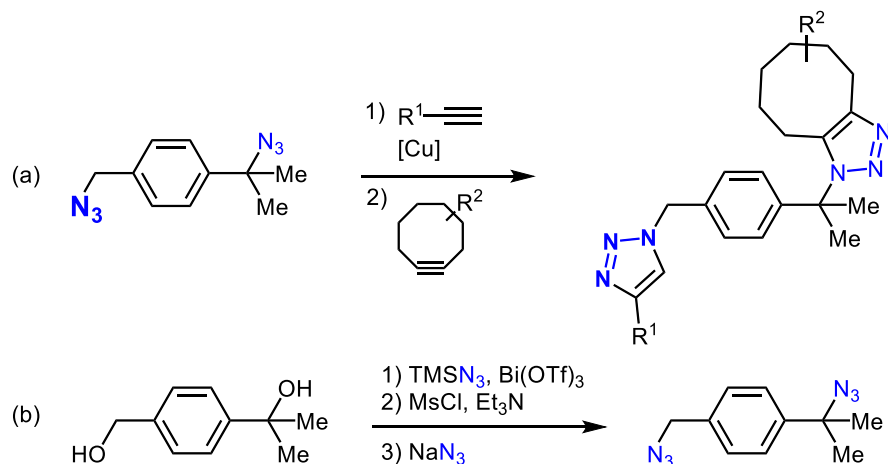
Scheme 1-27. Desymmetrized cyclization

この過剰反応は Scheme 1-10b で述べたように、CuAAC 反応が銅のアルキンへの配位による活性化を鍵とするため、トリアゾールの形成から銅触媒が再生する前にアルキンが接近し、トリアゾール近傍アジドが優先して反応したと考えられる。この現象は実際に、多分岐高分子合成の際に利用されている⁴⁰⁾。また、Zhu らは 2 価の銅触媒がヘテロ環に配位することで CuAAC 反応を促進させることを発見し、アジド近傍に配向基として配置することでアルキルアジド間での高位置選択的な環化反応に成功している (Scheme 1-28)⁴¹⁾。すなわち、2 価の銅触媒による環化反応がヘテロ環の近傍アジドでのみ進行した後、アスコルビン酸ナトリウムによって 2 価の銅触媒を 1 価へと還元することで残りのアジドでの CuAAC を行う方法である。



Scheme 1-28. Site-selective sequential CuAAC

一方、3 級アルキルアジドはその立体障害によって環化反応における反応速度が遅く、1 級アルキルアジド等と容易に区別できる (Scheme 1-29a)⁴²⁾。しかし、その調製には 1 級および 2 級アルキルアジドのような NaN₃ によるアジド化ではなく酸性条件下でのアジド化が必要であり、3 級アルキルアジドを併せ持つジアジドの調製は多段階を要する (Scheme 1-29b)。

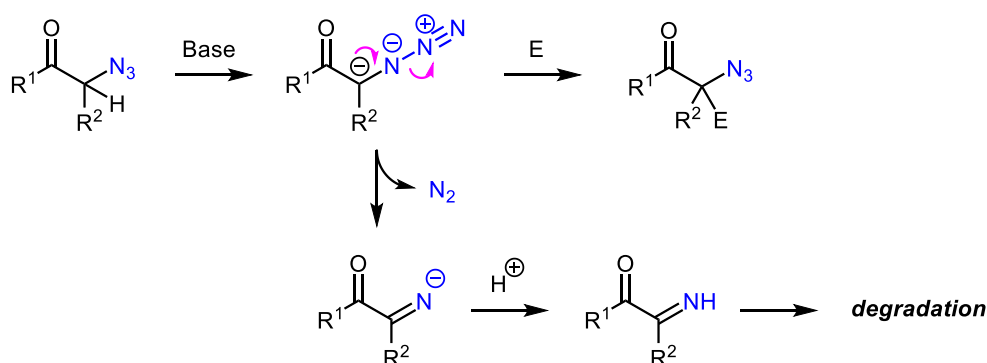


Scheme 1-29. Site-selective sequential ligation

上述したように、1 級および 2 級アルキルアジド間における位置選択的な変換反応は未だ例が少なく、非常に困難である。しかし、1 段階で一挙にアジドを導入可能な 1 級、2 級アルキルアジドを併せ持つマルチアルキルアジド化合物での位置選択的な変換反応の開発は、合成の簡便性、および有用性から次世代プラットフォーム分子の創出において非常に重要な分子変換技術であると言える。

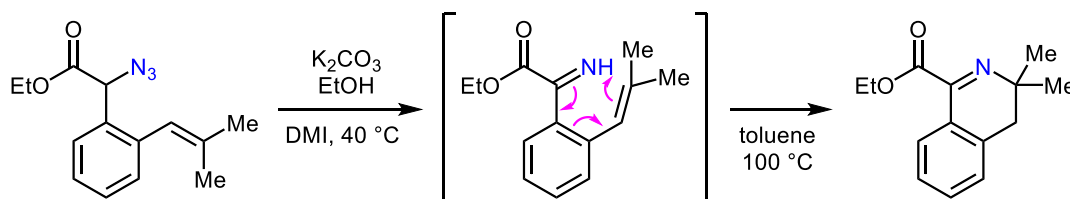
1-4 カルボニル隣接アジドの反応と性質

カルボニル基が隣接した α -アジドカルボニル種は、アジドがアミン保護基として利用できる性質から、 α -アミノ- β -ヒドロキシカルボン酸などの天然物に多く見られる α -アミノカルボニル構造を構築する上で有用な前駆体として利用されている。しかし、他のアルキルアジド類とは異なり、カルボニル隣接アジドは塩基性条件下で脱窒素を起こして不安定イミンへと変換されて分解することが報告されており (Scheme 1-30)⁴³⁾、 α -アミノ- β -ヒドロキシカルボン酸を合成する反応などでは「いかにアジドを分解させずに反応させるか」が重要視されている。



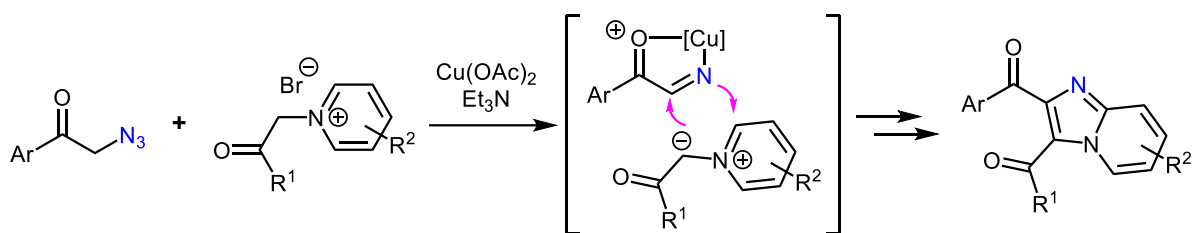
Scheme 1-30. Reactivity of α -azido carbonyl compounds

一方、最近では脱窒素後の不安定イミン中間体を利用する反応も報告されている⁴⁴⁾。例えば、千葉らは α -アジドエステルを塩基性条件下で加熱すると、分子内のアルケン部位と環化反応が進行したイソキノリン生成物が得られることを報告している (Scheme 1-31)^{44b)}。しかし、高温条件下でイミン中間体を利用することから、反応は生じるイミンが安定に存在できる芳香環に挟まれたアジド基質に限定される。



Scheme 1-31. 6π -electrocyclization of imine intermediate

また、Maurya らは銅を添加することで α -アジドケトンにイミニル銅中間体へと変換すれば、特殊な 1,3 双極子との反応のみではあるが形式的分子間 [3+2] 環化反応が行えることを報告している (Scheme 1-32)^{44d)}。

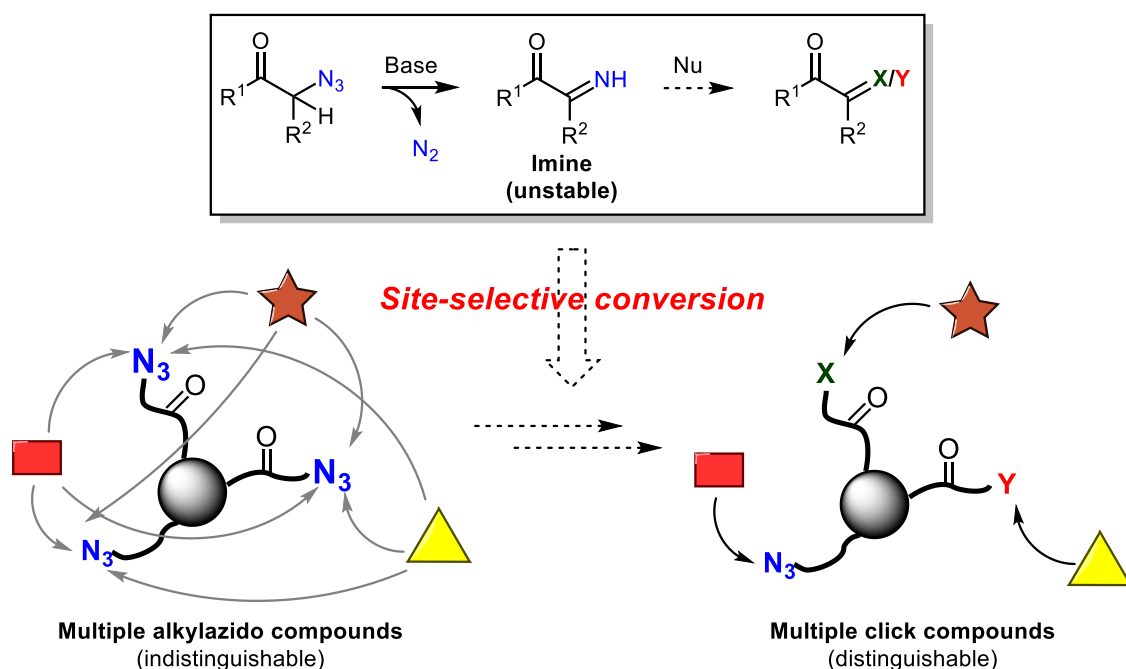


Scheme 1-32. [3+2] cycloaddition of iminyl copper intermediates

同様に、塩基性条件下でイミンを形成するアジドとして、ベンジルアジドについても報告されているが⁴⁵⁾、不安定中間体であるイミンを活用する例は極めて限定的である。

上述の通り、アルキルアジド間の区別は現在でも非常に困難であり、その位置選択的変換法の開発は重要な課題である。このような背景の下、アルキルアジドの中でも特異的な反応性を示すカルボニル隣接アジドの性質は非常に興味深い。

そこで本研究では、カルボニル隣接アジドが塩基性条件下で不安定なイミンへと変換される性質を利用し、マルチアルキルアジド化合物の中からカルボニル隣接位アジド選択的に異なる反応性を有するクリック官能基へと変換する反応を開発することで、合成が容易でありながら区別が困難であったマルチアルキルアジドから区別可能なマルチクリックプラットフォーム分子を創出することを目的とした(Scheme 1-33)。以下、第2章では位置選択的なジアゾ化法の条件探索と種々の基質への適用を行い、第3章では変換反応をオキシム化法へと拡張すると共に基質適用範囲の調査を行い、第4章では開発した反応を利用してプラットフォーム分子を創出し、その位置選択的な連結法について述べ、最後に本論文を総括する。



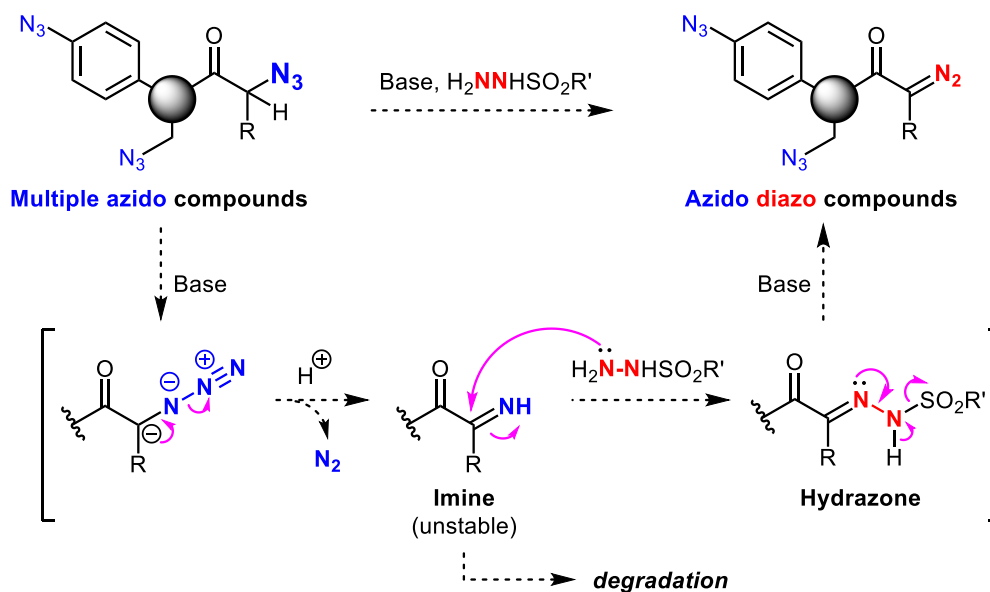
Scheme 1-33. Site-selective conversion of azido groups at carbonyl α -positions

第2章 カルボニル隣接アジド選択的ジアゾ化法の開発

2-1 モデル基質による反応の検討

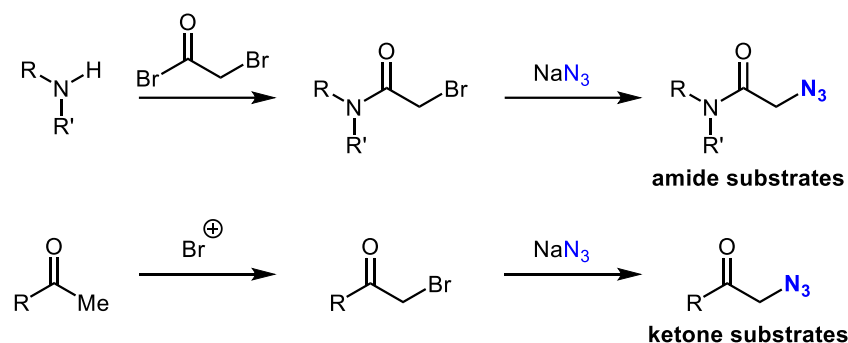
第1章で述べた通り、マルチアジド化合物におけるアジド基の位置選択的な変換反応は、その有用性に反して未開拓な部分が多く、特にアルキルアジドの区別は未だ困難である。しかし、その導入の容易さを考慮すると位置選択的な変換法の開発は簡便に利用可能なプラットフォーム分子の創出へ向けた重要な課題と言える。そこで、カルボニル隣接アジドの特異性を利用すれば、マルチアジドの中からカルボニル隣接位のみを選択的に別官能基へと変換できると考えた。特に、アジドとは異なる反応性を有するクリック官能基へと変換できれば、アジドとクリック官能基を併せ持つプラットフォーム分子へと容易に誘導できるようになる。

そこで本章では、カルボニル隣接アジドの性質を利用した位置選択的なジアゾ基への変換法の開発を行った。すなわち、塩基性条件下でカルボニル隣接アジドのみをイミンへと変換した後、求核剤としてヒドラジドを作用させ、縮合反応によってスルホニルヒドラゾンへと誘導する。スルホニルヒドラゾンは塩基性条件下で分解し⁴⁶⁾、ジアゾへと変換されることから、アジドの位置選択的なジアゾ化が可能と考えた(Scheme 2-1)。こうして得られるジアゾ基は C-H 挿入反応やシクロプロパン合成、高分子合成などにも利用できる有用な官能基であり⁴⁷⁾、アジドと区別して連結反応が行える²¹⁾ことから、次世代プラットフォーム分子創出への応用に適した官能基と言える。



Scheme 2-1. Site-selective conversion strategy

実際に位置選択的ジアゾ化を行う上で、イミン中間体が不安定であることに起因した大きな問題が2点考えられた。第一に、ヒドラジドは求核能力が低く⁴⁸⁾、ヒドラゾンの形成には通常、高温条件や長時間の攪拌が必要である。第二に、スルホニルヒドラゾンの分解反応には強塩基性条件か高温条件に付す必要がある。そこで、アジド基を1つ有するモノアジド化合物をモデル基質として、本反応の検討を始めることとした。尚、本研究で用いたアジド基質の一般的合成法を示した(Scheme 2-2)。アミド基質の場合はアミンと bromoacetyl bromide との反応でブロモ体へと誘導した後、NaN₃ でアジド化することで合成し、ケトン基質はアセチル部のブロモ化によって合成したブロモ体、もしくは市販のブロモ体をアジド化することで合成した。

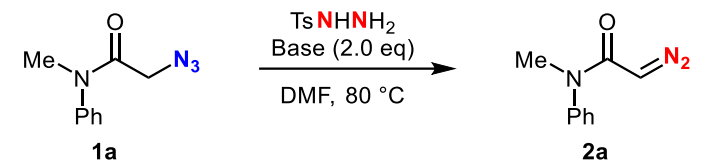


Scheme 2-2. Preparation of azido substrates

モデル反応の設計にあたり、カルボニル α 位水素原子の酸性度の低さから、脱窒素反応の進行にカルボニル類の中で最も強い塩基が必要と予想されるアミド体 **1a** を基質として検討を開始した(Table 2-1)。条件検討に際し、同様の脱窒素反応を鍵とする千葉らの報告⁴⁹⁾に用いられていた DMF を溶媒とし、TsNHNH₂ 存在下、種々の塩基を加えて加熱する条件を試みた。

まず K₂CO₃ を塩基として 24 時間加熱攪拌したところ、目的とするジアゾ生成物 **2a** を 51% の収率で得た(entry 1)。この際、その他の副生成物は確認できなかったことから、イミン中間体の分解によって収率が中程度に留まったと考えられる。続いて他の無機塩基についても検討したが、収率の向上は見られなかった。そこで、有機塩基である *i*Pr₂NEt を用いたところ、収率は向上したが(entry 2)、3 級アミン類ではこれ以上の収率の向上は見られなかった。さらに検討を進めた結果、2 級アミン類を用いることで収率良く反応が進行し、morpholine では 88% の収率で目的物が得られた(entries 3-6)。これは K₂CO₃ のような強塩基(pK_a = 10.33 in H₂O)に比べ、morpholine のような弱い塩基(pK_a = 8.36 in H₂O)はイミン中間体の分解を促進しなかったためと考えられる。しかし、求核性やその他の要因も収率に影響を与えていると予想でき、塩基性だけが収率をコントロールしているわけではないと考えられる。

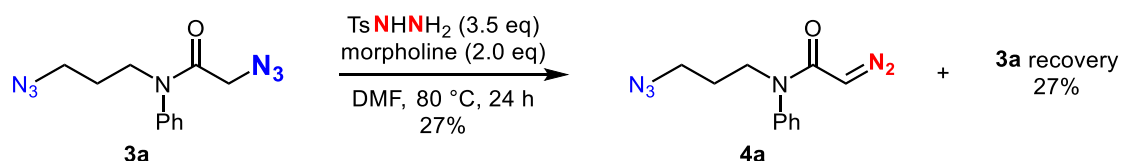
Table 2-1. Screening of reaction conditions for conversion from azido to diazo group



Entry	TsNHNH ₂ (eq)	Base	Time (h)	Yield (%)
1 ^a	3.0	K ₂ CO ₃	24	51
2	3.0	<i>t</i> -Pr ₂ NEt	27	59
3	3.0	pyrrolidine	26	52
4	3.0	Et ₂ NH	29	74
5	3.5	Et ₂ NH	24	76
6	3.5	morpholine	24	88

^a1.0 eq of base.

得られた entry 6 の条件を、アジドを 2 つ有するジアジド基質 **3a** へと適用した (Scheme 2-3)。しかし、原料は完全には消失せず、目的とするアジド-ジアゾ化合物 **4a** は 27%しか得られなかった。また、単離可能な副生成物も確認されなかったことから、基質および生成物のどちらかで分解が進行していると考え、加熱条件はマルチアジド化合物に適していないと判断した。そこで、より温和な条件での変換を検討することとした。



Scheme 2-3. Application to diazido compound

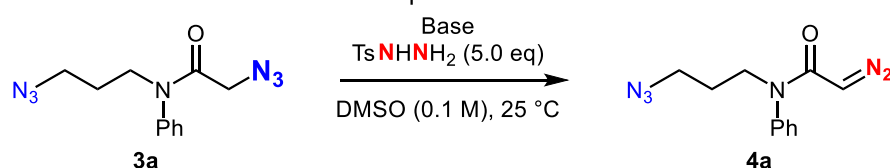
2-2 反応条件の検討

先の結果を受け、ジアジド **3a** を基質として再度条件探索を行うことにした。条件検討に際して、熱による分解を避け、不安定なイミン中間体へのヒドラジドの縮合反応を効率よく進行させるため、室温条件下、極性溶媒の DMSO を溶媒とすることで溶媒和による求核反応の促進を狙い、TsNHNH₂ を 5 当量用いる条件下、塩基の検討から開始した (Table 2-2)。

まず、*t*-BuOK で検討したところ、望みのアジド-ジアゾ生成物 **4a** を 56% の収率で得られた (entry 1)。しかし、アミドの加水分解物が副生成物として確認されたことに加えて、*t*-BuOK の条件ではベンジルアジドなども脱窒素反応が進行することが報告されている⁴⁵⁾ことから、より塩基性の弱い試薬を探索

することにした。そこで TBAF を塩基として⁵⁰⁾用いたところ副生成物は確認されず、entry 1 と同程度の収率で目的物が得られた(entry 2)。これはモノアジドの検討と同様、室温下においてもイミン中間体の分解が主な原因で収率が中程度に留まったと考えられる。そこで、イミン中間体の分解を避ける目的で TBAF より塩基性の低い DBU、TMG についても検討したが、反応は進行しなかったため(entries 3 and 4)、TBAF を塩基として用いることにした。続いて、DMSO や TBAF 試薬に含まれる微量の水の効果について検討したが、三水合物では水が過剰に存在するためか収率が低下し、微量の水を除去、もしくは添加した程度では収率に影響がないことを確認した(entries 5-7)。このことから、溶媒や試薬に含まれる微量の水は反応に大きく関与していないと判断した。

Table 2-2. Optimization of bases



Entry	Base	Time (h)	Yield (%)
1	^t BuOK (2.5 eq)	1	56
2	TBAF (5.0 eq)	2	58
3	DBU (5.0 eq)	48	0 ^a
4	TMG (5.0 eq)	48	0 ^a
5	TBAF·3H ₂ O (5.0 eq)	2	50
6	TBAF ^b (5.0 eq)	2	58
7 ^c	TBAF (5.0 eq)	2	59

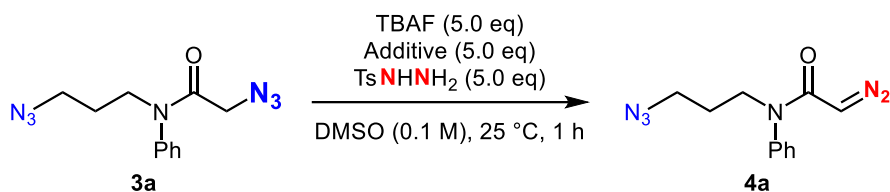
^aNo reaction. ^bTBAF was dried by molecular sieve.

^cWith H₂O (1.0 eq)

更なる収率向上を目指し検討を進めた結果、第 2 の塩基を加えることが効果的であることを見出したため、添加する第 2 塩基について調査した(Table 2-3)。添加した Et₃N (entry 1)から TMG (entry 5)までそれぞれの pK_a (in DMSO) は上から順に 9.1、9.2、10.9、11.1、13.6 となっており、塩基性の強さは収率に相関していないが、いずれも TBAF (pK_a = 15 in DMSO)よりも塩基性が低い。このことから、ヒドラゾン中間体の N-H 水素を引き抜く塩基は TBAF よりも弱い塩基性が適していたと考えられる。つまり、TBAF は反応で生じるアンモニウムカチオン種やスルフィン酸などの強酸性種を主にトラップし、第 2 の塩基がヒドラゾンの N-H 水素のような弱酸性種に作用したと考えた。続いて第 2 塩基の中で最も効果的であった pyrrolidine に関して調査を進めたところ、窒素原子にメチル基が存在すると収率が低下し(entry 6)、pyrrolidine のみでは反応が進行しなかった(entry 7)。これらの結果から、第 2 の塩基はイミン中間体形成以降に働いており、ヒドラゾンの N-H 水素引き抜きに加えて、求核能力の高い pyrrolidine が不安定イミンと反応して活性イ

ミニウム中間体を介することで、求核能力の低いヒドラジドの反応を補助する役割も重要であったと考えられる⁵¹⁾。

Table 2-3. Optimization of additives

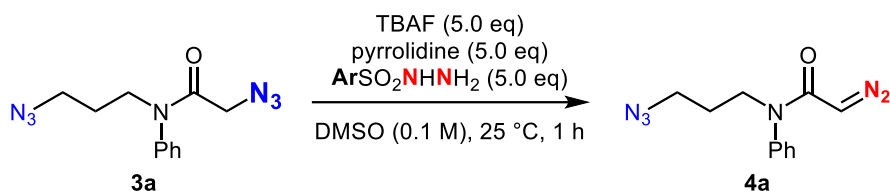


Entry	Additive	Yield (%)
1	Et ₃ N	72
2	morpholine	68
3	piperidine	71
4	pyrrolidine	77
5	TMG	73
6	<i>N</i> -methylpyrrolidine	66
7 ^a	pyrrolidine	0 ^b

^aTBAF was not added. ^bNo reaction.

続いてヒドラジドについても検討した(Table 2-4)。しかし、entries 2-4 ではヒドラジドが徐々に分解していく様子が TLC 分析によって確認され、entry 1 よりもアリールスルホニル基への電子供与性の高いメトキシ基を有するヒドラジド(entry 5)では若干の収率低下が見られた。これらの結果から、用いるヒドラジドには塩基性条件での分解に対する耐性⁵²⁾、およびヒドラゾン中間体から脱離するアリールスルホニル基の脱離能のバランスが重要であることがわかった。

Table 2-4. Optimization of sulfonylhydrazides

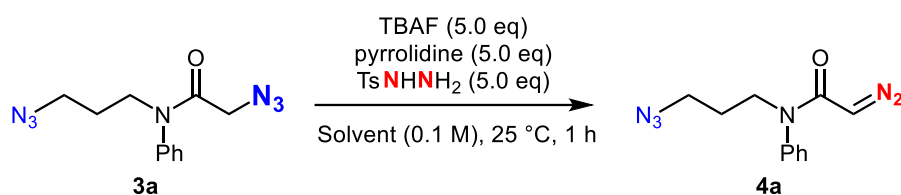


Entry	Ar	Yield (%)
1	4-methylbenzene	77
2	2,4,6-triisopropylbenzene	0 ^a
3	2,4,6-trimethylbenzene	28
4	2-nitrobenzene	0 ^a
5	4-methoxybenzene	71

^aNo reaction

溶媒条件も探索したが、非プロトン性の高極性溶媒以外では反応せず、DMSO 溶媒中で最も効率よく反応が進行した(Table 2-5)。このことから、不安定イミン中間体を捉えるため、求核剤の溶媒和によって求核能力を向上する DMSO が本反応には必須であると考えられる。

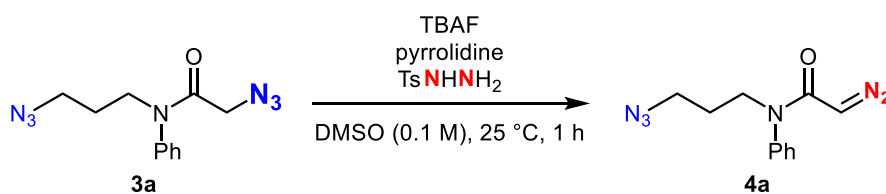
Table 2-5. Optimization of solvents



Entry	Solvent	Yield (%)
1	DMSO	77
2	DMF	55
3	THF	0 ^a
4	toluene	0 ^a
5	ethanol	0 ^b

^aObtained in trace amounts. ^bNo reaction.

続いて各試薬の当量について検討した(Table 2-6)。まず TBAF の当量を減じたところ、3.5 当量まで減らしても原料は消失し、同様の収率で目的物を得られることが判明した(entry 2)。そこで TBAF の当量を固定し、pyrrolidine の当量を変化させたところ、pyrrolidine は 5 当量から減らすと収率が低下することに加えて、当量を増やしても効果がないことが判明した(entries 3 and 4)。また TsNHNH₂ の当量についても調査したところ、5 当量から減らすと収率が低下した(entries 5 and 6)。そこで、再現性を得るため TBAF を 3.6 当量とし、0.2 M の濃度で反応させると収率 84%で **4a** が得られることがわかった(entry 7)。これはイミン中間体に対するヒドラジドの求核攻撃の頻度が向上したためだと考えられる。また、Entry 7 の条件は再現性に優れ、1.0 mmol スケールの反応でも 90%の収率で目的物を与えた。

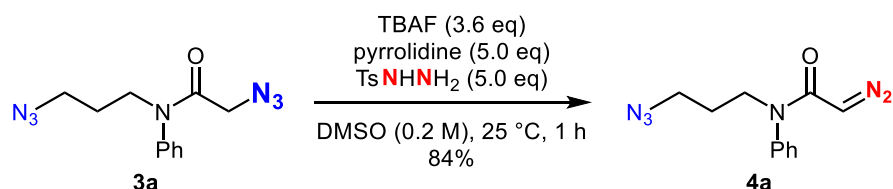
Table 2-6. Optimization of amount of reagents^a

Entry	TsNHNH ₂ (eq)	TBAF (eq)	pyrrolidine (eq)	Yield (%)
1	5.0	5.0	5.0	77
2	5.0	3.5	5.0	77
3	5.0	3.5	3.5	71
4	5.0	3.5	7.0	76
5	2.0	3.5	5.0	54
6	4.0	3.5	5.0	74
7 ^b	5.0	3.6	5.0	84 (90) ^c

^a0.1 mmol of **3a**. ^b0.2 M in DMSO. ^c1.0 mmol scale reaction.

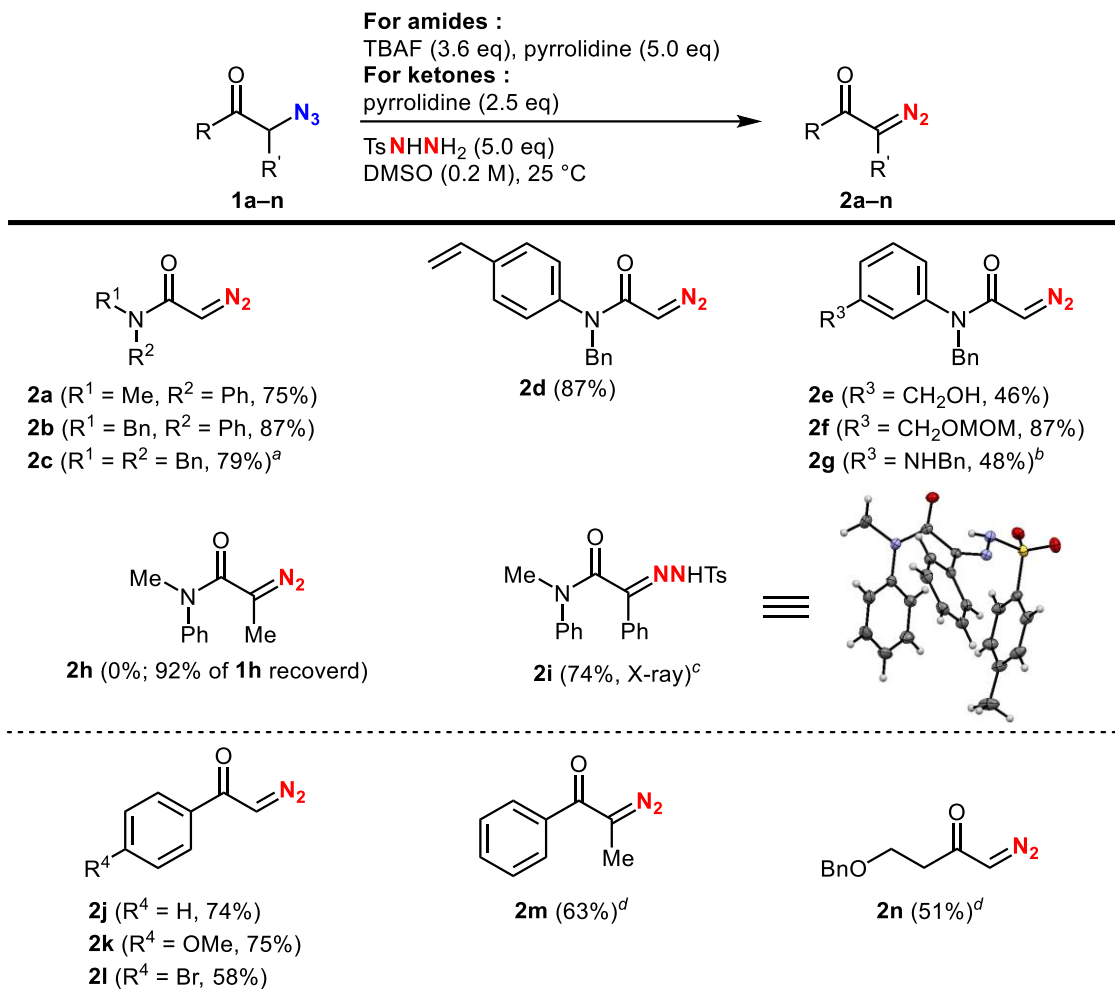
2-3 モノアジド基質

次に、先の検討で最適条件を見出したことから(Scheme 2-4)、基質適用範囲について検証することとした。



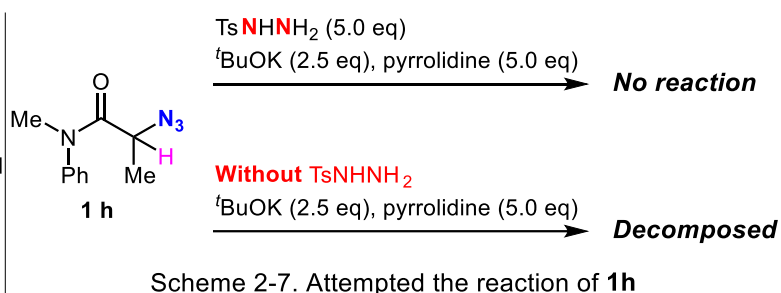
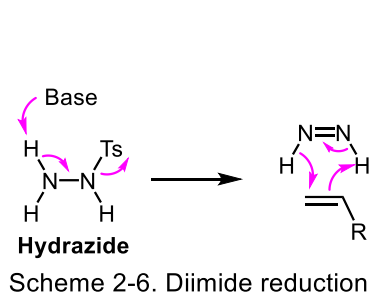
Scheme 2-4. Reaction of site-selective conversion of azido to diazo group

本反応は温和な条件下 1 段階でジアゾを与える新規ジアゾ化法としても興味深いため、まずは種々のモノアジド体について検討した(Scheme 2-5)。1a-c のアミド窒素上の置換基は反応に大きく影響せず、ジアゾ体 2a-c を収率よく与えた。続いてビニル基を有する 1d を検証したところ、2d が 87% の収率で得られた。この際、ビニル基の還元体は確認されず、アルケンを還元可能なジイミド⁵²⁾が本条件では生成していないと考えられる(Scheme 2-6)。続く水酸基を有する 1e では収率が中程度に留まった。原料は完全に消費されたことから、無保護の水酸基が求核能力の低いヒドラジド⁴⁸⁾の縮合反応を阻害したと考えた。そこで、水酸基を MOM 化した 1f で検討したところ、87% の収率で 2f が得られた。アミノ基を有する 1g についても検討したが、2e と同程度の収率となった。続いて 2 級アルキルアジドについて検討したところ、反応は進行せず 1h が 92% で原料回収となった。これはアミド α 位水素原子の酸性度が 1 級アルキルアジドよりも低下したためと考え、^tBuOK を用いて検討を行ったが同様に原料回収となった(Scheme 2-7)。更なる検討の結果、TsNHNH₂ 非存在下で原料の分解を確認でき、1h のようなアミド隣接 2 級アルキルアジドの α 位水素原子はヒドラジドの N-H 水素よりも酸性度が低いと考えられた。一方、フェニル基をアミド α 位炭素原子上に有する 1i は 1h と同じく 2 級アルキルアジドではあるものの、アジド置換炭素上の水素がベンジル位にも相当することで酸性度が高いため反応が進行した。しかし、反応終了後の処理でヒドラゾンが加水分解され、α-ケトアミドの生成が確認された。そこで、重曹水で処理したところ、加水分解が抑制されて収率よくヒドラゾン体 2i が得られた。2i はフェニル基によってヒドラゾンが安定化しており、2i を別途塩基性条件に付してもジアゾ化は進行しなかった。また、2i は X 線結晶構造解析によりその化学構造を確認した。



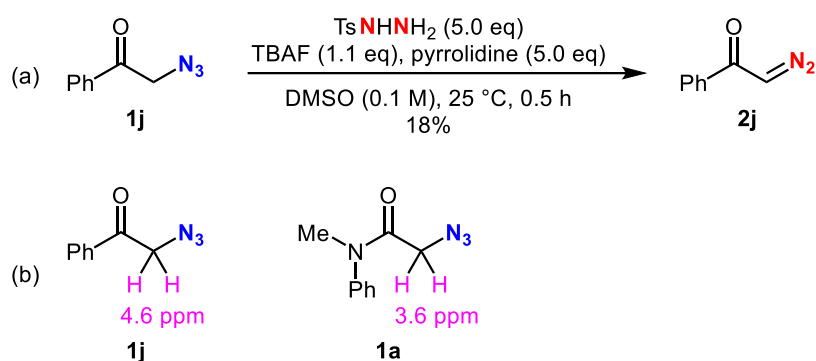
^a4.4 eq of TBAF. ^b5.0 eq of TBAF. ^cWithout pyrrolidine. ^d0.1 M in DMSO.

Scheme 2-5. Scope of monoazido substrates from azides to diazo compounds

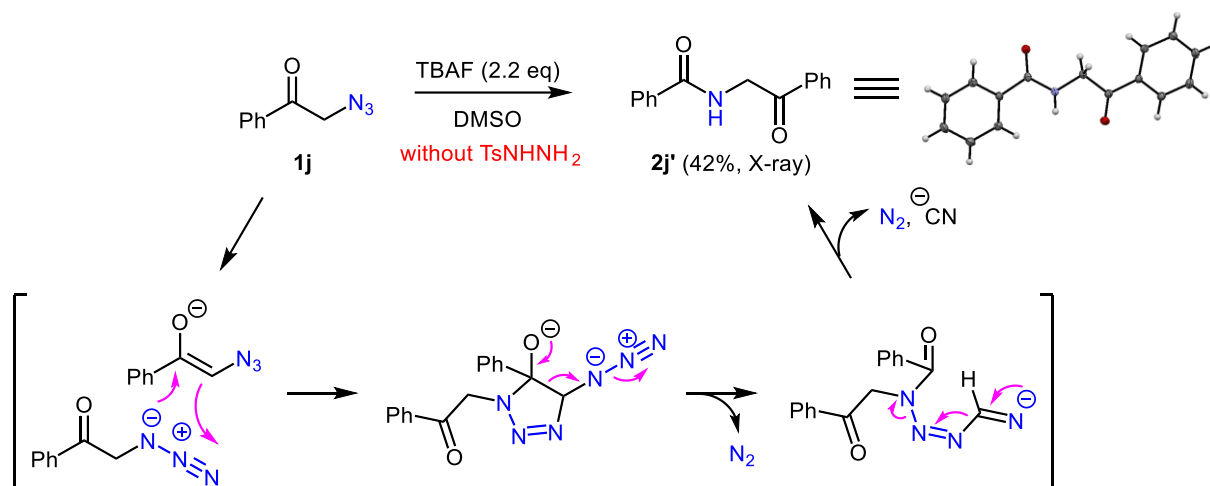


次に、ケトン隣接アジド **1j** についても同様に検討を開始したが、TBAF と pyrrolidine の混合条件では低収率となった (Scheme 2-8a)。これは両化合物の ¹H-NMR の比較から、ケトン隣接位水素 (**1j**; 4.6 ppm) がアミド隣接位水素 (**1a**; 3.6 ppm) よりも高い酸性度を有していると考えられることから (Scheme 2-8b)、ケトンの場合では TBAF はその強い塩基性のため適さないと考えた。また、調査の過程で、求核剤を添加せずに反応を行うと 2 量体 **2j'** が得られることがわかった (Scheme 2-9)。これはアミド基質よりも安定に存在できるエノレートがアジドと [3+2] 環化を起こし、窒素とシアニドを脱離することで生

成していると考えられる^{44b, 53})。この副反応が1つの原因として、ケトン基質の変換ではアミド基質よりも収率が低下したと考えた。そこで再度適切な塩基の検討を行った結果、pyrrolidineのみを用いると収率74%で目的の**2j**が得られた。以上の結果から、ケトンの基質に対してはpyrrolidineのみを用いた反応条件を適用することとした。続いて芳香環 *para* 位に置換基を持つ**1k**、**1l**で反応を行ったところ、それぞれ75%、58%の収率で目的物を与えた。2級アルキルアジドの反応においてアミド隣接アジドでは反応が進行しなかったが、カルボニル α 位水素の酸性度が向上するケトン**1m**では目的の変換が進行し、収率63%で**2m**が得られた。また、ベンジルオキシ基の β 脱離の可能性を有するジアルキルケトン**1n**についても、**2n**を51%の収率で得ることに成功した。

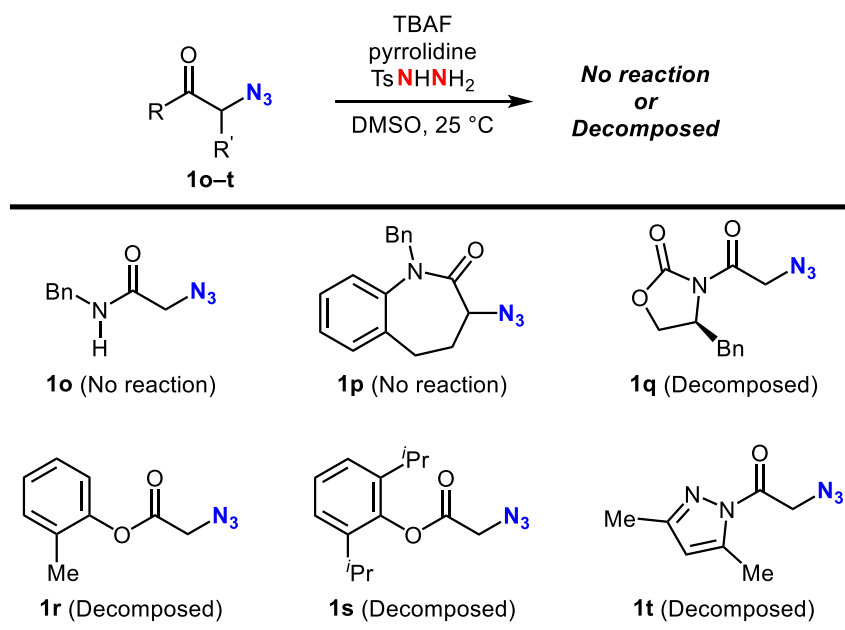


Scheme 2-8. Attempted the reaction of **1j**



Scheme 2-9. Dimerization of **1j** via [3+2] cycloaddition

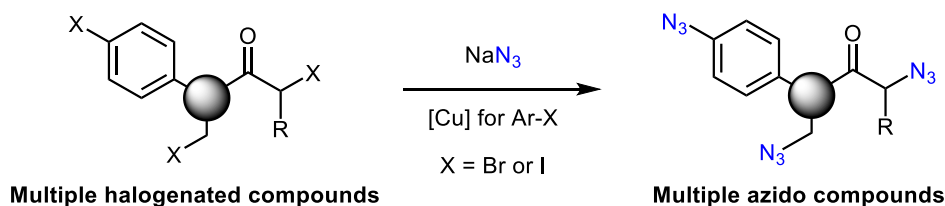
次に、検討したものの良好な結果が得られなかった基質について示した(Scheme 2-10)。2級アミド**1o**や環状2級アジド**1p**では反応が進行しなかった。また、オキサゾリジノン**1q**、エステル**1r**、**1s**やピラゾール**1t**などは加水分解が進行し、対応するアミンやアルコールが確認された。以上の結果から、2級アミドやエステル構造などは本反応条件には適さないと判断した。



Scheme 2-10. Limitation of azido substrates

2-4 マルチアジド基質

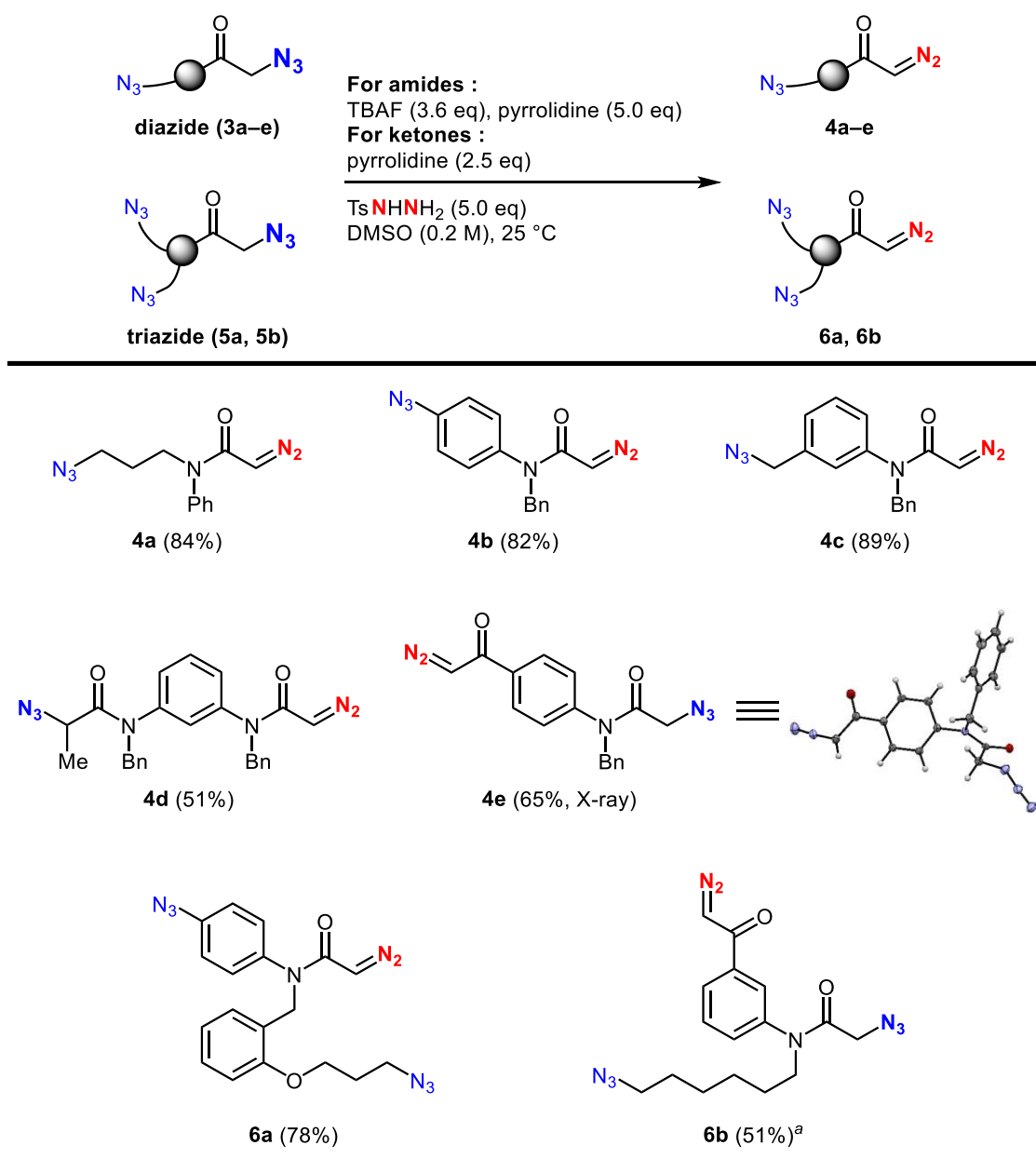
モノアジド基質で得られた基質適用範囲を考慮し、次に複数のアジド基を持つマルチアジド基質について、位置選択的なジアゾ化の検討を行った (Scheme 2-12)。なお、用いたマルチアジドについては、先述した導入の容易さを示すためマルチハロゲン化体に対して一挙にアジドを導入することで合成した (Scheme 2-11)。



Scheme 2-11. Preparation of multiple azido compounds via azidation at once

アリールアジドを有するジアジド **3b** は、**3a** と同様に活性水素がアミド隣接アジドにしか存在しないため位置選択的に反応が進行し、目的のアジド-ジアゾ化合物 **4b** が 82% の収率で得られた。本条件は強塩基で脱窒素が進行するベンジルアジド部位⁴⁵⁾存在下においても、TBAF の持つ塩基性がベンジルアジドの活性水素を引き抜く程強くはないため、**3c** の高位置選択的な反応が進行し、89% の収率でカルボニル隣接位のみジアゾへと変換された **4c** を与えた。本条件はカルボニル隣接位水素原子の酸性度を鍵とし、アミドに隣

接した 1 級および 2 級アルキルアジドを有するジアジド **3d** においても、1 級アルキルアジド選択的に反応が進行した。この際、2 級アルキルアジド部が変換された化合物は観察されず、主にアミドの加水分解物が副生成物として生じた。また、pyrrolidine のみを塩基に用いる条件であれば、アミド隣接アジド存在下ケトン隣接位のみを変換することが可能で、**3e** を位置選択的に変換した **4e** を 65% の収率で得られた。生成物 **4e** は X 線結晶構造解析にてその構造を決定した。



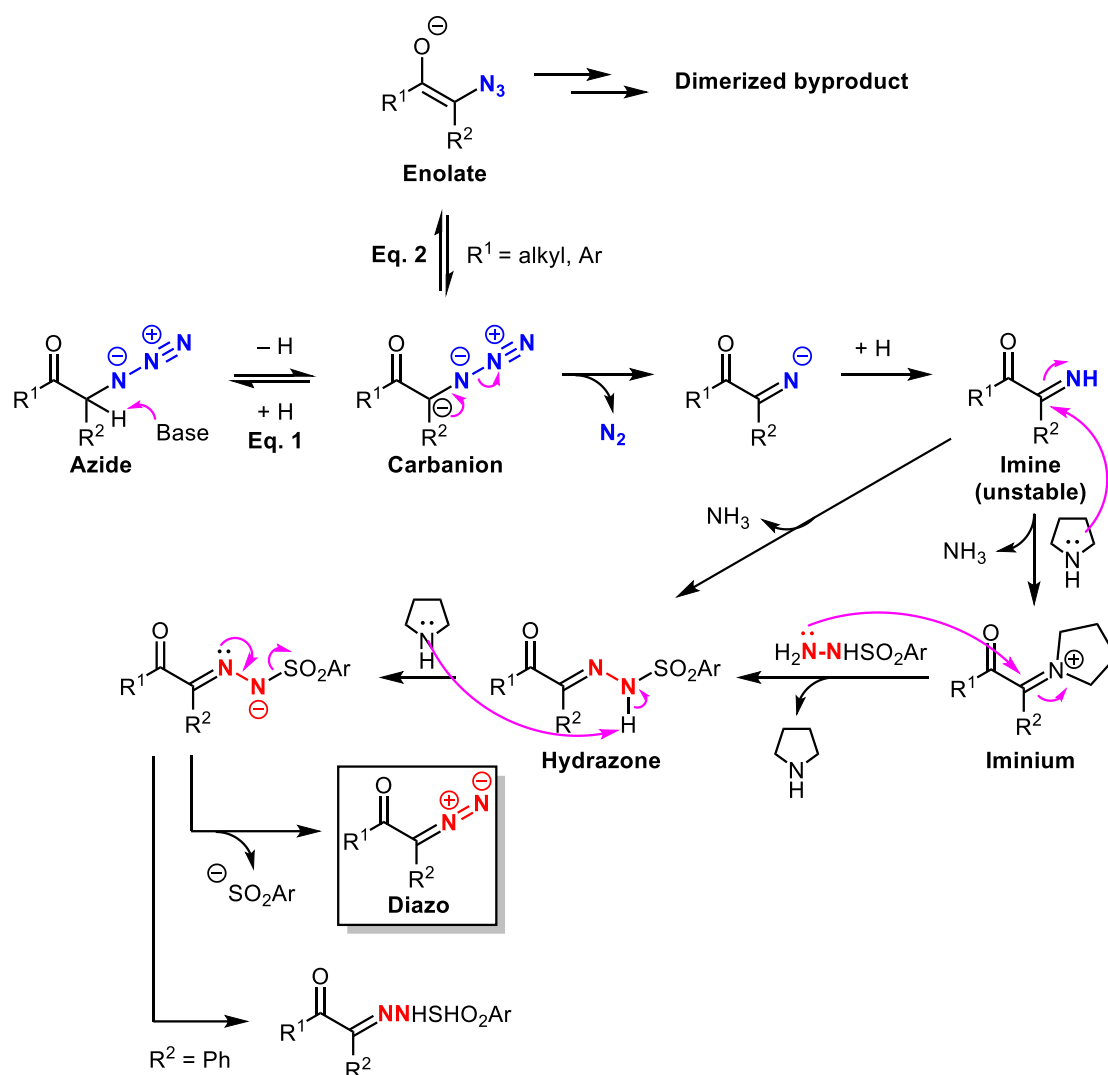
^a0.1 M in DMSO

Scheme 2-12. Site-selective conversion to diazo group of di- and triazido substrates

続いて、さらにアジド基を増やし、3つのアジド基を持つトリアジド基質について検討した。アリールアジドと2つのアルキルアジドを併せ持つトリアジド基質 **5a** では、カルボニル隣接位のみジアゾ化されたジアジド-ジアゾ

化合物 **6a** が 78% の収率で得られた。これは、化合物 **5a** 中のビスアルキルアジド部位はもともとクリック反応において区別が困難であったが、本変換によってアリールアジド、アルキルアジド、およびジアゾの反応性が異なる 3 種のクリック官能基を併せ持つ有用な化合物へと変換できたことを示す。また、SPAAC 反応においてすべてのアジド基が同じ速度で反応してしまう⁵⁴⁾ トリスアルキルアジド化合物 **5b** をケトン選択的な pyrrolidine のみの条件に付すことで、ケトン隣接位のみがジアゾへと変換されたジアジド-ジアゾ化合物 **6b** が 51% の収率で得られた。この際、その他の部位が変換された生成物は確認されなかったことから、先述した 2 量化反応などが副反応として進行することで中程度の収率であったと考えられた。

以上の検討から、予想される反応機構について考察する (Scheme 2-13)。本反応条件での過剰の塩基はカルボニル α 位水素の引き抜き時に生じる平衡状態をカルバニオンへと偏らせるためだと考えられる (Eq. 1)。こうして生じたアニオン種は基質によってエノレート状態が安定して存在するため、副反応として 2 量化が進行する。一方、不安定なアニオン種は脱窒素を促し、イミン中間体を生成する。この不安定イミン中間体はヒドラジドによって補足されるか、pyrrolidine によって捕捉されて活性イミニウム中間体を經由することでヒドラジドの縮合反応を促進し、スルホニルヒドラゾン形成する。生じたスルホニルヒドラゾンの N-H 水素は過剰量の pyrrolidine によって引き抜かれ、窒素アニオンが生成する。このアニオン種がフェニル基等で安定化されるとヒドラゾンとして生成物が得られるが、通常は不安定なため脱スルフィン酸による分解反応が進行してジアゾへと変換される。



Scheme 2-13. Possible reaction mechanism

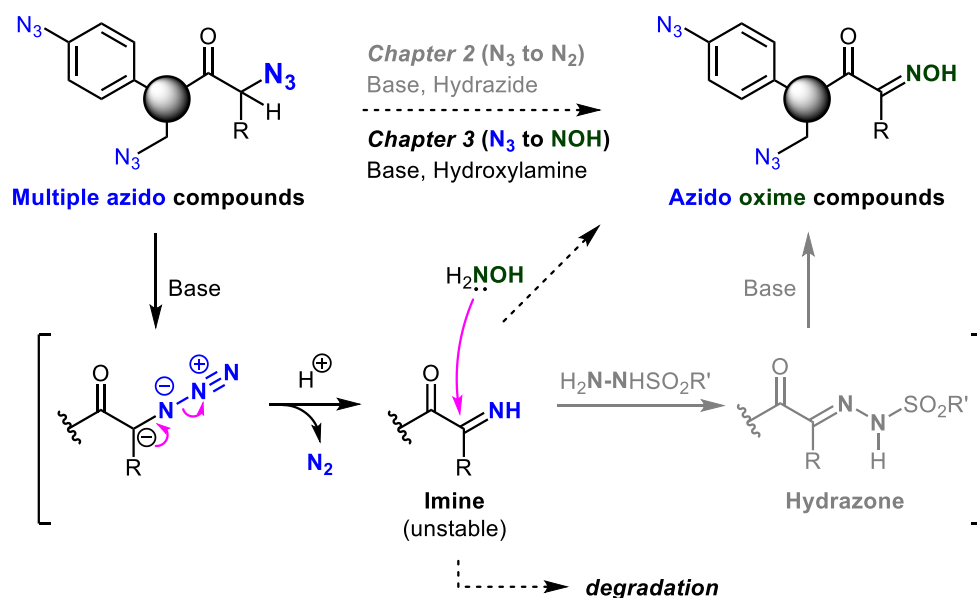
以上本章では、温和な条件下でカルボニル隣接アジドをジアゾへと変換する新たな反応を開発した。本反応は Raines らが報告しているホスフィン試薬を用いたアジド基からジアゾ基への変換法¹⁰⁾とは異なり、カルボニル隣接位活性水素の引き抜きによって起こるアジドの脱窒素を鍵反応とするため、不安定ジアゾを生じうるアリールアジドやアルキルアジドは反応せずに保持することができた。また、活性水素原子の酸性度が鍵となっており、同じく活性水素を有するベンジルアジドやアミド隣接 2 級アルキルアジドも脱窒素を起こさずに保持された。更に、用いる塩基を変えることで、アミド隣接アジド存在下においても、ケトン隣接アジドのみを選択的に変換できた。これらの特性を利用することで、従来反応の区別が困難とされたトリスアルキルアジド化合物であっても、反応位置を制御したアジド基の変換が可能となった。

第3章 カルボニル隣接アジド選択的オキシム化法への 拡張

3-1 反応条件の検討

第2章において、マルチアジド化合物におけるカルボニル隣接アジド選択的なジアゾ化法を確立した。本反応はカルボニル隣接アジドの脱窒素によって生成した不安定なイミン中間体を活用し、求核剤であるヒドラジドとの縮合反応によるスルホニルヒドラゾンの形成とその分解にて進行する。そこで中間体であるイミンに対する求核剤を変更すれば、様々なクリック官能基への変換が可能となり、より多様なプラットフォーム分子の創出につながると考えた。

本章では、位置選択的官能基変換法を拡張するため、ヒドロキシルアミンを求核剤としたカルボニル隣接アジド選択的なオキシム化法を検討することにした(Scheme 3-1)。オキシムは1,3-双極子として知られるニトリルオキシドやニトロンなどへの変換が容易であり、アジドと区別可能な連結官能基として利用できることから^{32a)}プラットフォーム分子創出への応用に適していると言える。特に、本反応によって合成できる α -オキシムカルボニル化合物は様々なヘテロ環合成に利用され⁵⁵⁾、中でもクリック官能基として近年注目されている1,2,4-トリアジンへも誘導できる⁵⁶⁾など有用性が高い。



Scheme 3-1. Site-selective conversion strategy of multiple azido compounds

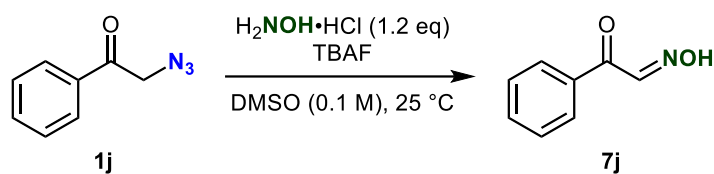
一方、オキシムへの変換を行う上で、ジアゾ化とは異なる問題点が浮上する。まず、アルドキシムは安定性に乏しいことである⁵⁷⁾。また、イミン中間体と類似する 2-オキソアルデヒド構造へのヒドロキシルアミンの縮合反応では、反応部位が制御できないという報告もある(Scheme 3-2)⁵⁸⁾。そこで、生成物の合成、および単離が困難と予想されるケトン体 **1j** を基質とし、反応条件を再度検討することとした(Table 3-1)



Scheme 3-2. Possible problem on regioselectivity of ketoxime synthesis

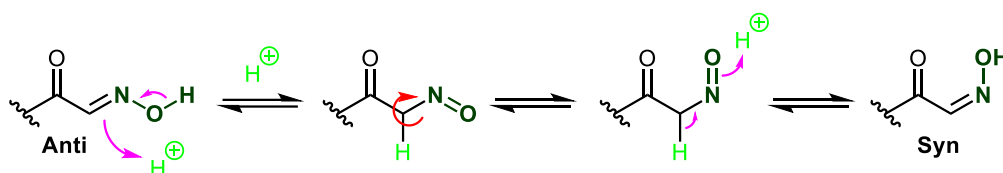
まず、ケトン類のジアゾ化で有効であった pyrrolidine を塩基とし、 $\text{H}_2\text{NOH}\cdot\text{HCl}$ によるオキシム化を行ったところ、60%の収率で目的のオキシム体 **7j** が単一異性体として得られた(entry 1)。この際、懸念していた反応点が異なる副生成物やジオキシム体(Scheme 3-2)は観察されなかった。これは、本反応ではアルデヒドよりも高い反応性を有するイミン部が存在するため、ヒドロキシルアミンの縮合反応は位置選択的に進行したと考えられる。また、生成物はアルミナを通した重クロロホルムで NMR 測定を行わない場合、オキシムの *syn-anti* 異性体の混合物として観測された。つまり、生成物であるオキシムは微量の酸が存在するだけで容易に異性化するため、幾何異性の判別は困難であると判断した(Scheme 3-3)。さらに、ジアゾ化の際と同様にその他の副生成物も確認されなかったことから、オキシム化においてもイミン中間体の分解が中程度の収率に留まった原因と考えられる。本反応はイミン中間体へのヒドロキシルアミンの縮合反応によって生成物が形成されるため、ジアゾ化法のようにヒドラゾンの N-H 水素の引き抜きに適した塩基を用いる必要がない。そこで、2章において脱窒素に適していた TBAF を用いたところ、entry 1 よりも若干ながら収率が向上した(entry 2)。続いて TBAF を塩基として、 $\text{H}_2\text{NOH}\cdot\text{HCl}$ の当量を増やしたところ収率が向上した(entry 3)。この収率向上には、 $\text{H}_2\text{NOH}\cdot\text{HCl}$ の増量が相対的に有効に働く TBAF の当量を減じたためと考え、 $\text{H}_2\text{NOH}\cdot\text{HCl}$ を当初の 1.2 当量のまま TBAF を減らし、entry 3 と同じ比率で行ったところ、狙い通り 76%の収率で **7j** が得られた(entry 4)。このことから $\text{H}_2\text{NOH}\cdot\text{HCl}$ の当量を固定し、TBAF の当量について検討を重ねたところ、1.8 当量の TBAF で原料が完全に消失し、80%の収率で目的物を与えた(entry 5)。更なる検討で TBAF の当量を下げると原料が残存したことや、ジアゾ化で有効であった 0.2 M の濃度では効果がなかったことから、entry 5 の条件を最適条件とした。

Table 3-1. Screening of azido to oxime group reaction



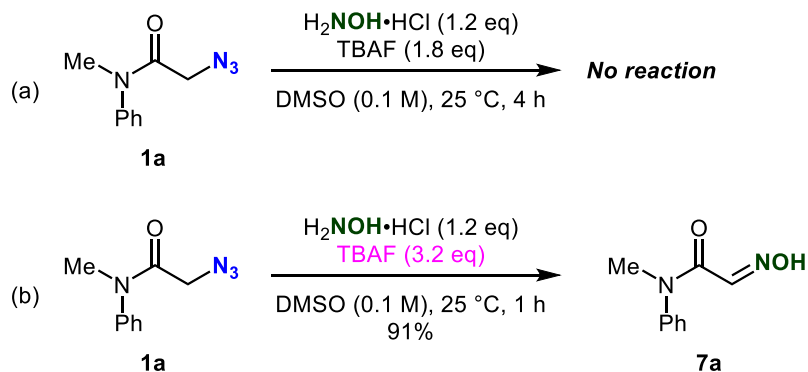
Entry	TBAF (eq)	Time (h)	Yield (%)
1 ^a	-	2	60
2	2.2	0.2	62
3 ^b	2.2	2	76
4	1.9	2	76
5	1.8	1	80

^aPyrrolidine (2.2 eq) as base. ^b1.5 eq of H₂NOH·HCl



Scheme 3-3. Oxime isomerization mechanism

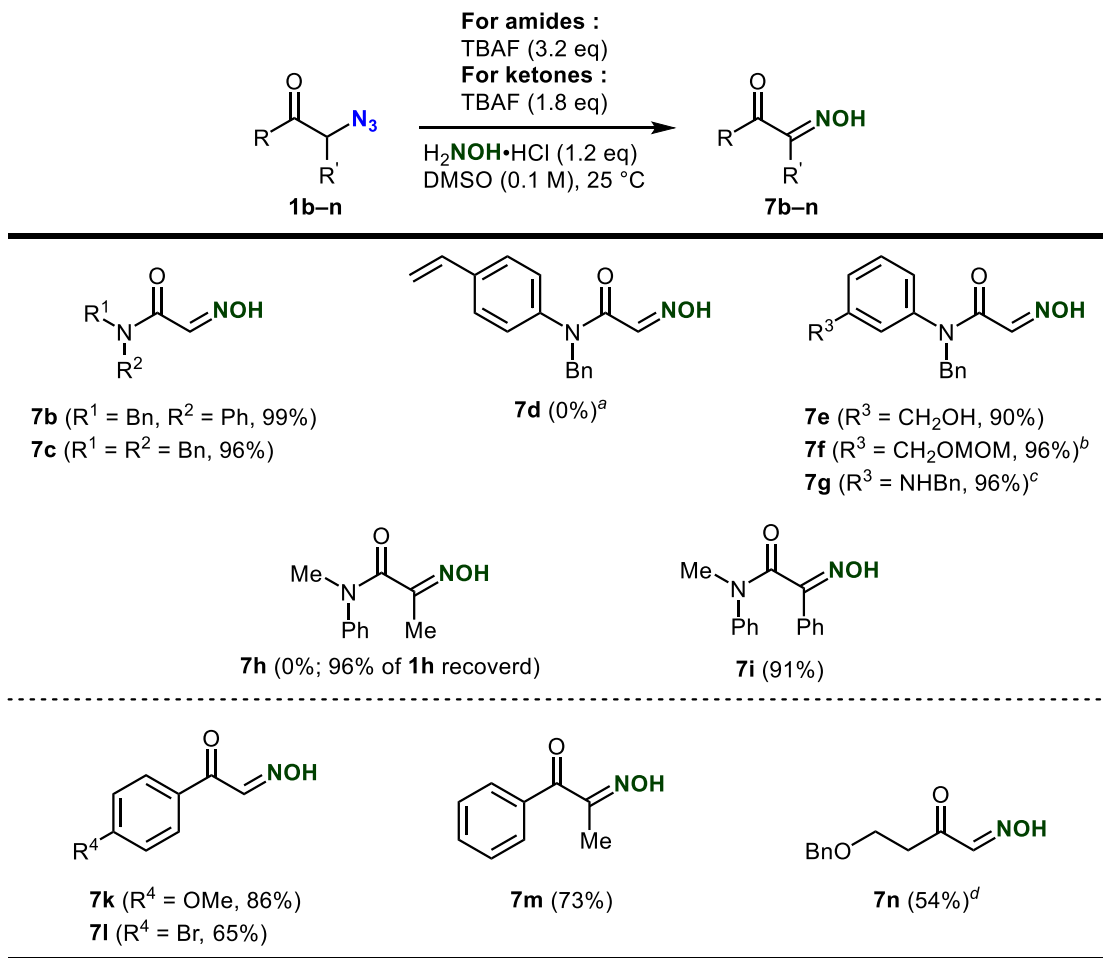
また、2章で述べた通り、本反応はカルボニル α 位水素原子の酸性度を鍵とするため、ケトン基質よりも酸性度が低いアミド基質 **1a** についても検討した。その結果、1.8 当量の TBAF では反応が進行せず、3.2 当量の TBAF で原料が消失し、目的物 **7a** を 91% で得られることがわかった (Scheme 3-4)。この結果から、TBAF の添加量を調整することで、アミド隣接アジド存在下におけるケトン隣接アジド選択的な変換が期待できた。



Scheme 3-4. Screening of azido to oxime group for amide substrate

3-2 モノアジド基質

ジアゾ化法と同様に、安定なアジドから 2-オキシオキシムを合成可能な新規オキシム化法としても興味深いため、種々のモノアジド体で検証を開始した(Scheme 3-5)。オキシム化においてもアミド窒素上の置換基は反応に大きく影響せず、**1b,1c** では目的の **7b, 7c** を収率よく与えた。続いてビニル基を有する **1d** について検討したところ、**7d** の生成を確認したが、微量の分離不可能な副生成物との混合物として得られた。ジアゾ化では中程度の収率にとどまった無保護水酸基を有する **1e** では、90%と高収率で **7e** が得られた。これはヒドロキシルアミンの求核能力がヒドラジドよりも優れている⁴⁸⁾からだと思われる。また、MOM 保護された **1f** やアミンを有する **1g** でも反応は良好に進行し、幾何異性体混合物として高収率で目的物 **7f, 7g** を与えた。この結果から、生成物によってはオキシムの幾何異性体混合物が生成すると判明したものの、この 2 例でしか確認されなかったため詳細な原因については不明であった。続く 2 級アルキルアジド **1h** はジアゾ化の際と同様に反応は進行せず、96%で原料回収となった。また、TBAF の当量を増やしても反応は進行せず、^tBuOK では原料は消費されたが目的物 **7h** は得られなかった。一方、アジド置換炭素にフェニル基を有する **1i** ではジアゾ化と同様に反応が進行し、**7i** を 91%の収率で与えた。次にケトン基質についても検討したところ、フェニル基 *para* 位に置換基を持つ **1k, 1l** に加えて、2 級アルキルアジド **1m** や置換基の β 脱離の可能性を有するジアルキルケトン **1n** についても良好な収率でオキシム体 **7k-n** が得られた。



^aInseparable mixture with unidentified byproduct.

^bProduct as geometric isomers (ratio = 4.9:1) was obtained.

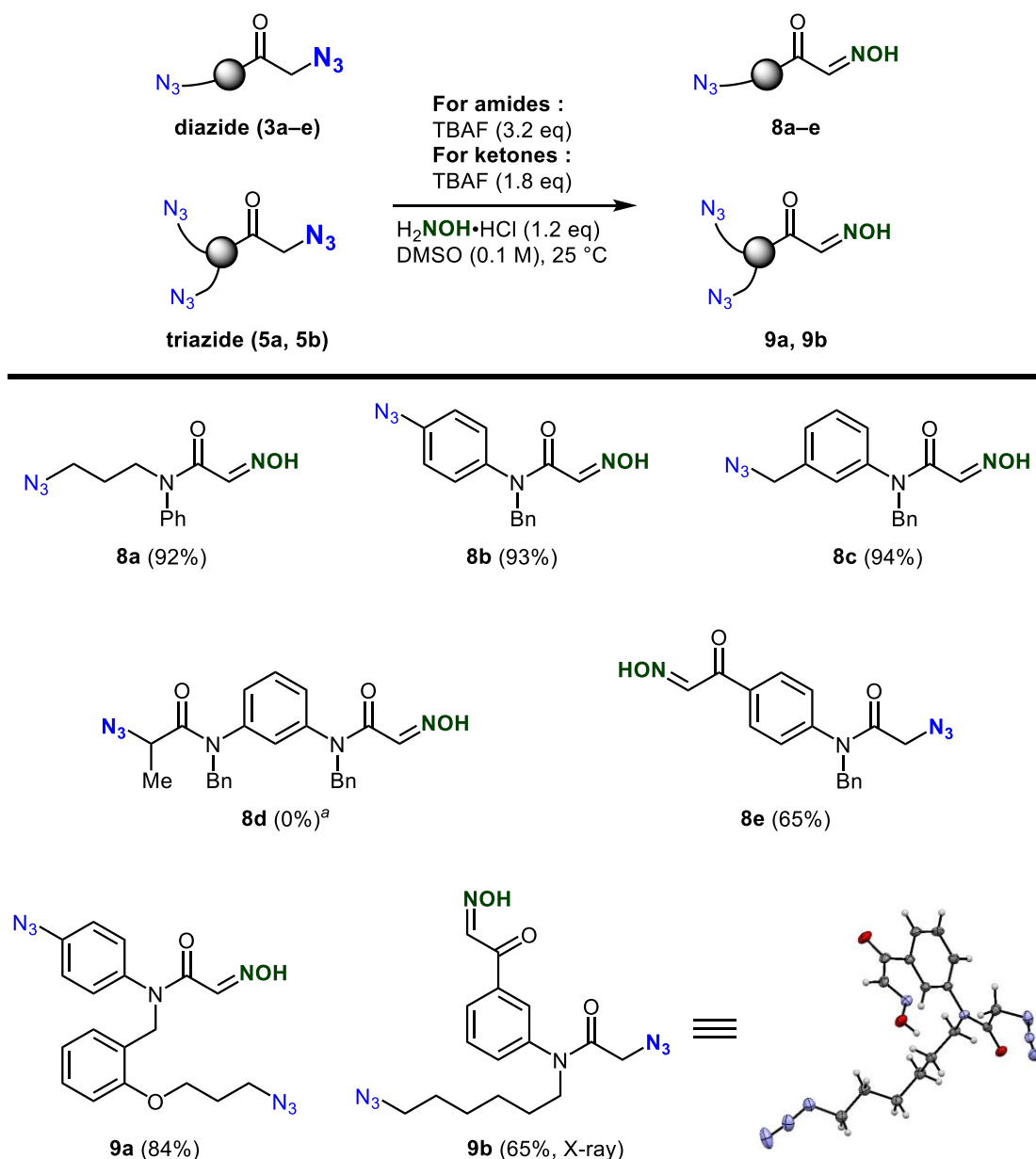
^cProduct as geometric isomers (ratio = 6.3:1) was obtained. ^d2.0 eq of TBAF.

Scheme 3-5. Scope and limitation of monoazido substrates from azido to oxime group

3-3 マルチアジド基質

モノアジド基質での良好な結果をうけ、マルチアジド化合物へ本オキシム化法を適用した(Scheme 3-6)。まず、活性水素がアミド隣接アジドにのみ存在するジアジド **3a,b** を検証したところ、問題なく反応が進行し、**8a** および **8b** を高収率で与えた。本反応においてもジアゾ化と同様、ベンジルアジドを有するジアジド **3c** はカルボニル隣接位のみが選択的に変換された **8c** を与えた。一方、アミドに隣接した 1 級および 2 級アルキルアジドを有するジアジド **3d** では、分離困難な混合物として得られ、**8d** が生成している確証は得られなかった。3-1 で期待した通り、ケトン隣接アジドとアミド隣接アジドを持つジアジド **3e** は 1.8 当量の TBAF を用いることでケトン隣接位のみオキ

シム化された **8e** が得られた。次にトリアジド基質について検討した。アリールアジドと 2 つのアルキルアジドを併せ持つトリアジド基質 **5a** はジアゾ化同様問題なく反応が進行し、区別可能なアリールアジド、アルキルアジド、およびオキシムの 3 種のクリック官能基を有する **9a** を 84% の収率で与えた。また、トリスアルキルアジド化合物 **5b** についても、ケトン隣接位のみを変換可能な条件にて収率 65% でジアジド-オキシム化合物 **9b** が得られた。**9b** は X 線結晶構造解析にてその構造を決定した。



^aComplex mixture.

Scheme 3-6. Site-selective conversion to oxime group of multiple azido substrates

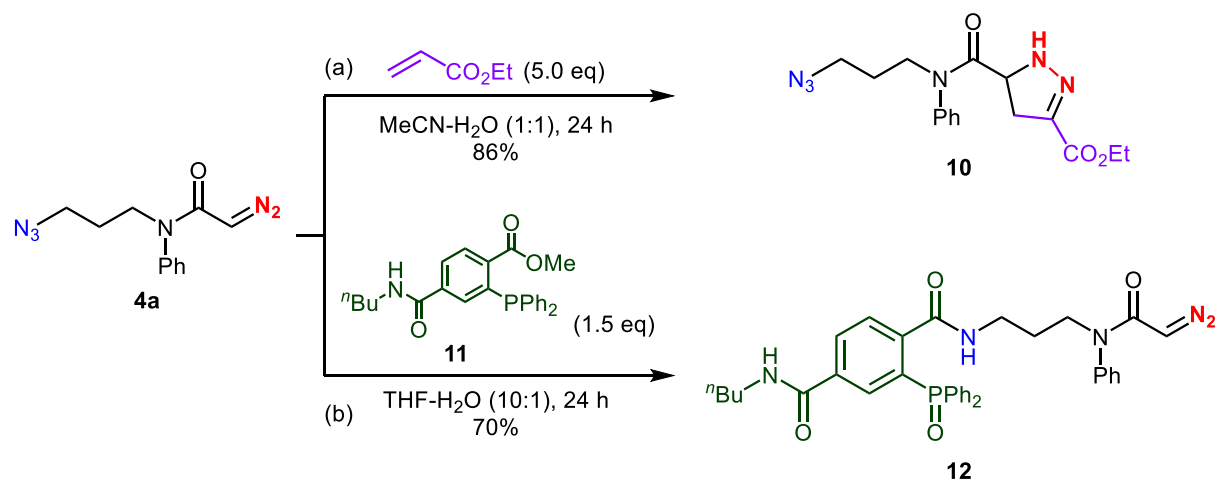
以上本章では、カルボニル隣接アジド選択的ジアゾ化法を拡張し、オキシムへの変換法を確立した。本反応では高反応性イミン中間体を利用するため、類似構造の 2-オキソアルデヒド類へのヒドロキシルアミンの縮合反応に比べて位置選択的に反応が進行した。また、ジアゾ化と同様に、アリールアジドだけでなく、様々なアルキルアジド存在下においても位置選択的にオキシム化が進行した。これらの結果から、塩基によってカルボニル隣接アジドを脱窒素させる本反応は求核剤を変更するだけで、様々な官能基へと変換できると予想される。

第4章 マルチアジド化合物を利用した位置選択的多成分集積化法の開発

4-1 デュアルクリック化合物の化学種選択的連結

カルボニル隣接アジドの性質に着目した変換反応の開発によって、本来区別が困難なマルチアジドにおける位置選択的変換を達成し、効率的にアジドとそれとは異なるクリック官能基の2種類を併せ持つ化合物を合成できた。そこで、1章でその有用性について触れた通り、効果的な多成分連結に活用できることを示すため、本反応によってマルチクリック化合物を合成し、プラットフォーム分子として利用した位置選択的な連結反応の実証実験に着手した。

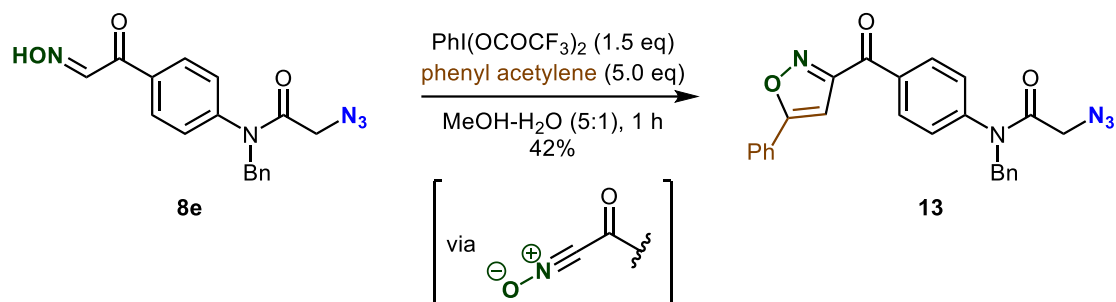
まず、トリアジドでの検討を行う前に、ジアジド基質から本反応によって1段階で合成したアジド-ジアゾ **4a** とアジド-オキシム **8e** のデュアルクリック化合物について検証することにした。**4a** は Raines らの報告^{21a)}に則って電子不足オレフィンであるアクリルエステルと反応させることで、ジアゾ部選択的に環化反応が進行したアジド-ピラゾリン化合物 **10** を86%の収率で与えた(Scheme 4-1a)。この際、ピラゾリンの二重結合はアミドよりも酸性度の高い水素原子を有するエステル側の水素原子が脱離することで形成され、単一異性体として生成物が得られた。一方、ホスフィン試薬 **11** を反応させると、アジド部選択的に Staudinger ライゲーション反応が進行したアミド-ジアゾ化合物 **12** が70%の収率で得られた(Scheme 4-1b)。



Scheme 4-1. Chemoselective conjugation using azido diazo compound

続いて **8e** のオキシム選択的連結反応を検討した(Scheme 4-2)。酸化剤によって **8e** のオキシム部をニトリルオキシドへと変換し、アルキンと環化反応

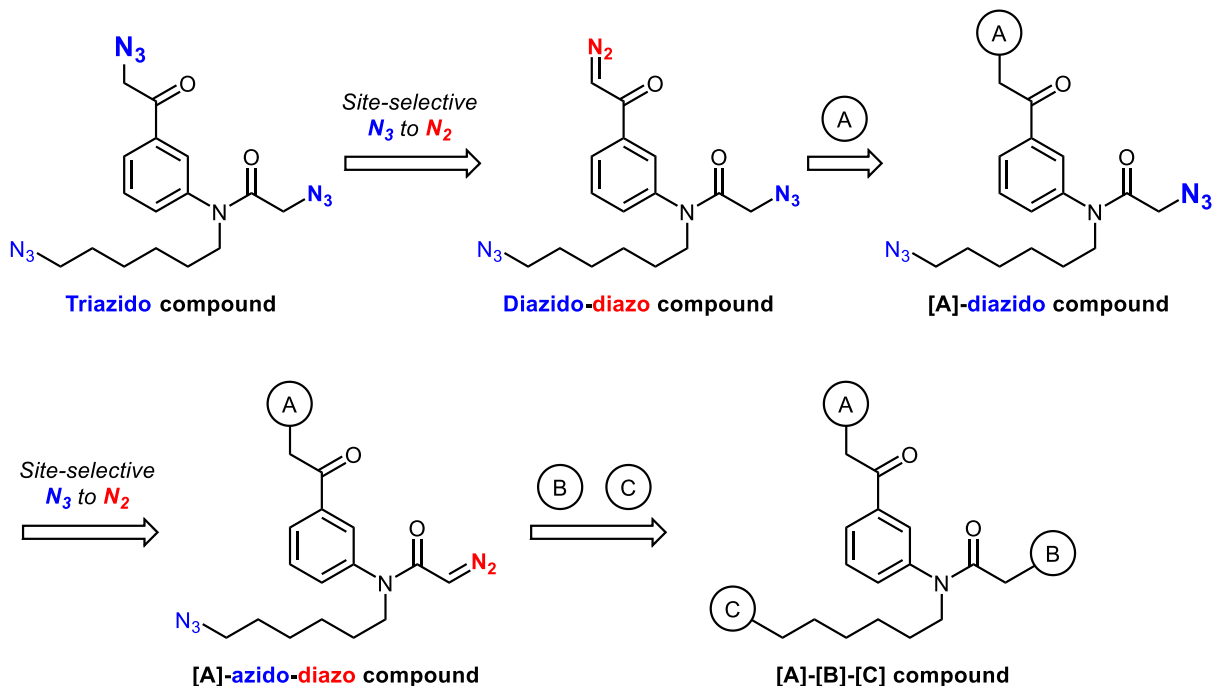
を行うことでオキシム部選択的に連結したアジド-イソキサゾール **13** が得られた(Scheme 4-2)。



Scheme 4-2. Chemoselective conjugation with azido oxime linker

4-2 多段階法による 3 成分集積化

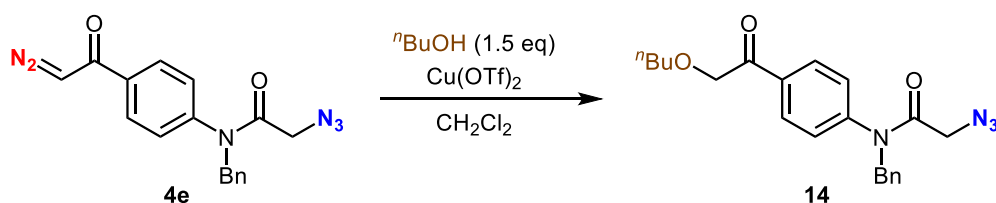
デュアルクリック化合物による化学種選択的連結が達成できたことから、本法をさらに展開し、トリアジド化合物の位置選択的なジアゾ化とジアゾ選択的連結を段階的に行うことで位置選択的な 3 成分集積化を検討することとした(Scheme 4-3)。即ち、トリアジド基質のケトン隣接位選択的なジアゾ化の後、ケトジアゾ部を利用した連結反応を行う。続いて、アミド隣接位選択的ジアゾ化によってアジド-ジアゾ化合物へと導いた後、ジアゾ選択的連結とアジド選択的連結によって異なる 3 成分を集積化する戦略である。



Scheme 4-3. Stepwise approaches to trifunctional molecule

そこで、実際の 3 成分集積化で利用するケトジアゾの反応性についてアジド-ジアゾ **4e** を用いて調査した。まず、金属カルベノイドによる挿入反応⁴⁷⁾を銅触媒によって検討した(Table 4-1)。連結分子であるアルコール存在下、室温で触媒量の $\text{Cu}(\text{OTf})_2$ を加えたところ、即座に原料が消失し、6%と低収率ではあるが目的のエーテル **14** の生成が確認された(entry 1)。続いて低温で反応を行うことでカルベノイドの生成速度を抑制しようとして試みたが、 $-78\text{ }^\circ\text{C}$ では反応は進行せず、徐々に昇温したところ反応は進行したが微量の **14** を確認するのみであった(entry 2)。また、触媒量を減じて検討したが収率は向上しなかった(entry 3)。アジド存在下でのアミドジアゾの金属カルベノイドによる反応は報告例があるため^{47a)}、触媒がアジドに作用しているとは考えにくく、ケトジアゾでの挿入反応は制御が困難であると判断した。

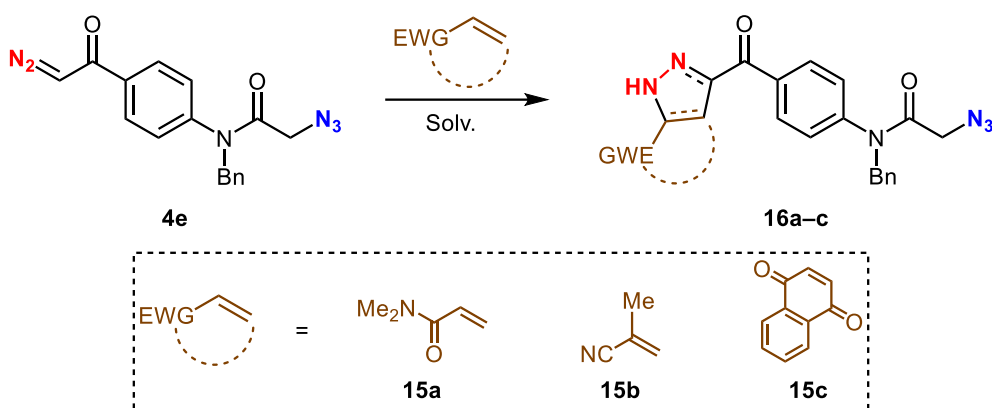
Table 4-1. Attempted insertion reaction via copper-carbenoid



Entry	$\text{Cu}(\text{OTf})_2$ (mol%)	Temp.	Time (h)	Yield
1	10	rt	0.5	6%
2	10	$-78\text{ }^\circ\text{C}$ to rt	5	trace
3	6	rt	1	trace

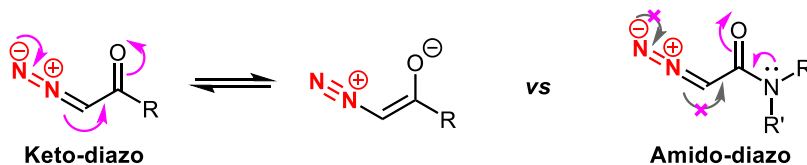
Table 4-1 の結果から、ケトジアゾとオレフィンとの[3+2]環化反応を検討することとし、アミドジアゾで利用するアクリルエステル以外のオレフィン類との反応を調査した(Table 4-2)。Scheme 4-1a と同様の条件でアクリルアミド **15a** との反応を試みたが、反応は全く進行しなかった(entry 1)。また、濃度条件を変更したが効果はなく(entry 2)、電子不足オレフィンであるアクリロニトリル **15b** やナフトキノ **15c** を用いても同様に反応は進行しなかった(entries 3 and 4)。これはアミドジアゾと異なり、ケトジアゾはケトン部のアクセプター性によって共鳴しているため、ジアゾの[3+2]環化への反応性が低下していると考えた(Scheme 4-4)。そこで、Wu らの条件⁵⁹⁾を参考に塩基性条件での環化反応を検討したところ反応が進行し、続く空気酸化によってピラゾール環の形成を行うことで、ナフトキノ **15c** と連結したアジド-ピラゾール **16c** を 75%の収率で得ることに成功した(entry 5)。

Table 4-2. Attempted [3+2] cycloaddition of diazo with olefines



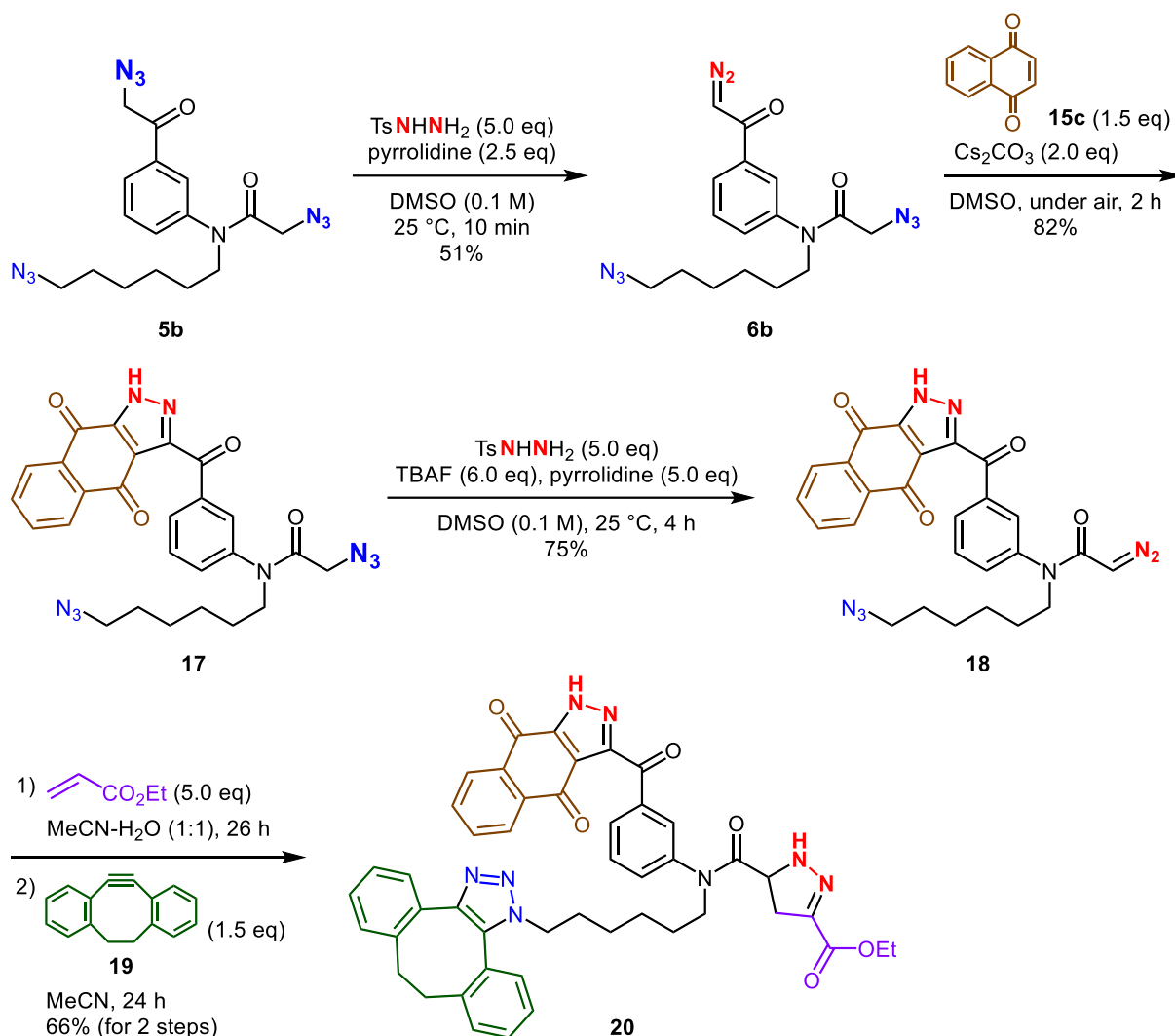
Entry	15a-c (eq)	Solv. (M)	Time (h)	Yield (%)
1	15a (5.0)	MeCN-H ₂ O (0.02)	72	0 ^a
2	15a (5.0)	MeCN-H ₂ O (0.1)	24	0 ^a
3	15b (5.0)	MeCN-H ₂ O (0.1)	24	0 ^a
4	15c (5.0)	MeCN-H ₂ O (0.1)	48	0 ^a
5 ^b	15c (1.5)	DMSO (0.05)	2	75

^aNo reaction. ^bReaction was carried out with Cs₂CO₃ (2.0 eq) under air



Scheme 4-4. Keto-diazo and amido-diazo groups

以上の検討から、見出した条件(Table 4-2, entry 5)にてケトジアゾ部の連結を行うこととし、トリアジド **5b** での3成分集積化を行った(Scheme 4-5)。まず、トリアジド **5b** のケトン隣接位選択的なジアゾ化によって **6b** を得た後、先の検討で見出した条件にてケトジアゾ部をナフトキノン **15c** と連結することでジアジド-ピラゾール **17** を合成した。続いて、アミド隣接位選択的なジアゾ化を試みたが、3.6 当量の TBAF では痕跡量の生成物しか確認できず、原料回収となった。これは TBAF による活性水素の引き抜きがカルボニル隣接位水素よりもピラゾールの N-H 水素原子を優先したことによって反応が阻害されていると考え、6.0 当量の TBAF を用いたところ原料が完全に消失し、望みのアジド-ジアゾ-ピラゾール化合物 **18** が 75%の収率で得られた。得られた **18** に対して、アクリルエステルのジアゾ選択的環化と歪アルキン **19** のアジド選択的環化反応を逐次行うことで、異なる3種の化合物を位置選択的に連結したピラゾール-ピラゾリン-トリアゾール生成物 **20** を単一生成物として合成することに成功した。

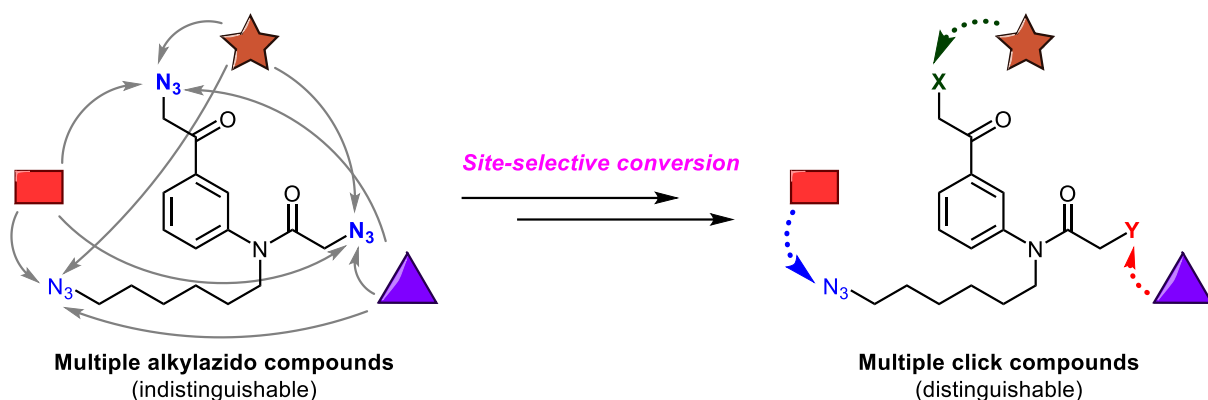


Scheme 4-5. Stepwise site-selective conjugation with three different components

4-3 トリプルクリック化合物の創成と one-pot 多成分連結

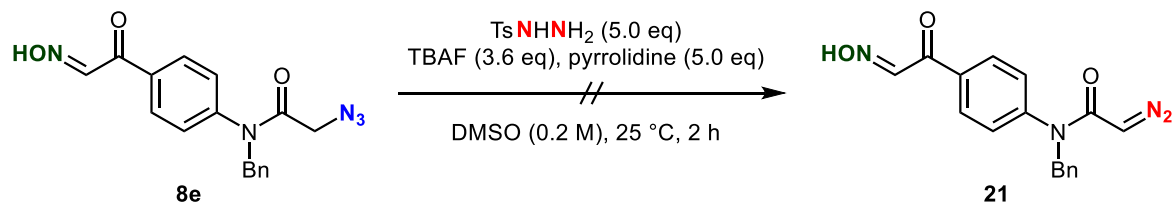
上述したように、本反応による位置選択的なジアゾ化とジアゾ選択的な連結反応を組み合わせた段階的な手法によって、トリアジド化合物をプラットフォーム分子として利用できることがわかった。しかし、本ジアゾ化法と分子連結を段階的に利用する必要があるため、連結分子によっては適用できない可能性がある。多成分を位置選択的かつ簡便に集積するには、1章で述べたような分子同士で相互干渉しないクリック官能基を複数有するプラットフォーム分子を利用することが理想的と言える。そこで、本反応による位置選択的なオキシム化とジアゾ化を組み合わせ、合成容易なトリアジド化合物から目的とするそれぞれが異なる反応性を有するクリック官能基を併せ持

ったトリプルクリックプラットフォーム分子の創出を行うこととした (Scheme 4-6)。



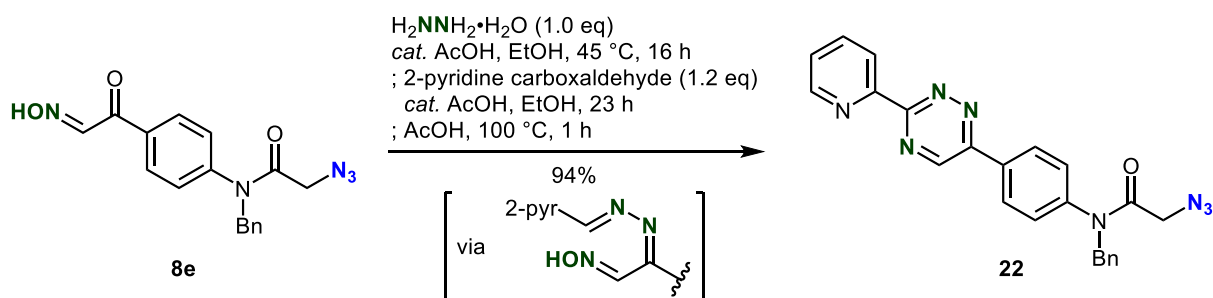
Scheme 4-6. One-pot approaches to trifunctional molecule using multiple click scaffold

トリアジド **5b** の選択的ジアゾ化とオキシム化によってアジド-ジアゾ-オキシム化合物が合成できれば、オキシム部のトランスオキシム化によるライゲーション、アクリレートとのジアゾ選択的環化、歪アルキンとのアジド選択的環化によって 3 成分集積化を可能とするプラットフォーム分子が創出できると考え、アジド-オキシム **8e** を基質としたオキシム存在下でのジアゾ化を検証した (Scheme 4-7)。しかし、目的とするジアゾ-オキシム **21** は得られず、有効な副生成物も確認できなかったことから、オキシム存在下での本ジアゾ化は困難であると判断した。



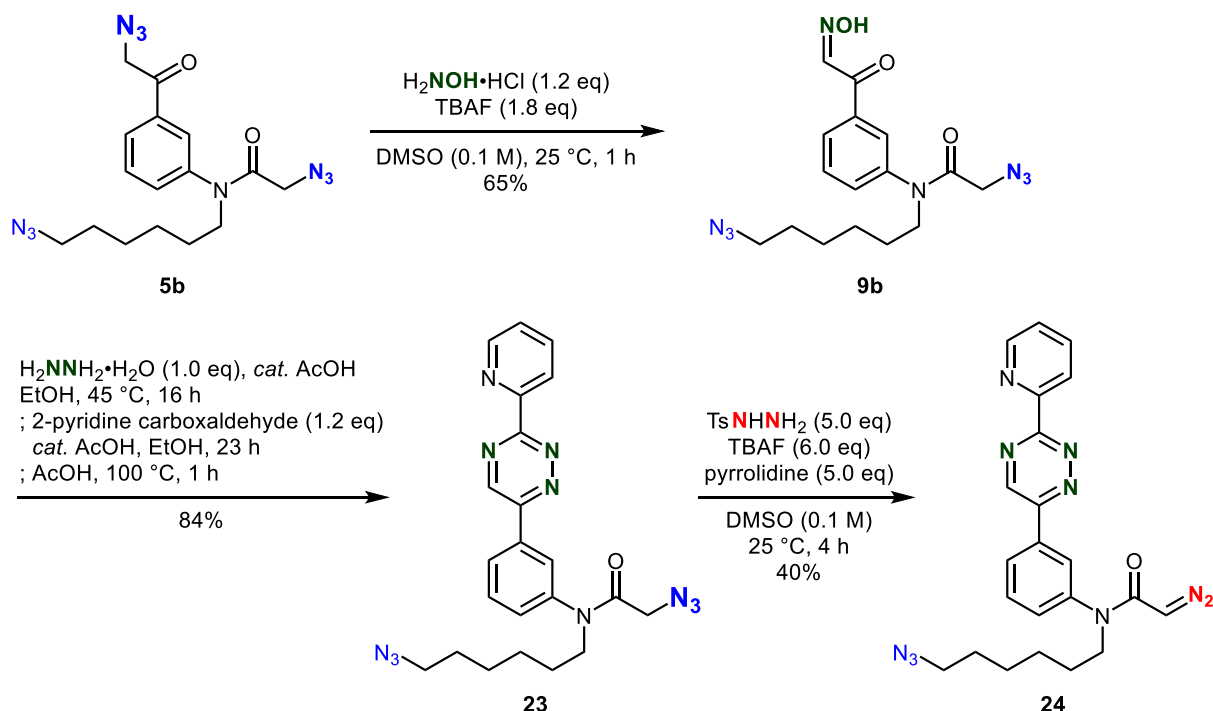
Scheme 4-7. Attempted diazo conversion of the substrate possessing oxime moiety

そこで、ケトオキシム部を DA/retro-DA 反応によるクリック連結が可能な 1,2,4-トリアジンに変換した後にアミド隣接アジドをジアゾ化することで、位置選択的な 3 成分集積化が可能と予想されるアジド-ジアゾ-トリアジン化合物へと導くことにした。それに先立ち、アジド存在下でのトリアジン合成についてアジド-オキシム **8e** を基質として検討を行った (Scheme 4-8)。Vrabelらの手法⁵⁶⁾に従い、ヒドラゾンの形成による 2-pyridine carboxaldehyde との脱水縮合と続く環化反応によってアジド-トリアジン化合物 **22** が合成できた。



Scheme 4-8. Chemoselective transformation from ketoxime to triazine

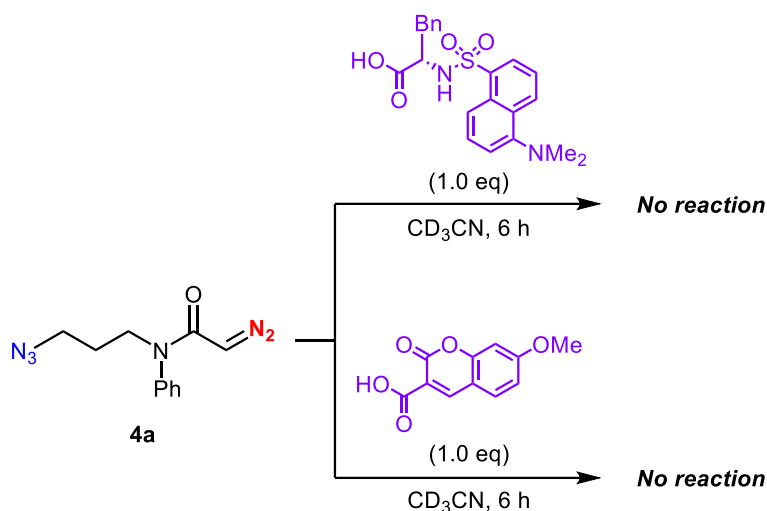
アジド存在下でのトリアジン合成が可能であったことから、実際にトリアジド **5b** を利用したアジド-ジアゾ-トリアジン化合物の合成を行った (Scheme 4-9)。まず、ケトン隣接位選択的なオキシム化によって **9b** を合成した後、Scheme 4-8 と同様の条件にてケトオキシムをトリアジンへと変換し、ジアジド-トリアジン **23** を合成した。続いてアミド隣接位選択的なジアゾ化を検討したが、ピラゾールの N-H 水素の様な活性水素が存在しないにも関わらず、Scheme 4-5 と同様に反応の進行が芳しくなかった。そこで、先の条件である 6.0 当量の TBAF を用いる条件に付すことで効果的に反応は進行し、アジド、ジアゾ、トリアジンの 3 種のクリック官能基を有するトリプルクリックプラットフォーム分子 **24** の合成に成功した。



Scheme 4-9. Synthesis of azido-diazo-triazine compound

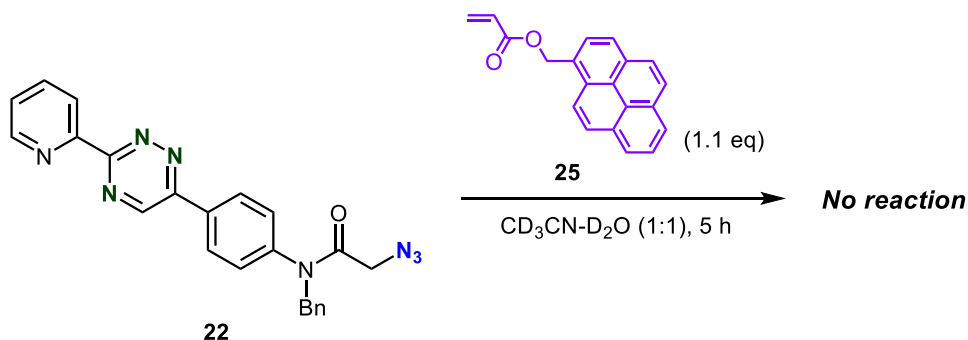
目的とする異なるクリック官能基を有するトリプルクリックプラットフォーム分子 **24** の合成に成功したため、**24** に対するワンポットでの 3 成分集積化を行うにあたり、各クリック官能基のカップリングパートナー分子に対する官能基選択性について検証することとした。まず、Raines らの報告 (Scheme 1-13b)^{21b)}にあるジアゾとカルボン酸の連結反応が可能であれば、入

手容易な蛍光部位を有するカルボン酸をカップリングパートナーとして選択できる。そこで、市販の蛍光性カルボン酸である dansyl-L-phenylalanine と coumarin-3-carboxylic acid を用いて連結反応を試みた(Scheme 4-10)。しかし、 ^1H NMR によって反応を追跡した結果、反応は進行しなかった。これは、dansyl-L-phenylalanine のジメチルアミノ基や coumarin-3-carboxylic acid のメトキシ基などの置換基効果によってカルボン酸の酸性度が低下したためと考えられる。そこで、カルボン酸の利用は断念し、既に反応性について検証したアクリルエステルをカップリングパートナーとして選択し、トリアジンとの反応性について調査することとした。



Scheme 4-10. Attempted esterification of diazo with carboxylic acids

アジド-トリアジン化合物 **22** を基質とし、合成したアクリレート **25** との反応性を検討した(Scheme 4-11)。 ^1H NMR によって反応を追跡したところ、アジド置換炭素上の水素ピーク、およびトリアジン芳香環上水素ピークなどに変化はなく(Figure 4-1)、アクリレートはトリアジンと反応せず、ジアゾ選択的に反応が行えると判断した。



Scheme 4-11. Investigation into reactivity of azido-triazine **22** with pyrene-acrylate **25**

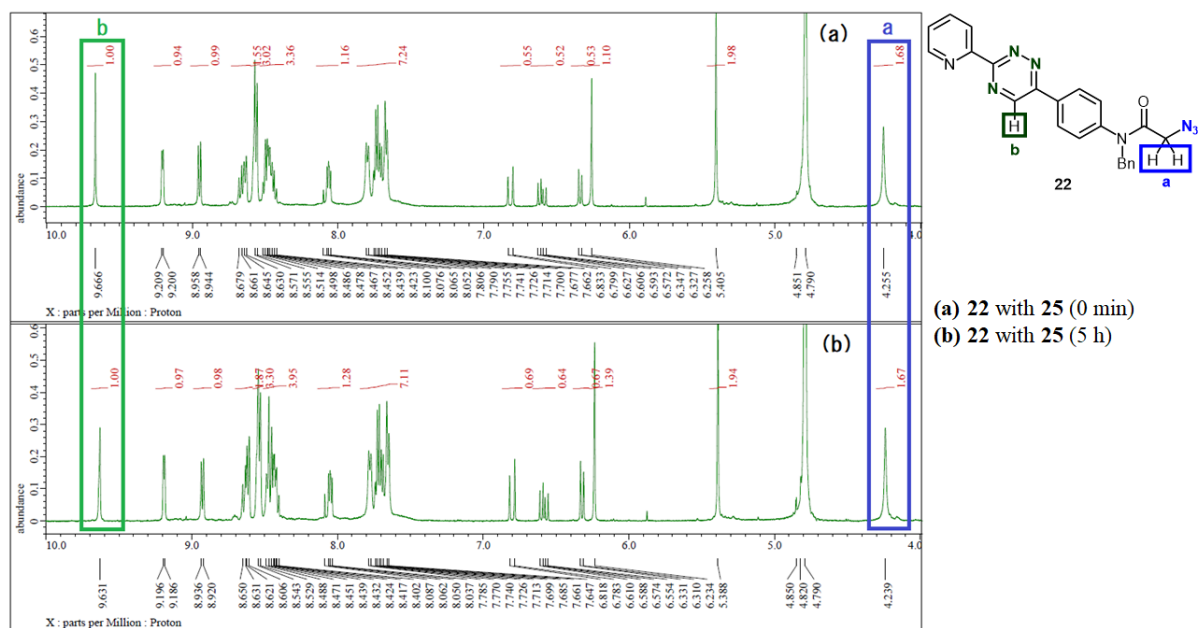
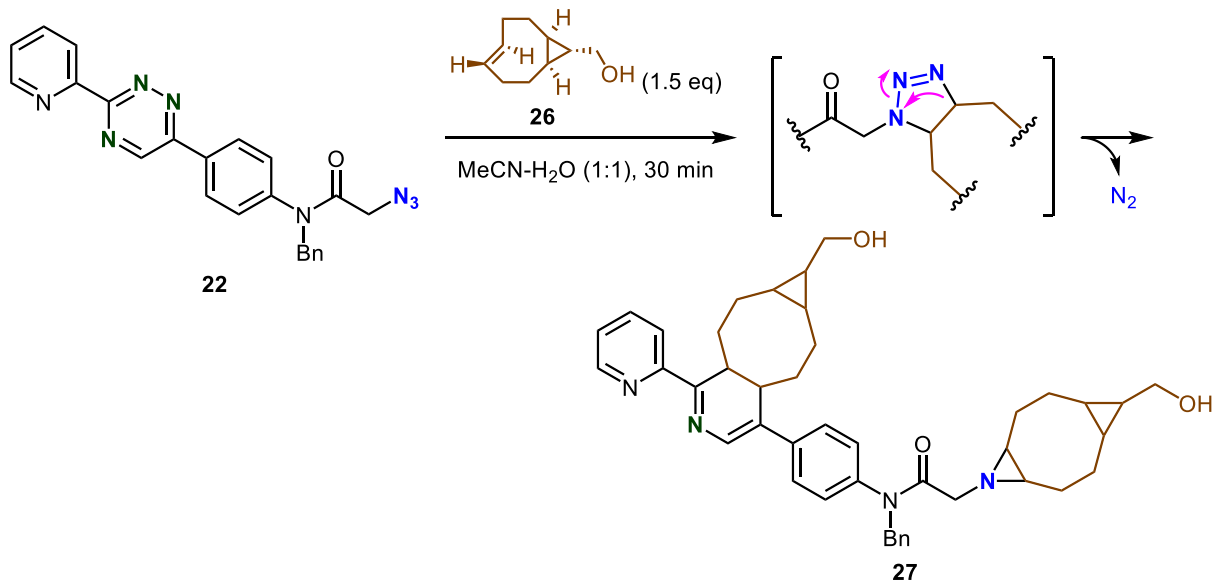


Figure 4-1. ^1H NMR spectra of reaction of azido-triazine **22** with pyrene-acrylate **25** in $\text{CD}_3\text{CN-D}_2\text{O}$ (1:1).

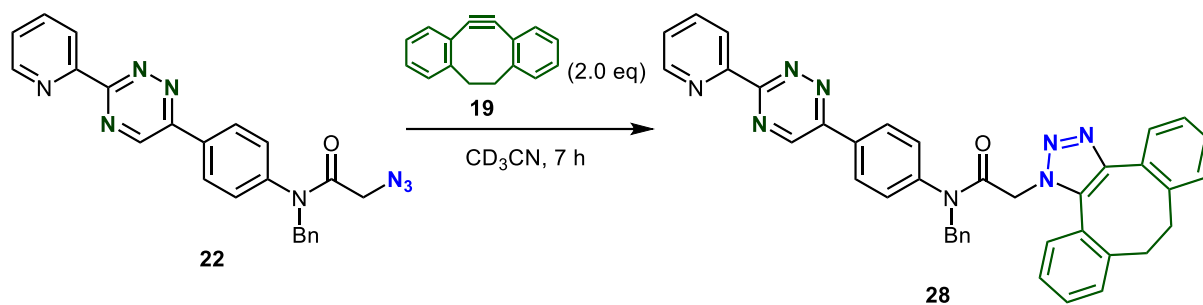
続いて、**22**と *trans*-シクロアルケン **26**との反応を検討した(Scheme 4-12)。しかし、予想に反して官能基選択性は発現せず、トリアジン部と DA/retro-DA 反応、アジド部と [3+2]環化/脱窒素反応が進行したと考えられる生成物 **27**が確認された。この結果から、トリアジン部と *trans*-シクロアルケンの反応はアジド部の連結反応後に行う必要があるとわかった。



Scheme 4-12. Overreaction of azido-triazine **22** with *trans*-cyclooctene **26**

また、**22**とアジドのカップリングパートナーである歪アルキン **19**との反応性についても検証した(Scheme 4-13)。**19**の添加後40分にてアジド置換炭素上の水素ピークは消失したのに対して、トリアジンの芳香環上水素ピークは7時間経過しても全く変化がなかったことを ^1H NMRで確認した(Figure 4-2)。仮にトリアジン部で環化および脱窒素が進行した場合、芳香環の電子

不足状態が解消されて芳香環上の水素ピークは高磁場シフトするため^{26, 56}、トリアジンと歪アルキンは干渉しないと判断した。



Scheme 4-13. Investigation into reactivity of azido-triazine **22** with cyclooctyne **19**

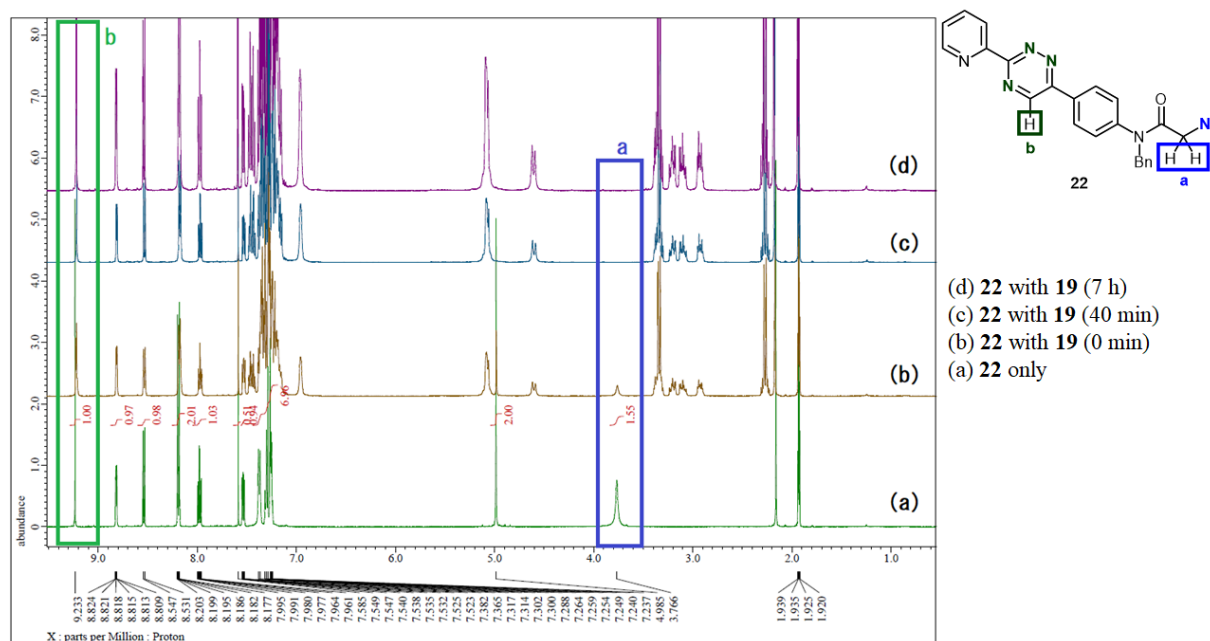
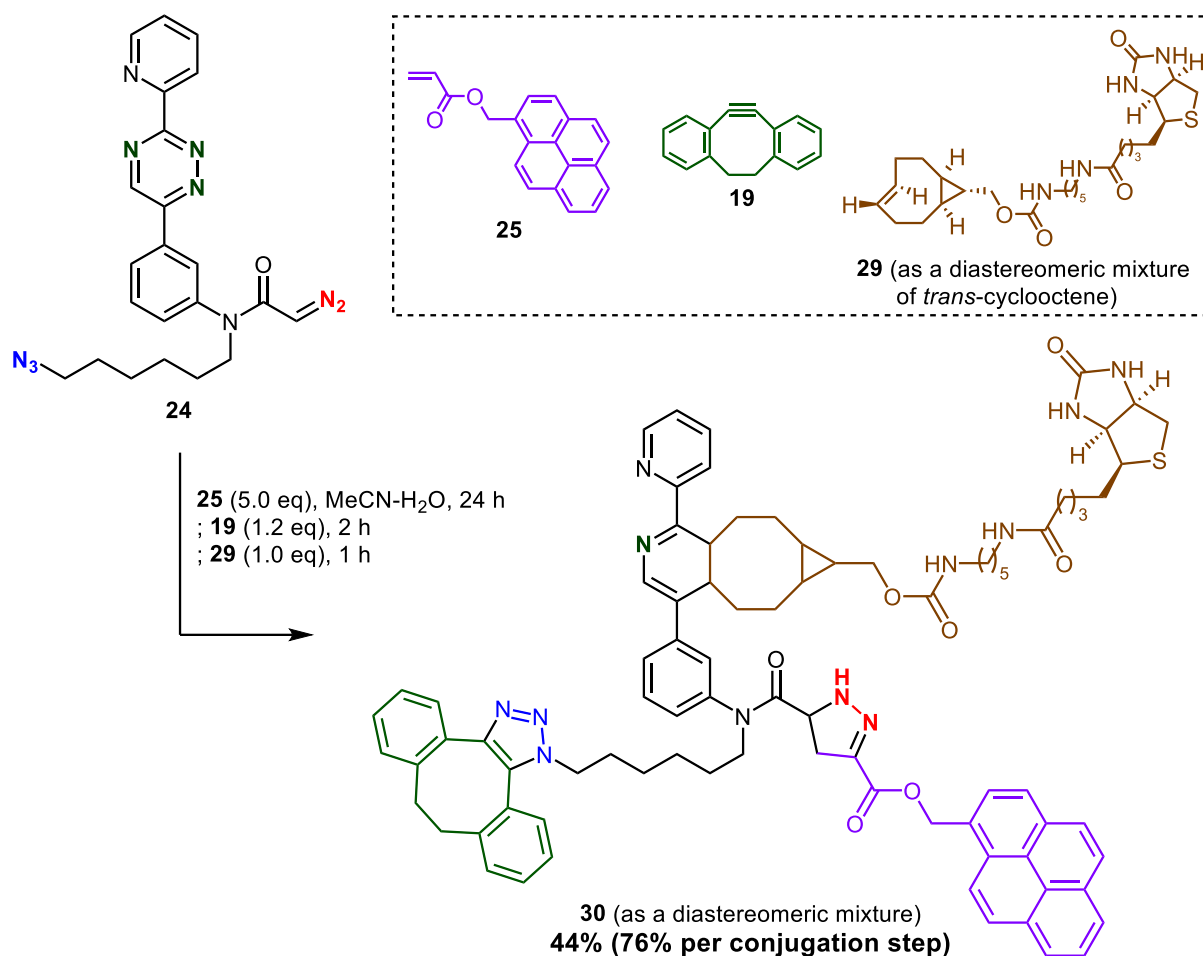


Figure 4-2. ¹H NMR spectra of reaction of azido-triazine **22** with dibenzocyclooctyne **19** in CD₃CN.

これらの検討から、第1にジアゾとアクリレートの[3+2]環化、第2にアジドと歪アルキンの[3+2]環化、第3にトリアジンと *trans*-シクロアルケンのDA/retro-DA反応を順に行うことで3成分の集積化が可能と判断した。そこで実用性についても実証するため有用な化合物を持ったカップリングパートナーを採用し、実際にプラットフォーム分子**24**の反応溶液にピレンを有するアクリレート**25**、シクロオクチン**19**、ビオチンを有する *trans*-シクロアルケン**29**を順次加える手法で3成分集積化を行った(Scheme 4-14)。その結果、予想通り**24**に3つの異なる分子が集積した生成物**30**をジアステレオマー混合物として44%の収率(1段階毎に76%の収率)で得ることに成功した。以上の結果によって、目的とする簡便に多成分連結を可能とするトリプルクリックプラットフォーム分子の創出を達成した。



Scheme 4-14. One-pot reagent-free sequential triple click conjugation

以上本章では、開発した位置選択的変換反応によってジアジドから合成したデュアルクリック化合物が官能基選択的な分子連結に有効であることを示した。また、ケトン隣接アジド、アミド隣接アジド、アルキルアジドで構成されたトリスアルキルアジド化合物を利用すれば、ジアゾ化とジアゾ選択的連結を繰り返す段階法によって 3 つの異なる成分を位置選択的に連結できることを明らかにした。さらに、本反応のオキシム化とジアゾ化を組み合わせることで、トリスアルキルアジド化合物をアジド、ジアゾ、トリアジンの 3 種のクリック官能基を有するプラットフォーム分子へと誘導することに成功した。合成したプラットフォーム分子に対し、連結反応に別途試薬を用いることなく各カップリングパートナーを適切な順序で加えるだけで、3 成分が位置選択的にプラットフォーム分子に集積化された化合物を得ることができ、有用なプラットフォーム分子であることを実証した。

第 5 章 総括

アジドは様々な含窒素化合物の合成や剛直な分子連結に広く利用されている有用官能基である。近年、2種の成分を連結するだけでなく、多数の機能性分子を1つのプラットフォーム分子に集積することで簡便に多機能性化合物を合成する手法が注目されている。中でも、アルキルアジドを複数有する合成容易なマルチアジド化合物は有効なプラットフォーム分子となり得るが、その高い反応性のため反応位置を区別して利用することは大きな課題である。このような背景から本研究では、カルボニル隣接位のアジド基が示す塩基性条件下での特異な反応性に着目し、アジド基の位置選択的なクリック官能基への変換法の開発によって有用なプラットフォーム分子の創出を行った。

第2章では、カルボニル隣接アジド基のジアゾ基への位置選択的な変換法を開発した。塩基性条件下でのカルボニル隣接アジドの分解により生成する不安定なイミン中間体を活用し、ヒドラジドとの縮合と同一塩基性条件を利用した分解反応により、ジアゾ基への変換を達成した。しかし、当初見出した加熱条件はマルチアジドへの適用が困難であったため、室温下にて再度条件検討を行ったところ、TBAFとpyrrolidineの2つの塩基を組み合わせる条件を見出し、高収率でのカルボニル隣接位選択的なジアゾ化法を確立した。本ジアゾ化法は温和な条件で様々な官能基を許容し、活性水素を持たないアリールアジドやアルキルアジド存在下のみならず、用いる塩基を変更することでケトン-アミド間においても高い位置選択性を発現した。

第3章では、反応で生じるイミン中間体に対する求核剤を変更し、位置選択的なオキシム化法へと拡張した。ジアゾ化にて見出したpyrrolidineを用いる条件では中程度の収率にとどまったものの、TBAFを用いることで高収率にて目的とするオキシム化合物を得た。また、塩基の当量を調節することで、ケトンとアミドの反応位置を区別することができ、位置選択的なアジドからオキシムへの変換に成功した。

第4章では、2章ならびに3章にて確立した反応を活用し、多成分の位置選択的な集積化を可能とするプラットフォーム分子を創出した。ジアジド分子より誘導した2種類のクリック官能基を持つデュアルクリック化合物を利用し、官能基選択的連結反応を行うことで、区別が困難であったマルチアジド化合物を、位置選択的な分子連結が可能な分子へ変換できることを示した。また、ケトン隣接アジド、アミド隣接アジド、アルキルアジドで構成さ

れたトリスアルキルアジド化合物を利用し、ケトンおよびアミド部位を段階的にジアゾ化／ジアゾ選択的連結を行う方法にて、3つの異なる成分の位置選択的な分子連結を達成した。更に、ジアゾ化とオキシム化を組み合わせることで、アジド、ジアゾ、トリアジンの3種のクリック官能基を有するプラットフォーム分子の創出に成功し、これを用いることで、知る限りワンポットでの位置選択的な3成分集積化では初となる、連結試薬を必要としない集積化を達成した。

以上、本研究ではカルボニル基に隣接するアジド基が塩基性条件下で脱窒素を起こしてイミンへと変換される性質を利用し、課題とされてきたマルチアジド分子におけるアジド基の位置選択的な変換法を開発した。本反応はアジド置換炭素上の水素原子の酸性度が鍵となっており、活性水素を持たないアルキルアジドやアリールアジドを保持したままカルボニル隣接位選択的に変換できただけでなく、用いる塩基やその当量を調節することでカルボニル隣接アジド間での区別を可能とした。本反応によってマルチアジド化合物の反応位置を制御した利用が可能となり、効率的にクリック官能基とアジド基を併せ持つマルチクリックプラットフォーム分子へと誘導できた。合成したプラットフォーム分子は実際に簡便かつ位置選択的な多成分連結反応が可能であったことから、これまで合成に多大な労力を要した、ケミカルバイオロジーにおける同時多角的検出を可能とするプローブ分子や、多機能性材料の開発を加速するものと期待される。

第 6 章 実験の部

6-1 General Information

Analysis and Reagents: ^1H and ^{13}C NMR spectra were recorded using a JEOL JNM-ECP500 spectrometer (500 MHz for ^1H NMR, 126 MHz for ^{13}C NMR, and 202 MHz for ^{31}P NMR). Chemical shifts are reported as δ values in ppm and calibrated with respect to the residual solvent peak (CDCl_3 : δ 7.26 for ^1H NMR and δ 77.00 for ^{13}C NMR, CD_3OD : δ 3.30 for ^1H NMR and δ 49.0 for ^{13}C NMR). ^{31}P NMR spectra were calibrated with an external reference (phosphoric acid in benzene- d_6 as δ 0.0). The abbreviations used are as follows: s (singlet), d (doublet), t (triplet), q (quartet), br (broad), and m (complex multiplet). Melting points were measured using a Yanaco Micro melting point apparatus. Infrared spectra were measured using a JASCO FT-IR-4200 spectrometer. Mass spectra were recorded using a JEOL JMS-700 MStation [EI-magnetic sector (70 eV), CI-magnetic sector, and ESI-TOF], and Bruker Autoflex II (MALDI-spiral TOF). All measurements of single crystal X-ray diffraction analysis were made on a Rigaku R-AXIS RAPID diffractometer using multi-layer mirror monochromated $\text{Mo-K}\alpha$ radiation. The data were collected at a temperature of -150 or -170 °C. UV-visible spectra were recorded using JASCO V-630. The progress of the reactions was monitored by silica gel thin layer chromatography (TLC) (Merck TLC Silica gel 60 F₂₅₄). Phosphomolybdic acid-cerium(IV) sulfate sulfuric acid solution was used for the TLC stains, and TLC was also monitored with UV lamp. Flash column chromatography was performed using neutral silica gel N60 from Kanto Chemical Co. Inc. If not specified as neutral silica gel column chromatography, Merck Silica gel 60 and packed column of Biotage® SNAP Ultra with HP-Sphere™ 25 μm were used. If necessary, further purification of the crude materials was performed using a LC-908 recycling gel permeation chromatography (GPC) equipped with a JAIGEL 2H-40 column (chloroform elution) made by Japan Analytical Industry Co., Ltd. All reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd, TCI (Tokyo Chemical Industry, Co. Ltd), Kanto Chemical Co. Inc., and Nacalai Tesque. Anhydrous solvents such as tetrahydrofuran (THF), toluene, acetonitrile, and dichloromethane were purchased from Kanto Chemical and Wako Pure Chemical. Dimethyl sulfoxide (DMSO) was distilled under reduced pressure after refluxing in the presence of calcium hydride.

5,6-dihydro-11,12-didehydrodibenzo[*a,e*]-cyclooctyne (**19**)^{23a,60}, ((1*R*,8*S*,9*r*,*E*)-

bicyclo[6.1.0]non-4-en-9-yl)methanol (**26**)⁶¹⁾, and pyren-1-ylmethyl acrylate (**25**)⁶²⁾ were prepared according to the reported methods.

Caution: Organic azides, especially multiple azido compounds as well as diazo compounds are potentially hazardous and explosive. Although I have never experienced such an explosion with those used in this study, all manipulation should be carefully conducted behind a safety shield in a hood. Sodium azide should be handled with plastic spatula. At azidation stage of azido compound preparation, complete removal of residual halogenated solvent used in the last steps or extractions should be in mind to avoid generation of explosive species such as diazidomethane from dichloromethane.⁶³⁾

Storage of TBAF: Tetrabutylammonium fluoride (TBAF) was purchased from TCI (Tokyo Chemical Industry, Co. Ltd) as 1 mol/L solution of THF. Because I encountered irreproducible results when I used old solution, probably due to the decomposition of TBAF by the reagent itself or contaminated water from moisture,⁶⁴⁾ the newly purchased bottle of TBAF solution was repacked in small subsection vial bottles. These were filled with nitrogen gas, and were stored in the refrigerator. With these small batch bottles, I successfully obtained reproducible results as described in the text.

NOTE: Volume and the ratio of DMSO solvent in the reaction mixture is very important to succeed. However, I still used THF solution of TBAF, because use of commercial solid TBAF hydrate or removal of THF from the reagent solution prior to use gave low yields or irreproducible results. Short path silica gel column chromatography can afford the desired products in good yields. Exposure to the silica gel column for a long time reduced the product yields.

6-2 Synthesis of Diazo Compounds

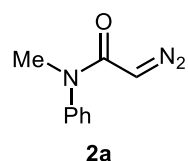
General Procedure for Synthesis of Diazo Compounds

From Amides: TBAF (3.6 eq, 1.0 M in THF) was added dropwise to a stirred solution of α -azido amide (1.0 eq), *p*-toluenesulfonyl (tosyl) hydrazide (5.0 eq), and pyrrolidine (5.0 eq) in DMSO (0.2 M based on an azido substrate unless otherwise noted) at 25 °C (set by a water bath) under the nitrogen gas atmosphere. After completion of the reaction checked by TLC, the mixture was diluted with ether and quenched with water. The solution was extracted three times with ether

and was washed with water and brine. The collected organic layer was dried over anhydrous sodium sulfate. Concentration and purification by flash neutral silica gel column chromatography gave the diazo product.

From Ketones: Pyrrolidine (2.5 eq) was added dropwise to a stirred solution of α -azido ketone (1.0 eq) and *p*-toluenesulfonyl hydrazide (5.0 eq) in DMSO (0.2 M based on an azido substrate unless otherwise noted) at 25 °C (set by a water bath) under the nitrogen gas atmosphere. The purification procedure was followed for amides.

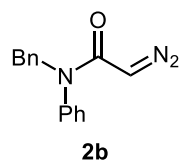
2-Diazo-*N*-methyl-*N*-phenylacetamide (**2a**)⁶⁵⁾



A total of 13.2 mg of **2a** (75%) was obtained from the reaction with azide **1a** (19.0 mg, 0.10 mmol), tosyl hydrazide (93.6 mg, 0.50 mmol, 5.0 eq), pyrrolidine (42.0 μ L, 0.50 mmol, 5.0 eq), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 eq) in DMSO (0.5 mL, 0.2 M) for 1.5 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 8/1).

Pale yellow oil; R_f value 0.57 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 2106, 1622, 1591, 1387 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.41 (t, 2H, $J = 7.5$ Hz), 7.33 (t, 1H, $J = 7.5$ Hz), 7.20 (m, 2H), 4.51 (s, 1H), 3.32 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 165.7, 143.1, 129.8, 127.9, 127.3, 47.3, 37.1; HRMS (CI) calcd for $\text{C}_9\text{H}_{10}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$ 176.0824, found 176.0826.

N-Benzyl-2-diazo-*N*-phenylacetamide (**2b**)⁶⁵⁾

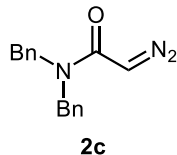


A total of 21.8 mg of **2b** (87%) was obtained from the reaction with azide **1b** (26.6 mg, 0.10 mmol), tosyl hydrazide (93.5 mg, 0.50 mmol, 5.0 eq), pyrrolidine (42.0 μ L, 0.50 mmol, 5.0 eq), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 eq) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 8/1).

Pale yellow amorphous solid; R_f value 0.63 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 3478, 2106, 1624, 1593, 1399 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.34–7.22 (m, 8H), 7.03–7.01 (m, 2H), 4.93 (s, 2H), 4.45 (s, 1H); ^{13}C NMR (126

MHz, CDCl₃) δ 165.8, 141.4, 137.5, 129.6, 128.6, 128.43, 128.36, 128.1, 127.3, 52.9, 47.4; HRMS (CI) calcd for C₁₅H₁₄N₃O [M+H]⁺ 252.1137, found 252.1143.

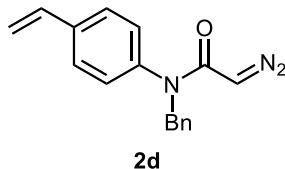
N,N-Dibenzyl-2-diazoacetamide (**2c**)



A total of 20.9 mg of **2c** (79%) was obtained from the reaction with azide **1c** (28.0 mg, 0.10 mmol), tosyl hydrazide (93.7 mg, 0.50 mmol, 5.0 eq), pyrrolidine (42.0 μ L, 0.50 mmol, 5.0 eq), and TBAF (0.44 mL, 1.0 M in THF, 0.44 mmol, 4.4 eq) in DMSO (0.5 mL, 0.2 M) for 3 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1 to 6/1).

Pale yellow oil; R_f value 0.63 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 2106, 1605, 1428, 1213 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃) δ 7.37–7.34 (m, 4H), 7.31–7.28 (m, 2H), 7.23 (br-s, 4H), 4.99 (s, 1H), 4.62–4.29 (br-m, 4H); ¹³C NMR (126 MHz, CDCl₃) δ 166.5, 136.6 (br), 128.8, 127.6, 126.4 (br), 49.4 (br), 47.0; HRMS (CI) calcd for C₁₆H₁₆N₃O [M+H]⁺ 266.1293, found 266.1295.

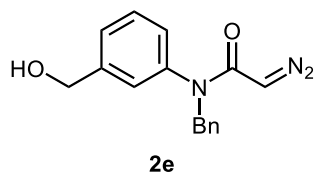
N-Benzyl-2-diazo-*N*-(4-vinylphenyl)acetamide (**2d**)



A total of 23.9 mg of **2d** (87%) was obtained from the reaction with azide **1d** (29.1 mg, 0.10 mmol), tosyl hydrazide (93.1 mg, 0.50 mmol, 5.0 eq), pyrrolidine (42.0 μ L, 0.50 mmol, 5.0 eq), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 eq) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 10/1 to 8/1).

Pale yellow oil; R_f value 0.8 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 2106, 1624, 1600, 1509, 1396 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃) δ 7.35 (d, 2H, J = 8.5 Hz), 7.29–7.22 (m, 5H), 6.97 (d, 2H, J = 8.0 Hz), 6.67 (dd, 1H, J = 17.0, 11.0 Hz), 5.74 (d, 1H, J = 17.0 Hz), 5.29 (d, 1H, J = 11.0 Hz), 4.92 (s, 2H), 4.49 (s, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 165.8, 140.7, 137.4, 137.3, 135.5, 128.6, 128.5, 128.4, 127.4, 127.2, 115.2, 52.8, 47.4; LRMS (EI, M = C₁₇H₁₅N₃O) m/z 277 (M⁺, 2%), 249 (48), 158 (10), 130 (11), 91 (100); HRMS (EI) calcd for C₁₇H₁₅N₃O (M⁺) 277.1215, found 277.1208.

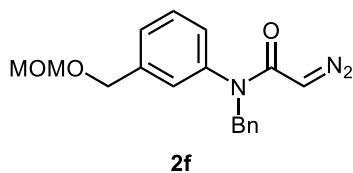
N-Benzyl-2-diazo-*N*-(3-(hydroxymethyl)phenyl)acetamide (**2e**)



A total of 13.0 mg of **2e** (46%) was obtained from the reaction with azide **1e** (29.5 mg, 0.10 mmol), tosyl hydrazide (93.2 mg, 0.50 mmol, 5.0 eq), pyrrolidine (42.0 μ L, 0.50 mmol, 5.0 eq), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 eq) in DMSO (0.5 mL, 0.2 M) for 3 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 1/1) and GPC for further purification.

Pale yellow oil; R_f value 0.5 (hexane/ethyl acetate = 1/2); IR (NaCl, neat) ν_{\max} 3396, 3117, 2106, 1584, 1403 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.32–7.21 (m, 7H), 7.05 (s, 1H), 6.93 (ddd, 1H, $J = 5.0, 1.5, 1.5$ Hz), 4.92 (s, 2H), 4.66 (d, 2H, $J = 5.5$ Hz), 4.46 (s, 1H), 1.82–1.78 (m, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 165.9, 142.9, 141.5, 137.4, 129.6, 128.5, 128.4, 127.4, 126.5, 126.4, 64.3, 52.9, 47.5; HRMS (CI) calcd for $\text{C}_{16}\text{H}_{16}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 282.1243, found 282.1236.

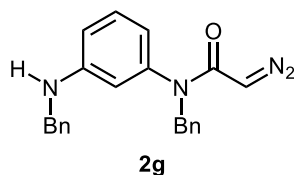
N-Benzyl-2-diazo-*N*-(3-((methoxymethoxy)methyl)phenyl)-acetamide (**2f**)



A total of 28.1 mg of **2f** (87%) was obtained from the reaction with azide **1f** (34.0 mg, 0.10 mmol), tosyl hydrazide (93.6 mg, 0.50 mmol, 5.0 eq), pyrrolidine (42.0 μ L, 0.50 mmol, 5.0 eq), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 eq) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 10/1 to 6/1 to 4/1).

Pale yellow oil; R_f value 0.6 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 2932, 2885, 2107, 1625, 1603, 1587, 1399 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31–7.21 (m, 7H), 7.04 (s, 1H), 6.93 (ddd, 1H, $J = 6.0, 2.5, 1.5$ Hz), 4.92 (s, 2H), 4.66 (s, 2H), 4.53 (s, 2H), 4.46 (s, 1H), 3.37 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 165.8, 141.5, 139.9, 137.4, 129.6, 128.6, 128.3, 127.6, 127.4, 127.32, 127.30, 95.8, 68.3, 55.4, 52.8, 47.4; HRMS (MALDI-TOF) calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{NaO}_3$ $[\text{M}+\text{Na}]^+$ 348.1324, found 348.1314.

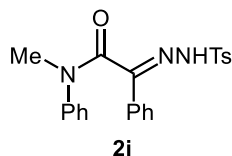
N-Benzyl-*N*-(3-(benzylamino)phenyl)-2-diazoacetamide (**2g**)



A total of 17.2 mg of **2g** (48%) was obtained from the reaction with azide **1g** (37.0 mg, 0.10 mmol), tosyl hydrazide (93.2 mg, 0.50 mmol, 5.0 eq), pyrrolidine (42.0 μ L, 0.50 mmol, 5.0 eq), and TBAF (0.50 mL, 1.0 M in THF, 0.50 mmol, 5.0 eq) in DMSO (0.5 mL, 0.2 M) for 6 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 10/1 to 8/1 to 6/1).

Pale yellow oil; R_f value 0.77 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 2102, 1597, 1492, 1399, 1346 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.34 (dd, 2H, $J = 7.0, 5.5$ Hz), 7.33–7.21 (m, 8H), 7.08 (dd, 1H, $J = 8.0, 8.0$ Hz), 6.55 (dd, 1H, $J = 8.5, 2.0$ Hz), 6.35 (dd, 1H, $J = 7.5, 1.0$ Hz), 6.21 (dd, 1H, $J = 2.0, 2.0$ Hz), 4.86 (s, 2H), 4.52 (s, 1H), 4.23 (s, 2H), 4.19 (br, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 165.9, 148.9, 142.5, 138.6, 137.8, 130.1, 128.7, 128.5, 128.3, 127.40, 127.36, 127.2, 116.8, 112.6, 112.2, 52.7, 47.9, 47.3; HRMS (MALDI-TOF) calcd for $\text{C}_{22}\text{H}_{20}\text{N}_4\text{ONa}$ $[\text{M}+\text{Na}]^+$ 379.1535, found 379.1529.

N-Methyl-*N*,2-diphenyl-2-(2-tosylhydrazineylidene)acetamide (**2i**)

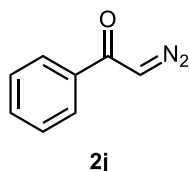


TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 eq) was added dropwise to a stirred solution of azide **1i** (26.6 mg, 0.10 mmol) and tosyl hydrazide (93.5 mg, 0.50 mmol, 5.0 eq) in DMSO (0.5 mL, 0.2 M) at 25 $^{\circ}\text{C}$ under a nitrogen atmosphere. The reaction mixture was diluted with diethyl ether and quenched with a saturated aqueous sodium bicarbonate solution after stirring for 1 h. The mixture was extracted three times with ether and was washed with water and brine. The collected organic layer was dried over anhydrous sodium sulfate. Concentration and purification by neutral silica gel column chromatography (hexane/ethyl acetate = 5/1 to 2/1) followed by GPC for further purification gave tosyl hydrazone **2i** (30.1 mg, 0.0739 mmol, 74%). Recrystallization for X-ray analysis was performed with hexane/ether by the vapor diffusion method.

Colorless crystal; R_f value 0.27 (hexane/ethyl acetate = 1/1); mp 183–184 $^{\circ}\text{C}$; IR (NaCl, neat) ν_{\max} 1640, 1594, 1496, 1389, 1348, 1169, 1082, 915 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3 , major isomer) δ 8.70 (d, 1H, $J = 5.0$ Hz), 7.84 (d, 2H, $J = 8.0$

Hz), 7.27–7.26 (m, 2H), 7.23–7.18 (m, 3H), 7.14–7.07 (m, 5H), 6.93–6.71 (m, 2H), 3.43 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3 , major rotamer) δ 163.6, 150.9, 144.1, 140.4, 135.2, 132.5, 129.8, 129.6, 129.2, 128.3, 128.1, 128.0, 126.1, 125.8, 36.4, 21.6; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{21}\text{N}_3\text{NaO}_3\text{S}$ $[\text{M}+\text{Na}]^+$ 430.1201, found 430.1197.

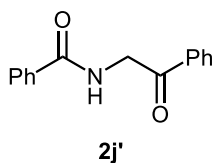
α -Diazo acetophenone (**2j**)^{10a,59)}



A total of 10.7 mg of **2j** (74%) was obtained from the reaction with azide **1j** (16.0 mg, 0.10 mmol), tosyl hydrazide (93.5 mg, 0.50 mmol, 5.0 eq), and pyrrolidine (21.0 μL , 0.25 mmol, 2.5 eq) in DMSO (0.5 mL, 0.2 M) for 0.5 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 15/1).

Pale yellow solid; R_f value 0.37 (hexane/ethyl acetate = 3/1); mp 44.6–45.1 $^\circ\text{C}$; IR (NaCl, neat) ν_{max} 2106, 1613, 1364, 1227 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.77–7.76 (m, 2H), 7.55 (tt, 1H, $J = 7.5, 1.5$ Hz), 7.47–7.44 (m, 2H), 5.91 (s, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 186.3, 136.6, 132.7, 128.6, 126.7, 54.2; HRMS (CI) calcd for $\text{C}_8\text{H}_7\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 147.0558, found 147.0547.

N-(2-Oxo-2-phenylethyl)benzamide (**2j'**)

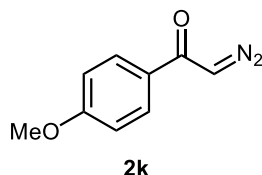


To a stirred solution of azido ketone **1j** (16.2 mg, 0.10 mmol) in DMSO (1.0 mL, 0.1 M) was added TBAF (0.22 mL, 1.0 M in THF, 0.22 mmol, 2.2 eq) at 25 $^\circ\text{C}$. After 15 min, the reaction was quenched with water, and the mixture was extracted twice with ether. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. Concentration and purification by neutral silica gel column chromatography (hexane/ethyl acetate = 10/1 to 5/1) gave 5.0 mg of compound **2j'** (42%). Recrystallization for X-ray analysis was performed with hexane/ethyl acetate by the vapor diffusion method.

Yellow crystal; R_f value 0.27 (hexane/ethyl acetate = 2/1); mp 115–116 $^\circ\text{C}$; IR (NaCl, neat) ν_{max} 3330, 3061, 2924, 1698, 1645, 1537, 1488, 1225 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.03 (dd, 2H, $J = 8.5, 1.0$ Hz), 7.88 (dd, 2H, $J = 8.0, 1.5$ Hz), 7.05 (m, 1H), 7.55–7.51 (m, 3H), 7.47 (dd, 2H, $J = 8.0, 6.5$ Hz), 7.34 (br, 1H), 4.96

(d, 2H, $J = 4.0$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 194.2, 167.4, 134.3, 134.2, 133.8, 131.8, 129.0, 128.6, 128.0, 127.1, 46.9; LRMS (EI, $M = \text{C}_{15}\text{H}_{13}\text{NO}_2$) m/z 239 (20%, M^+), 211 (18), 134 (20), 105 (100); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_2$ (M^+) 239.0946, found 239.0952.

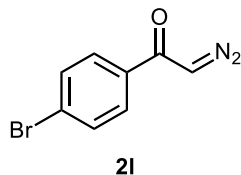
2-Diazo-1-(4-methoxyphenyl)ethan-1-one (**2k**)^{10a,59)}



A total of 13.2 mg of **2k** (75%) was obtained from azide **1k** (19.1 mg, 0.10 mmol), tosyl hydrazide (93.9 mg, 0.50 mmol, 5.0 eq), and pyrrolidine (21.0 μL , 0.25 mmol, 2.5 eq) in DMSO (0.5 mL, 0.2M) for 3 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1 to 6/1)

Pale yellow solid; R_f value 0.50 (hexane/ethyl acetate = 1/1); mp 75–76 °C; IR (NaCl, neat) ν_{max} 3099, 2115, 1611, 1590, 1567, 1388, 1372 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.74 (d, 2H, $J = 9.0$ Hz), 6.93 (d, 2H, $J = 9.0$ Hz), 5.85 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 185.2, 163.2, 129.4, 128.7, 113.8, 55.4, 53.5; LRMS (EI, $M = \text{C}_9\text{H}_8\text{N}_2\text{O}_2$) m/z 176 (79%, M^+), 135 (100), 120 (28), 91 (35), 77 (52); HRMS (EI) calcd for $\text{C}_9\text{H}_8\text{N}_2\text{O}_2$ (M^+) 176.0586, found 176.0589.

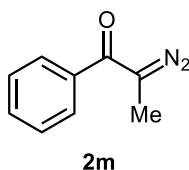
1-(4-Bromophenyl)-2-diazoethan-1-one (**2l**)^{10a,59)}



A total of 13.0 mg of **2l** (58%) was obtained from the reaction with azide **1l** (17.4 mg, 0.10 mmol), tosyl hydrazide (93.1 mg, 0.50 mmol, 5.0 eq), and pyrrolidine (21.0 μL , 0.25 mmol, 2.5 eq) in DMSO (0.5 mL, 0.2 M) for 0.5 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1).

Pale yellow solid; R_f value 0.37 (hexane/ethyl acetate = 3/1); mp 110–111 °C; IR (KBr, disc) ν_{max} 3115, 2118, 1608, 1590, 1401, 1379, 1070 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.63 (d, 2H, $J = 8.5$ Hz), 7.59 (d, 2H, $J = 8.5$ Hz), 5.88 (s, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 185.1, 135.3, 131.9, 128.2, 127.6, 54.4; LRMS (EI, $M = \text{C}_8\text{H}_5\text{BrN}_2\text{O}$) m/z 226 (42%, M^+ of ^{81}Br), 224 (42, M^+ of ^{79}Br), 185 (55), 183 (56), 89 (100); HRMS (EI) calcd for $\text{C}_8\text{H}_5^{79}\text{BrN}_2\text{O}$ (M^+) 223.9585, found 223.9589.

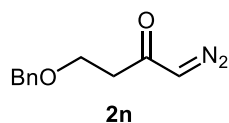
2-Diazo-1-phenylpropan-1-one (**2m**)



A total of 10.0 mg of **2m** (63%) was obtained from the reaction with azide **1m** (17.4 mg, 0.10 mmol), tosyl azide (93.1 mg, 0.50 mmol, 5.0 eq), and pyrrolidine (21.0 μ L, 0.25 mmol, 2.5 eq) in DMSO (1.0 mL, 0.1 M) for 0.5 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 20/1).

Pale yellow oil; R_f value 0.40 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{\max} 2071, 1606, 1344, 1003 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.59–7.57 (m, 2H), 7.50–7.47 (m, 1H), 7.44–7.41 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 190.2, 137.6, 131.3, 128.5, 127.1, 29.7, 9.5; LRMS (EI, $M = \text{C}_9\text{H}_8\text{N}_2\text{O}$) m/z 160 (16%, M^+), 132 (24), 104 (100), 103 (78), 77 (59), 51 (32); HRMS (EI) calcd for $\text{C}_9\text{H}_8\text{N}_2\text{O}$ (M^+) 160.0637, found 160.0631.

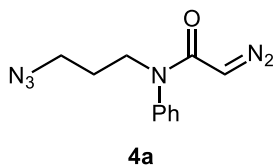
4-(Benzyloxy)-1-diazobutan-2-one (**2n**)



A total of 10.3 mg of **2n** (51%) was obtained from the reaction with azide **1n** (21.8 mg, 0.10 mmol), tosyl hydrazide (93.5 mg, 0.50 mmol, 5.0 eq), and pyrrolidine (21.0 μ L, 0.25 mmol, 2.5 eq) in DMSO (1.0 mL, 0.1 M) for 4 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1).

Pale yellow oil; R_f value 0.60 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 2866, 2104, 1637, 1369, 1322, 1097 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.36–7.27 (m, 5H), 5.36 (s, 1H), 4.52 (s, 2H), 3.76 (t, 2H, $J = 6.5$ Hz), 2.59 (br-s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 193.0, 137.9, 128.4, 127.68, 127.66, 73.2, 65.8, 55.1, 41.3; HRMS (CI) calcd for $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}_2$ [$M+H$] $^+$ 205.0977, found 205.0979.

N-(3-Azidopropyl)-2-diazo-*N*-phenylacetamide (**4a**)



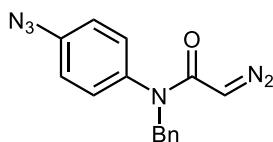
The following is a 0.10 mmol scale reaction: 20.5 mg of **4a** (84%) was obtained from the reaction with diazide **3a** (25.8 mg, 0.10 mmol), tosyl hydrazide (93.8 mg, 0.50 mmol, 5.0 eq), pyrrolidine (42.0 μ L, 0.50 mmol, 5.0 eq), and TBAF (0.36 mL,

1.0 M in THF, 0.36 mmol, 3.6 eq) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 8/1 to 5/1).

The following is a 1.0 mmol scale reaction: 219.5 mg of **4a** (90%) was obtained from the reaction with diazide **3a** (259.1 mg, 1.0 mmol), tosyl hydrazide (931.9 mg, 5.0 mmol, 5.0 eq), pyrrolidine (0.42 mL, 5.0 mmol, 5.0 eq), and TBAF (3.6 mL, 1.0 M in THF, 3.6 mmol, 3.6 eq) in DMSO (5.0 mL, 0.2M) for 1 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 5/1 to 4/1 to 3/1 to 2/1).

Pale yellow oil; R_f value 0.63 (hexane/ethyl acetate= 1/1); IR (NaCl, neat) ν_{\max} 2102, 1622, 1592, 1401, 1263 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.43 (dd, 2H, $J = 8.0, 7.5$ Hz), 7.37 (t, 1H, $J = 8.0$ Hz), 7.19 (d, 2H, $J = 7.5$ Hz), 4.42 (s, 1H), 3.84 (t, 2H, $J = 7.0$ Hz), 3.36 (t, 2H, $J = 6.5$ Hz), 1.83 (tt, 2H, $J = 7.0, 6.5$ Hz); ^{13}C NMR (126MHz, CDCl_3) δ 165.9, 141.3, 129.9, 128.3, 128.2, 49.1, 47.4, 46.7, 27.7; HRMS (CI) calcd for $\text{C}_{11}\text{H}_{13}\text{N}_6\text{O}$ $[\text{M}+\text{H}]^+$ 245.1151, found 245.1152.

N-(4-Azidophenyl)-*N*-benzyl-2-diazoacetamide (**4b**)

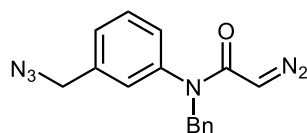


4b

A total of 23.9 mg of **4b** (82%) was obtained from the reaction with diazide **3b** (30.6 mg, 0.10 mmol), tosyl hydrazide (93.6 mg, 0.50 mmol, 5.0 eq), pyrrolidine (42.0 μL , 0.50 mmol, 5.0 eq), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 eq) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 15/1 to 10/1).

Pale yellow oil; R_f value 0.37 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{\max} 2107, 1623, 1505, 1397, 1294, 1280 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.29–7.24 (m, 3H), 7.21–7.19 (m, 2H), 7.00–6.95 (m, 4H), 4.89 (s, 2H), 4.43 (s, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 165.8, 139.9, 137.8, 137.2, 129.9, 128.6, 128.4, 127.5, 120.0, 52.8, 47.4; LRMS (EI, $\text{M} = \text{C}_{15}\text{H}_{12}\text{N}_6\text{O}$) m/z 292 (3%, M^+), 264 (52), 236 (27), 223 (24), 196 (18), 91 (100), 84 (19); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{12}\text{N}_6\text{O}$ (M^+) 292.1073, found 292.1071.

N-(3-(Azidomethyl)phenyl)-*N*-benzyl-2-diazoacetamide (**4c**)

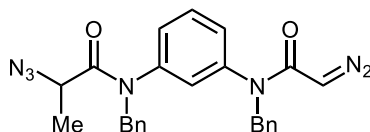


4c

A total of 27.1 mg of **4c** (89%) was obtained from the reaction with diazide **3c** (32.1 mg, 0.10 mmol), tosyl hydrazide (93.8 mg, 0.50 mmol, 5.0 eq), pyrrolidine (42.0 μ L, 0.50 mmol, 5.0 eq), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 eq) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1 to 8/1).

Pale yellow oil; R_f value 0.23 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{\max} 2104, 1623, 1397, 706 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.35 (t, 1H, $J = 8.0$ Hz), 7.29–7.24 (m, 4H), 7.23–7.21 (m, 2H), 7.00–6.98 (m, 2H), 4.93 (s, 2H), 4.44 (s, 1H), 4.29 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 165.7, 141.9, 137.3, 137.1, 130.1, 128.6, 128.5, 128.3, 128.1, 127.9, 127.5, 54.0, 52.9, 47.6; HRMS (CI) calcd for $\text{C}_{16}\text{H}_{15}\text{N}_6\text{O}$ $[\text{M}+\text{H}]^+$ 307.1307, found 307.1304.

2-Azido-*N*-benzyl-*N*-(3-(*N*-benzyl-2-diazoacetamido)phenyl)-propanamide (**4d**)

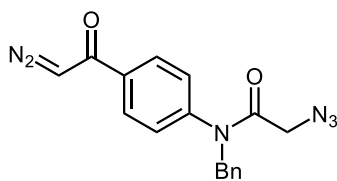


4d

A total of 23.1 mg of **4d** (51%) was obtained from the reaction with diazide **3d** (46.9 mg, 0.10 mmol), tosyl hydrazide (93.5 mg, 0.50 mmol, 5.0 eq), pyrrolidine (42.0 μ L, 0.50 mmol, 5.0 eq), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 eq) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 10/1 to 4/1) and GPC for further purification.

Pale yellow oil; R_f value 0.67 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 2107, 1665, 1595, 1395, 702 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.36 (t, 1H, $J = 7.5$ Hz), 7.25–7.22 (m, 6H), 7.10–7.03 (m, 6H), 6.40 (s, 1H), 4.94–4.75 (m, 4H), 3.90 (s, 1H), 3.25 (q, 1H, $J = 6.0$ Hz), 1.29 (d, 3H, $J = 6.0$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 169.9, 165.3, 142.2, 141.2, 136.7, 136.1, 130.9, 129.4, 129.0, 128.6, 128.5, 128.0, 127.8, 127.7, 127.5, 54.1, 53.0, 52.4, 47.4, 16.3; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{23}\text{N}_7\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 476.1811, found 476.1804.

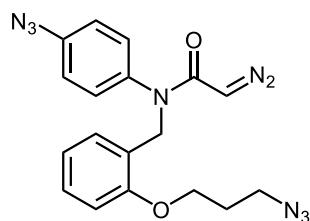
2-Azido-*N*-benzyl-*N*-(4-(2-diazoacetyl)phenyl)acetamide (**4e**)



4e

A total of 21.5 mg of **4e** (65%) as a pale yellow oil was obtained from the reaction with diazide **3e** (34.8 mg, 0.10 mmol), tosyl hydrazide (93.5 mg, 0.50 mmol, 5.0 eq), and pyrrolidine (21.0 μ L, 0.25 mmol, 2.5 eq) in DMSO (0.5 mL, 0.2 M) for 0.5 h followed by neutral silica gel column chromatography (hexane/ethyl acetate = 2/1). Solid **4e** was obtained after storage in a refrigerator. Recrystallization for X-ray analysis was performed with hexane/ethyl acetate by the vapor diffusion method. Pale yellow solid; R_f value 0.37 (hexane/ethyl acetate = 1/1); mp 65–66 °C; IR (NaCl, neat) ν_{\max} 2105, 1671, 1602, 1361 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.74 (d, 2H, $J = 8.0$ Hz), 7.28–7.26 (m, 3H), 7.17 (dd, 2H, $J = 4.0, 3.5$ Hz), 7.06 (d, 2H, $J = 7.5$ Hz), 5.87 (s, 1H), 4.91 (s, 2H), 3.60 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 184.7, 166.9, 144.0, 136.6, 136.0, 128.9, 128.6, 128.5, 128.3, 127.9, 54.8, 53.3, 50.9; LRMS (EI, $M = \text{C}_{17}\text{H}_{14}\text{N}_6\text{O}_2$) m/z 334 (18%, M^+), 250 (21), 222 (27), 187 (28), 174 (62), 118 (71), 91 (100); HRMS (EI) calcd for $\text{C}_{17}\text{H}_{14}\text{N}_6\text{O}_2$ (M^+) 334.1178, found 334.1177.

N-(4-Azidophenyl)-*N*-(2-(3-azidopropoxy)benzyl)-2-diazoacetamide (**6a**)



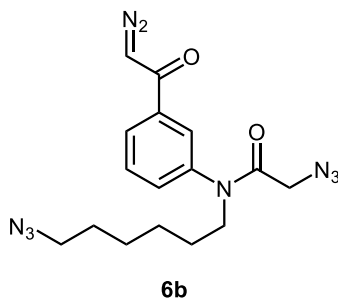
6a

A total of 30.6 mg of **6a** (78%) was obtained from triazide **5a** (40.6 mg, 0.10 mmol), tosyl hydrazide (93.7 mg, 0.50 mmol, 5.0 eq), pyrrolidine (42.0 μ L, 0.50 mmol, 5.0 eq), and TBAF (0.36 mL, 1.0 M in THF, 0.36 mmol, 3.6 eq) in DMSO (0.5 mL, 0.2 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1 to 8/1 to 6/1).

Pale yellow oil; R_f value 0.77 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 2103, 1623, 1505, 1396, 1287, 1244 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.26–7.25 (m, 1H), 7.20 (ddd, 1H, $J = 8.0, 8.0, 1.5$ Hz), 7.02 (d, 2H, $J = 8.5$ Hz), 6.94 (d, 2H, $J = 8.5$ Hz), 6.89 (dd, 1H, $J = 7.5, 7.5$ Hz), 6.78 (d, 1H, $J = 8.0$ Hz), 4.96 (s, 2H), 4.44 (s, 1H), 3.91 (t, 2H, $J = 6.0$ Hz), 3.38 (t, 2H, $J = 7.0$ Hz), 1.89

(tt, 2H, $J = 7.5, 6.0$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 165.6, 156.3, 139.8, 138.2, 130.4, 129.8, 128.8, 125.2, 120.8, 119.8, 110.9, 64.2, 48.0, 47.4, 47.3, 28.7; LRMS (EI, $M = \text{C}_{18}\text{H}_{17}\text{N}_9\text{O}_2$) m/z 391 (9%, M^+), 363 (42), 335 (26), 162 (24), 134 (100), 105 (45); HRMS (EI) calcd for $\text{C}_{18}\text{H}_{17}\text{N}_9\text{O}_2$ (M^+) 391.1505, found 391.1503.

2-Azido-*N*-(6-azidohexyl)-*N*-(3-(2-diazoacetyl)phenyl)acetamide (**6b**)



A total of 124.5 mg of **6b** (51%) was obtained from the reaction with triazide **5b** (253.1 mg, 0.658 mmol), tosyl hydrazide (613.0 mg, 3.29 mmol, 5.0 eq), and pyrrolidine (137.5 μL , 1.65 mmol, 2.5 eq) in DMSO (6.6 mL, 0.1 M) for 15 min followed by neutral silica gel column chromatography (hexane/ethyl acetate = 3/1 to 2/1).

Pale yellow oil; R_f value 0.4 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 2105, 1670, 1578, 1362 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.72 (d, 1H, $J = 7.5$ Hz), 7.63 (s, 1H), 7.55 (dd, 1H, $J = 7.0, 7.0$ Hz), 7.35 (d, 1H, $J = 8.0$ Hz), 5.92 (s, 1H), 3.73 (t, 2H, $J = 7.5$ Hz), 3.54 (s, 2H), 3.24 (t, 2H, $J = 6.5$ Hz), 1.60–1.50 (m, 4H), 1.40–1.31 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ 184.5, 166.9, 141.3, 138.6, 132.0, 130.5, 126.7, 126.3, 55.0, 51.2, 50.9, 49.6, 28.7, 27.4, 26.3, 26.2; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{19}\text{N}_9\text{NaO}_2$ [$M+\text{Na}$] $^+$ 392.1559, found 392.1556.

6-3 Synthesis of Oximes

NOTE: Stereochemistry of oximes (*E/Z*) was not determined. However, the products were obtained as a single stereoisomer unless otherwise noted. The chloroform-*d* should be passed through alumina prior to NMR experiments, otherwise the products isomerized to *E/Z* mixtures.

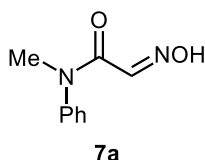
General Procedure for Synthesis of Oximes

From amides: TBAF (3.2 eq, 1.0 M in THF) was added to a stirred solution of α -azido amide (1.0 eq) and hydroxylammonium chloride (1.2 eq) in DMSO (0.1 M based on azido substrate) at 25 $^\circ\text{C}$ (set by water bath) under the nitrogen gas

atmosphere. After completion of the reaction checked by TLC, the mixture was diluted with ether and quenched with water. The solution was extracted three times with ether, and was washed with water and brine. The collected organic layer was dried over anhydrous sodium sulfate. Concentration and purification by flash neutral silica gel column chromatography gave the oxime product.

From ketones: TBAF (1.8 eq, 1.0 M in THF) was added dropwise to a stirred solution of α -azido ketone (1.0 eq) and hydroxylammonium chloride (1.2 eq) in DMSO (0.1 M based on azido substrate) at 25 °C (set by water bath) under the nitrogen gas atmosphere. After completion of the reaction checked by TLC, the mixture was diluted with ether and quenched with water. The solution was extracted three times with ether, and was washed with water and brine. The collected organic layer was dried over anhydrous sodium sulfate. Concentration and purification by flash neutral silica gel column chromatography gave the oxime product.

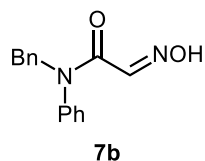
2-(Hydroxyimino)-*N*-methyl-*N*-phenylacetamide (**7a**)



A total of 16.1 mg of **7a** (91%) was obtained from the reaction with azide **1a** (19.0 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.32 mL, 1.0 M in THF, 0.32 mmol, 3.2 eq) in DMSO (1.0 mL, 1.0 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1 to 3/1 to 1/1 to 1/2).

White solid; R_f value 0.20 (hexane/ethyl acetate = 1/1); mp 168–170 °C; IR (NaCl, neat) ν_{\max} 3165, 1654, 1590, 1474, 1389, 1065 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 10.2 (s, 1H), 7.48 (s, 1H), 7.43 (dd, 2H, $J = 7.5, 7.5$ Hz), 7.37 (t, 1H, $J = 7.3$ Hz), 7.19 (d, 2H, $J = 7.5$ Hz), 3.38 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 161.5, 142.2, 141.8, 130.0, 128.3, 127.0, 37.5; LRMS (EI, $M = \text{C}_9\text{H}_{10}\text{N}_2\text{O}_2$) m/z 178 (69%, M^+), 161 (70), 106 (100); HRMS (EI) calcd for $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_2$ (M^+) 178.0742, found 178.0736.

N-Benzyl-2-(hydroxyimino)-*N*-phenylacetamide (**7b**)

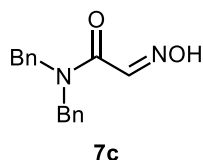


A total of 25.1 mg of **7b** (99%) was obtained from the reaction with azide **1b** (26.5

mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.27 mL, 1.0 M in THF, 0.27 mmol, 2.7 eq) in DMSO (1.0 mL, 1.0 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1 to 3/1 to 1/1).

Colorless amorphous solid; R_f value 0.4 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 3298, 3063, 1656, 1593, 1495, 1454, 1253 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.45 (s, 1H), 7.34–7.32 (m, 3H), 7.26–7.24 (m, 3H), 7.21–7.19 (m, 2H), 6.99–6.47 (m, 2H), 4.98 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 161.3, 142.4, 140.1, 136.3, 129.8, 128.9, 128.5, 128.4, 128.2, 127.6, 53.1; HRMS (CI) calcd for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 255.1134, found 255.1140.

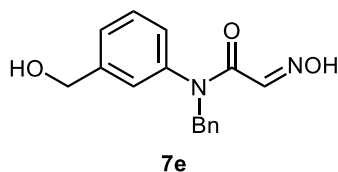
N,N-Dibenzyl-2-(hydroxyimino)acetamide (**7c**)



A total of 25.8 mg of **7c** (96%) was obtained from the reaction with azide **1c** (28.0 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.32 mL, 1.0 M in THF, 0.32 mmol, 3.2 eq) in DMSO (1.0 mL, 1.0 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1 to 3/1).

White amorphous solid; R_f value 0.53 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 3061, 3030, 2925, 1644, 1604, 1496, 1454 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.92 (s, 1H), 7.38–7.26 (m, 7H), 7.26–7.18 (m, 3H), 4.60 (s, 2H), 4.59 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 163.0, 143.4, 136.1, 135.8, 128.9, 128.7, 128.5, 127.9, 127.7, 127.0, 50.0, 48.0; HRMS (CI) calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 269.1290, found 269.1295.

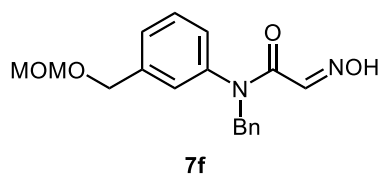
N-Benzyl-2-(hydroxyimino)-*N*-(3-(hydroxymethyl)phenyl)acetamide (**7e**)



A total of 25.5 mg of **7e** (90%) as single isomer was obtained from the reaction with azide **1e** (29.5 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.32 mL, 1.0 M in THF, 0.32 mmol, 3.2 eq) in DMSO (1.0 mL, 1.0 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 2/1 to 1/1 to 1/2 with 2% methanol).

White powder; R_f value 0.3 (hexane/ethyl acetate = 1/2); mp 137–138 °C; IR (NaCl, neat) ν_{\max} 2870, 1655, 1602, 1586, 1453 cm^{-1} ; ^1H NMR (500 MHz, CD_3OD) δ 7.36–7.32 (m, 3H), 7.28–7.20 (m, 5H), 7.14 (s, 1H), 6.95–6.94 (m, 1H), 5.01 (s, 2H), 4.56 (s, 2H); ^{13}C NMR (126 MHz, CD_3OD) δ 163.9, 145.2, 143.0, 141.7, 138.0, 130.7, 129.7, 129.5, 128.7, 128.2, 127.9, 127.4, 64.3, 54.0; HRMS (CI) calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 285.1239, found 285.1230.

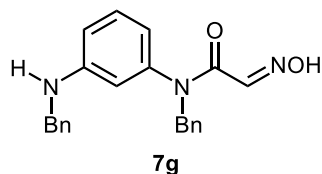
N-Benzyl-2-(hydroxyimino)-*N*-(3-((methoxymethoxy)methyl)phenyl)acetamide (**7f**)



A total of 31.5 mg of **7f** (96%, ratio of isomers = 6.3 : 1 based on ^1H NMR) as isomeric mixture was obtained from the reaction with azide **1f** (34.0 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.32 mL, 1.0 M in THF, 0.32 mmol, 3.2 eq) in DMSO (1.0 mL, 1.0 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 6/1 to 2/1 to 1/2).

Colorless amorphous solid; R_f value 0.33 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 3316, 2935, 2887, 1660, 1453, 1047 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) peaks from major isomer are listed. δ 7.45 (s, 1H), 7.30 (d, 2H, $J = 5.0$ Hz), 7.26–7.18 (m, 5H), 7.02 (s, 1H), 6.88 (m, 1H), 4.97 (s, 2H), 4.65 (s, 2H), 4.53 (s, 2H), 3.36 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) Peaks from major isomer are listed. δ 161.5, 142.1, 140.2, 140.1, 136.3, 129.7, 128.9, 128.4, 127.6, 127.4, 127.1, 95.7, 68.1, 55.4, 53.1; LRMS (EI, $\text{M} = \text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4$) m/z 328 (2%, M^+), 311 (9), 194 (16), 91 (100); HRMS (EI) calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_4$ (M^+) 328.1423, found 328.1427.

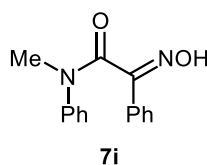
N-Benzyl-*N*-(3-(benzylamino)phenyl)-2-(hydroxyimino)acetamide (**7g**)



A total of 34.4 mg of **7g** (96%, isomeric ratio = 4.9 : 1 based on ^1H NMR) as isomeric mixture was obtained from the reaction with azide **1g** (37.0 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.32 mL, 1.0 M in THF, 0.32 mmol, 3.2 eq) in DMSO (1.0 mL, 1.0 M) for 2 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 5/1 to 3/1 to 2/1 to 1/1).

Yellow amorphous solid; R_f value 0.3 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 3354, 3061, 6029, 1656, 1602, 1495, 1453 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) Peaks from major isomer are listed. δ 10.7 (br, 1H), 7.54 (s, 1H), 7.35 (dd, 2H, $J = 7.5, 6.5$ Hz), 7.31–7.26 (m, 3H), 7.25–7.19 (m, 5H), 7.07 (dd, 1H, $J = 8.0, 8.0$ Hz), 6.54 (dd, 1H, $J = 8.0, 1.5$ Hz), 6.30 (d, 1H, $J = 6.5$ Hz), 6.20 (s, 1H), 4.90 (s, 2H), 4.20 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) Peaks from major isomer are listed. δ 161.4, 149.1, 142.4, 141.4, 138.4, 136.7, 130.3, 128.9, 128.7, 128.3, 127.45, 127.42, 127.39, 116.7, 112.9, 111.9, 52.9, 47.9; HRMS (MALDI-TOF) calcd for $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_2\text{Na}$ $[\text{M}+\text{Na}]^+$ 382.1531, found 382.1526.

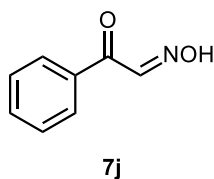
2-(Hydroxyimino)-*N*-methyl-*N*,2-diphenylacetamide (**7i**)



Total of 23.2 mg of **7i** (91%) was obtained from the reaction with azide **1i** (26.6 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.32 mL, 1.0 M in THF, 0.32 mmol, 3.2 eq) in DMSO (1.0 mL, 0.1 M) for 2 h. However in this case, the reaction mixture was diluted with diethyl ether and quenched with saturated aqueous solution of sodium bicarbonate. This quenching method was important to prevent the generation of hydrolyzed material of oxime **7i**. The mixture were extracted three times with ether and was washed with water and brine. The collected organic layer was dried over anhydrous sodium sulfate. Concentration and purification by neutral silica gel column chromatography (hexane/ethyl acetate = 5/1 to 2/1 with 1% of triethylamine) afforded the product as above.

Colorless oil; R_f value 0.4 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 3238, 3061, 1649, 1594, 1496 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.60 (br, 1H), 7.66 (br, 1H), 7.55–7.41 (m, 2H), 7.40 (dd, 1H, $J = 7.5, 7.0$ Hz), 7.33 (dd, 1H, $J = 7.5, 7.5$ Hz), 7.20–7.15 (m, 3H), 7.01 (br, 2H), 3.45 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.3, 167.8, 141.8, 134.9, 131.1, 129.4, 129.3, 128.4, 127.8, 127.3, 126.5, 36.7; HRMS (EI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2$ (M^+) 254.1055, found 254.1055.

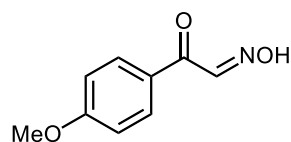
2-Oxo-2-phenylacetaldehyde oxime (**7j**)



A total of 11.9 mg of **7j** (80%) was obtained from the reaction with azide **1j** (16.1 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.18 mL, 1.0 M in THF, 0.18 mmol, 1.8 eq) in DMSO (1.0 mL, 1.0 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 15/1 to 8/1).

Yellow powder; R_f value 0.60 (hexane/ethyl acetate = 1/1); mp 124–125 °C; IR (NaCl, neat) ν_{\max} 3272, 2893, 1676, 1594, 1460, 1240 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.09–8.03 (m, 4H), 7.61 (t, 1H, $J = 7.3$ Hz), 7.48 (dd, 2H, $J = 8.0, 8.0$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 188.6, 148.4, 135.7, 133.7, 129.9, 128.5; LRMS (EI, $M = \text{C}_8\text{H}_7\text{NO}_2$) m/z 149 (36%, M^+), 105 (100), 77 (63); HRMS (EI) calcd for $\text{C}_8\text{H}_7\text{NO}_2$ [M^+] 149.0477, found 149.0475.

2-(4-Methoxyphenyl)-2-oxoacetaldehyde oxime (**7k**)

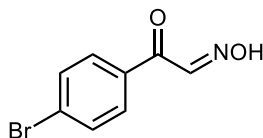


7k

A total of 15.3 mg of **7k** (86%) was obtained from the reaction with azide **1k** (19.0 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.18 mL, 1.0 M in THF, 0.18 mmol, 1.8 eq) in DMSO (1.0 mL, 1.0 M) for 5 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1 to 5/1).

Yellow powder; R_f value 0.50 (hexane/ethyl acetate = 1/1); mp 119–121 °C; IR (NaCl, neat) ν_{\max} 3225, 3176, 3044, 2984, 1597, 1571, 1259 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.56 (s, 1H), 8.09–8.05 (m, 3H), 6.95 (d, 2H, $J = 8.5$ Hz), 3.89 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 186.6, 164.1, 148.7, 132.4, 128.6, 113.8, 55.5; LRMS (EI, $M = \text{C}_9\text{H}_9\text{NO}_3$) m/z 179 (28%, M^+), 135 (100%); HRMS (EI) calcd for $\text{C}_9\text{H}_9\text{NO}_3$ [M^+] 179.0582, found 179.0582.

2-(4-Bromophenyl)-2-oxoacetaldehyde oxime (**7l**)



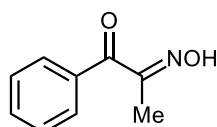
7l

A total of 14.9 mg of **7l** (65%) was obtained from the reaction with azide **1l** (24.0 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.18 mL, 1.0 M in THF, 0.18 mmol, 1.8 eq) in DMSO (1.0 mL, 1.0 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 15/1 to

8/1).

Pale yellow powder; R_f value 0.5 (hexane/ethyl acetate = 2/1); mp 155–156 °C; IR (KBr, disc) ν_{\max} 3242, 3092, 1673, 1583, 1248 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.97 (s, 1H), 7.95 (d, 2H, $J = 9.0$ Hz), 7.62 (d, 2H, $J = 9.0$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 187.6, 148.9, 134.3, 131.7, 131.5, 129.0; LRMS (EI, $M = \text{C}_8\text{H}_6\text{BrNO}_2$) m/z 229 (23%, M^+ of ^{81}Br), 227 (24, M^+ of ^{79}Br), 185 (96), 183 (100), 157 (37), 155 (37), 84 (84); HRMS (EI) calcd for $\text{C}_8\text{H}_6^{79}\text{BrNO}_2$ (M^+) 226.9582, found 226.9588.

2-(Hydroxyimino)-1-phenylpropan-1-one (**7m**)

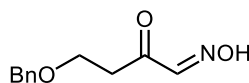


7m

A total of 11.8 mg of **7m** (73%) was obtained from the reaction with azide **1m** (17.4 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.18 mL, 1.0 M in THF, 0.18 mmol, 1.8 eq) in DMSO (1.0 mL, 1.0 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 15/1 to 8/1).

White solid; R_f value 0.50 (hexane/ethyl acetate = 2/1); mp 113–114 °C; IR (NaCl, neat) ν_{\max} 3252, 2925, 1661, 1447, 1365, 1000 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.43 (s, 1H), 7.89 (d, 2H, $J = 7.0$ Hz), 7.57 (t, 1H, $J = 7.5$ Hz), 7.45 (dd, 2H, $J = 7.0, 7.5$ Hz), 2.17 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 191.8, 156.9, 136.3, 132.8, 130.2, 128.2, 10.2; LRMS (EI, $M = \text{C}_9\text{H}_9\text{NO}_2$) m/z 163 (30%, M^+), 105 (100), 77 (78); HRMS (EI) calcd for $\text{C}_9\text{H}_9\text{NO}_2$ (M^+) 163.0633, found 163.0624.

4-(Benzyloxy)-2-oxobutanal oxime (**7n**)



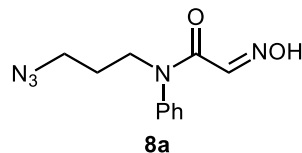
7n

A total of 11.2 mg of **7n** (54%) was obtained from the reaction with azide **1n** (21.9 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.20 mL, 1.0 M in THF, 0.20 mmol, 2.0 eq) in DMSO (1.0 mL, 1.0 M) for 2 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1 to 6/1).

Colorless oil; R_f value 0.33 (hexane/ethyl acetate = 2/1); IR (NaCl, neat) ν_{\max} 3270, 3209, 3061, 2871, 1684, 1454 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.64 (br, 1H), 7.56 (s, 1H), 7.37–7.31 (m, 5H), 4.58 (s, 2H), 3.87 (t, 2H, $J = 7.0$ Hz), 3.22 (m,

2H); ^{13}C NMR (126 MHz, CDCl_3) δ 196.6, 149.0, 137.0, 128.5, 128.1, 73.6, 65.0, 38.0; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{12}\text{NO}_3$ $[\text{M}-\text{H}]^-$ 206.0817, found 206.0812.

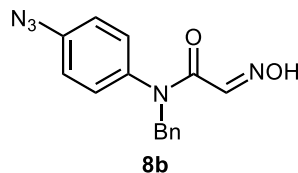
N-(3-Azidopropyl)-2-(hydroxyimino)-*N*-phenylacetamide (**8a**)



A total of 22.7 mg of **8a** (92%) as single isomer was obtained from the reaction with diazide **3a** (25.9 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.32 mL, 1.0 M in THF, 0.32 mmol, 3.2 eq) in DMSO (1.0 mL, 1.0 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 5/1 to 1/1).

White solid; R_f value 0.15 (hexane/ethyl acetate = 1/1); mp 98–100 °C; IR (NaCl, neat) ν_{max} 3260, 2936, 2098, 1659, 1593, 1493, 1254 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 10.35 (s, 1H), 7.45–7.37 (m, 4H), 7.16 (d, 2H, $J = 7.5$ Hz), 3.87 (t, 2H, $J = 7.5$ Hz), 3.34 (t, 2H, $J = 7.0$ Hz), 1.85 (tt, 2H, $J = 7.5, 7.0$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 161.4, 142.2, 140.2, 130.1, 128.6, 127.8, 49.0, 47.2, 27.0; LRMS (EI, $\text{M} = \text{C}_{11}\text{H}_{13}\text{N}_5\text{O}_2$) m/z 247 (5%, M^+), 164 (26), 147 (21), 119 (28), 106 (100); HRMS (EI) calcd for $\text{C}_{11}\text{H}_{13}\text{N}_5\text{O}_2$ $[\text{M}^+]$ 247.1069, found 247.1078.

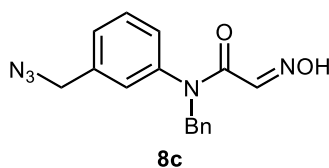
N-(4-Azidophenyl)-*N*-benzyl-2-(hydroxyimino)acetamide (**8b**)



A total of 27.4 mg of **8b** (93%) was obtained from the reaction with diazide **3b** (30.6 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.32 mL, 1.0 M in THF, 0.32 mmol, 3.2 eq) in DMSO (1.0 mL, 1.0 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 6/1 to 3/1 to 1/1).

Pale yellow amorphous solid; R_f value 0.43 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 3298, 3063, 2930, 2122, 1663, 1505, 1298, 1280 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.44 (s, 1H), 7.26–7.25 (m, 3H), 7.19 (dd, 2H, $J = 7.5, 3.5$ Hz), 6.99–6.94 (m, 4H), 4.96 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 161.3, 142.5, 140.4, 136.6, 136.1, 129.7, 129.0, 128.6, 127.8, 120.2, 53.1; LRMS (EI, $\text{M} = \text{C}_{15}\text{H}_{13}\text{N}_5\text{O}_2$) m/z 295 (2%, M^+), 282 (9), 267 (38), 223 (11), 91 (100); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{13}\text{N}_5\text{O}_2$ (M^+) 295.1069, found 295.1078.

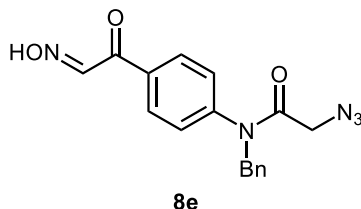
N-(3-(Azidomethyl)phenyl)-*N*-benzyl-2-(hydroxyimino)acetamide (**8c**)



A total of 28.9 mg of **8c** (94%) was obtained from the reaction with diazide **3c** (32.0 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.32 mL, 1.0 M in THF, 0.32 mmol, 3.2 eq) in DMSO (1.0 mL, 1.0 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 5/1 to 3/1 to 1/1).

Colorless amorphous solid; R_f value 0.43 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 3298, 3062, 2932, 2101, 1656, 1451, 1258 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 10.4 (br, 1H), 7.44 (s, 1H), 7.35 (dd, 1H, $J = 8.5, 7.5$ Hz), 7.29–7.26 (m, 3H), 7.26–7.24 (m, 2H), 7.20–7.15 (m, 2H), 6.95–6.94 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 161.3, 142.2, 140.6, 137.4, 136.1, 130.2, 128.9, 128.51, 128.46, 128.14, 128.11, 127.77, 127.67, 53.8, 53.1; LRMS (EI, $M = \text{C}_{16}\text{H}_{15}\text{N}_5\text{O}_2$) m/z 309 (7%, M^+), 292 (20), 237 (19), 209 (30), 91 (100); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{15}\text{N}_5\text{O}_2$ (M^+) 309.1226, found 309.1225.

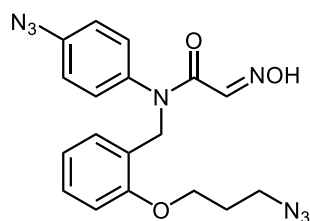
2-Azido-*N*-benzyl-*N*-(4-(2-(hydroxyimino)acetyl)phenyl)acetamide (**8e**)



A total of 21.8 mg of **8e** (65%) was obtained from the reaction with diazide **3e** (34.9 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.18 mL, 1.0 M in THF, 0.18 mmol, 1.8 eq) in DMSO (1.0 mL, 1.0 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 10/1 to 6/1 to 2/1).

Yellow oil; R_f value 0.55 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 3282, 3060, 2107, 1657, 1600, 1426, 1260 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.38 (br, 1H), 8.06 (d, 2H, $J = 8.5$ Hz), 7.96 (s, 1H), 7.26–7.25 (m, 3H), 7.17–7.15 (m, 2H), 7.06 (d, 2H, $J = 8.0$ Hz), 4.92 (s, 2H), 3.62 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 188.1, 167.5, 148.4, 144.0, 135.8, 135.5, 131.8, 128.7, 128.6, 127.9, 127.8, 53.3, 50.9; HRMS (CI) calcd for $\text{C}_{17}\text{H}_{16}\text{N}_5\text{O}_3$ [$M+H$] $^+$ 338.1253, found 338.1255.

N-(4-Azidophenyl)-*N*-(2-(3-azidopropoxy)benzyl)-2-(hydroxyimino)acetamide (**9a**)

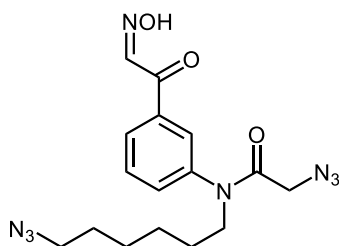


9a

A total of 33.0 mg of **9a** (84%) was obtained from the reaction with triazide **5a** (40.6 mg, 0.10 mmol), hydroxylammonium chloride (8.3 mg, 0.12 mmol, 1.2 eq), and TBAF (0.32 mL, 1.0 M in THF, 0.32 mmol, 3.2 eq) in DMSO (1.0 mL, 1.0 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 6/1 to 3/1 to 2/1 to 1/1).

Pale yellow amorphous solid; R_f value 0.3 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 2932, 2877, 2099, 1663, 1505, 1297, 1247 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 10.0 (br, 1H), 7.43 (s, 1H), 7.21 (dd, 1H, $J = 7.5, 7.0$ Hz), 7.17 (d, 1H, $J = 7.5$ Hz), 6.97–6.93 (m, 4H), 6.85 (dd, 1H, $J = 7.5, 7.5$ Hz), 6.78 (d, 1H, $J = 8.0$ Hz), 5.03 (s, 2H), 3.91 (t, 2H, $J = 5.5$ Hz), 3.40 (t, 2H, $J = 6.5$ Hz), 1.89 (t, 2H, $J = 6.5, 6.0$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 161.1, 156.5, 142.5, 140.2, 136.7, 130.9, 129.7, 129.2, 124.0, 120.8, 119.9, 110.9, 64.2, 48.0, 47.6, 28.6; LRMS (EI, $M = \text{C}_{18}\text{H}_{18}\text{N}_8\text{O}_3$) m/z 394 (2%, M^+), 366 (9), 162 (23), 134 (100), 105 (35); HRMS (EI) calcd for $\text{C}_{18}\text{H}_{18}\text{N}_8\text{O}_3$ (M^+) 394.1502, found 194.1505.

2-Azido-*N*-(6-azidoheptyl)-*N*-(3-(2-(hydroxyimino)acetyl)phenyl)acetamide (**9b**)



9b

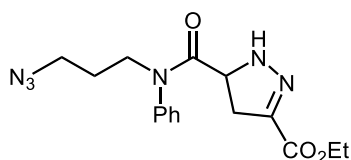
A total of 1.12 g of **9b** (65%) as single isomer was obtained from the reaction with triazide **5b** (1.78 g, 4.64 mmol), hydroxylammonium chloride (387.4 mg, 5.57 mmol, 1.2 eq), and TBAF (8.4 mL, 1.0 M in THF, 8.40 mmol, 1.8 eq) in DMSO (46 mL, 1.0 M) for 1 h followed by neutral silica gel chromatography (hexane/ethyl acetate = 4/1 to 3/1). Recrystallization for X-ray analysis was performed with hexane/dichloromethane.

Pale yellow solid; R_f value 0.2 (hexane/ethyl acetate = 2/1); mp 85–86 °C; IR (NaCl,

neat) ν_{\max} 3265, 2935, 2861, 2105, 1655, 1444, 1256 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 10.1 (s, 1H), 8.05 (d, 1H, $J = 8.0$ Hz), 7.98 (s, 1H), 7.95 (s, 1H), 7.59 (dd, 1H, $J = 8.5, 7.0$ Hz), 7.42–7.40 (m, 1H), 3.76 (t, 2H, $J = 7.5$ Hz), 3.66 (s, 2H), 3.26 (t, 2H, $J = 7.0$ Hz), 1.55 (tt, 4H, $J = 7.0, 7.0$ Hz), 1.40–1.32 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ 188.0, 167.6, 149.0, 139.8, 137.6, 131.9, 130.7, 130.4, 130.0, 51.5, 51.3, 49.7, 28.6, 27.2, 26.3, 26.1; HRMS (CI) calcd for $\text{C}_{16}\text{H}_{21}\text{N}_8\text{O}_3$ $[\text{M}+\text{H}]^+$ 373.1737, found 373.1729.

6-4 Synthesis of Conjugated Compounds

Ethyl 5-((3-Azidopropyl)(phenyl)carbamoyl)-4,5-dihydro-1H-pyrazole-3-carboxylate (**10**)

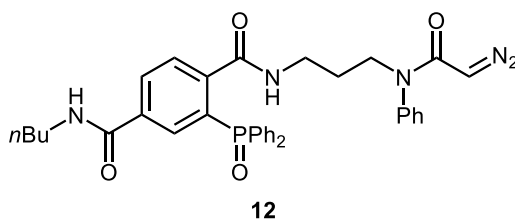


10

To a stirred solution of alkyl azido α -diazo amido compound **4a** (11.2 mg, 0.05 mmol) in acetonitrile/water (2.5 mL, 0.02 M, 1/1) was added ethyl acrylate (27.5 μL , 0.25 mmol, 5.0 eq), and the mixture was stirred at room temperature for 24 h. After removal of solvent in vacuo, the resulting crude material was purified by neutral silica gel column chromatography (hexane/ethyl acetate = 3/1 to 2/1 to 1/1), and 13.5 mg of pyrazoline **10** (86%) was obtained.

Pale yellow oil; R_f value 0.37 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 3323, 2096, 1700, 1660, 1258, 1119 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.49 (dd, 2H, $J = 8.0, 7.5$ Hz), 7.42 (dd, 1H, $J = 7.0, 6.5$ Hz), 7.20 (d, 2H, $J = 7.5$ Hz), 6.43 (s, 1H), 4.41 (dd, 1H, $J = 7.5, 7.0$ Hz), 4.25 (q, 2H, $J = 7.5$ Hz), 3.85 (ddd, 1H, $J = 14.5, 7.5, 7.0$ Hz), 3.74 (ddd, 1H, $J = 14.0, 7.5, 7.0$ Hz), 3.34 (dd, 2H, $J = 7.0, 6.5$ Hz), 3.08 (dd, 1H, $J = 17.0, 7.5$ Hz), 2.77 (dd, 1H, $J = 17.0, 7.5$ Hz), 1.82 (tt, 1H, $J = 7.5, 7.0$ Hz), 1.31 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 170.8, 162.1, 142.6, 140.5, 130.4, 128.9, 128.5, 61.3, 60.5, 49.1, 47.8, 36.5, 27.0, 14.2; LRMS (EI, $\text{M} = \text{C}_{16}\text{H}_{20}\text{N}_6\text{O}_3$) m/z 344 (3%, M^+), 299 (19), 176 (25), 141 (87), 106 (48), 95 (100); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{20}\text{N}_6\text{O}_3$ (M^+) 344.1597, found 344.1594.

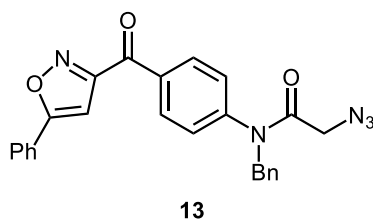
*N*⁴-Butyl-*N*¹-(3-(2-diazo-*N*-phenylacetamido)propyl)-2-(diphenylphosphoryl)terephthalamide (**12**)



To a stirred solution of alkyl azido α -diazo amido compound **4a** (11.2 mg, 0.05 mmol) in THF/water (1.0 mL, 0.05 M, 10/1) was added phosphine reagent **11** (31.8 mg, 0.075 mmol, 1.5 eq), and the mixture was stirred at room temperature for 24 h. The resulting mixture was transferred to another flask with ethyl acetate and was concentrated in vacuo. The obtained crude material was purified by neutral silica gel column chromatography (hexane/ethyl acetate = 1/1 to dichloromethane/methanol = 15/1) followed by GPC, and 20.0 mg of the ligation product **12** (70%) was obtained.

Pale yellow amorphous solid; R_f value 0.17 (dichloromethane/methanol = 15/1); IR (NaCl, neat) ν_{\max} 3286, 3061, 2931, 2106, 1645, 1542, 1407 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.32 (t, 1H, $J = 6.0$ Hz), 7.99 (d, 1H, $J = 8.5$ Hz), 7.87 (dd, 1H, $J = 13.5, 1.0$ Hz), 7.83 (dd, 1H, $J = 8.0, 4.0$ Hz), 7.65–7.61 (m, 4H), 7.53–7.50 (m, 2H), 7.44–7.38 (m, 6H), 7.35–7.32 (m, 1H), 7.13 (d, 2H, $J = 7.0$ Hz), 6.53 (br-s, 1H), 4.37 (s, 1H), 3.69 (t, 2H, $J = 7.0$ Hz), 3.34 (dd, 2H, $J = 12.0, 7.0$ Hz), 2.94 (dd, 2H, $J = 13.0, 7.0$ Hz), 1.50 (ddt, 2H, $J = 7.5, 7.5, 7.5$ Hz), 1.42 (ddt, 2H, $J = 7.0, 7.0, 7.0$ Hz), 1.31 (qdd, 2H, $J = 7.5, 7.5, 7.5$ Hz), 0.90 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 166.8 (d, $J = 3.1$ Hz), 166.0, 165.6, 143.0 (d, $J = 8.4$ Hz), 141.1, 135.9 (d, $J = 10.8$ Hz), 132.4 (d, $J = 10.8$ Hz), 132.2 (d, $J = 2.4$ Hz), 131.9 (d, $J = 10.8$ Hz), 131.5, 130.8 (d, $J = 2.4$ Hz), 130.7, 130.4 (d, $J = 8.4$ Hz), 129.8, 128.55, 128.45, 128.32, 128.26, 47.3, 46.4, 39.8, 36.8, 31.4, 27.0, 20.0, 13.7; ^{31}P NMR (202 MHz, benzene- d_6) δ 32.9; HRMS (ESI) calcd for $\text{C}_{35}\text{H}_{36}\text{N}_5\text{NaO}_4\text{P}$ $[\text{M}+\text{Na}]^+$ 644.2403, found 644.2403.

2-Azido-*N*-benzyl-*N*-(4-(5-phenylisoxazole-3-carbonyl)phenyl)acetamide (**13**)

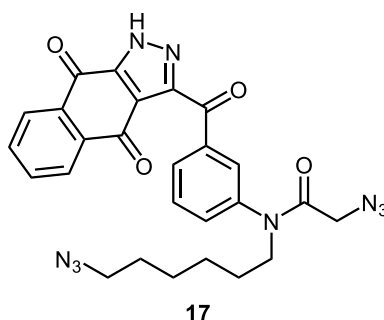


To a solution of **8e** (16.9 mg, 0.050 mmol) and phenyl acetylene (27.5 μL , 0.25 mmol, 5.0 eq) in methanol/water (0.50 mL, 5/1, 0.1 M) was added

[bis(trifluoroacetoxy)iodo]benzene (33.2 mg, 0.075 mmol, 1.5 eq) at room temperature. After 1 h, the solvent was removed under reduced pressure to obtain crude material, which was purified by neutral silica gel column chromatography (hexane/ethyl acetate = 8/1 to 5/1) followed by GPC purification to afford 9.1 mg of **13** (42%).

Colorless oil; R_f value 0.57 (hexane/ethyl acetate = 2/1); IR (NaCl, neat) ν_{\max} 2105, 1669, 1600, 1441, 1251 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.37 (dd, 2H, $J = 7.0, 6.5$ Hz), 7.85 (dd, 2H, $J = 8.0, 3.0$ Hz), 7.54–7.51 (m, 3H), 7.30–7.28 (m, 3H), 7.21 (dd, 2H, $J = 7.5, 7.0$ Hz), 7.17 (d, 2H, $J = 8.0$ Hz), 7.06 (s, 1H), 4.96 (s, 2H), 3.67 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 184.4, 171.1, 166.9, 162.1, 145.3, 136.1, 135.6, 132.4, 130.9, 129.2, 128.9, 128.7, 128.3, 128.0, 126.4, 126.0, 100.1, 53.3, 50.9; LRMS (EI, $M = \text{C}_{25}\text{H}_{19}\text{N}_5\text{O}_3$) m/z 437 (M^+ , 1%), 353 (17), 277 (11), 208 (10), 146 (20), 91 (100); HRMS (EI) calcd for $\text{C}_{25}\text{H}_{19}\text{N}_5\text{O}_3$ (M^+) 437.1488, found 437.1485.

2-Azido-*N*-(6-azidohexyl)-*N*-(3-(4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]indazole-3-carbonyl)phenyl)acetamide (**17**)

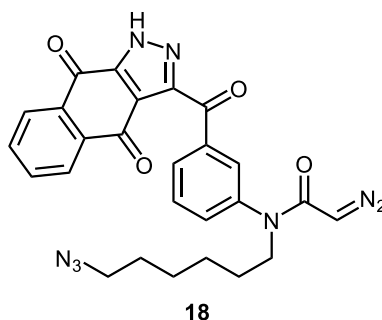


To a stirred solution of diazido diazo compound **6b** (159.9 mg, 0.433 mmol) and 1,4-naphthoquinone (103.7 mg, 0.649 mmol, 1.5 eq) in DMSO (8.7 mL, 0.05 M) was added cesium carbonate (282.6 mg, 0.866 mmol, 2.0 eq) at room temperature under open-air conditions. After 2 h, the reaction was quenched with water, and the mixture was extracted three times with dichloromethane. The combined organic layer was washed three times with water and brine. The collected organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 2/1 to 1/1 to 1/1 + 5% methanol) gave 185.4 mg of pyrazole **17** (82%).

Pale blown amorphous solid; R_f value 0.2 (dichloromethane/methanol = 20/1); IR (NaCl, neat) ν_{\max} 2934, 2105, 1681, 1582, 1331, 1255, 917 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.27–8.24 (m, 2H), 8.17 (d, 1H, $J = 8.0$ Hz), 7.88 (s, 1H), 7.85–7.79 (m, 2H), 7.65 (dd, 1H, $J = 8.0, 7.5$ Hz), 7.47 (d, 1H, $J = 8.5$ Hz), 3.76 (t, 2H, $J = 7.5$ Hz), 3.64 (s, 2H), 3.30 (t, 2H, $J = 7.0$ Hz), 1.58–1.53 (m, 4H), 1.38–1.34 (m,

4H); ^{13}C NMR (126 MHz, CDCl_3) δ 185.6, 177.8, 176.0, 167.4, 140.5, 138.0, 135.2, 134.5, 133.9, 133.0, 132.4, 130.55, 130.50, 130.3, 127.9, 127.0, 121.2, 51.4, 51.2, 49.6, 28.7, 27.3, 26.4, 26.2; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{23}\text{N}_9\text{NaO}_4$ $[\text{M}+\text{Na}]^+$ 548.1771, found 548.1778.

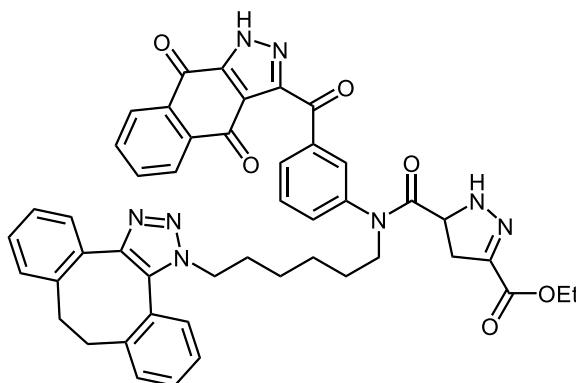
N-(6-Azidohexyl)-2-diazo-*N*-(3-(4,9-dioxo-4,9-dihydro-1*H*benzo[*f*]indazole-3-carbonyl)phenyl)acetamide (**18**)



To a solution of diazide **17** (133.9 mg, 0.255 mmol), tosyl hydrazide (237.8 mg, 1.27 mmol, 5.0 eq), and pyrrolidine (106 μL , 1.27 mmol, 5.0 eq) in DMSO (2.55 mL, 0.1 M) was added dropwise TBAF (1.53 mL, 1.0 M in THF, 1.53 mmol, 6.0 eq) at 25 $^\circ\text{C}$. After 4 h, the reaction mixture was diluted with dichloromethane and water. The mixture was extracted three times with dichloromethane, and the organic layer was washed twice with water. The collected organic layer was dried over anhydrous sodium sulfate. Concentration and purification by neutral silica gel column chromatography (dichloromethane to dichloromethane/methanol = 20/1) followed by GPC gave 97.2 mg of **18** (75%).

Pale blown amorphous solid; R_f value 0.47 (dichloromethane/methanol = 20/1); IR (NaCl, neat) ν_{max} 2934, 2860, 2106, 1682, 1578, 1407 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.27–8.25 (m, 1H), 8.22–8.21 (m, 1H), 8.12 (d, 1H, $J = 8.0$ Hz), 7.86 (s, 1H), 7.84–7.78 (m, 2H), 7.61 (dd, 1H, $J = 8.0, 7.5$ Hz), 7.49 (d, 1H, $J = 8.0$ Hz), 4.50–4.48 (m, 1H), 3.78 (t, 2H, $J = 7.0$ Hz), 3.29–3.26 (m, 2H), 1.57–1.51 (m, 4H), 1.39–1.30 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ 185.9, 178.0, 176.0, 166.0, 141.5, 137.8, 135.0, 134.4, 133.9, 133.4, 132.5, 130.8, 130.2, 129.6, 127.7, 127.1, 121.1, 51.4, 49.1, 48.0, 28.7, 27.9, 26.4, 26.2; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{22}\text{N}_8\text{NaO}_4$ $[\text{M}+\text{Na}]^+$ 533.1662, found 533.1653.

Ethyl 5-((6-(8,9-Dihydro-1*H*-dibenzo[3,4:7,8]cycloocta[1,2-*d*]-[1,2,3]triazol-1-yl)hexyl)(3-(4,9-dioxo-4,9-dihydro-1*H*-benzo[*f*]-indazole-3-carbonyl)phenyl)carbamoyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylate (**20**)



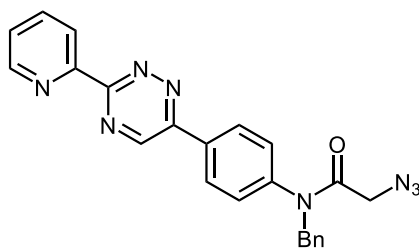
20

To a stirred solution of diazo azide **18** (55.6 mg, 0.109 mmol) in acetonitrile/water (5.5 mL, 1/1, 0.02 M) was added ethyl acrylate (59.5 μ L, 0.545 mmol, 5.0 eq) at room temperature. After 26 h, the wet organic solvent was removed under reduced pressure. Then, the resulting crude material was dissolved in acetonitrile (2.2 mL, 0.05 M). To a stirred acetonitrile solution was added dibenzocyclooctyne (5,6-dihydro-11,12-didehydrodibenzo[*a,e*]-cyclooctyne, 33.3 mg, 0.163 mmol, 1.5 eq based on **18**) at room temperature. After 24 h, the organic solvent was removed under reduced pressure to obtain crude material, which was purified by neutral silica gel column chromatography (hexane/ethyl acetate = 1/1 to dichloromethane to dichloromethane/methanol = 20/1) followed by GPC to afford 58.9 mg of **20** (66%).

Pale yellow amorphous solid; R_f value 0.23 (dichloromethane/methanol = 20/1); IR (NaCl, neat) ν_{\max} 3330, 3065, 2933, 2860, 1682, 1581, 1454, 1434, 1334, 1221 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.24 (d, 1H, $J = 7.5$ Hz), 8.19–8.15 (m, 2H), 7.91 (s, 1H), 7.78 (dd, 1H, $J = 7.5$ Hz), 7.73 (dd, 1H, $J = 7.5$ Hz), 7.65 (dd, 1H, $J = 8.0$ Hz), 7.62–7.57 (m, 1H), 7.33–7.30 (m, 2H), 7.23–7.12 (m, 6H), 4.43–4.41 (m, 2H), 4.27–4.24 (m, 1H), 4.19 (q, 2H, $J = 7.5$ Hz), 3.38–3.35 (m, 1H), 3.26–3.17 (m, 1H), 3.08 (dd, 2H, $J = 11.0$ Hz), 2.95–2.86 (m, 2H), 1.86 (br-s, 1H), 1.70 (m, 1H), 1.54–1.45 (m, 2H), 1.31–1.18 (m, 9H); ^{13}C NMR (126 MHz, CDCl_3) δ 185.7, 177.9, 175.9, 170.4, 162.1, 146.4, 142.3, 141.5, 140.44, 140.40, 138.6, 137.57, 137.55, 134.8, 134.6, 134.07, and 134.04 (conformers), 133.6, 133.02, 132.99, 132.41, 131.84, 131.80, 130.8, 130.6, 130.2, 129.8, 129.36, 129.31, 128.8, 128.1, 127.8, 126.8, 126.5, 126.1, 121.5, 61.3, 60.8, and 60.7 (conformers), 50.1, 50.0, 48.1, 36.5, 32.8, 29.3, and 29.2 (conformers), 26.99 and 26.96 (conformers), 25.7, 25.61, and 25.55 (conformers), 14.13; HRMS (ESI) calcd for $\text{C}_{47}\text{H}_{42}\text{N}_8\text{NaO}_6$

[M+Na]⁺ 837.3125, found 837.3107.

2-Azido-*N*-benzyl-*N*-(4-(3-(pyridin-2-yl)-1,2,4-triazin-6-yl)phenyl)acetamide (**22**)



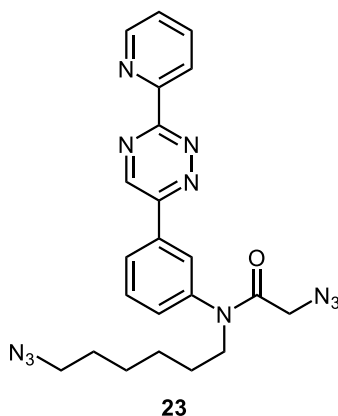
22

To a stirred solution of azido oxime **8e** (101 mg, 0.30 mmol) and hydrazine monohydrate (14.6 μ L, 0.30 mmol, 1.0 eq) in ethanol (0.45 mL, 0.67 M) was added one drop of acetic acid, and the mixture was heated at 45 °C for 16 h. Then, concentration of the reaction mixture *in vacuo* gave crude hydrazone (110 mg) which was submitted to the next step without further purification.

To a stirred solution of crude hydrazone and 2-pyridinecarboxaldehyde (34.5 μ L, 0.359 mmol, 1.2 eq) in ethanol (2.0 mL, 0.15 M) was added three drops of acetic acid. After 23 h, the reaction mixture was concentrated *in vacuo*. The obtained crude material was dissolved in acetic acid (0.50 mL, 0.60 M), and the stirred mixture was heated at 100 °C. After 1 h, the reaction mixture was diluted with water, and was quenched with saturated aqueous solution of sodium bicarbonate. The organic components were extracted three times with dichloromethane and washed with brine, and then was dried over anhydrous sodium sulfate. Concentration of the collected organic layer *in vacuo* and purification by silica gel column chromatography (hexane/ethyl acetate = 1/1 to 1/2 with 2% methanol to dichloromethane/methanol = 20/1) gave 119 mg of **22** (94% for 3 steps).

Brown amorphous solid; R_f value 0.13 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 2105, 1670, 1402, 1255 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃) δ 9.17 (s, 1H), 8.90 (m, 1H), 8.74 (d, 1H, $J = 8.0$ Hz), 8.19 (ddd, 2H, $J = 9.5, 2.5, 2.5$ Hz), 7.96 (ddd, 1H, $J = 8.0, 7.5, 2.0$ Hz), 7.52–7.50 (m, 1H), 7.32–7.28 (m, 3H), 7.24–7.21 (m, 4H), 4.97 (s, 2H), 3.68 (s, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 167.0, 162.0, 154.8, 152.0, 150.6, 146.9, 143.0, 137.3, 136.1, 133.4, 129.3, 129.0, 128.7, 128.5, 128.0, 125.9, 124.0, 53.4, 51.0; LRMS (EI, M = C₂₃H₁₈N₈O) m/z 422 (2%, M⁺), 394 (12), 338 (23), 206 (26), 91 (100); HRMS (EI) calcd for C₂₃H₁₈N₈O (M⁺) 422.1604, found 422.1602.

2-Azido-*N*-(6-azidohexyl)-*N*-(3-(3-(pyridin-2-yl)-1,2,4-triazin-6-yl)phenyl)acetamide (**23**)

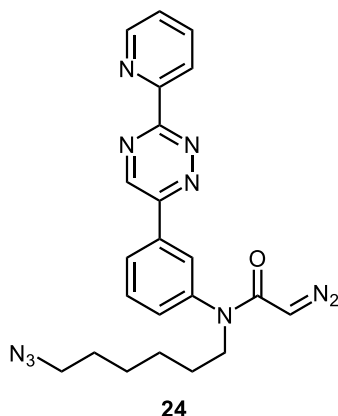


To a stirred solution of oxime **9b** (933 mg, 2.5 mmol) and hydrazine monohydrate (0.12 mL, 2.5 mmol, 1.0 eq) in ethanol (3.8 mL, 0.67 M) was added one drop of acetic acid, and the mixture was heated at 45 °C for 16 h. Then, concentration of the reaction mixture *in vacuo* gave crude hydrazone (1.10 g) which was submitted to the next step without further purification.

To a stirred solution of crude hydrazone and 2-pyridinecarboxaldehyde (0.29 mL, 3.0 mmol, 1.2 eq) in ethanol (16.7 mL, 0.15 M) was added three drops of acetic acid. After 23 h, the reaction mixture was concentrated *in vacuo*. The obtained crude material was dissolved in acetic acid (4.2 mL, 0.60 M), and the mixture stirred was heated at 100 °C. After 1 h, the reaction mixture was diluted with water, and was quenched with saturated aqueous solution of sodium bicarbonate. The organic components were extracted three times with dichloromethane and washed with brine, and then was dried over anhydrous sodium sulfate. Concentration of the organic layer followed by purification by silica gel column chromatography (hexane/ethyl acetate = 1/1 to 1/2 with 2% methanol to dichloromethane/methanol = 20/1) gave 959 mg of **23** (84% for 3 steps).

Brown oil; R_f value 0.13 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 2934, 2103, 1669, 1584, 1403, 1258 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.21 (s, 2H), 8.91 (d, 1H, $J = 4.0$ Hz), 8.75 (d, 1H, $J = 8.0$ Hz), 8.14–8.13 (m, 2H), 7.96 (ddd, 1H, $J = 8.0, 7.5, 2.0$ Hz), 7.69 (dd, 1H, $J = 8.0, 8.0$ Hz), 7.51 (dd, 1H, $J = 7.5, 7.0$ Hz), 7.38 (d, 1H, $J = 8.5$ Hz), 3.80 (t, 2H, $J = 8.0$ Hz), 3.64 (s, 2H), 3.23 (t, 2H, $J = 7.0$ Hz), 1.58 (tt, 4H, $J = 7.5, 7.5$ Hz), 1.36 (t, 4H, $J = 3.5$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 166.9, 162.2, 154.6, 152.0, 150.6, 147.0, 142.0, 137.3, 135.2, 131.2, 130.6, 126.8, 126.5, 125.9, 124.1, 51.2, 50.9, 49.7, 28.6, 27.4, 26.3, 26.2; HRMS (MALDI-TOF) calcd for $\text{C}_{22}\text{H}_{23}\text{N}_{11}\text{ONa}$ $[\text{M}+\text{Na}]^+$ 480.1983, found 480.1973.

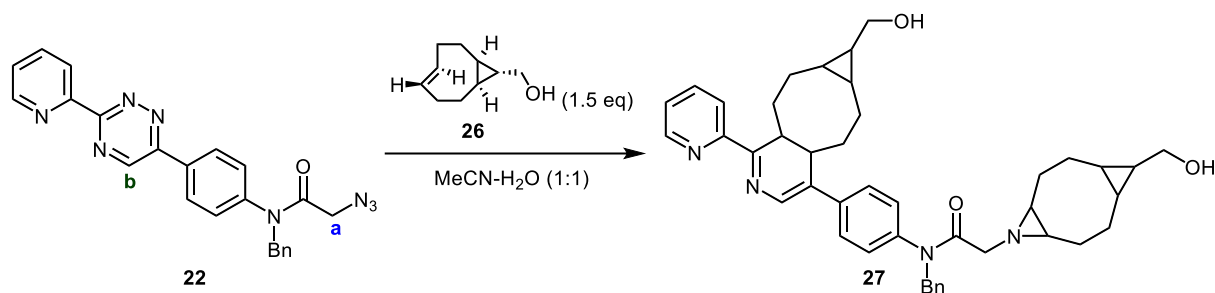
N-(6-Azidohexyl)-2-diazo-*N*-(3-(3-(pyridin-2-yl)-1,2,4-triazin-6-yl)phenyl)acetamide (**24**)



To a stirred solution of diazide **23** (666 mg, 1.46 mmol), *p*-toluenesulfonyl hydrazide (1.36 g, 7.28 mmol, 5.0 eq), and pyrrolidine (0.61 mL, 7.28 mmol, 5.0 eq) in DMSO (15 mL, 0.1 M) was added TBAF (8.7 mL, 1.0 M in THF, 8.74 mmol, 6.0 eq) dropwise at 25 °C. After 4 h, the resulting mixture was diluted with dichloromethane and was quenched with water. Organic components were extracted 3 times with dichloromethane and washed twice with water. Drying collected organic layer over anhydrous sodium sulfate followed by concentration *in vacuo* and purification by neutral silica gel column chromatography (hexane/ethyl acetate = 1/1 to dichloromethane elution to dichloromethane/methanol = 20/1) and GPC gave 256 mg of **24** (40%).

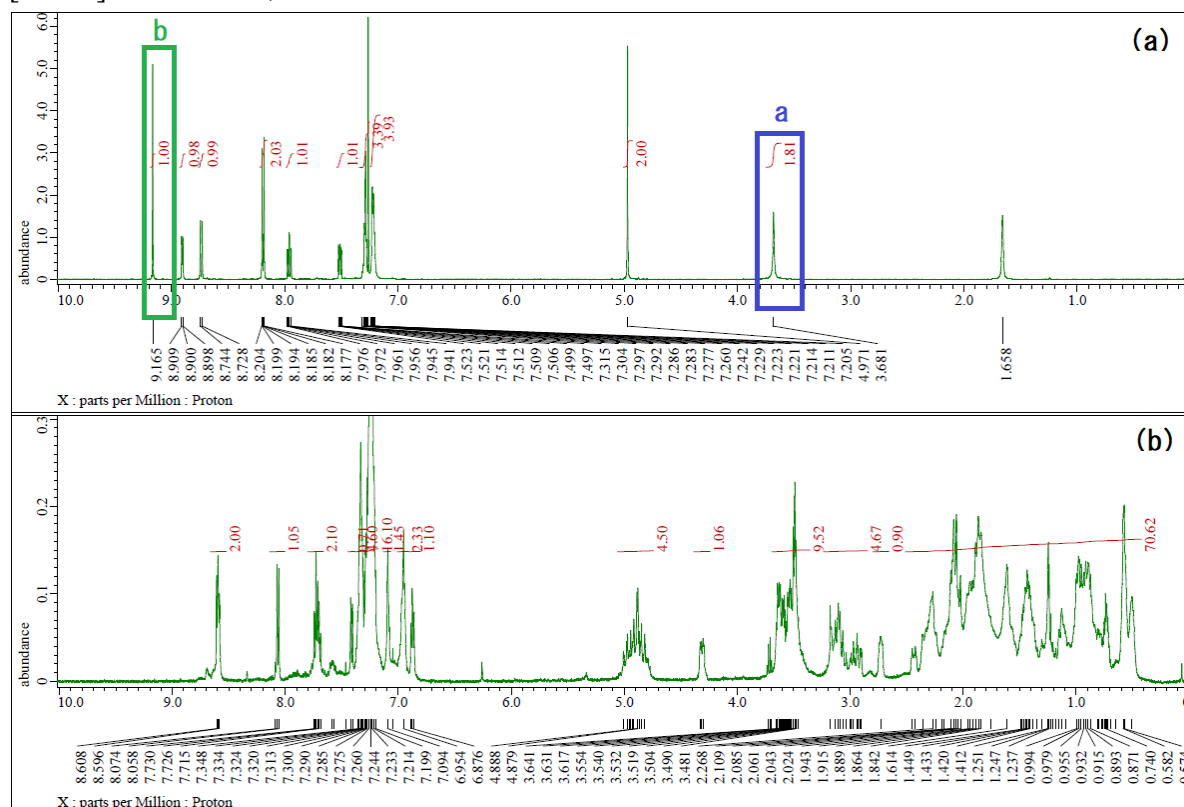
Yellow amorphous solid; R_f value 0.33 (dichloromethane/methanol = 15/1); IR (NaCl, neat) ν_{\max} 2934, 2860, 2102, 1621, 1584, 1402 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 9.20 (s, 1H), 8.92 (d, 1H, $J = 4.5$ Hz), 8.76 (d, 1H, $J = 8.5$ Hz), 8.12–8.10 (m, 2H), 7.97 (ddd, 1H, $J = 8.0, 8.0, 2.0$ Hz), 7.66 (dd, 1H, $J = 8.5, 8.0$ Hz), 7.52 (ddd, 1H, $J = 7.5, 7.5, 1.0$ Hz), 7.42–7.40 (m, 1H), 4.50 (s, 1H), 3.83 (t, 2H, $J = 7.5$ Hz), 3.23 (t, 2H, $J = 7.0$ Hz), 1.60–1.56 (m, 4H), 1.37 (t, 4H, $J = 4.0, 3.0$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 165.4, 162.0, 154.9, 152.0, 150.6, 147.0, 142.9, 137.3, 134.8, 131.1, 130.9, 126.8, 126.2, 125.9, 124.0, 51.2, 49.1, 47.7, 28.7, 28.0, 26.4, 26.2; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{23}\text{N}_{11}\text{ONa}$ $[\text{M}+\text{Na}]^+$ 465.1876, found 465.1857.

Model study of Azido triazine **22** with cyclopropane-fused trans-cyclooctene **26**

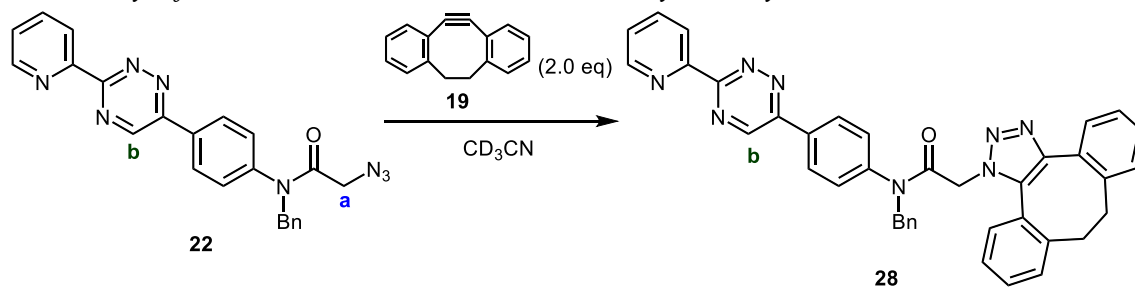


To a solution of azido triazine **22** (20.8 mg, 0.05 mmol) in acetonitrile/water (1.0 mL, 1/1 vol., 0.05 M) was added *trans*-cyclooctene **26** (11.1 mg, 0.075 mmol, 1.5 eq) at room temperature. After 30 min, concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 1/1 to dichloromethane to dichloromethane/methanol = 20/1) followed by GPC to afford 12.5 mg of **27** (50% based on **22**) as stereomixture. Loss of triazine and azido structures were confirmed by ¹H NMR (Figure 6-1), and IR spectra as well as HRMS.

Pale yellow amorphous solid; R_f value 0.17 (dichloromethane/methanol = 15/1); IR (NaCl, neat) ν_{max} 2925, 2856, 1662, 1509 cm⁻¹; HRMS (ESI) calcd for C₂₃H₁₈N₈O [M+H]⁺ 671.3961, found 671.3910.



Model study of Azido triazine **22** with dibenzocyclooctyne **19**



Azido triazine **22** (15.2 mg, 0.0375 mmol) was dissolved in acetonitrile- d_3 (0.75 mL, 0.05 M) in an NMR tube (Figures 6-2a, 6-3a). And then, dibenzocyclooctyne **19** (15.3 mg, 0.075 mmol, 2.0 eq) was added to the mixture (Figure 6-2b). The reaction was monitored the disappearance of the peaks of the protons on each click functional groups (protons **a** and **b**) by ^1H NMR after 40 min (Figure 6-2c) and 7 h (Figures 6-2d, and 6-3b).

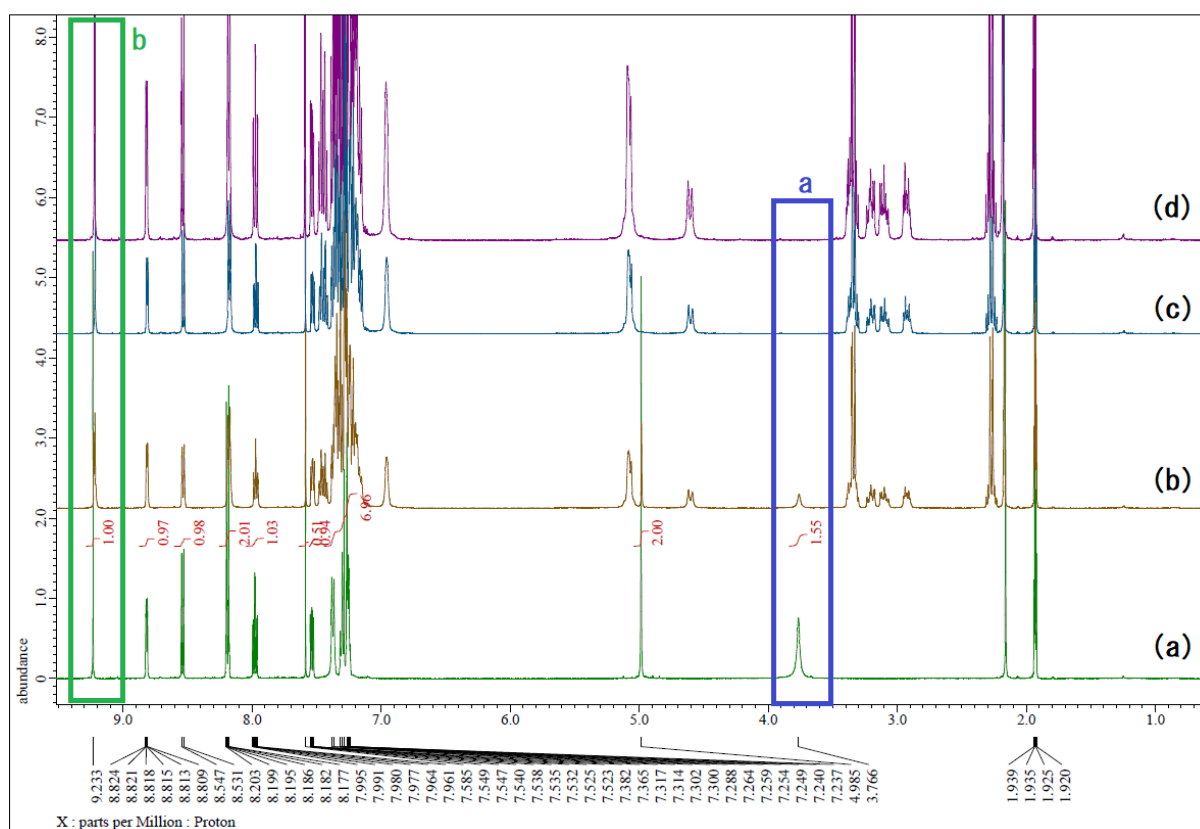


Figure 6-2. ^1H NMR experiments (a) **22** in CD_3CN , (b) soon after addition of **19**, (c) after 40 min, and (d) after 7 h

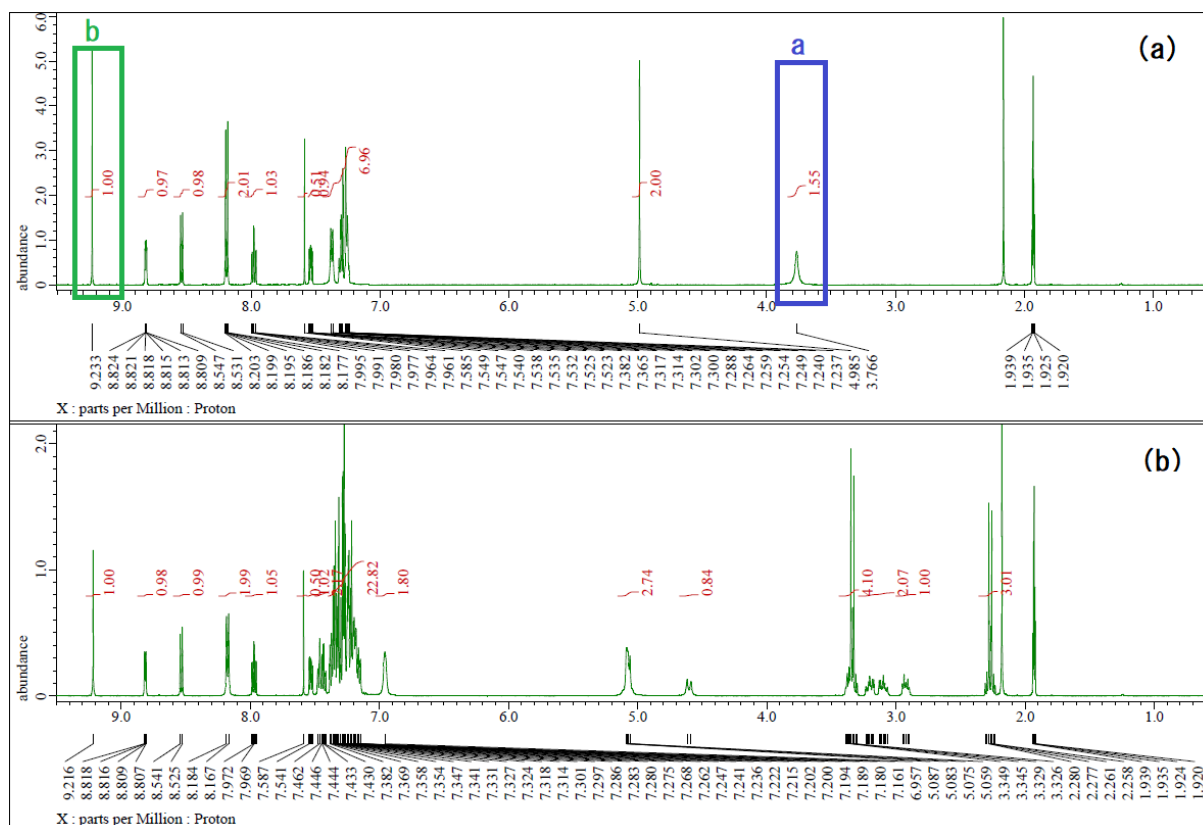
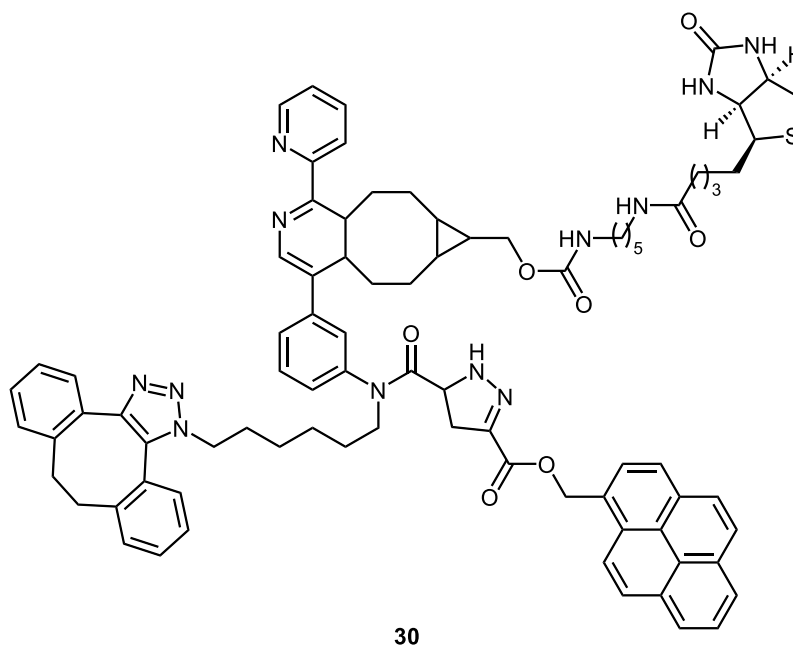


Figure 6-3. Comparison of NMR charts of the reaction (a) before addition of **19**, and (b) 7 h after addition of **19**

Four component coupling product (**30**)



To a solution of azido-diazo-triazine **24** (16.4 mg, 0.0361 mmol) in acetonitrile-water (2.9 mL, 1:1, 0.013 M) was added 1-pyrenemethyl acrylate **25** (52.4 mg,

0.181 mmol, 5.0 eq) at room temperature. After 24 h, dibenzocyclooctyne **19** (9.1 mg, 0.0433 mmol, 1.2 eq) was added to the resulting mixture at same temperature. Then after 2 h, *trans*-alkene-biotin tag **29** (18.3 mg, 0.0361 mmol, 1.0 eq) dissolved in acetonitrile-water (1.0 mL + rinsed with 0.5 mL×2, 1:1) at same temperature. After 1 h, the solvent was removed under reduced pressure followed by silica gel column chromatography (hexane/ethyl acetate = 1/1 to dichloromethane elution to dichloromethane/methanol = 20/1 to 15/1 to 10/1) gave **30** (22.1 mg, 0.0157 mmol, 44%) as diastereomeric mixture.

Yellow amorphous solid; R_f value 0.3 (dichloromethane/methanol = 10/1); IR (NaCl, neat) ν_{\max} 3309, 2930, 1699, 1654, 1460, 1245 cm^{-1} ; UV-vis (CHCl_3) λ_{\max} = 267, 278, 302 (sh), 315, 329, 346, 376 (sh); ^1H NMR (500 MHz, CDCl_3) See NMR spectra section; HRMS (MALDI-TOF) calcd for $\text{C}_{84}\text{H}_{90}\text{N}_{12}\text{O}_7\text{SNa}$ $[\text{M}+\text{Na}]^+$ 1433.6668, found 1433.6659.

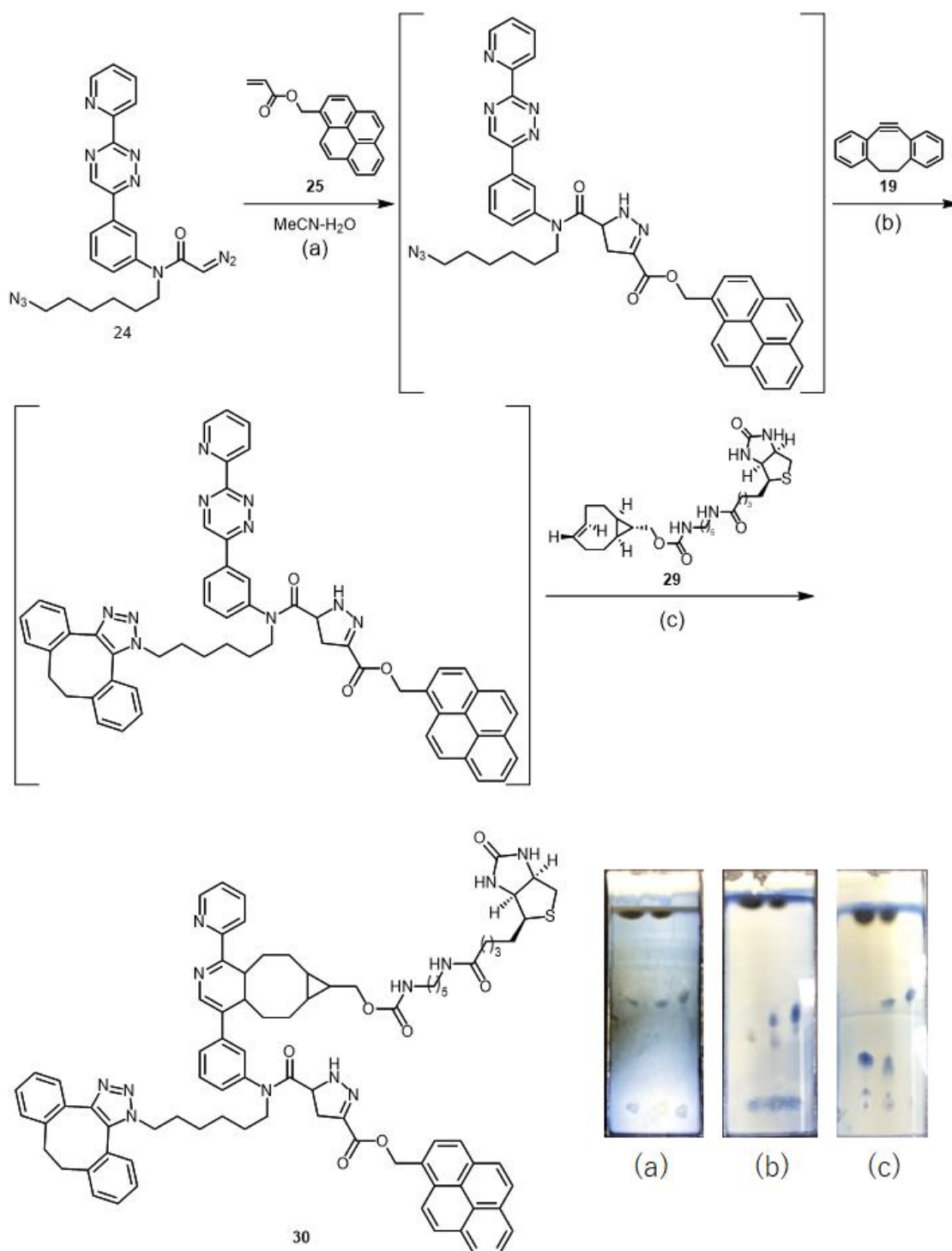


Figure 6-4. TLC analysis of the progress of three-component integration reaction (left: reaction mixture, middle: reaction mixture + starting material scaffold **24**, right: reference sample of **24**) (a) 24 h after addition of acrylate **25** [(dichloromethane/methanol = 20/1)×2], (b) 2 h after addition of dibenzocyclooctyne **19** [(dichloromethane/methanol = 20/1)×2], (c) 1 h after addition of biotin-connected cyclopropane fused *trans*-cyclooctene **29** (dichloromethane/methanol = 10/1).

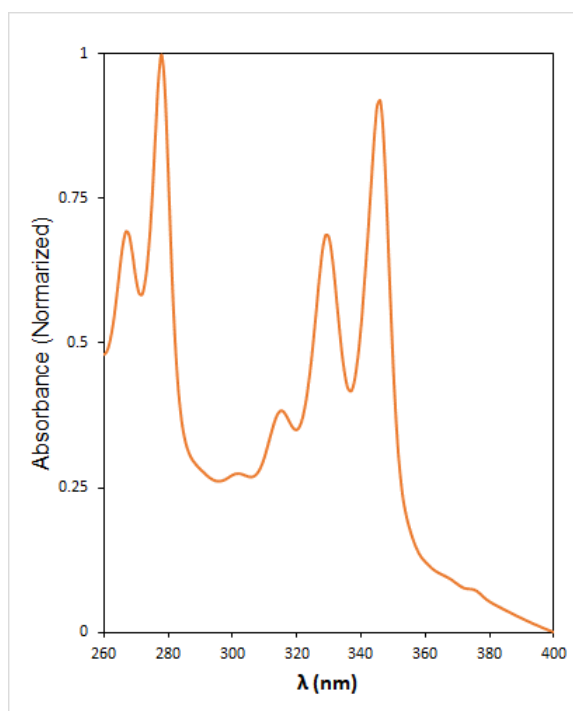


Figure 6-5. UV-vis spectrum of **30** (0.019 μ M in chloroform)

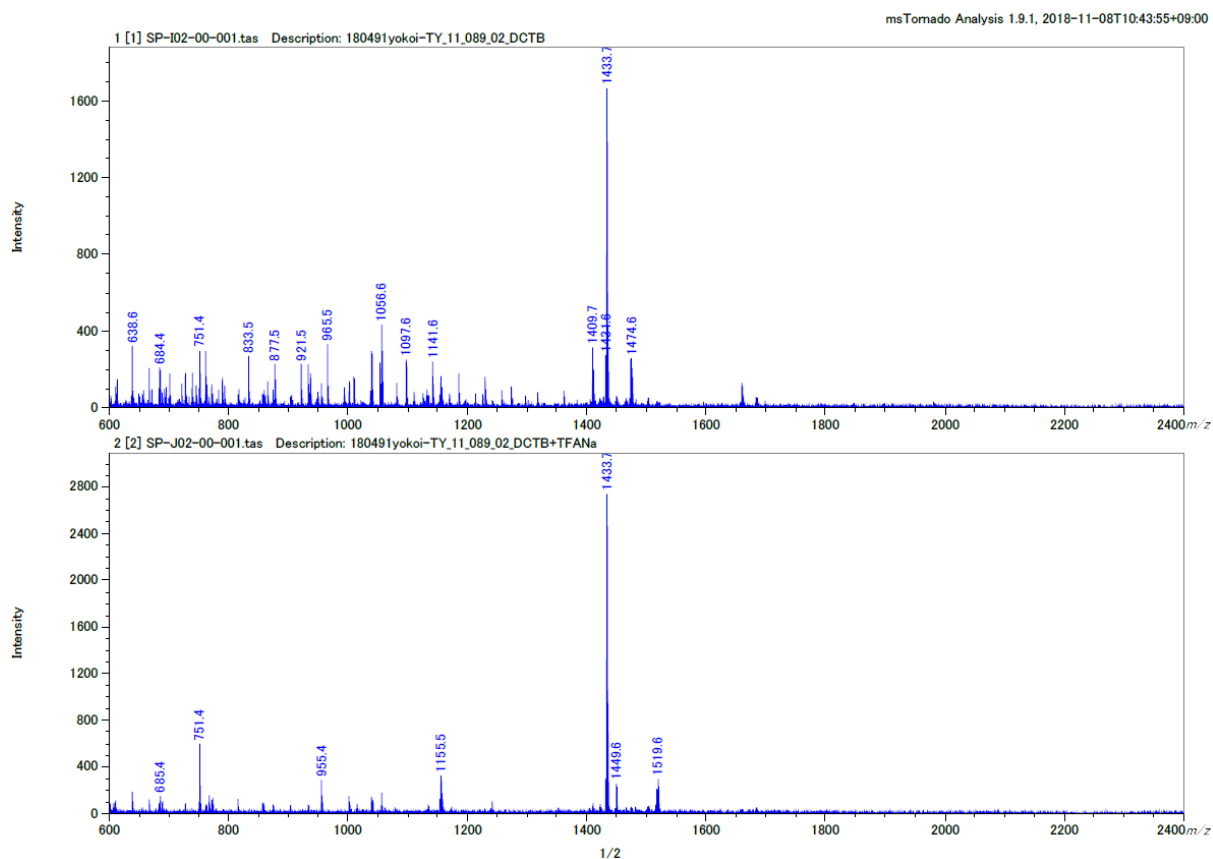


Figure 6-6. Mass spectra of **30** by MALDI-Spiral TOFMS: (top) with DCTB (3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile), (bottom) with DCTB + sodium trifluoroacetate

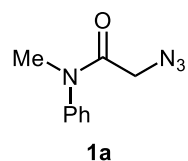
6-5 Preparation of Substrates

General Procedure for Synthesis of Azido Acetamides from Amines

The following is reaction 1: in a two-neck flask, amine was dissolved in dichloromethane under a nitrogen atmosphere and the solution was cooled to 0 °C. Then, a solution of bromoacetyl bromide or 2-bromopropionyl bromide in dichloromethane was added slowly to the reaction mixture, in which precipitate was formed immediately. The reaction mixture was warmed to room temperature and was stirred for 1 h. The reaction was quenched with a saturated aqueous sodium bicarbonate solution, and the mixture was washed with saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate. Concentration in vacuo gave the crude bromoacetamide product, which was used in the next step without further purification. (Beware of residual dichloromethane; see also the caution statement above.)

The following is reaction 2: to a stirred solution of crude bromoacetamide in DMSO was added sodium azide at ambient temperature. After completion of the reaction (reaction time noted in each compound section), the reaction was quenched with water, and the mixture was extracted three times with ether. The organic layer was washed with water and brine, and the combined organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography gave α -azido acetamide.

2-Azido-*N*-methyl-*N*-phenylacetamide (**1a**)

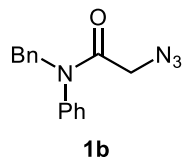


Following the general procedure, 916mg of **1a** (97% from amine for 2 steps) was obtained from the reactions with (1) *N*-methyl aniline (0.54 mL, 5.0 mmol, 1.0 eq), bromoacetyl bromide (0.50 mL, 5.7 mmol, 1.14 eq) dissolved in dichloromethane (20 mL), and dichloromethane solvent (40 mL, 0.13M); (2) crude bromoacetamide (1.230 g), sodium azide (810.3 mg, 12.5 mmol, 2.5 eq), and DMSO (25 mL, 0.2 M) for 20 min followed by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 2/1).

Pale yellow oil; R_f value 0.67 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 2924, 2106, 1668, 1595, 1495, 1390, 1267, 1124 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.44 (dd, 2H, $J = 7.5, 7.5$ Hz), 7.38 (t, 1H, $J = 7.5$ Hz), 7.19 (d, 2H, $J = 7.5$ Hz), 3.61 (s, 2H), 3.31 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.3, 142.1, 130.2, 128.6,

127.0, 50.6, 37.5; LRMS (EI, M = C₉H₁₀N₄O) *m/z* 190 (1.1%, M⁺), 162 (29), 134 (100), 105 (83), 77 (64); HRMS (EI) calcd for C₉H₁₀N₄O (M⁺) 190.0855, found 190.0858.

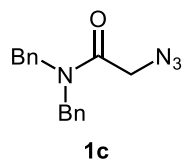
2-Azido-*N*-benzyl-*N*-phenylacetamide (**1b**)



Following the general procedure, 1.30 g of **1b** (98% from amine for 2 steps) was obtained from the reactions with (1) *N*-benzylaniline (916 mg, 5.0 mmol, 1.0 eq), bromoacetyl bromide (0.50 mL, 5.7 mmol, 1.14 eq) dissolved in dichloromethane (20 mL), and dichloromethane solvent (40 mL, 0.13 M); (2) crude bromoacetamide (1.5380 g), sodium azide (817.5 mg, 12.6 mmol, 2.5 eq), and DMSO (25 mL, 0.2 M) for 20 min followed by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 3/1).

Pale yellow oil; *R_f* value 0.2 (hexane/ethyl acetate = 5/1); IR (NaCl, neat) ν_{\max} 2104, 1670, 1496, 1399, 1260 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.35–7.33 (m, 3H), 7.29–7.26 (m, 3H), 7.20–7.18 (m, 2H), 6.97–6.95 (m, 2H), 4.90 (s, 2H), 3.59 (s, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 167.2, 140.2, 136.5, 129.9, 129.0, 128.8, 128.5, 128.2, 127.7, 53.4, 50.8; LRMS (EI, M = C₁₅H₁₄N₄O) *m/z* 266 (8%, M⁺), 182 (53), 119 (58), 91 (100), 77 (45); HRMS (EI) calcd for C₁₅H₁₄N₄O (M⁺) 266.1168, found 266.1162.

2-Azido-*N,N*-dibenzylacetamide (**1c**)

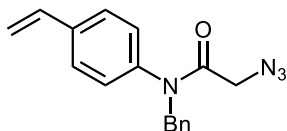


Following the general procedure, 1.38 g of **1c** (99% from amine for 2 steps) was obtained from the reactions with (1) *N,N*-dibenzyl amine (0.96 mL, 5.0 mmol, 1.0 eq), bromoacetyl bromide (0.495 mL, 5.7 mmol, 1.14 eq) dissolved in dichloromethane (20 mL), and dichloromethane solvent (40 mL, 0.13 M); (2) crude bromoacetamide (1.666 g), sodium azide (812 mg, 12.5 mmol, 2.5 eq), and DMSO (25 mL, 0.2 M) for 20 min followed by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 2/1).

Colorless oil; *R_f* value 0.8 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 2104, 1658, 1450, 1213 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.40–7.29 (m, 6H), 7.26–7.24

(m, 2H), 7.34 (d, 2H, $J = 7.0$ Hz), 4.65 (s, 2H), 4.37 (s, 2H), 3.98 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.9, 136.4, 135.4, 129.2, 128.7, 128.5, 128.0, 127.8, 126.2, 50.6, 49.3, 48.9; LRMS (EI, $M = \text{C}_{16}\text{H}_{16}\text{N}_4\text{O}$) m/z 280 (1.8%, M^+), 196 (51), 91 (100); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}$ (M^+) 280.1324, found 280.1306.

2-Azido-*N*-benzyl-*N*-(4-vinylphenyl)acetamide (**1d**)



1d

To a stirred solution of 4-vinyl aniline (0.58 mL, 4.95 mmol) in ethanol (8.3 mL, 0.6 M) was added benzaldehyde (0.76 mL, 7.50 mmol, 1.5 eq), and the mixture was stirred at room temperature for 1 h. Then, the mixture was cooled down to 0 °C, and sodium borohydride (631 mg, 15.0 mmol, 3.0 eq) was added carefully. After the mixture stirred at room temperature for 12 h, the resulting mixture was poured into a saturated aqueous sodium bicarbonate solution. The organic components were extracted twice with ethyl acetate and were washed with brine. The combined organic layer was dried over magnesium sulfate. Concentration in vacuo gave benzylamine (1.27 g) as a crude material, which was submitted to the next step without purification.

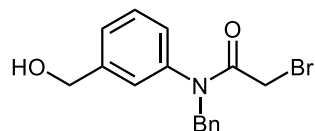
To a stirred solution of *N*-benzyl-4-vinylaniline (1.27 g) in dichloromethane (40 mL) was added bromoacetyl bromide (0.49 mL, 5.64 mmol, 1.14 eq) dissolved in dichloromethane (20 mL) at 0 °C. After the mixture stirred at room temperature for 1 h, the reaction was quenched with a saturated aqueous sodium bicarbonate solution and was dried over anhydrous sodium sulfate. Concentration in vacuo gave bromoacetamide (1.66 g) as a crude material, which was submitted to the next step without purification.

To a stirred solution of the bromide (1.66 g) in DMSO (25 mL, 0.2 M) was added sodium azide (646 mg, 9.90 mmol, 2.0 eq) at room temperature. After 1 h, the reaction was quenched with water, and the organic components were extracted three times with ether. The organic layer was washed with water and brine. The combined organic layer was then dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (11% to 14% to 25% ethyl acetate in hexane) gave 551 mg of **1d** (38% for 3 steps).

Pale yellow oil; R_f value 0.47 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{max} 2103, 1669, 1508, 1397 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.37 (d, 2H, $J = 8.5$ Hz), 7.29–7.26 (m, 3H), 7.19 (d, 1H, $J = 7.5$ Hz), 7.19 (d, 1H, $J = 6.0$ Hz), 6.91 (d, 2H, $J = 8.5$ Hz), 6.67 (dd, 1H, $J = 18.0, 11.0$ Hz), 5.75 (d, 1H, $J = 18.0$ Hz), 5.32

(d, 1H, $J = 11.0$ Hz), 4.89 (s, 2H), 3.61 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.2, 139.5, 138.0, 136.5, 135.4, 129.0, 128.5, 128.3, 127.7, 127.6, 115.6, 53.3, 50.8; LRMS (EI, $M = \text{C}_{17}\text{H}_{16}\text{N}_4\text{O}$) m/z 292 (4%, M^+), 208 (10), 145 (11), 118 (12), 91 (100); HRMS (EI) calcd for $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}$ (M^+) 292.1324, found 292.1324.

N-Benzyl-2-bromo-*N*-(3-(hydroxymethyl)phenyl)acetamide (**1e-1**)

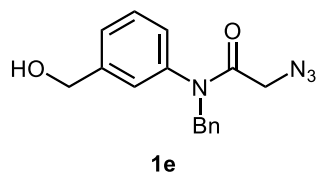


To a stirred solution of 3-aminobenzyl alcohol (616 mg, 5.0 mmol) in ethanol (8.3 mL, 0.6 M) was added benzaldehyde (0.61 mL, 5.0 mmol, 1.2 eq) at room temperature. After 2 h, the mixture was cooled to 0 °C, and then sodium borohydride (632 mg, 15.0 mmol, 3.0 eq) was added carefully. After the mixture stirred at room temperature for 12 h, the resulting mixture was poured into a saturated aqueous sodium bicarbonate solution. The organic components were extracted three times with ethyl acetate and were washed with brine. The combined organic layer was dried over anhydrous sodium sulfate. Concentration in vacuo gave (3-(benzylamino)phenyl)methanol (1.14 g) as a crude material, which was submitted to the next step without purification.

To a solution of the crude amine (1.14 g) in dichloromethane (40 mL, 0.13 M) was added bromoacetyl bromide (0.49 mL, 5.7 mmol, 1.14 eq) dissolved in dichloromethane (20 mL) at 0 °C. After the mixture stirred at room temperature for 1 h, the reaction was quenched with a saturated aqueous sodium bicarbonate solution at 0 °C. The resulting mixture was washed with a saturated aqueous sodium bicarbonate solution and was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 8/1 to 5/1 to 3/1 to 2/1 to 1/1) gave 522 mg of **1e-1** (31% from amine for 2 steps).

Colorless oil; R_f value 0.40 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{max} 3410, 1656, 1439, 1401, 700 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.35–7.31 (m, 2H), 7.29–7.24 (m, 3H), 7.19–7.18 (m, 2H), 7.10 (s, 1H), 6.95 (d, 1H, $J = 7.0$ Hz), 4.88 (s, 2H), 4.67 (s, 2H), 3.67 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 166.4, 143.0, 141.3, 136.5, 129.8, 128.8, 128.5, 127.6, 127.2, 126.9, 126.2, 64.2, 53.6, 27.4; LRMS (EI, $M = \text{C}_{16}\text{H}_{16}\text{BrNO}_2$) m/z 335 (0.8%, M^+ of ^{81}Br), 333 (0.8, M^+ of ^{79}Br), 254 (61), 236 (51), 132 (40), 91 (100); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{16}^{79}\text{BrNO}_2$ (M^+) 333.0364, found 333.0368.

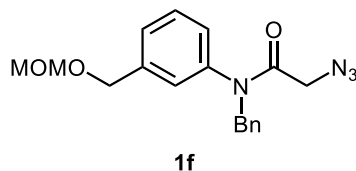
2-Azido-*N*-benzyl-*N*-(3-(hydroxymethyl)phenyl)acetamide (**1e**)



To a stirred solution of bromide **1e-1** (790.6 mg, 2.4 mmol) in DMSO (12 mL, 0.2 M) at ambient temperature was added sodium azide (308 mg, 4.73 mmol, 2.0 eq). After 0.5 h, the resulting mixture was poured into water, and the mixture was extracted three times with ether. The organic layer was washed with water and brine. The combined organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (33% to 50% ethyl acetate in hexane) gave 700 mg of **1e** (99%).

Colorless oil; R_f value 0.17 (hexane/ethyl acetate = 2/1); IR (NaCl, neat) ν_{\max} 2926, 2870, 2104, 1662, 1404, 1265 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.34–7.32 (m, 2H), 7.30–7.26 (m, 3H), 7.18 (d, 1H, $J = 7.5$ Hz), 7.18 (d, 1H, $J = 6.5$ Hz), 7.01 (s, 1H), 6.85–6.83 (m, 1H), 4.89 (s, 2H), 4.67 (d, 2H, $J = 6.0$ Hz), 3.60 (s, 2H), 1.94 (br, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.2, 143.2, 140.4, 136.5, 130.0, 129.0, 128.5, 127.7, 127.2, 127.0, 126.2, 64.2, 53.4, 50.8; LRMS (EI, $M = \text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_2$) m/z 296 (1%, M^+), 268 (3), 238 (6), 136 (10), 118 (12), 91 (100); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{16}\text{N}_4\text{O}_2$ (M^+) 296.1273, found 296.1271.

2-Azido-*N*-benzyl-*N*-(3-((methoxymethoxy)methyl)phenyl)-acetamide (**1f**)

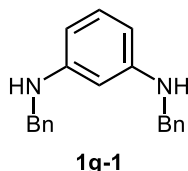


To a stirred solution of alcohol **1e** (479 mg, 1.61 mmol) and tetrabutyl ammonium iodide (119 mg, 0.323 mmol, 0.2 eq) in dichloromethane (16 mL, 0.1 M) were added *N,N*-diisopropylethylamine (1.13 mL, 6.46 mmol, 4.0 eq) and chloromethyl methyl ether (0.365 mL, 4.84 mmol, 3.0 eq) at 0 °C. After the mixture stirred at room temperature for 3 h, the resulting mixture was quenched by a saturated aqueous ammonium chloride solution. The organic components were extracted twice with dichloromethane and were washed with water and brine. The combined organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (25% to 33% to 50% ethyl acetate in hexane) gave 449 mg of **1f** (82%).

Colorless oil; R_f value 0.43 (hexane/ethyl acetate = 2/1); IR (NaCl, neat) ν_{\max} 2932, 2886, 2105, 1671, 1046 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.32 (d, 2H, $J = 5.0$

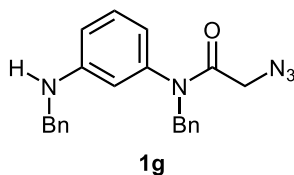
Hz), 7.29–7.23 (m, 3H), 7.20–7.18 (m, 2H), 6.98 (s, 1H), 6.58 (m, 1H), 4.89 (s, 2H), 4.66 (s, 2H), 4.53 (s, 2H), 3.60 (s, 2H), 3.37 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 167.1, 140.3, 136.5, 129.8, 129.0, 128.4, 127.8, 127.6, 127.3, 127.1, 95.8, 68.1, 55.4, 53.3, 50.8; LRMS (EI, M = C₁₈H₂₀N₄O₃) *m/z* 340 (0.2%, M⁺), 312 (2), 250 (15), 91 (100); HRMS (EI) calcd for C₁₈H₂₀N₄O₃ (M⁺) 340.1535, found 340.1528.

2-Azido-*N*-benzyl-*N*-phenylacetamide (**1g-1**)⁶⁶⁾



To a stirred solution of 1,3-phenylenediamine (1.08 g, 10 mmol) in ethanol (16.7 mL, 0.6 M) was added benzaldehyde (3.1 mL, 30 mmol, 3.0 eq), and the mixture was stirred at room temperature for 0.5 h with a covered flask to protect from light. Then, the mixture was cooled to 0 °C, and sodium borohydride (1.69 g, 40 mmol, 4.0 eq) was added carefully. After the mixture stirred at room temperature for 12 h, the resulting mixture was poured into a saturated aqueous sodium bicarbonate solution. The organic components were extracted three times with ethyl acetate and were washed with brine. The combined organic layer was dried over magnesium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 6/1) gave 2.75 g of *N,N'*-dibenzylamine **1g-1** (95%). This compound was soon submitted to the next step without collecting analytical data.

2-Azido-*N*-benzyl-*N*-(3-(benzylamino)phenyl)acetamide (**1g**)



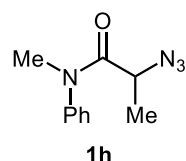
To a stirred solution of diamine **1g-1** (787 mg, 2.73 mmol) in dichloromethane (23 mL) was added bromoacetyl bromide (0.28 mL, 2.87 mmol, 1.05 eq) dissolved in dichloromethane (10 mL) at 0 °C. After the mixture stirred at room temperature for 1 h, the reaction was quenched with a saturated aqueous sodium bicarbonate solution and was dried over anhydrous sodium sulfate. Concentration in vacuo gave bromoacetamide (1.09 g) as a crude material, which was submitted to the next step without purification.

To a stirred solution of the bromide (1.09 g) in DMSO (14 mL, 0.2 M) was added sodium azide (354 mg, 5.46 mmol, 2.0 eq) at room temperature. After 1 h, the

reaction was quenched with water, and the organic components were extracted three times with ether. The organic layer was washed with water and brine. The combined organic layer was then dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (14% to 20% to 25% to 33% ethyl acetate in hexane) gave 429 mg of **1g** (42%).

White solid; R_f value 0.43 (hexane/ethyl acetate = 2/1); mp 73.6–74.3 °C; IR (NaCl, neat) ν_{\max} 3373, 3033, 2103, 1661, 1602, 1494 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.38–7.34 (m, 2H), 7.31–7.28 (m, 3H), 7.27–7.24 (m, 3H), 7.19 (dd, 2H, $J = 7.5, 6.5$ Hz), 7.09 (dd, 2H, $J = 8.0, 8.0$ Hz), 6.58 (dd, 1H, $J = 8.0, 2.0$ Hz), 6.26 (dd, 1H, $J = 7.5, 1.0$ Hz), 6.10 (dd, 1H, $J = 2.5, 1.5$ Hz), 4.82 (s, 2H), 4.22 (s, 3H), 3.57 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.3, 149.1, 141.3, 138.4, 136.9, 130.4, 129.0, 128.7, 128.4, 127.53, 127.50, 127.3, 116.5, 113.3, 111.7, 53.2, 50.7, 47.9; LRMS (EI, $M = \text{C}_{22}\text{H}_{21}\text{N}_5\text{O}$) m/z 371 (2%, M^+), 343 (88), 252 (37), 91 (100); HRMS (EI) calcd for $\text{C}_{22}\text{H}_{21}\text{N}_5\text{O}$ (M^+) 371.1746, found 371.1751.

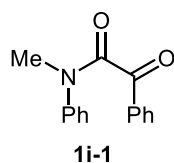
2-azido-*N*-methyl-*N*-phenylpropanamide (**1h**)



Following the general procedure, 387mg of **1h** (96% from amine for 2 steps) was obtained from the reactions with (1) *N*-methyl aniline (0.22 mL, 2.0 mmol, 1.0 eq), 2-bromopropionyl bromide (0.24 mL, 2.3 mmol, 1.14 eq) dissolved in dichloromethane (8 mL), and dichloromethane solvent (16 mL, 0.13M); (2) crude bromoacetamide (526 mg), sodium azide (323.4 mg, 4.97 mmol, 2.5 eq), and DMSO (10 mL, 0.2 M) for 20 min followed by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 2/1).

Pale yellow oil; R_f value 0.3 (hexane/ethyl acetate = 5/1); IR (NaCl, neat) ν_{\max} 2111, 1666, 1495, 1390, 1238 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.44 (dd, 2H, $J = 7.5, 7.5$ Hz), 7.38 (t, 1H, $J = 7.5$ Hz), 7.21 (m, 2H), 3.63 (q, 1H, $J = 7.0$ Hz), 3.30 (s, 3H), 1.83 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 170.7, 142.7, 130.1, 128.4, 127.1, 53.6, 37.7, 16.5; LRMS (EI, $M = \text{C}_{10}\text{H}_{12}\text{N}_4\text{O}$) m/z 204 (26%, M^+), 175 (43), 134 (100), 106 (78), 77 (54); HRMS (EI) calcd for $\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}$ (M^+) 204.1011, found 204.1033.

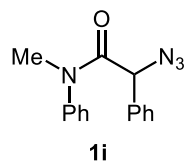
N-Methyl-2-oxo-*N*,2-diphenylacetamide (**1i-1**)^{44c)}



To a stirred solution of benzoylformic acid (750 mg, 5.0 mmol) in dichloromethane (5 mL, 1M) were added a catalytic amount of DMF (1 drop) and oxalyl chloride (0.475 mL, 5.5 mmol, 1.1 eq) at room temperature. The reaction mixture was stirred at room temperature until generation of gas was stopped (1.5 h). Then, the reaction mixture was cooled to 0 °C. To the cooled mixture were added *N*-methyl aniline (0.81 mL, 7.5 mmol, 1.5 eq) and triethylamine (1.75 mL, 12.5 mmol, 2.5 eq). Then, the mixture was stirred at room temperature for 1 h. The reaction was quenched with water, and the mixture was extracted three times with ethyl acetate. The combined organic layer was washed with brine and was dried over magnesium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 3/1 to 1/1) gave 1.195 g of **1i-1** (100%).

White solid; R_f value 0.63 (hexane/ethyl acetate = 1/1); mp 61–62 °C; IR (NaCl, neat) ν_{\max} 1680, 1651, 1595, 1495, 1234 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3 , major rotamer listed as similar to the referred report) δ 7.85 (m, 2H), 7.57 (m, 1H), 7.46–7.42 (m, 2H), 7.25–7.20 (m, 3H), 7.14–7.13 (m, 2H), 3.49 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3 , major rotamer listed as the referred report) δ 190.8, 167.0, 141.1, 134.2, 133.4, 129.5, 129.4, 128.7, 128.1, 126.7, 36.2; LRMS (EI, $M = \text{C}_{15}\text{H}_{13}\text{NO}_2$) m/z 239 (26%, M^+), 134 (51), 105 (100), 77 (46); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{13}\text{NO}_2$ (M^+) 239.0946, found 239.0968.

2-Azido-*N*-methyl-*N*,2-diphenylacetamide (**1i**)



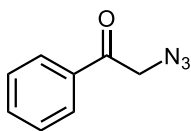
To an ice-cooled stirred solution of **1i-1** (1.13 g, 4.70 mmol) in ethanol and dichloromethane (11.5 mL, 2/1, 0.4 M) was added sodium borohydride (242 mg, 6.39 mmol, 1.36 eq), and the reaction mixture was stirred at room temperature. After 1 h, the reaction was quenched by the careful addition of a saturated aqueous ammonium chloride solution, and the mixture was extracted three times with ethyl acetate. The combined organic extract was washed with brine and was dried over magnesium sulfate. Removal of organic solvents gave the crude material, which was used for the next step without further purification.

To an ice-cooled stirred solution of the crude alcohol in dichloromethane (4.7 mL, 1 M) were added triethylamine (1.94 mL, 13.8 mmol, 2.94 eq) and methanesulfonyl chloride (0.462 mL, 5.97 mmol, 1.27 eq, with slow addition), and the reaction mixture was stirred at the same temperature. After 1 h, the reaction was quenched with water, and organic materials were extracted three times with ethyl acetate. The combined organic layer was washed with brine and was dried over magnesium sulfate. Removal of organic solvents afforded the crude mesylate compound, which was submitted to the next step without further purification. (Beware of residual dichloromethane; see also the caution statement above.)

To an ice-cooled stirred solution of the crude mesylate material in DMF (4.7 mL, 1 M) was added sodium azide (657 mg, 7.03 mmol, 1.5 eq), and the mixture was stirred at room temperature. After 3 h, the reaction was quenched with water, and the organic components were extracted three times with ether. The combined extracts were washed with water and brine. The combined organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 5/1) gave 1.01 g of **1i** (80% for 3 steps).

White solid; R_f value 0.60 (hexane/ethyl acetate = 2/1); mp 81–82 °C; IR (NaCl, neat) ν_{\max} 2098, 1666, 1491, 1387, 1236 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.36–7.29 (m, 6H), 7.13–7.11 (m, 2H), 6.90 (br-s, 2H), 4.61 (s, 1H), 3.30 (s, 3H); ^{13}C NMR (126 MHz, CDCl_3) δ 168.8, 142.1, 134.2, 129.7, 129.0, 128.9, 128.5, 128.0, 127.6, 62.8, 37.8; HRMS (CI) calcd for $\text{C}_{15}\text{H}_{15}\text{N}_4\text{O}$ $[\text{M}+\text{H}]^+$ 267.1246, found 267.1262.

Phenacyl azide (**1j**)



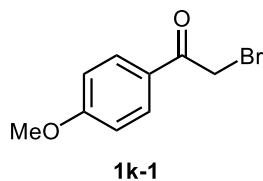
1j

To a stirred solution of phenacyl bromide (1.50 g, 7.54 mmol) in DMSO (38 mL, 0.2 M) at ambient temperature was added sodium azide (1.20 g, 18.8 mmol, 2.5 eq). After 15 min, the resulting mixture was poured into water with ice and the mixture was extracted twice with ether. The organic layer was washed with water and brine. The combined organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 5/1) gave 1.14 g of **1j** (94%).

Pale yellow oil; R_f value 0.53 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{\max} 2104, 1697, 1218 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.91 (dd, 2H, $J = 8.0, 1.5$ Hz), 7.65–7.62 (m, 1H), 7.50 (dd, 2H, $J = 8.0, 8.0$ Hz), 4.58 (s, 2H); ^{13}C NMR (126

MHz, CDCl₃) δ 193.2, 134.2, 134.1, 129.0, 127.9, 54.8; HRMS (CI) calcd for C₈H₈N₃O [M+H]⁺ 162.0667, found 162.0675.

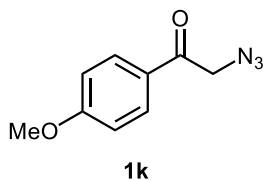
2-Bromo-1-(4-methoxyphenyl)ethan-1-one (**1k-1**)⁶⁷⁾



To a stirred solution of 4'-methoxyacetophenone (750.7 mg, 5.0 mmol) in 1,4-dioxane (8.2 mL, 0.6 M) was added bromine (0.28 mL, 5.45 mmol, 1.09 eq) dissolved in ether (6.6 mL), and the mixture was heated up to 40 °C. After 2 h, the resulting mixture was cooled to room temperature and was washed five times with water. Then, the organic layer was dried over anhydrous sodium sulfate. Concentration to obtain the crude solid material, which was recrystallized from ether, gave 329 mg of **1k-1** (29%).

Colorless crystal; R_f value 0.50 (hexane/ethyl acetate = 2/1); mp 70–71 °C; IR (NaCl, neat) ν_{\max} 1686, 1600, 1261, 1206, 1170, 1022 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.97 (d, 2H, *J* = 8.5 Hz), 6.96 (d, 2H, *J* = 8.5 Hz), 4.40 (s, 2H), 3.89 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 190.0, 164.1, 131.4, 126.9, 114.0, 55.6, 30.7; LRMS (EI, M = C₉H₉BrO₂) *m/z* 230 (46%, M⁺ for ⁸¹Br), 228 (46, M⁺ for ⁷⁹Br), 135 (100); HRMS (EI) calcd for C₉H₉⁸¹BrO₂ (M⁺) 229.9765, found 229.9767.

2-Azido-1-(4-methoxyphenyl)ethan-1-one (**1k**)

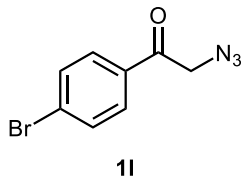


To a stirred solution of **1k-1** (267 mg, 1.16 mmol) in DMSO (5.8 mL, 0.2 M) at ambient temperature was added sodium azide (190 mg, 2.91 mmol, 2.5 eq). After 20 min, the reaction was quenched with water, and the organic components were extracted three times with ether. The combined organic layer was washed with water and brine and was dried over anhydrous sodium sulfate. Concentration to obtain crude solid material, which was recrystallized from hexane, gave 159 mg of **1k** (71%).

Pale yellow crystal; R_f value 0.60 (hexane/ethyl acetate = 1/1); mp 73 °C; IR (NaCl, neat) ν_{\max} 2123, 1683, 1600, 1239, 1180, 1019, 945, 825 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.89 (d, 2H, *J* = 9.0 Hz), 6.96 (d, 2H, *J* = 9.0 Hz), 4.51 (s, 2H), 3.89 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 191.6, 164.2, 130.3, 127.3, 114.1, 55.6, 54.5;

LRMS (EI, M = C₉H₉N₃O₂) *m/z* 191 (2%, M⁺), 135 (100), 92 (34), 77 (35); HRMS (EI) calcd for C₉H₉N₃O₂ (M⁺) 191.0695, found 191.0692.

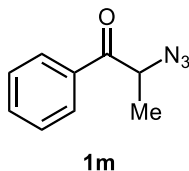
2-Azido-1-(4-bromophenyl)ethan-1-one (**1l**)⁶⁸⁾



To a stirred solution of 4-bromo phenacyl bromide (1.39 g, 5.0 mmol) in DMSO (25 mL, 0.2 M) at ambient temperature was added sodium azide (814 mg, 12.5 mmol, 2.5 eq). After 10 min, the reaction was quenched with water, and the organic components were extracted three times with ether. The combined organic layer was washed with water and brine and was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 8/1) gave 1.05 g of **1l** (87%).

Pale yellow solid; *R_f* value 0.40 (hexane/ethyl acetate = 5/1); mp 79 °C; IR (KBr, disc) ν_{\max} 2918, 2118, 1694, 1588, 1401, 1224, 1072, 1011, 815 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, 2H, *J* = 9.0 Hz), 7.65 (d, 2H, *J* = 9.0 Hz), 4.53 (s, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 192.3, 133.0, 132.4, 129.5, 129.4, 54.8; HRMS (CI) calcd for C₈H₇⁷⁹BrN₃O [M+H]⁺ 239.9772, found 239.9767.

2-Azido-1-phenylpropan-1-one (**1m**)

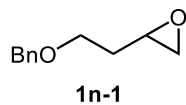


To a stirred solution of 2-bromopropiophenone (0.76 mL, 5.0 mmol) in DMSO (25 mL, 0.2 M) at ambient temperature was added sodium azide (813 mg, 12.5 mmol, 2.5 eq). After 0.5 h, the reaction was quenched with water, and the organic components were extracted three times with ether. The combined organic layer was washed with water and brine and was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 10/1) gave 757mg of **1m** (87%).

Pale yellow oil; *R_f* value 0.40 (hexane/ethyl acetate = 5/1); IR (NaCl, neat) ν_{\max} 2123, 2094, 1690, 1217, 964 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.96–7.94 (m, 2H), 7.62 (t, 1H, *J* = 7.5 Hz), 7.51 (dd, 2H, *J* = 7.5, 7.5 Hz), 4.72 (q, 1H, *J* = 7.0 Hz), 1.57 (t, 3H, *J* = 7.0 Hz); ¹³C NMR (126 MHz, CDCl₃) δ 196.7, 134.2, 133.9, 128.9, 128.6, 58.3, 16.5; HRMS (CI) calcd for C₉H₁₀N₃O[M+H]⁺ 176.0824, found

176.0829.

2-(2-(Benzyloxy)ethyl)oxirane (**1n-1**)



To a stirred solution of D-aspartic acid (1.33 g, 10.0 mmol) in aqueous sulfuric acid (3.5 mL of conc sulfuric acid, 66 mmol, 6.6 eq, diluted with 27 mL of water) at $-5\text{ }^{\circ}\text{C}$ was added potassium bromide (5.4 g, 45 mmol, 4.5 eq) followed by the slow addition of an aqueous solution of sodium nitrite (1.2 g, 18 mmol, 1.8 eq, dissolved in 2.4 mL of water). After 3 h at $0\text{ }^{\circ}\text{C}$, the brown mixture was extracted four times with ethyl acetate. The combined organic layer was dried over magnesium sulfate. Concentration in vacuo gave the brominated product (1.70 g) as a white solid. The compound was used without purification.

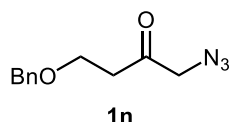
To a stirred solution of crude α -bromo carboxylic acid in THF (23 mL) was slowly added borane–THF complex (0.92 M in THF, 28.1 mL, 25.9 mmol, 3.0 eq) at $0\text{ }^{\circ}\text{C}$. The white solution formed was stirred for 1 h at $0\text{ }^{\circ}\text{C}$, and then the cooling bath was removed to warm up to room temperature. After 2 h, the mixture was cooled again to $0\text{ }^{\circ}\text{C}$, and potassium carbonate (2.59 g) dissolved in water (10 mL) was slowly added. The suspension was stirred for 10 min at room temperature, and then the mixture was filtered through Celite; the precipitate was rinsed twice with diethyl ether. The obtained organic filtrate was washed with brine and was dried over magnesium sulfate. Concentration gave the crude bromohydrin product (1.17 g) as a pale yellow oil. The material was submitted to the next step without further purification.⁶⁹⁾

To suspension of sodium hydride (60% in material oil, 500 mg, 20.8 mmol, 3.0 eq) in THF (10 mL) at $-16\text{ }^{\circ}\text{C}$ was added a solution of crude bromohydrin in THF (10 mL) dropwise. After 30 min, benzyl bromide (0.91 mL, 7.6 mmol, 1.1 eq) and tetrabutylammonium iodide (2.56 g, 6.93 mmol, 1.0 eq) were successively added to the reaction mixture at $-10\text{ }^{\circ}\text{C}$, and the mixture was warmed up to room temperature. After an additional 3 h, water (10 mL) followed by saturated ammonium chloride aqueous solution (10 mL) was added carefully to the reaction mixture. After 1 h, the organic materials were extracted twice with ethyl acetate. The combined organic layer was dried over magnesium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 8/1 to 6/1) gave 692 mg of **1n-1** (39% for 3 steps). Although this is a chiral product, optical rotation value was not measured because its chirality disappeared in next step.

Colorless oil; R_f value 0.60 (hexane/ethyl acetate = 5/1); IR (NaCl, neat) ν_{max} 2860, 2359, 1455, 1362, 1103, 833, 739, 698 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ

7.37–7.33 (m, 4H), 7.32–7.27 (m, 1H), 4.53 (s, 2H), 3.67–3.60 (m, 2H), 3.08 (ddt, 1H, $J = 6.0, 4.5, 3.0$ Hz), 2.79 (dd, 1H, $J = 5.0, 4.5$ Hz), 2.53 (dd, 1H, $J = 5.0, 3.0$ Hz), 1.92 (m, 1H), 1.78 (ddt, 1H, $J = 14.0, 6.0, 6.0$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 138.2, 128.4, 127.6, 73.1, 67.0, 50.1, 47.1, 32.9; HRMS (CI) calcd for $\text{C}_{11}\text{H}_{15}\text{O}_2$ $[\text{M}+\text{H}]^+$ 179.1072, found 179.1076.

1-Azido-4-(benzyloxy)butan-2-one (**1n**)

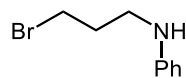


To a stirred solution of **1n-1** (542 mg, 3.04 mmol) in methanol/water (10.9 mL, 8/1, 0.3 M) were added ammonium chloride (326 mg, 6.08 mmol, 2.0 eq) and sodium azide (1.58 g, 24.3 mmol, 8.0 eq) successively at room temperature. Then the reaction mixture was warmed to 40 °C. After 10 h, the resulting mixture was cooled to room temperature and then was diluted with water. The organic materials were extracted twice with ether. The combined organic layer was dried over magnesium sulfate. Concentration in vacuo gave crude azidohydrin (620 mg), which was submitted to the next step without further purification.

To a solution of oxalyl chloride (0.29 mL, 3.36 mmol, 1.2 eq) in dichloromethane (1.7 mL) under a nitrogen atmosphere was added DMSO (0.40 mL, 5.6 mmol, 2.0 eq), and the obtained crude material was dissolved in dichloromethane (7.6 mL, 0.4 M) dropwise at -78 °C. After 20 min, triethylamine (1.95 mL, 14.0 mmol, 5.0 eq) was added slowly to the reaction mixture at the same temperature, and the mixture was warmed up to room temperature. After 30 min, the reaction mixture was diluted with dichloromethane and was washed with saturated aqueous ammonium chloride solution and twice with brine. The combined organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 4/1 to 2/1) gave 571 mg of **1n** (86% for 2 steps).

Colorless oil; R_f value 0.33 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{max} 2869, 2103, 1728, 1281, 1101, 740, 699 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.37–7.34 (m, 2H), 7.31–7.29 (m, 3H), 4.51 (s, 2H), 4.00 (s, 2H), 3.76 (t, 2H, $J = 6.0$ Hz), 2.70 (t, 2H, $J = 5.5$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 203.1, 137.6, 128.5, 127.8, 127.7, 73.3, 64.9, 58.1, 40.4; HRMS (CI) calcd for $\text{C}_{11}\text{H}_{14}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 220.1086, found 220.1086.

N-(3-Bromopropyl)aniline (**3a-1**)

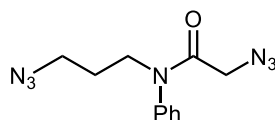


3a-1

A stirred solution of aniline (0.455 mL, 5.0 mmol) and 1,3-dibromopropane (3.05 mL, 30.0 mmol, 6.0 eq) in acetonitrile (10 mL, 0.5 M) was heated up to reflux for 3 h. After the mixture cooled to room temperature, the reaction mixture was diluted with water and was extracted three times with ether. The combined organic layer was dried over magnesium sulfate. Concentration and purification by silica gel column chromatography (hexane with 5% ether to hexane/ethyl acetate = 5/1) gave **3a-1** (386 mg, 1.80mmol, 36%).

Colorless oil; R_f value 0.5 (hexane/ethyl acetate = 5/1); IR (NaCl, neat) ν_{\max} 3404, 1603, 1506, 1255 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.20 (m, 2H), 6.73 (tt, 1H, $J = 7.5, 1.0$ Hz), 6.65 (m, 2H), 3.52 (t, 2H, $J = 6.5$ Hz), 3.35 (t, 2H, $J = 6.0$ Hz), 2.16 (tt, 2H, $J = 6.5, 6.0$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 147.6, 129.3, 117.7, 112.9, 42.0, 31.9, 31.2; LRMS (EI, $M = \text{C}_9\text{H}_{12}\text{BrN}$) m/z 215 (1.2%, M^+ of ^{81}Br), 213 (1.4, M^+ of ^{79}Br), 106 (100), 77 (15); HRMS (EI) calcd for $\text{C}_9\text{H}_{12}^{81}\text{BrN}$ (M^+) 215.0133, found 215.0123.

2-Azido-*N*-(3-azidopropyl)-*N*-phenylacetamide (**3a**)



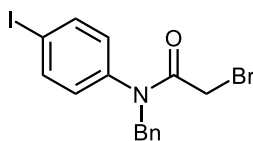
3a

According to the general procedure, 390 mg of **3a** (91% from amine for 2 steps) was obtained from the reactions with (1) **3a-1** (352 mg, 1.65 mmol, 1.0 eq), bromoacetyl bromide (0.165 mL, 1.88 mmol, 1.14 eq), which dissolved in dichloromethane (6 mL), and dichloromethane solvent (14 mL, 0.12 M); (2) crude bromoacetamide (574 mg), sodium azide (375 mg, 5.76 mmol, 3.5 eq), and DMSO (8.3 mL, 0.2 M) for 1 h followed by silica gel column chromatography (hexane/ethyl acetate = 4/1 to 2/1).

Pale yellow oil; R_f value 0.5 (hexane/ethyl acetate = 2/1); IR (NaCl, neat) ν_{\max} 2935, 2104, 1670, 1493, 1406, 1261 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.48–7.40 (m, 3H), 7.18–7.16 (m, 2H), 3.81 (t, 2H, $J = 7.5$ Hz), 3.57 (s, 2H), 3.37 (t, 2H, $J = 7.0$ Hz), 1.85 (tt, 2H, $J = 7.5, 7.0$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 167.4, 140.4, 130.3, 128.9, 127.8, 50.8, 49.0, 47.3, 27.1; HRMS (CI) calcd for $\text{C}_{11}\text{H}_{14}\text{N}_7\text{O}$

[M+H]⁺ 260.1260, found 260.1264.

N-Benzyl-2-bromo-*N*-(4-iodophenyl)acetamide (**3b-1**)



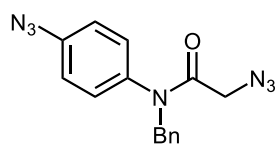
3b-1

To a stirred solution of 4-iodoaniline (1.09 g, 5.0 mmol) in methanol (8.3 mL, 0.6 M) was added benzaldehyde (0.51 mL, 5.0 mmol, 1.0 eq) at room temperature. After 0.5 h, the mixture was cooled to 0 °C. Sodium borohydride (631 mg, 15.0 mmol, 3.0 eq) was added to the mixture carefully, and then the mixture was warmed up to room temperature. After 12 h, the resulting mixture was poured into a saturated aqueous sodium bicarbonate solution. The organic components were extracted three times with ethyl acetate and were washed with brine. The collected organic layer was dried over anhydrous sodium sulfate. Concentration in vacuo gave *N*-benzyl-4-iodoaniline (1.06 g) as a crude material, which was submitted to the next step without further purification.

To a stirred solution of the crude amine (1.06 g) in dichloromethane (30.0 mL, 0.2 M) was added bromoacetyl bromide (0.34 mL, 3.92 mmol, 1.14 eq) dissolved in dichloromethane (11.5 mL) at 0 °C. After the mixture stirred at room temperature for 2 h, the reaction mixture was quenched with a saturated aqueous sodium bicarbonate solution at 0 °C. The resulting mixture was washed with a saturated aqueous sodium bicarbonate solution, and the organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 5/1 with 5% toluene) gave 1.33 g of **3b-1** (62%).

White solid; R_f value 0.27 (hexane/ethyl acetate = 5/1); mp 90–91 °C; IR (NaCl, neat) ν_{\max} 1663, 1482, 1006 cm^{-1} ; ¹H NMR (500 MHz, CDCl₃) δ 7.68 (d, 2H, J = 8.5 Hz), 7.30–7.26 (m, 3H), 7.18–7.16 (m, 2H), 6.80 (d, 2H, J = 8.5 Hz), 4.86 (s, 2H), 3.65 (s, 2H); ¹³C NMR (126 MHz, CDCl₃) δ 166.2, 140.8, 139.0, 136.2, 130.1, 128.9, 128.6, 127.8, 94.3, 53.5, 26.9; LRMS (EI, M = C₁₅H₁₃BrINO) m/z 431 (5%, M⁺ of ⁸¹Br), 429 (5, M⁺ of ⁷⁹Br), 352 (2), 350 (100), 223 (26), 91 (77); HRMS (EI) calcd for C₁₅H₁₃⁷⁹BrINO (M⁺) 428.9225, found 428.9224.

2-Azido-*N*-(4-azidophenyl)-*N*-benzylacetamide (**3b**)

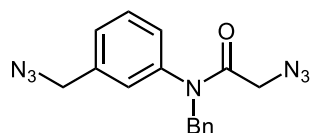


3b

To a stirred solution of **3b-1** (215 mg, 0.50 mmol) in DMSO/water (3.3 mL, 5/1, 0.15 M) were added sodium azide (98.2 mg, 1.5 mmol, 3.0 eq), copper(I) iodide (19.8 mg, 0.1 mmol, 0.2 eq), sodium L-ascorbate (9.9 mg, 0.05 mmol, 0.1 eq), and *N,N'*-dimethylethylenediamine (16.1 μ L, 0.15 mmol, 0.3 eq) successively at room temperature. After 12 h, the resulting mixture was poured into water, and the organic components were extracted three times with ether. The organic layer was washed with brine followed by drying over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 4/1) gave 138 mg of **3b** (90%).

Pale yellow oil; R_f value 0.57 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{\max} 2103, 1672, 1505, 1279, 1256 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.28–7.26 (m, 3H), 7.18–7.16 (m, 2H), 6.99 (d, 2H, $J = 8.5$ Hz), 6.92 (d, 2H, $J = 8.5$ Hz), 4.87 (s, 2H), 3.58 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.2, 140.7, 136.7, 136.3, 129.7, 129.1, 128.6, 127.8, 120.3, 53.4, 50.8; LRMS (EI, $M = \text{C}_{15}\text{H}_{13}\text{N}_7\text{O}$) m/z 307 (7%, M^+), 279 (58), 118 (28), 91 (100); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{13}\text{N}_7\text{O}$ (M^+) 307.1182, found 307.1174.

2-Azido-*N*-(3-(azidomethyl)phenyl)-*N*-benzylacetamide (**3c**)



3c

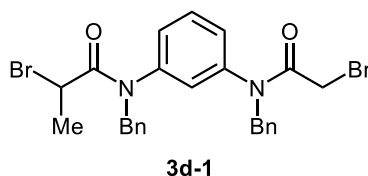
To a stirred solution of **1e-1** (66.8 mg, 0.2 mmol) were added *p*-toluenesulfonyl chloride (45.9 mg, 0.24 mmol, 1.2 eq), 4-dimethylaminopyridine (3.2 mg, 0.02 mmol, 0.1 eq) in dichloromethane (2.0 mL, 0.1 M), and triethylamine (37 μ L, 0.26 mmol, 1.3 eq) dropwise at 0 $^\circ\text{C}$. After the mixture stirred at room temperature for 4 h, the reaction was quenched with water at 0 $^\circ\text{C}$. The organic components were extracted twice with dichloromethane and then were washed with water and brine. The combined organic layer was dried over anhydrous sodium sulfate. Concentration in vacuo gave crude tosylate (61.8 mg), which was submitted to the next step without purification. (Beware of residual dichloromethane; see also the caution statement above.)

To a stirred solution of the crude tosylate (61.8 mg) in DMSO (0.64 mL, 0.2 M)

was added sodium azide (20.9 mg, 0.316 mmol, 2.5 eq) at room temperature. After 1 h, the reaction was quenched with water, and the organic components were extracted three times with ether. The combined organic layer was washed with water and brine and then was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 8/1 to 4/1) gave 41.4 mg of **3c** (65% for 2 steps).

Pale yellow oil; R_f value 0.83 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 2103, 1670, 1400, 1263, 1217, 707 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.37 (t, 1H, $J = 8.0$ Hz), 7.31–7.26 (m, 4H), 7.19–7.17 (m, 2H), 6.94–6.92 (m, 2H), 4.90 (s, 2H), 4.30 (s, 2H), 3.59 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 167.1, 140.8, 137.6, 136.3, 130.5, 129.1, 128.6, 128.5, 128.1, 127.83, 127.78, 53.9, 53.4, 50.9; HRMS (CI) calcd for $\text{C}_{16}\text{H}_{16}\text{N}_7\text{O}$ $[\text{M}+\text{H}]^+$ 322.1416, found 322.1413.

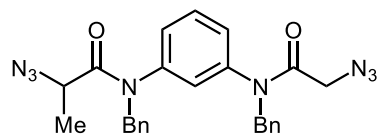
N-Benzyl-*N*-(3-(*N*-benzyl-2-bromoacetamido)phenyl)-2-bromopropanamide (**3d-1**)



To a stirred solution of the diamine **1g-1** (2.33 g, 8.08 mmol) in dichloromethane (77.0 mL, 0.083 M) was added bromoacetyl bromide (0.70 mL, 8.08 mmol, 1.0 eq) dissolved in dichloromethane (10.0 mL) dropwise at 0 °C. After the mixture stirred at room temperature for 1 h, 2-bromopropionyl bromide (0.85 mL, 8.08 mmol, 1.0 eq) dissolved in dichloromethane (10.0 mL) was added to the reaction mixture at 0 °C. After the mixture stirred at room temperature for 1 h, the reaction was quenched with a saturated aqueous sodium bicarbonate solution at 0 °C. The resulting mixture was washed with a saturated aqueous sodium bicarbonate solution and was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 5/1 to 3/1 to 2/1) gave 1.64 g of **3d-1** (37%).

Colorless viscous oil; R_f value 0.30 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{\max} 1664, 1596, 1391, 701 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.37 (t, 1H, $J = 8.0$ Hz), 7.26–7.25 (m, 6H), 7.10–7.09 (m, 6H), 6.60 (br-s, 1H), 5.07–4.56 (m, 4H), 3.93 (br-s, 1H), 3.44 (s, 2H), 1.71 (br-d, 3H, $J = 6.5$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 168.9, 166.0, 141.7, 141.5, 136.1, 135.9, 130.8, 129.4, 128.87, 128.85, 128.75, 128.63, 128.58, 128.4, 127.95, 127.91, 53.33, 53.31, 38.9, 27.0, 21.6; LRMS (EI, $\text{M} = \text{C}_{25}\text{H}_{24}\text{Br}_2\text{N}_2\text{O}_2$) m/z 546 (1.3%, M^+ of $^{81}\text{Br}\times 2$), 544 (3, M^+ of $^{81}\text{Br}+^{79}\text{Br}$), 542 (1.3, M^+ of $^{79}\text{Br}\times 2$), 465 (85), 463 (85), 223 (25), 91 (100); HRMS (EI) calcd for $\text{C}_{25}\text{H}_{24}^{79}\text{Br}_2\text{N}_2\text{O}_2$ (M^+) 542.0205, found 542.0198.

2-Azido-*N*-(3-(2-azido-*N*-benzylacetamido)phenyl)-*N*-benzylpropanamide (**3d**)

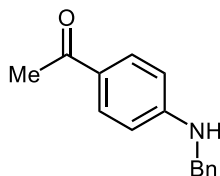


3d

To a stirred solution of **3d-1** (157 mg, 0.289 mmol) in DMSO (1.4 mL, 0.2 M) was added sodium azide (58.0 mg, 0.867 mmol, 2.5 eq) at room temperature. After 1 h, the reaction was quenched with water, and the organic components were extracted three times with ether. The organic layer was washed with water and brine. The combined organic layer was then dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 2/1) gave 129 mg of **3d** (95%).

White solid; R_f value 0.30 (hexane/ethyl acetate = 3/1); mp 104–105 °C; IR (NaCl, neat) ν_{\max} 2105, 1667, 1397, 1235, 703 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.39 (t, 1H, $J = 8.0$ Hz), 7.28–7.25 (m, 5H), 7.10–7.01 (m, 7H), 6.31 (s, 1H), 4.91–4.71 (br, 4H), 3.22–3.15 (m, 3H), 1.30 (br-d, 3H, $J = 6.5$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 169.7, 166.8, 141.6, 141.0, 136.0, 135.8, 131.3, 129.4, 129.0, 128.9, 128.7, 128.6, 128.5, 128.1, 128.0, 54.0, 53.1, 53.0, 50.7, 16.2; HRMS (CI) calcd for $\text{C}_{25}\text{H}_{25}\text{N}_8\text{O}_2$ $[\text{M}+\text{H}]^+$ 469.2100, found 469.2095.

1-(4-(Benzylamino)phenyl)ethan-1-one (**3e-1**)

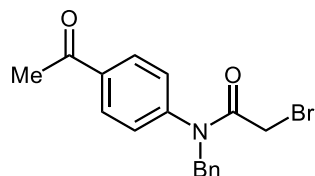


3e-1

To a stirred solution of 4'-aminoacetophenone (4.10 g, 30.3 mmol, 3.0 eq) in acetonitrile (20 mL, 1.5 M) were added potassium carbonate (2.09 g, 15.2 mmol, 1.5 eq) and benzyl bromide (1.20 mL, 10.1 mmol) successively at room temperature. After 26 h at room temperature, the insoluble potassium carbonate was removed by filtration through filter paper and was washed with ethyl acetate. The collected filtrate was concentrated and was purified by silica gel column chromatography (hexane/ethyl acetate = 2/1) to obtain 2.00 g of **3e-1** (88% based on benzyl bromide). Orange solid; R_f value 0.60 (hexane/ethyl acetate = 1/1); mp 90.1–91.8 °C; IR (NaCl, neat) ν_{\max} 3349, 1650, 1596, 1358, 1280, 1179 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, 2H, $J = 8.5$ Hz), 7.38–7.34 (m, 4H), 7.32–7.29 (m, 1H), 6.60 (d, 2H, $J = 8.5$ Hz), 4.63 (s, 1H), 4.41 (s, 2H), 2.49 (s, 3H); ^{13}C NMR (126 MHz,

CDCl₃) δ 196.4, 151.9, 138.2, 130.7, 128.8, 127.5, 127.3, 126.8, 111.5, 47.5, 26.0; LRMS (EI, M = C₁₅H₁₅NO) m/z 225 (77%, M⁺), 210 (62), 91 (100); HRMS (EI) calcd for C₁₅H₁₅NO (M⁺) 225.1154, found 225.1155.

N-(4-Acetylphenyl)-*N*-benzyl-2-bromoacetamide (**3e-2**)

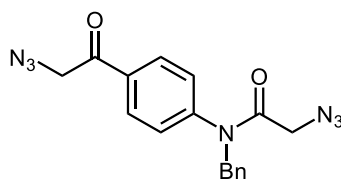


3e-2

To a stirred biphasic solution of **3e-1** (2.00 g, 8.86 mmol) in dichloromethane and water (125 mL, 1/4, 0.07 M) was added potassium carbonate (368 mg, 2.66 mmol, 0.2 eq) at 0 °C. Then, bromoacetyl bromide (1.15 mL, 13.3 mmol, 1.5 eq) dissolved in dichloromethane (45 mL) was added dropwise over 40 min at the same temperature. After 2 h, the mixture was warmed at room temperature. After 12 h, the reaction mixture was diluted with dichloromethane and was washed twice with water. The combined organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 2/1) gave 3.01 g of **3e-2** (98%).

White solid; R_f value 0.50 (hexane/ethyl acetate = 1/1); mp 79–80 °C; IR (NaCl, neat) ν_{\max} 1666, 1600, 1265 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.94 (d, 2H, J = 9.0 Hz), 7.27–7.26 (m, 3H), 7.18–7.175 (m, 4H), 4.92 (s, 2H), 3.67 (s, 2H), 2.60 (s, 2H); ¹³CNMR (126 MHz, CDCl₃) δ 196.8, 166.1, 145.2, 136.9, 136.1, 129.8, 128.8, 128.6, 128.4, 127.8, 53.5, 26.9, 26.7; HRMS (CI) calcd for C₁₇H₁₇⁷⁹BrNO₂ [M+H]⁺ 346.0443, found 346.0439.

2-Azido-*N*-(4-(2-azidoacetyl)phenyl)-*N*-benzylacetamide (**3e**)



3e

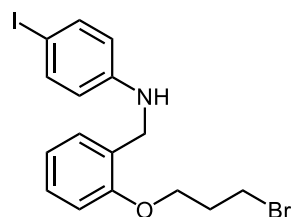
To a stirred solution of *N*-benzyl-4-aminoacetophenone (175 mg, 0.500 mmol) in THF (6.4 mL) was added trimethylphenylammonium tribromide (207 mg, 0.550 mmol, 1.1 eq) at 0 °C. After 12 h, the resulting precipitate was removed by filtration and was washed with ethyl acetate. Then the filtrate was washed with water and brine. The combined organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl

acetate = 4/1 to 2/1) gave 97.2 mg of dibromide (46%) as a colorless oil. Because the dibromide product was relatively unstable, this was soon submitted to the next step without collecting analytical data.

To a stirred solution of the dibromide (273 mg, 0.642 mmol) in DMSO (6.5 mL, 0.1 M) was added sodium azide (104 mg, 1.60 mmol, 2.5 eq) at room temperature. After 1.5 h, the reaction was quenched with water. The organic components were extracted three times with ether and were washed with brine. The combined organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 4/1 to 2/1) gave 176 mg of **3e** (79%).

Pale yellow oil; R_f value 0.60 (hexane/EtOAc = 1/1); IR (NaCl, neat) ν_{\max} 2105, 1672, 1600, 1215 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.90 (d, 2H, $J = 8.5$ Hz), 7.29–7.26 (m, 3H), 7.17–7.13 (m, 4H), 4.93 (s, 2H), 4.52 (s, 2H), 3.62 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 192.1, 166.8, 145.2, 135.8, 134.0, 129.5, 128.6, 127.9, 54.8, 53.2, 50.8; HRMS (CI) calcd for $\text{C}_{17}\text{H}_{16}\text{N}_7\text{O}_2$ $[\text{M}+\text{H}]^+$ 350.1365, found 350.1360.

N-(2-(3-Bromopropoxy)benzyl)-4-iodoaniline (**5a-1**)



5a-1

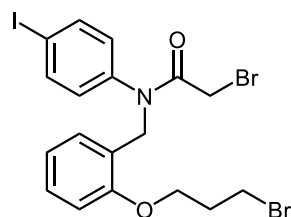
To a stirred solution of salicylaldehyde (1.23 g, 10 mmol) and potassium carbonate (2.77 g, 20 mmol, 2.0 eq) in DMF (29 mL, 0.34 M) was added 1,3-dibromopropane (4.1 mL, 40 mmol, 4.0 eq) at 0 °C. After 24 h at room temperature, the resulting mixture was diluted with ethyl acetate and was washed with water, 1 N HCl (twice), a saturated aqueous sodium bicarbonate solution, and brine. The combined organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane elution to hexane with 12% ethyl acetate) gave 1.86 g of 2(3-bromopropoxy)benzaldehyde (76%). This product was soon submitted to the next step without collecting analytical data.

To a stirred solution of 4-iodoaniline (1.36 g, 6.23 mmol) and the synthesized aldehyde above (1.82 g, 7.48 mmol, 1.2 eq) in ethanol (31 mL, 0.2 M) was added acetic acid (0.43 mL, 7.48 mmol, 1.2 eq) at room temperature. After 1 h, sodium cyanoborohydride (620 mg, 9.35 mmol, 1.5 eq) was added to the reaction mixture at 0 °C. After the mixture stirred at room temperature for 13 h, the resulting mixture

was poured into a saturated aqueous sodium bicarbonate solution. The organic components were extracted twice with ether and were washed with brine. The combined organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 5/1 with 2% trimethylamine) gave 2.71 g of **5a-1** (97%).

White oil; R_f value 0.67 (hexane/ethyl acetate = 2/1); IR (NaCl, neat) ν_{\max} 3418, 1589, 1434, 1454, 1238, 811, 752 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.40–7.39 (m, 2H), 7.28–7.24 (m, 2H), 6.92 (dd, 2H, $J = 12.5, 7.5$ Hz), 6.43 (d, 2H, $J = 9.0$ Hz), 4.30 (s, 2H), 4.17 (t, 2H, $J = 5.5$ Hz), 4.13 (br-s, 1H), 3.58 (t, 2H, $J = 6.5$ Hz), 2.33 (tt, 2H, $J = 6.5, 6.0$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 156.3, 147.5, 137.7, 128.9, 128.6, 126.6, 120.8, 115.3, 111.2, 78.2, 65.1, 43.4, 32.0, 30.1; LRMS (EI, $M = \text{C}_{16}\text{H}_{17}\text{BrINO}$) m/z 447 (99%, M^+ of ^{81}Br), 445 (100, M^+ of ^{79}Br), 229 (60), 227 (61) 107 (60), 91 (34); HRMS (EI) calcd for $\text{C}_{16}\text{H}_{17}^{79}\text{BrINO}$ (M^+) 444.9538, found 444.9536.

2-Bromo-*N*-(2-(3-bromopropoxy)benzyl)-*N*-(4-iodophenyl)-acetamide (**5a-2**)

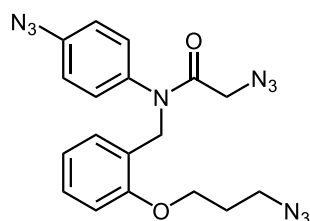


5a-2

To a stirred solution of the **5a-1** (2.57 g, 5.76 mmol) in dichloromethane (49 mL) was added bromoacetyl bromide (0.57 mL, 6.57 mmol, 1.14 eq) dissolved in dichloromethane (20 mL) at 0 °C. After the mixture stirred at room temperature for 1 h, the reaction was quenched with saturated aqueous sodium bicarbonate at 0 °C. The resulting mixture was washed with a saturated aqueous sodium bicarbonate solution. The combined organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane elution to hexane with 14% to 20% to 23% ethyl acetate) gave 3.28 g of **5a-2** (quant). Colorless oil; R_f value 0.33 (hexane/ethyl acetate = 3/1); IR (NaCl, neat) ν_{\max} 1664, 1483, 1244, 1005, 754 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.65 (d, 2H, $J = 8.5$ Hz), 7.22 (dd, 1H, $J = 8.5, 8.0$ Hz), 7.17 (d, 1H, $J = 7.5$ Hz), 6.87 (t, 1H, $J = 7.5$ Hz), 6.82–6.80 (m, 3H), 4.93 (s, 2H), 3.96 (t, 2H, $J = 5.5$ Hz), 3.63 (s, 2H), 3.47 (t, 2H, $J = 6.5$ Hz), 2.14 (tt, 2H, $J = 6.5, 5.5$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 165.9, 156.6, 140.9, 138.7, 131.1, 130.2, 129.3, 124.1, 120.8, 111.1, 94.1, 65.1, 48.0, 32.0, 30.2, 27.0; LRMS (EI, $M = \text{C}_{18}\text{H}_{18}\text{Br}_2\text{INO}_2$) m/z 569 (0.4%, M^+ of $^{81}\text{Br}\times 2$), 567 (0.8, M^+ of $^{81}\text{Br}+^{79}\text{Br}$), 565 (0.4, M^+ of $^{79}\text{Br}\times 2$), 488 (99), 486 (100), 229 (39), 227

(40), 107 (38); HRMS (EI) calcd for $C_{18}H_{18}^{79}Br_2INO_2$ (M^+) 564.8749, found 564.8738.

2-Azido-*N*-(4-azidophenyl)-*N*-(2-(3-azidopropoxy)benzyl)-acetamide (**5a**)

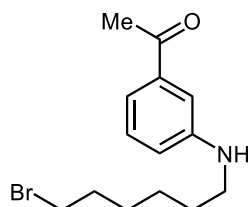


5a

To a stirred solution of **5a-2** (3.23 g, 5.69 mmol) in DMSO/water (10/1, 56 mL, 0.1 M) were added sodium azide (1.66 g, 25.6 mmol, 4.5 eq), copper(I) iodide (217 mg, 1.13 mmol, 0.2 eq), sodium L-ascorbate (116 mg, 0.569 mmol, 0.1 eq), and *N,N'*-dimethylenediamine (183 μ L, 1.71 mmol, 0.3 eq) successively at room temperature. After 16 h, the reaction mixture was poured into water and was extracted three times with ether. The combined organic layer was washed with brine and then was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 3/1) gave 2.03 g of **5a** (88%).

Colorless oil; *R_f* value 0.50 (hexane/ethyl acetate = 2/1); IR (NaCl, neat) ν_{\max} 2101, 1671, 1505, 1279, 1246 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$) δ 7.22 (ddd, 1H, $J = 8.0, 7.5, 1.5$ Hz), 7.15 (dd, 1H, $J = 7.5, 1.5$ Hz), 6.97–6.92 (m, 4H), 6.86 (dd, 1H, $J = 7.5, 7.5$ Hz), 6.79 (d, 1H, $J = 8.0$ Hz), 4.96 (s, 2H), 3.91 (t, 2H, $J = 6.0$ Hz), 3.56 (s, 2H), 3.40 (t, 2H, $J = 6.5$ Hz), 1.89 (tt, 2H, $J = 6.5, 6.0$ Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.9, 156.6, 140.5, 136.8, 131.2, 129.7, 129.3, 124.2, 120.8, 120.1, 111.1, 64.3, 50.9, 48.0, 47.7, 28.6; LRMS (EI, $M = C_{18}H_{18}N_{10}O_2$) m/z 406 (11%, M^+), 162 (81), 134 (100), 105 (83); HRMS (EI) calcd for $C_{18}H_{18}N_{10}O_2$ (M^+) 406.1614, found 406.1617.

1-(3-((6-Bromohexyl)amino)phenyl)ethan-1-one (**5b-1**)



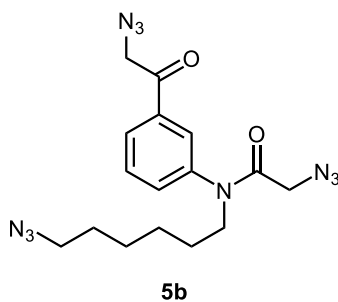
5b-1

To a stirred solution of 3'-aminoacetophenone (1.35 g, 10.0 mmol) in acetonitrile (20 mL, 0.5 M) was added 1,6-dibromohexane (9.10 mL, 60.0 mmol, 6.0 eq), and

the mixture was heated to 90 °C. After 3 h, water (100 mL) was added to the mixture at room temperature for quenching the reaction. The organic components were extracted three times with ethyl acetate and was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane elution to hexane/ethyl acetate = 5/1) gave 1.19 g of **5b-1** (40%).

Yellow oil; R_f value 0.65 (hexane/ethyl acetate = 1/1); IR (NaCl, neat) ν_{\max} 3386, 2932, 2856, 1677, 1603 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.28–7.23 (m, 2H), 7.18 (br, 1H), 6.80 (dd, 1H, $J = 7.0, 2.0, 2.0$ Hz), 3.42 (t, 2H, $J = 6.5$ Hz), 3.16 (t, 2H, $J = 7.0$ Hz), 2.57 (s, 3H), 1.87 (tt, 2H, $J = 7.5, 7.0$ Hz), 1.65 (tt, 2H, $J = 7.5, 6.5$ Hz), 1.52–1.41 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ 198.7, 148.3, 138.1, 129.3, 117.8, 117.6, 111.4, 43.8, 33.8, 32.6, 29.1, 27.9, 26.8, 26.2; LRMS (EI, $\text{M} = \text{C}_{14}\text{H}_{20}\text{BrNO}$) m/z 299 (12%, M^+ of ^{81}Br), 297 (12, M^+ of ^{79}Br), 218 (9), 148 (100); HRMS (EI) calcd for $\text{C}_{14}\text{H}_{20}\text{BrNO}$ (M^+) 297.0728, found 297.0726.

2-Azido-*N*-(3-(2-azidoacetyl)phenyl)-*N*-(6-azidohexyl)acetamide (**5b**)



To stirred solution of **5b-1** (2.13 g, 7.13 mmol) in dichloromethane (66 mL, 0.1 M) was added bromoacetyl bromide (0.71 mL, 8.13 mmol, 1.14 eq) dissolved in dichloromethane (20 mL) at 0 °C. After the mixture stirred at room temperature for 1 h, the reaction mixture was quenched with a saturated aqueous sodium bicarbonate solution at 0 °C. The resulting mixture was washed with a saturated aqueous sodium bicarbonate solution, and the organic layer was dried over anhydrous sodium sulfate. Concentration in vacuo gave crude amide (3.12 g), which was submitted to the next step without further purification.

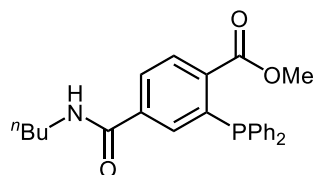
To a solution of crude ketone in THF (92 mL, 0.08 M) under a nitrogen atmosphere was added trimethylphenylammonium bromide (2.95 g, 7.84 mmol, 1.1 eq) at 0 °C. After 13 h, the reaction mixture was filtered through Celite, and then the filtrate was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate. Concentration in vacuo gave crude tribromide (4.4826 g), which was submitted to the next step.

To a solution of crude tribromide in DMSO (36 mL, 0.2 M) was added sodium azide (1.85 g, 28.5 mmol, 4.0 eq) at room temperature. After 1 h, the reaction was

quenched with water, and the organic components were extracted three times with ether. The combined organic layer was washed with water and brine and then was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (13% to 20% to 25% to 35% ethyl acetate in hexane) gave 1.94 g of **5b** (71% for 3 steps).

Colorless oil; R_f value 0.50 (hexane/EtOAc = 1/1); IR (NaCl, neat) ν_{\max} 2935, 2858, 2103, 1670, 1438, 1263 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.90 (d, 1H, $J = 8.0$ Hz), 7.76 (s, 1H), 7.62 (dd, 1H, $J = 8.0, 8.0$ Hz), 7.44 (d, 1H, $J = 8.0$ Hz), 4.58 (s, 2H), 3.73 (t, 2H, $J = 7.5$ Hz), 3.53 (s, 2H), 3.23 (t, 2H, $J = 7.0$ Hz), 1.57–1.50 (m, 4H), 1.40–1.30 (m, 4H); ^{13}C NMR (126 MHz, CDCl_3) δ 192.1, 166.7, 141.6, 136.1, 133.5, 130.9, 128.0, 127.3, 55.0, 51.2, 50.8, 49.6, 28.6, 27.3, 26.3, 26.1; HRMS (CI) calcd for $\text{C}_{16}\text{H}_{21}\text{N}_{10}\text{O}_2$ $[\text{M}+\text{H}]^+$ 385.1849, found 385.1841.

Methyl 4-(Butylcarbamoyl)-2-(diphenylphosphaneyl)benzoate (**11**)



11

To a stirred solution of 1-methyl-2-aminoterephthalate (976 mg, 5.0 mmol) in aq 4 M HCl (26.9 mL) was added NaNO_2 (380 mg, 5.5 mmol, 1.1 eq) dissolved in water (9.8 mL) dropwise at 0 °C. After 30 min, potassium iodide (4.15 g, 25 mmol, 5.0 eq) in water (33 mL, 0.15 M) cooled at -15 °C was slowly added to the reaction mixture at 0 °C. After the mixture was stirred at room temperature for 4 h, the reaction was quenched with a saturated aqueous sodium bicarbonate solution. The precipitated solid was collected by filtration and was washed with iced water. The obtained solid was recrystallized from methanol/water (1/1) to give 901 mg of 3-iodo-4-(methoxycarbonyl)benzoic acid (59%) as a yellow solid. Analytical data were identical to those reported.^{8,9)}

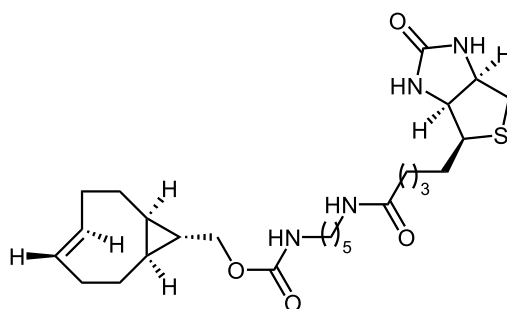
In a flame-dried flask, obtained 3-iodo-4-(methoxycarbonyl)benzoic acid (980 mg, 2.91 mmol) was dissolved in methanol (29 mL, 0.1 M). To the stirred solution were added palladium(II) acetate (76.2 mg, 0.291 mmol, 0.1 eq), triethylamine (0.82 mL, 5.82 mmol, 2.0 eq), and diphenylphosphine (0.56 mL, 2.91 mmol, 1.0 eq) at room temperature. The reaction mixture was stirred at reflux for 10 h, and then the resulting mixture was cooled down to room temperature. The crude material obtained after concentration in vacuo was dissolved with dichloromethane and was washed with water and aq 1 M HCl. After removal of organic solvent, the resulting material was dissolved by methanol and an equal volume of water was added to the

solution. The solution was cooled to 4 °C for 2 h, and the resulting solid was collected by filtration to afford 663 mg of methyl 3-(diphenylphosphaneyl)-4-(methoxycarbonyl)benzoic acid^{8,9}) as blown powder, which was submitted to the next step without further purification.

To a stirred solution of 3-(diphenylphosphaneyl)-4-(methoxycarbonyl)-benzoic acid (657 mg) in dichloromethane (80 mL) were added N-(3-(dimethylamino)propyl)-N'-ethylcarbodiimide hydrochloride (427 mg, 2.22 mmol, 1.23 eq), and 4-dimethylaminopyridine (22.1 mg, 0.186 mmol, 0.1 eq) at room temperature. Then, a solution of *n*-butylamine (0.196 mL, 1.98 mmol, 1.1 eq) in dichloromethane (10 mL) was added to the mixture. After 18 h, the reaction mixture was diluted with dichloromethane and was washed with 10% HCl (twice), saturated aqueous sodium bicarbonate (twice), water, and brine. The combined organic layer was dried over anhydrous sodium sulfate. Concentration and purification by silica gel column chromatography (hexane/ethyl acetate = 4/1 to 3/1) gave 473 mg of **11** (39% from iodide for 2 steps).

Yellow solid; R_f value 0.6 (hexane/ethyl acetate = 1/1); mp 78–79 °C; IR (NaCl, neat) ν_{\max} 3299, 2955, 1720, 1638, 1541, 1434, 1288 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.10 (dd, 1H, $J = 8.5, 4.0$ Hz), 7.80 (dd, 1H, $J = 8.0, 1.5$ Hz), 7.38–7.33 (m, 6H), 7.29–7.26 (m, 4H), 7.12 (dd, 1H, $J = 3.5, 1.5$ Hz), 5.70 (br-s, 1H), 3.75 (s, 3H), 3.31 (dd, 2H, $J = 12.5, 6.5$ Hz), 1.47–1.41 (m, 2H), 1.24 (ddt, 2H, $J = 15.5, 7.5, 7.5$ Hz), 0.90 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR (126 MHz, CDCl_3) δ 166.5 (d, $J = 2.4$ Hz), 166.3, 141.5 (d, $J = 28.8$ Hz), 137.5, 137.2 (d, $J = 10.7$ Hz), 136.3 (d, $J = 18.0$ Hz), 133.8 (d, $J = 20.4$ Hz), 132.0, 131.0 (d, $J = 2.4$ Hz), 129.0, 128.6 (d, $J = 7.2$ Hz), 127.1, 52.3, 39.6, 31.2, 19.9, 13.7; ^{31}P NMR (202 MHz, benzene- d_6) δ -2.90; HRMS (ESI) calcd for $\text{C}_{25}\text{H}_{27}\text{NO}_3\text{P}$ $[\text{M}+\text{H}]^+$ 420.1729, found 420.1730.

Biotin-conjugated *trans*-cyclooctene (**29**)



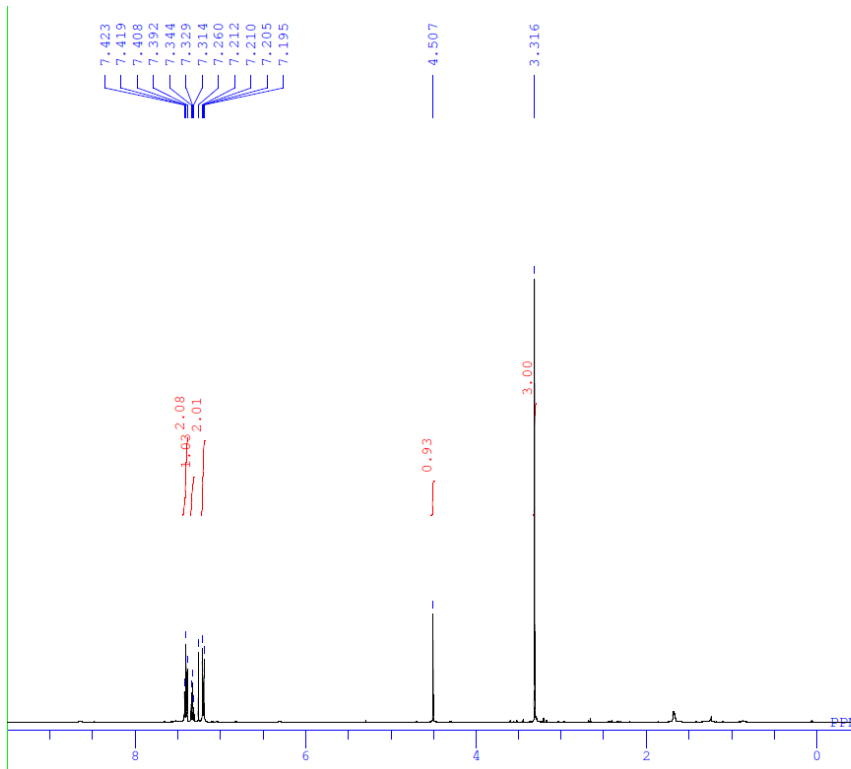
29

To a solution of 5-(*(+)*-biotinamido)pentylamine trifluoroacetic acid salt⁷⁰) (264 mg, 0.596 mmol) and racemic (*rel*-1*R*,8*S*,9*R*,4*E*)-bicyclo[6.1.0]non-4-ene-9-ylmethyl (4-nitrophenyl) carbonate^{61a}) (227 mg, 0.716 mmol, 1.2 eq) in DMF (60 mL, 0.01

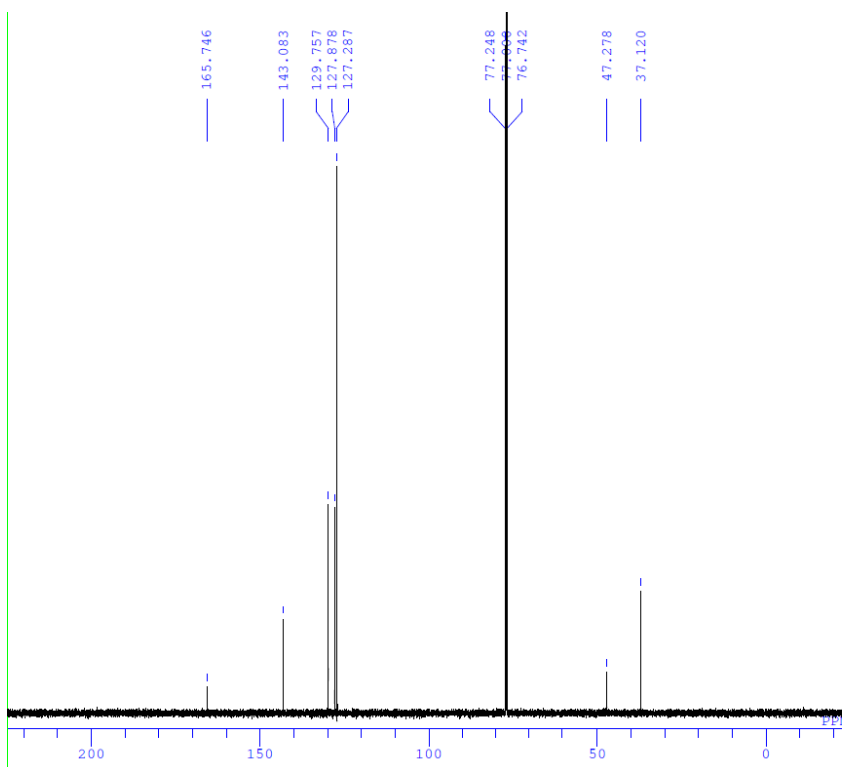
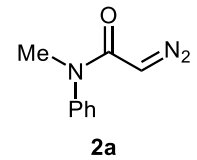
M) was added triethylamine (0.25 mL, 1.79 mmol, 3.0 eq) at room temperature. After 24 h, to the mixture was added triethylamine (0.25 mL, 1.79 mmol, 3.0 eq) again. After 24 h, the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane elution to dichloromethane/methanol = 15/1) gave **29** (157 mg, 0.310 mmol, 52%). Although residual nitrophenol was inseparable even after GPC purification, which also ended large loss of the product (down to ca. 5%), the obtained material was used in the next reaction without further purification.

White amorphous solid; R_f value 0.17 (dichloromethane/methanol = 10/1); IR (NaCl, neat) ν_{\max} 3301, 2926, 2854, 1702, 1642, 1545, 1267 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 6.49–6.41 (br, 1H), 6.22 (br, 1H), 5.85 (ddd, 1H, $J = 17, 8.0, 6.5$ Hz), 5.62–5.55 (br, 1H), 5.12 (ddd, 1H, $J = 14.0, 10.0, 3.5$ Hz), 4.88 (br, 1H), 4.51 (dd, 1H, $J = 7.0, 5.0$ Hz), 4.31 (dd, 1H, $J = 4.5, 2.0$ Hz), 3.91 (d, 2H, $J = 8.0$ Hz), 3.22–3.20 (m, 2H), 3.15 (m, 4H), 2.90 (dd, 1H, $J = 8.0, 5.0$ Hz), 2.73 (d, 1H, $J = 13.0$ Hz), 2.35 (d, 1H, $J = 14.0$ Hz), 2.27–2.24 (m, 2H), 2.21–2.18 (m, 2H), 1.95–1.87 (m, 2H), 1.73–1.65 (m, 4H), 1.52–1.41 (m, 6H), 1.34 (m, 2H), 0.87–0.81 (m, 2H), 0.55–0.51 (m, 2H), 0.41 (m, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ 173.2, 163.9, 157.0, 138.3, 131.2, 70.5, 69.4 (assigned to diastereomer), 61.8, 60.2, 55.6, 40.5, 39.2, 38.7, 35.9, 33.8, 32.6, 29.7, 29.6, 29.0, 28.1, 28.0, 27.6, 25.6, 24.7, 23.8, 21.9, 20.9; HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{23}\text{N}_{11}\text{ONa}$ $[\text{M}+\text{Na}]^+$ 529.2824, found 529.2821.

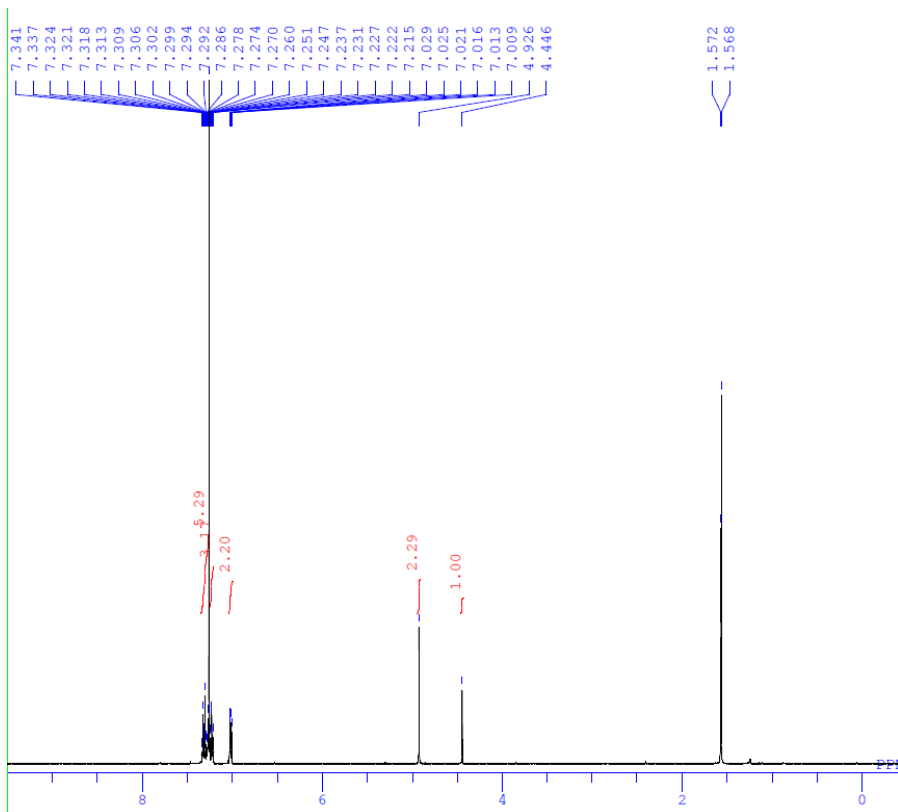
6-6 NMR Spectra



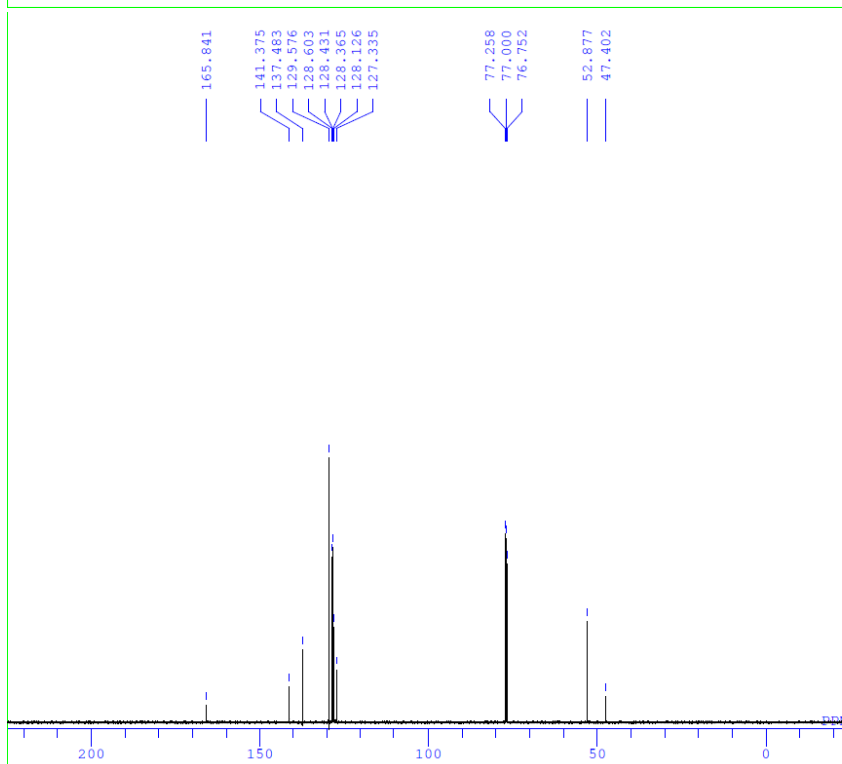
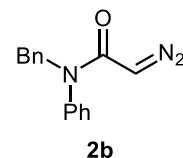
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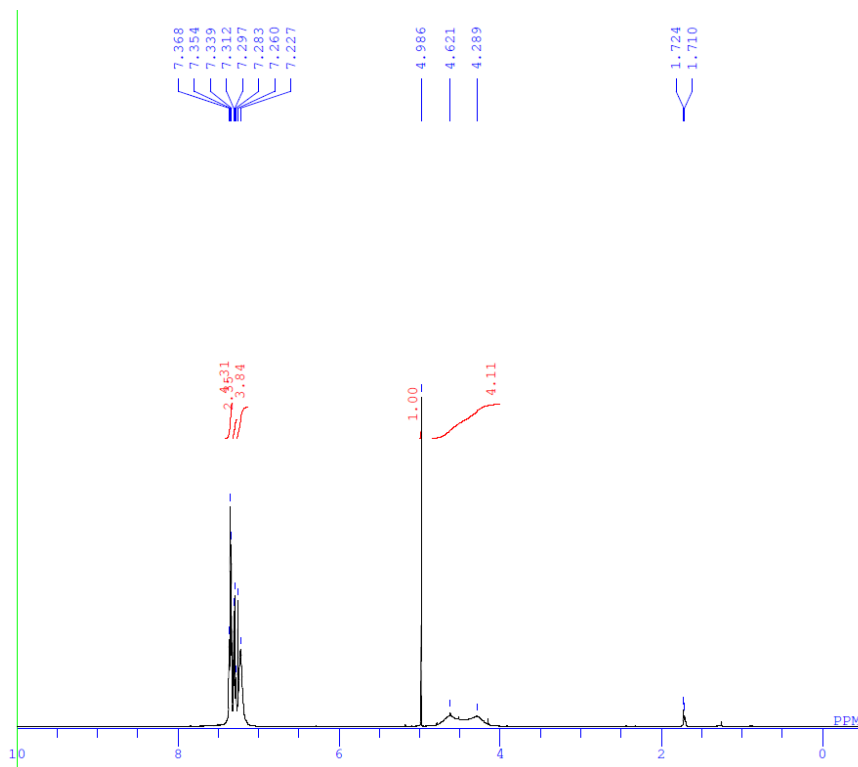
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 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60



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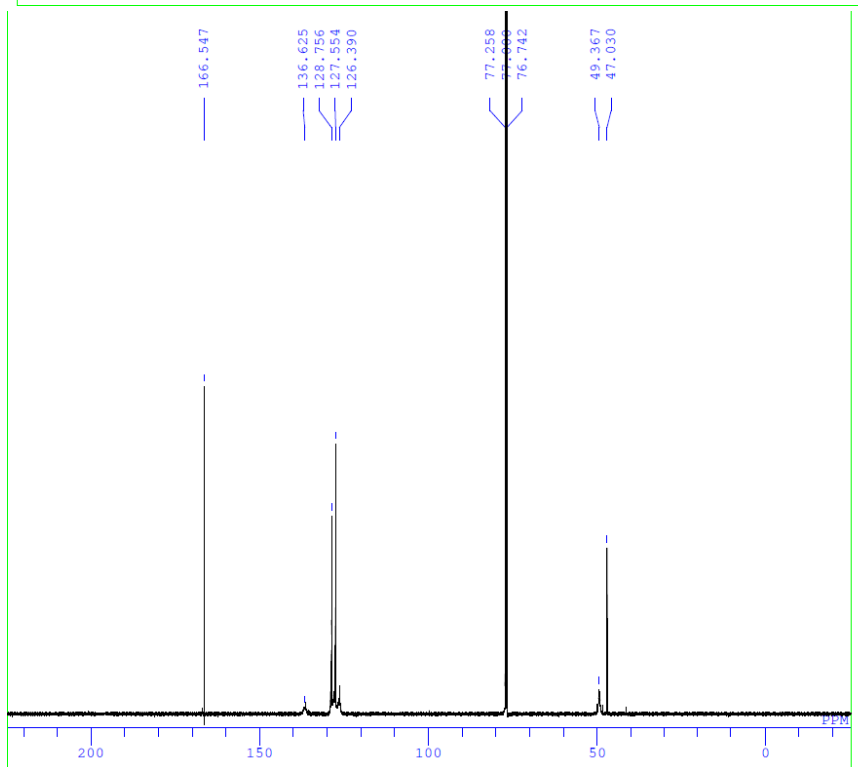
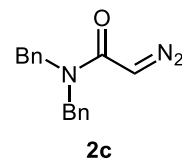


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RGAIN 60



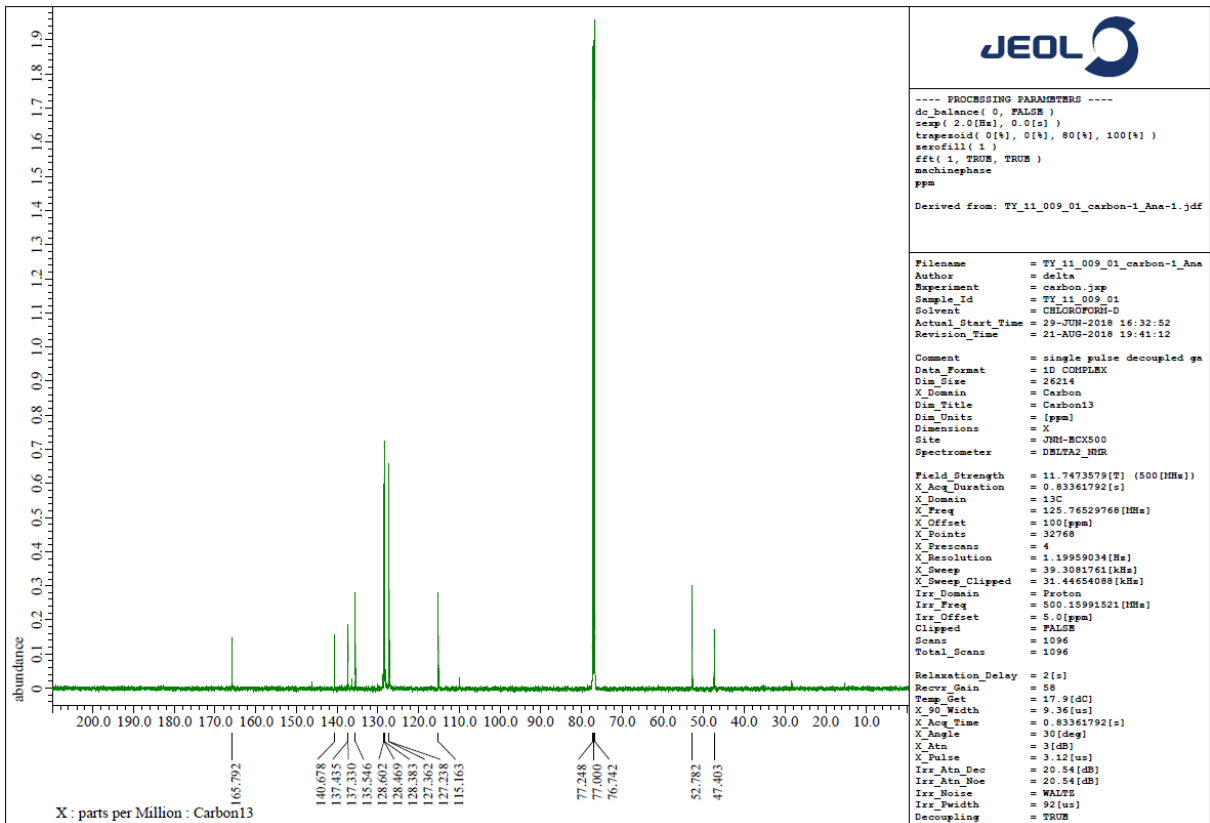
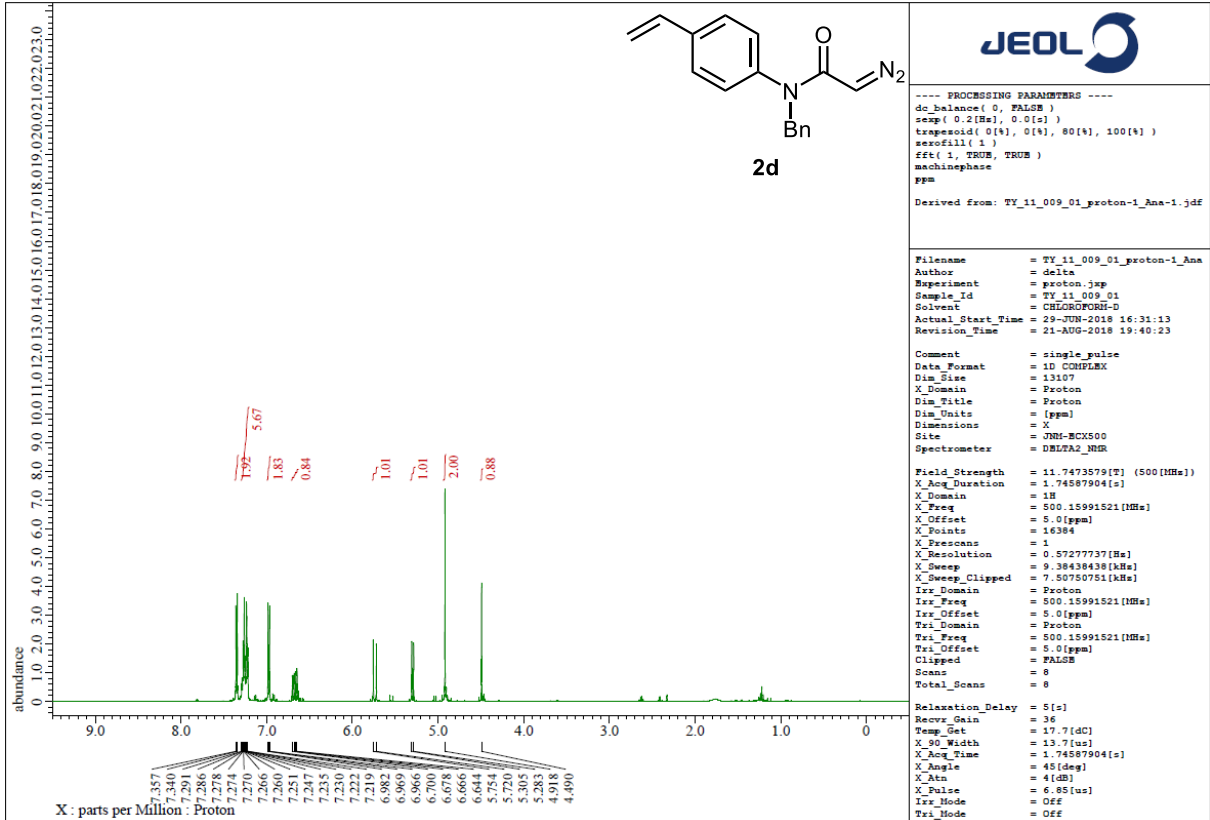
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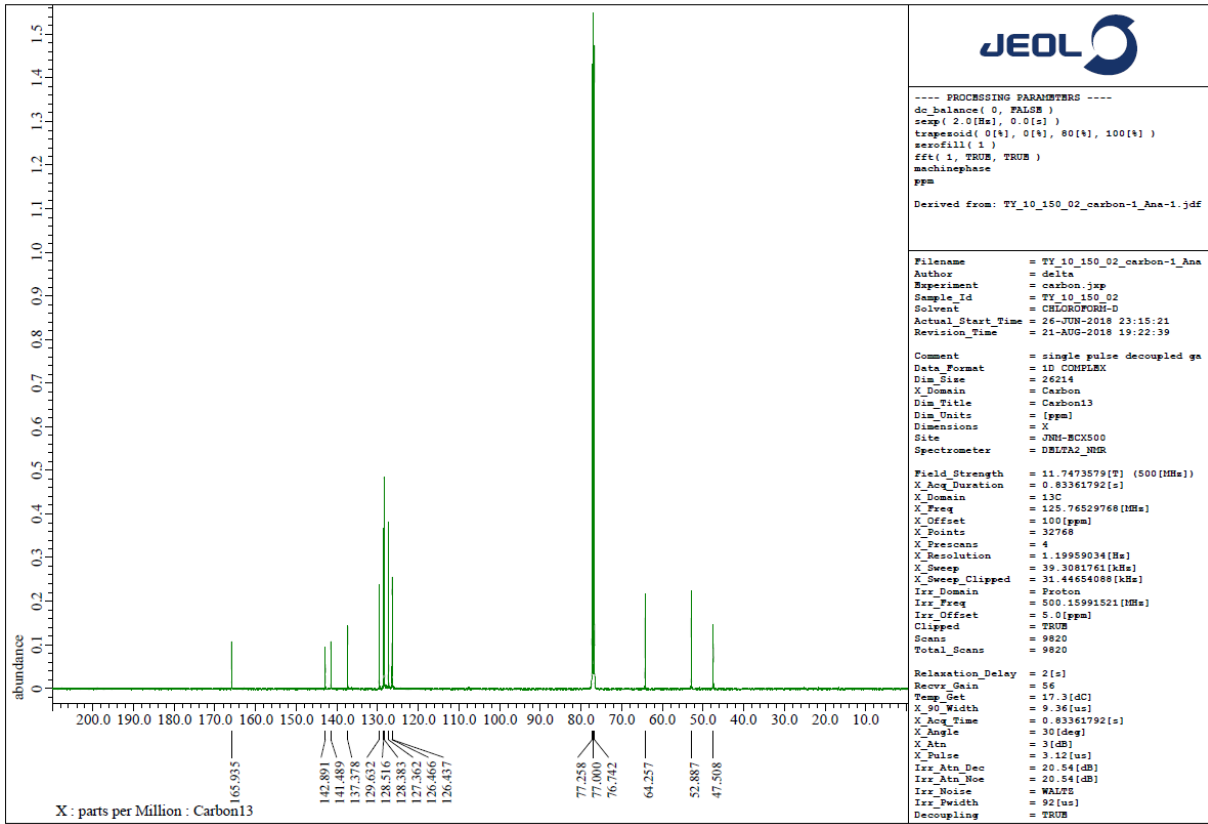
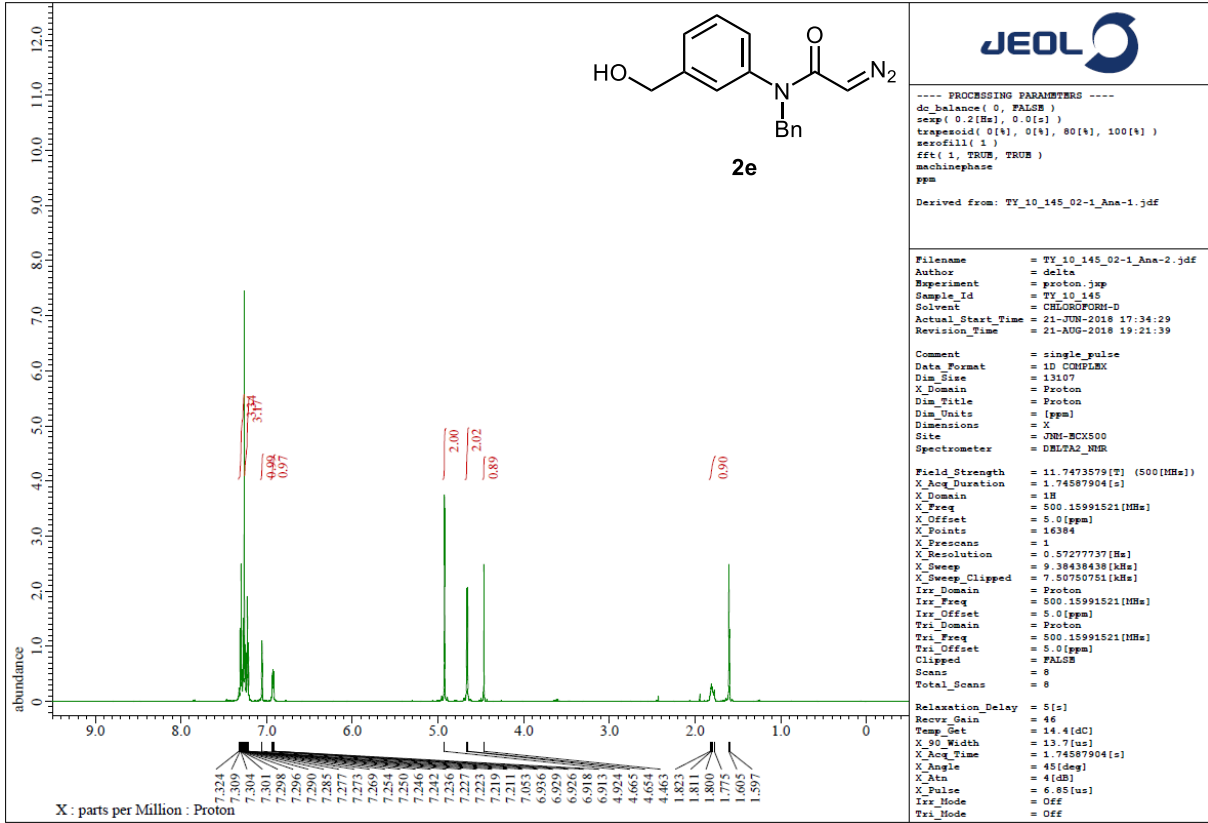
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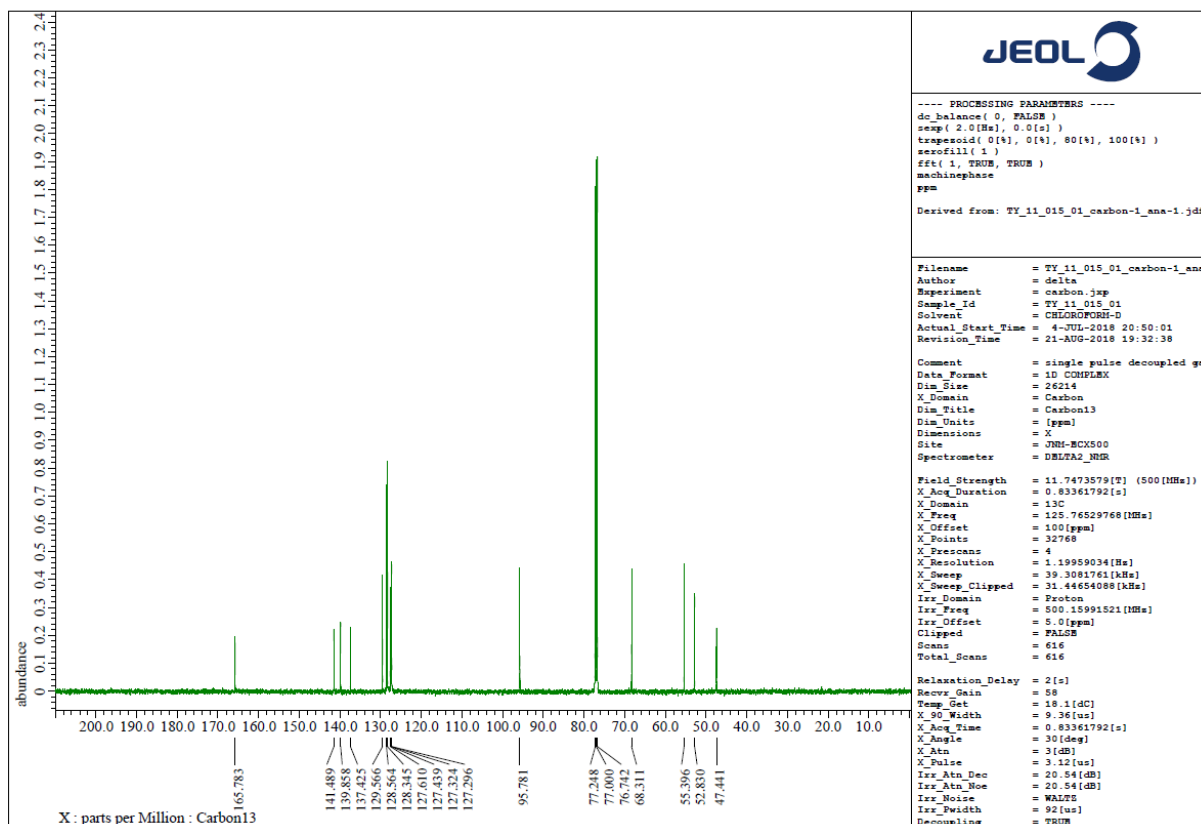
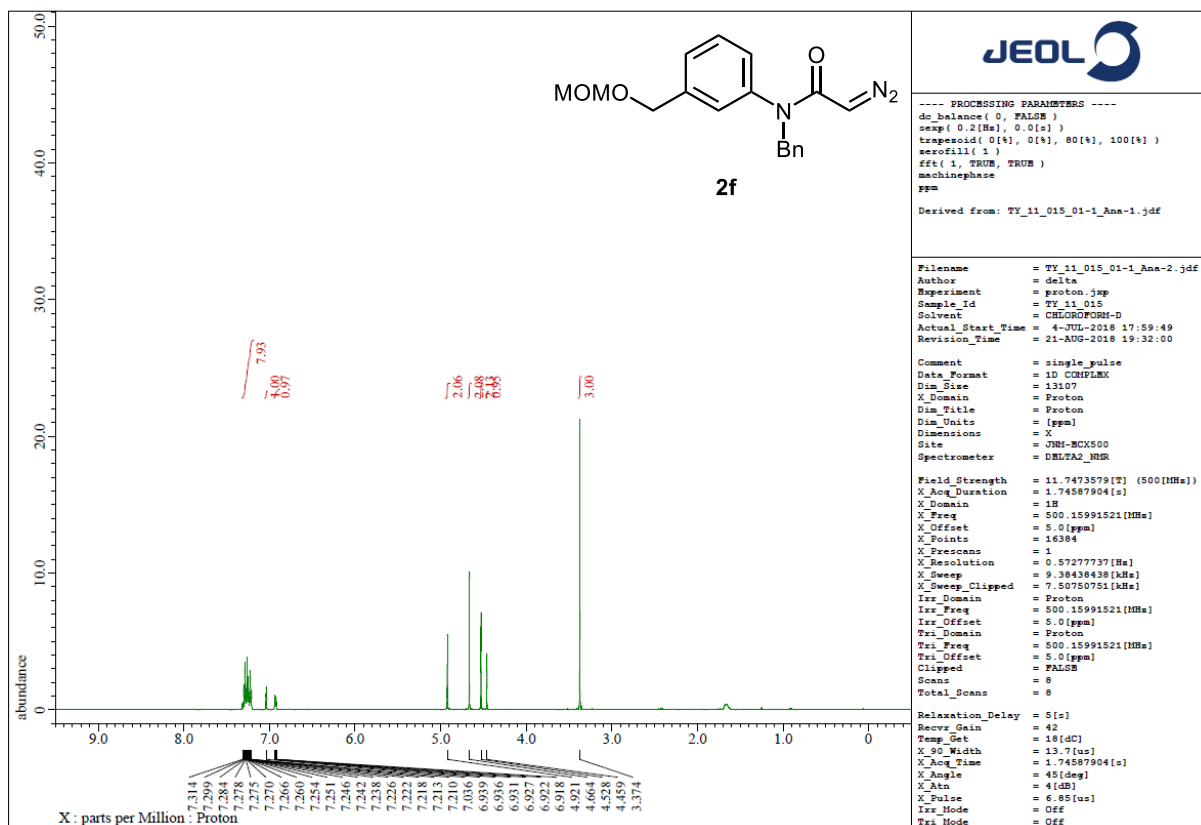


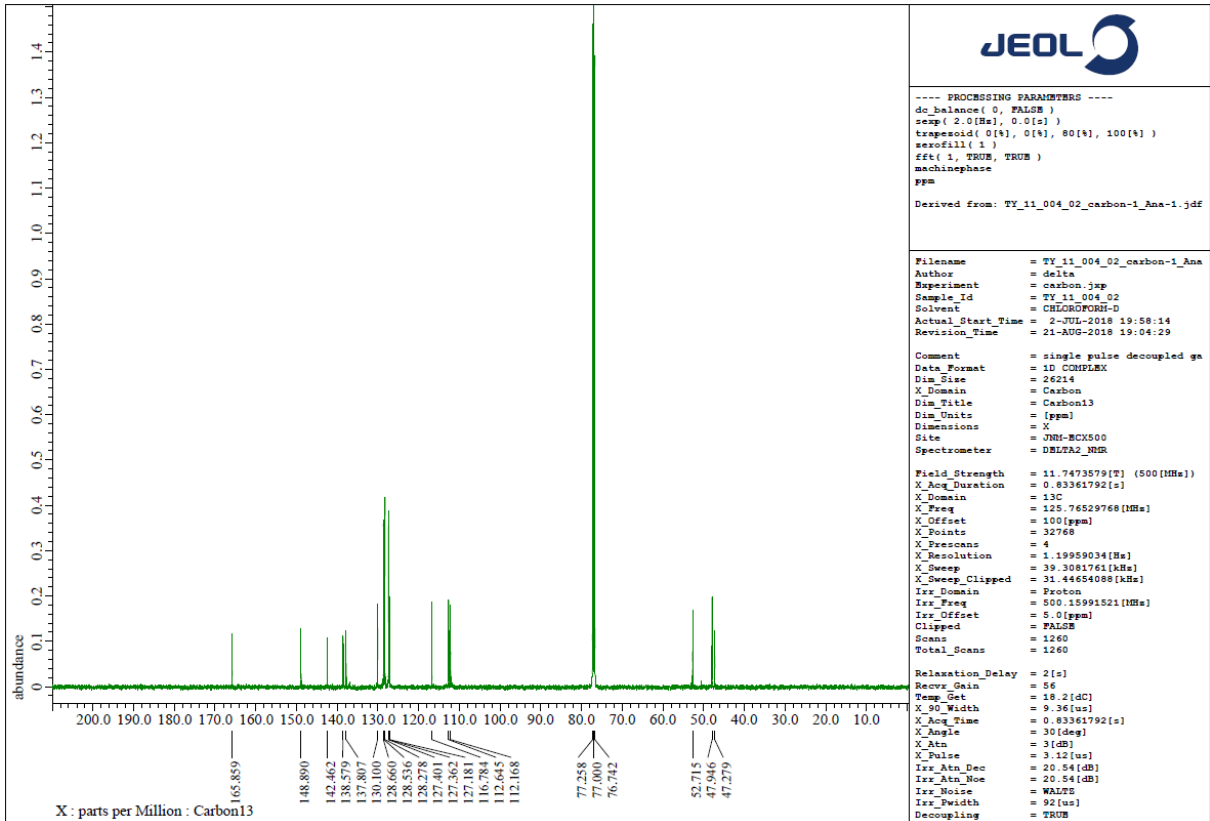
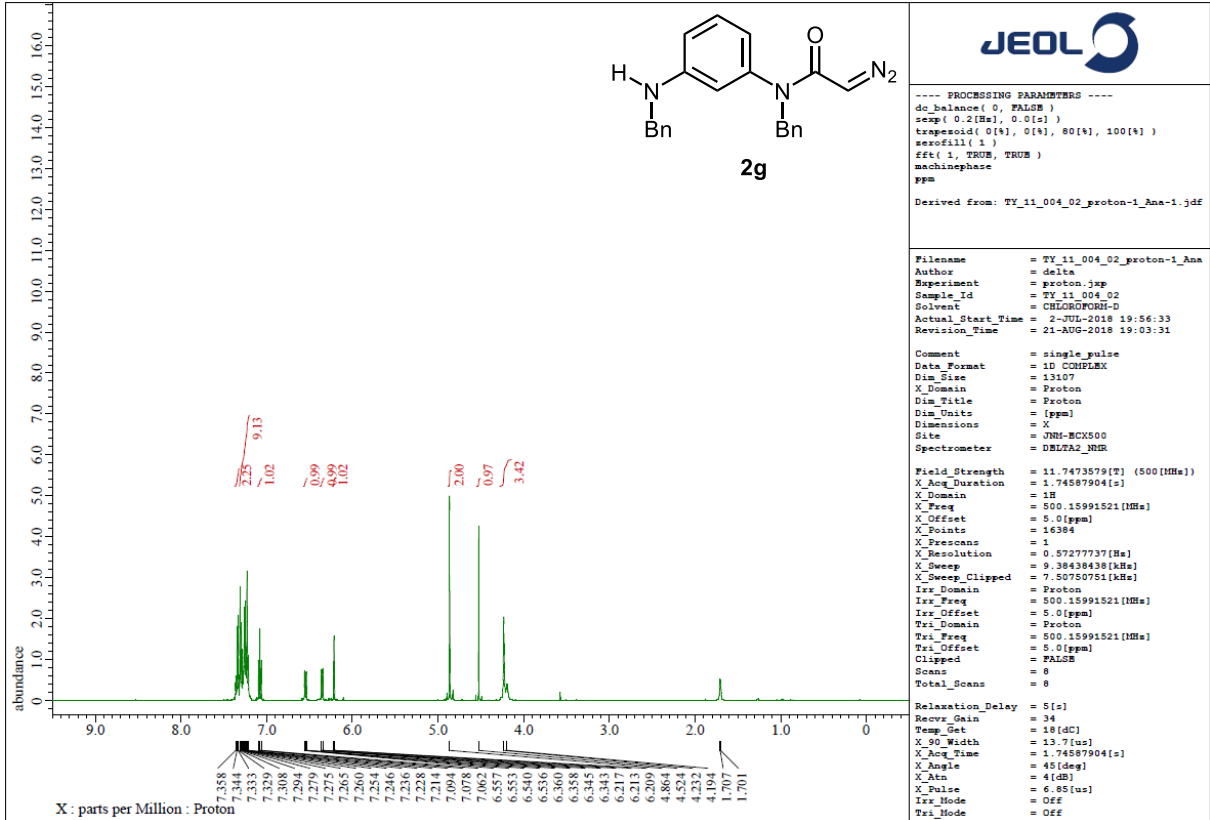
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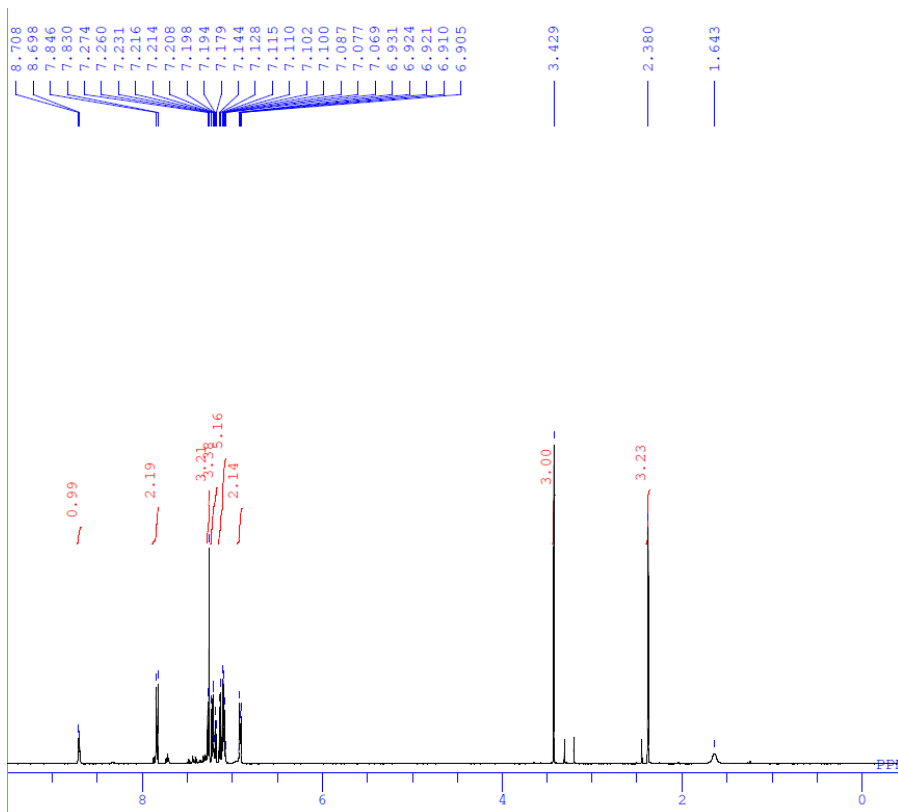
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PD 10.0000 sec
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EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
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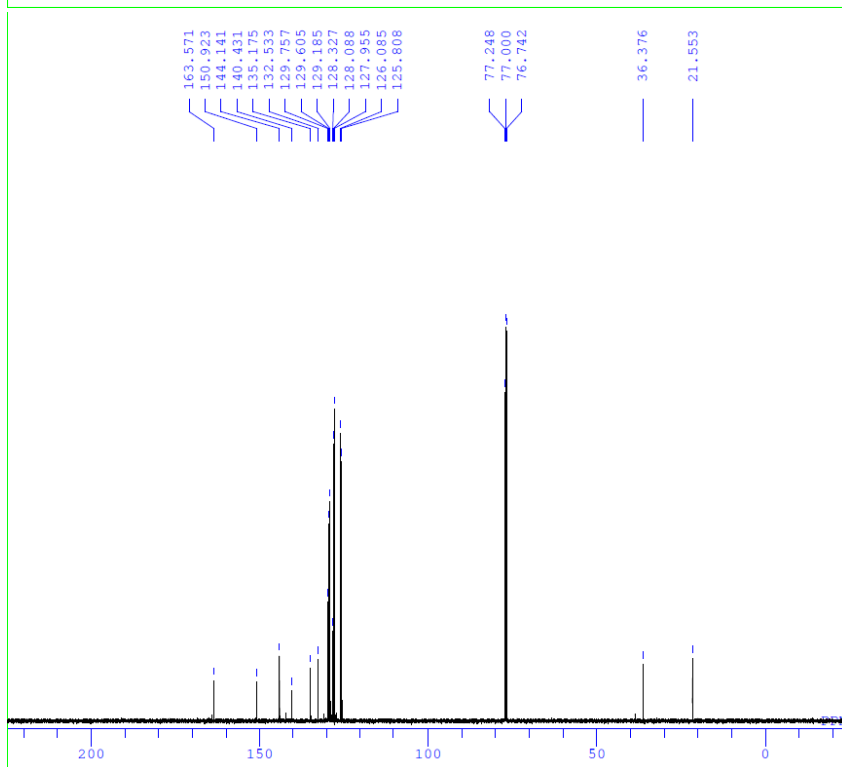
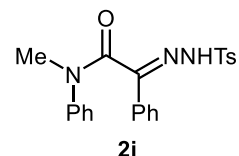




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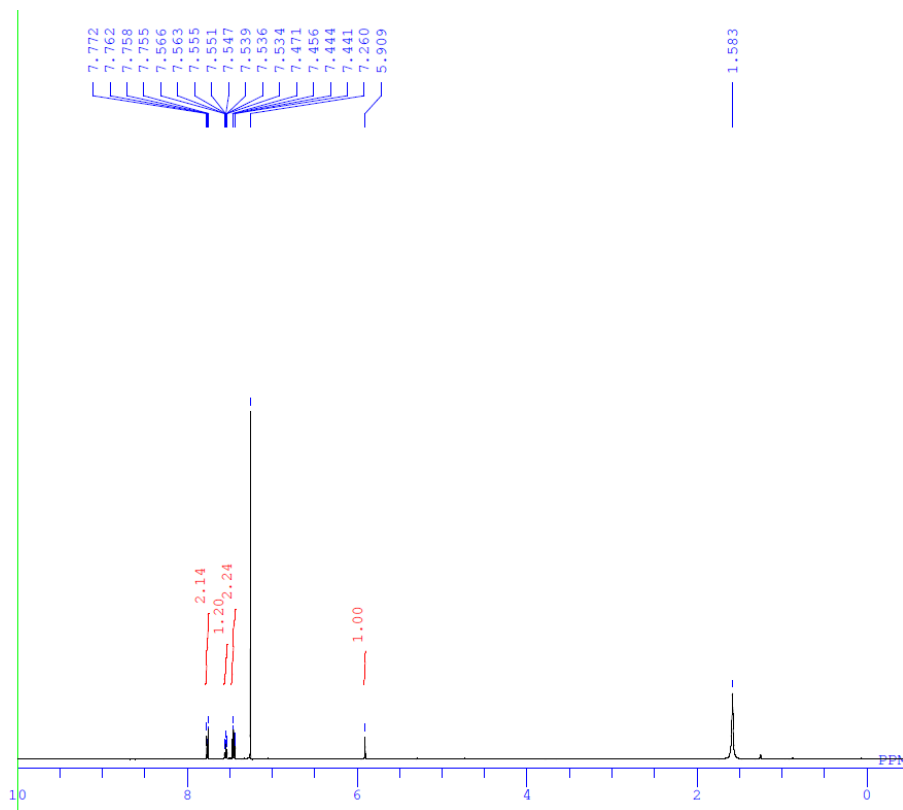
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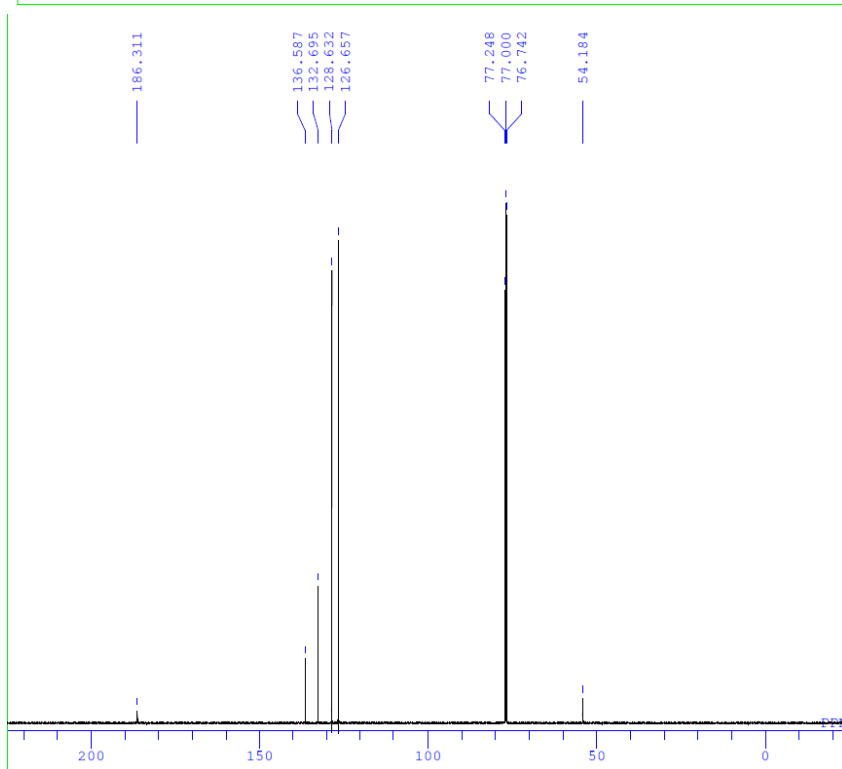
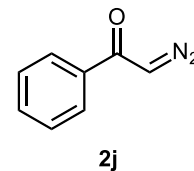
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RGAIN 60

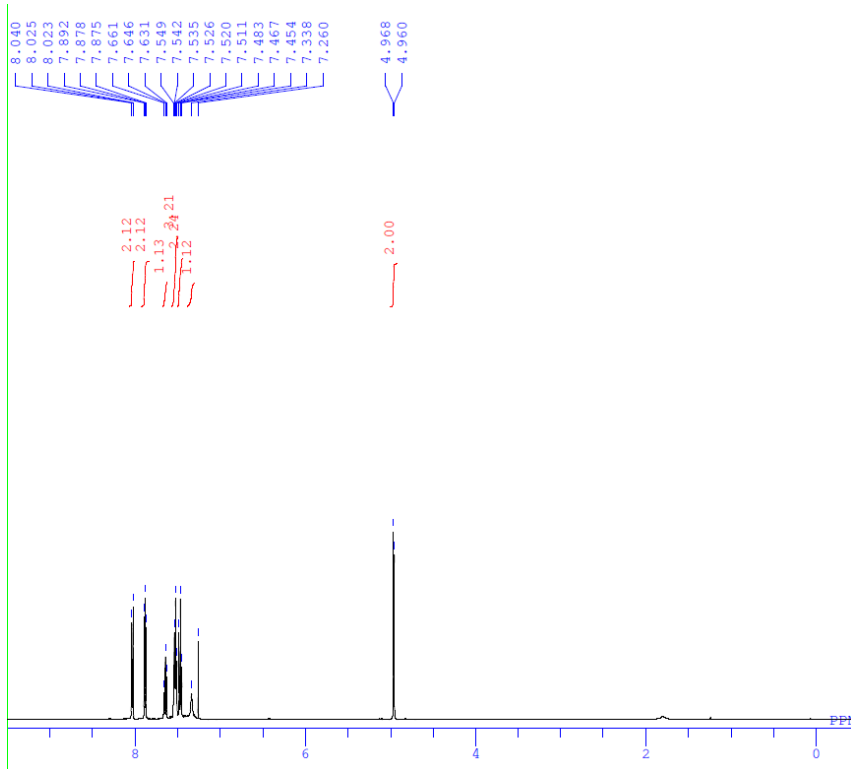
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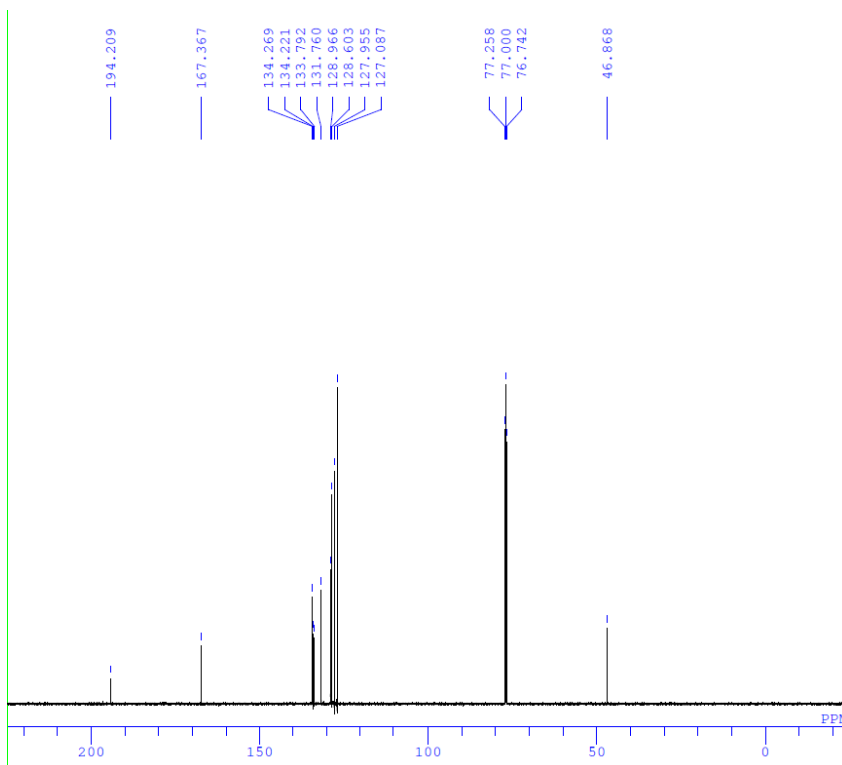
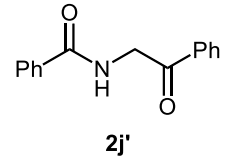


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 RGAIN 60



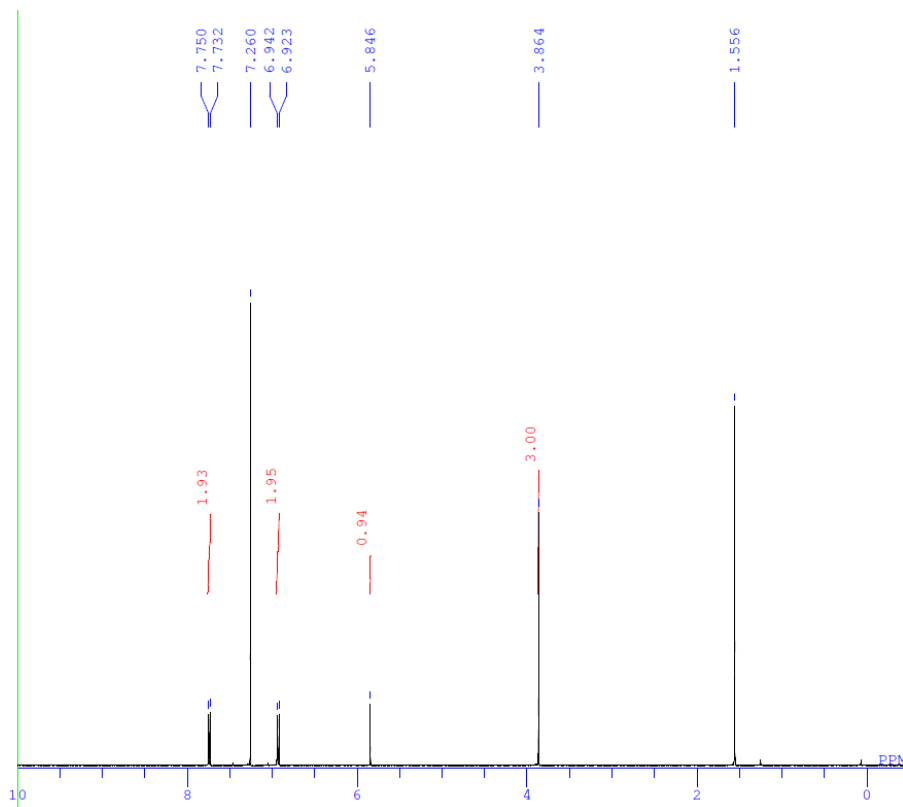
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PD 5.0000 sec
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RGAIN 36
  
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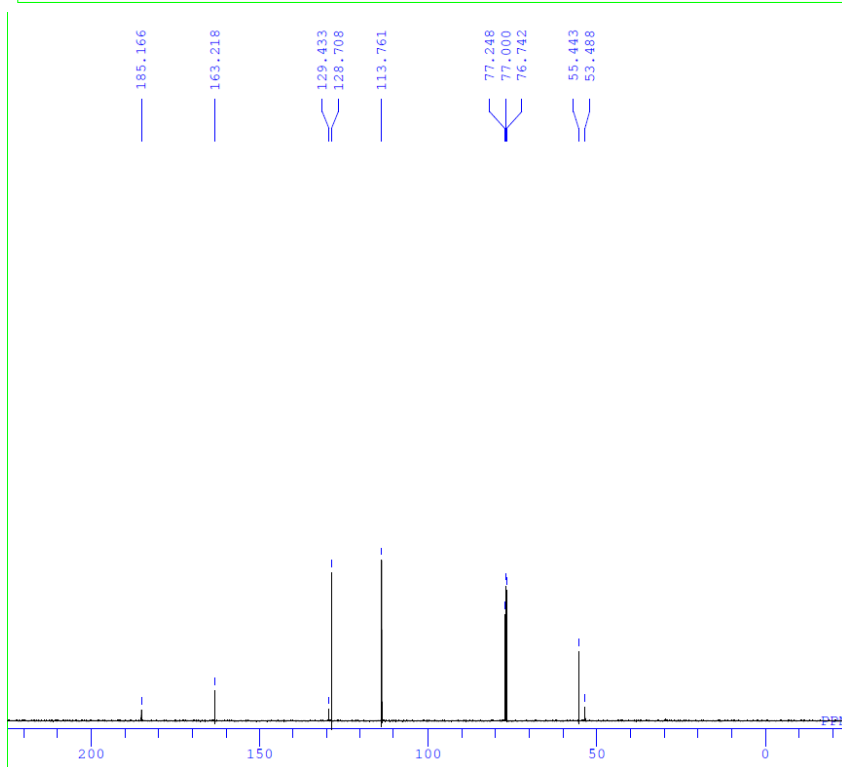
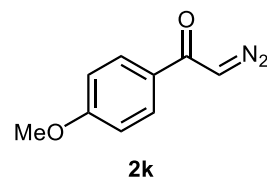
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DATIM 2018-04-12 13:18:15
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 1680
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 15.3 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
```



```

DFILE TY_09_031_01-1-1.als
COMNT diazo
DATIM 2017-07-19 17:00:58
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 19.0 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 50

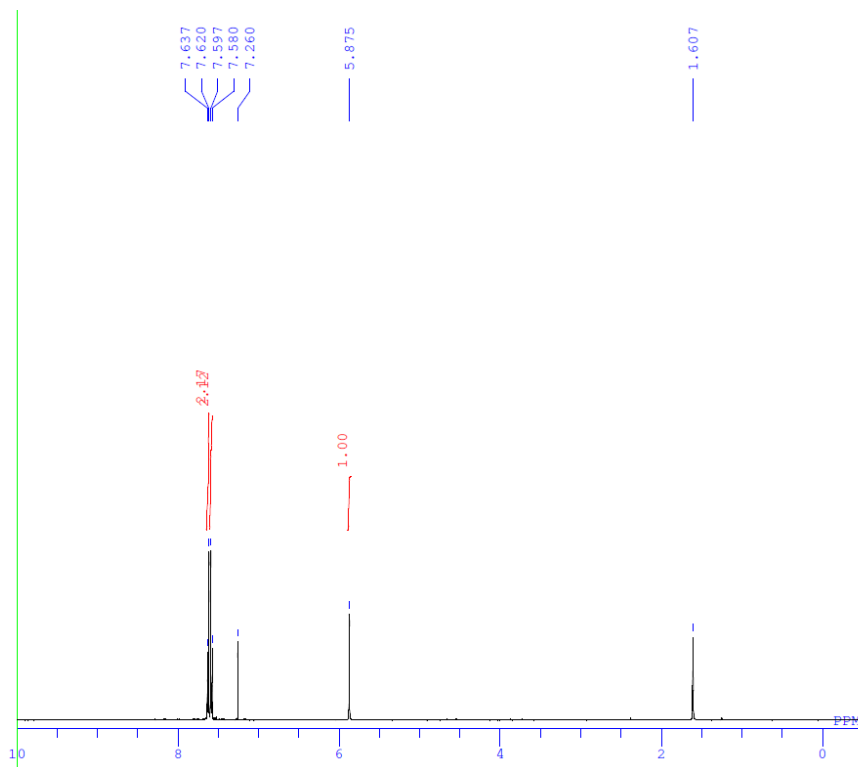
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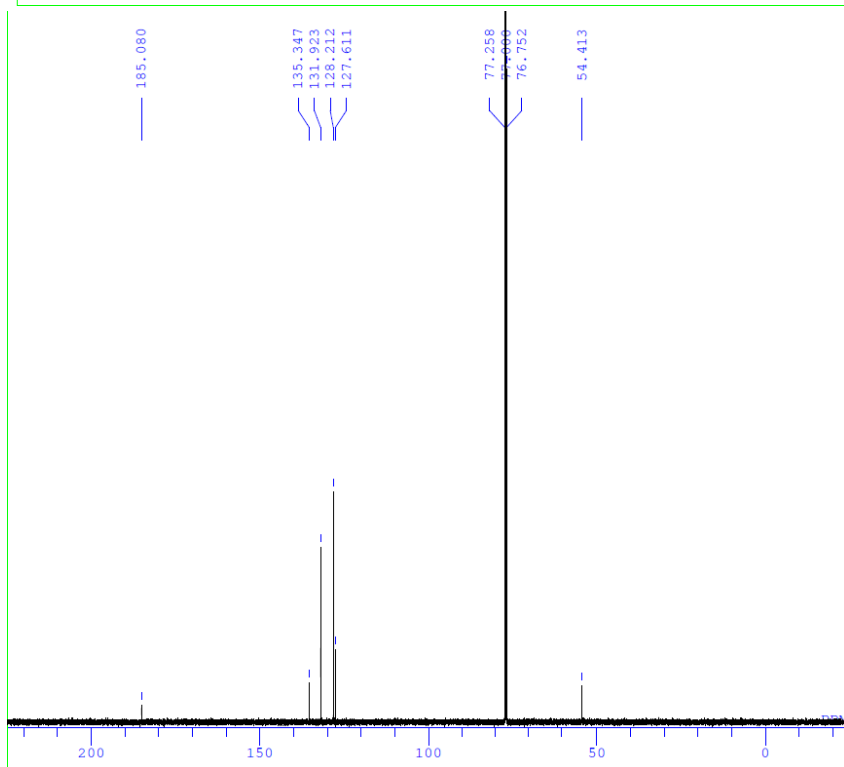
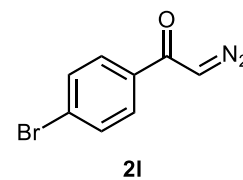
```

DFILE TY_09_031_01_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2017-07-20 09:56:39
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 1680
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 18.1 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60

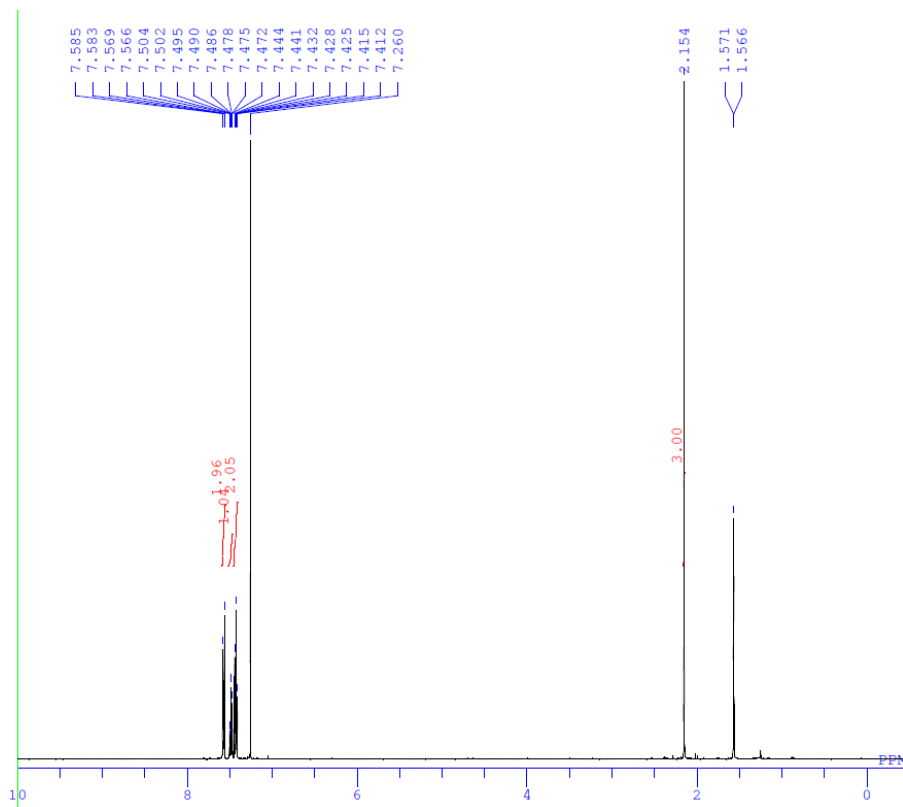
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DFILE TY_09_054_02_proton-1-1.als
 COMNT single_pulse
 DATIM 2017-08-05 14:19:17
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 19.3 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 44

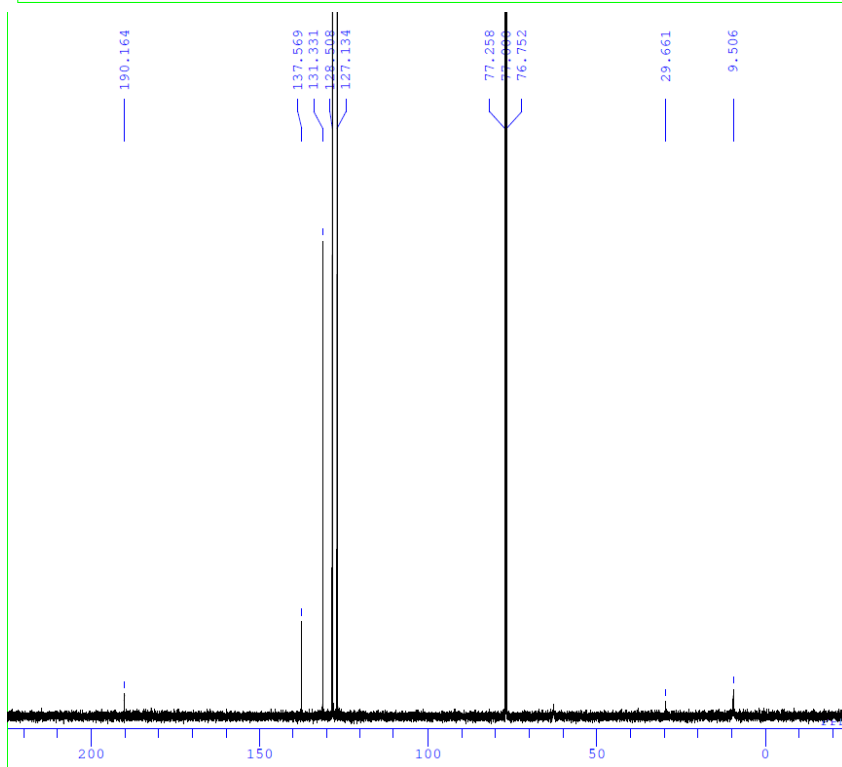
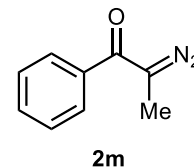


DFILE TY_09_054_02_carbon-1-1.als
 COMNT single_pulse decoupled gated
 DATIM 2017-08-05 14:20:58
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 1780
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 19.9 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60



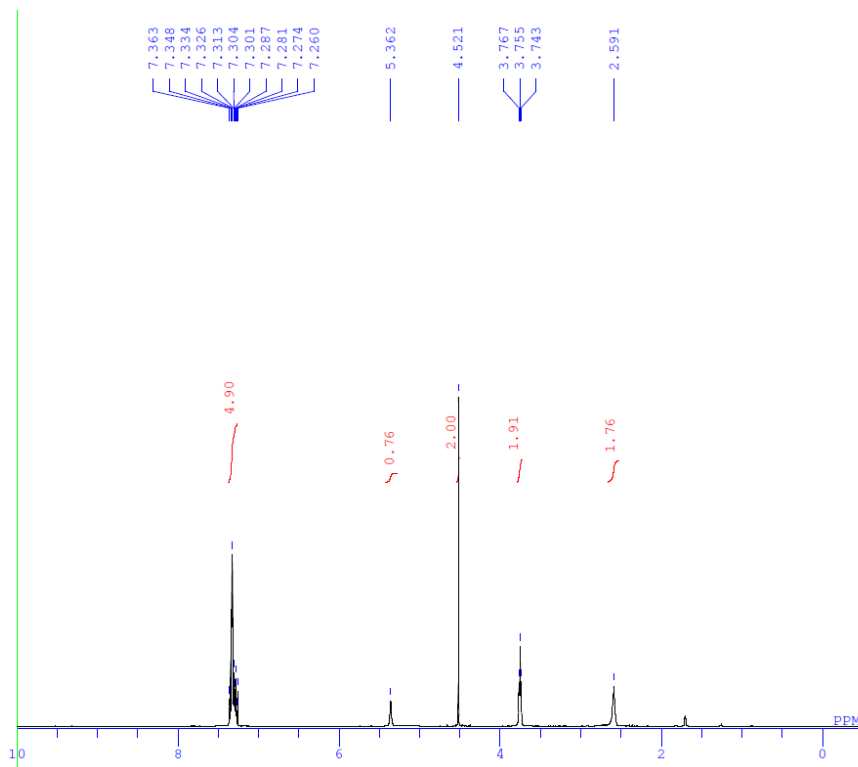
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DFILE TY_09_036_01-1-1.als
COMNT diazo?
DATIM 2017-07-21 13:03:43
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 18.4 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 48
  
```



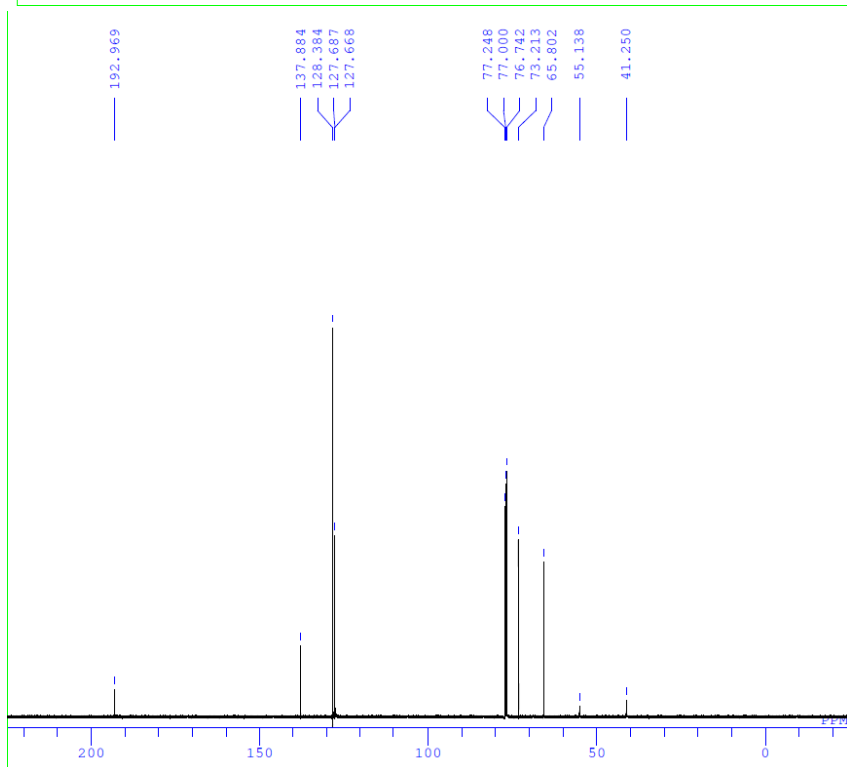
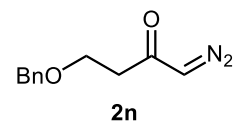
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DFILE TY_09_038_01_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2017-07-25 10:00:23
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 1580
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 18.5 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
```



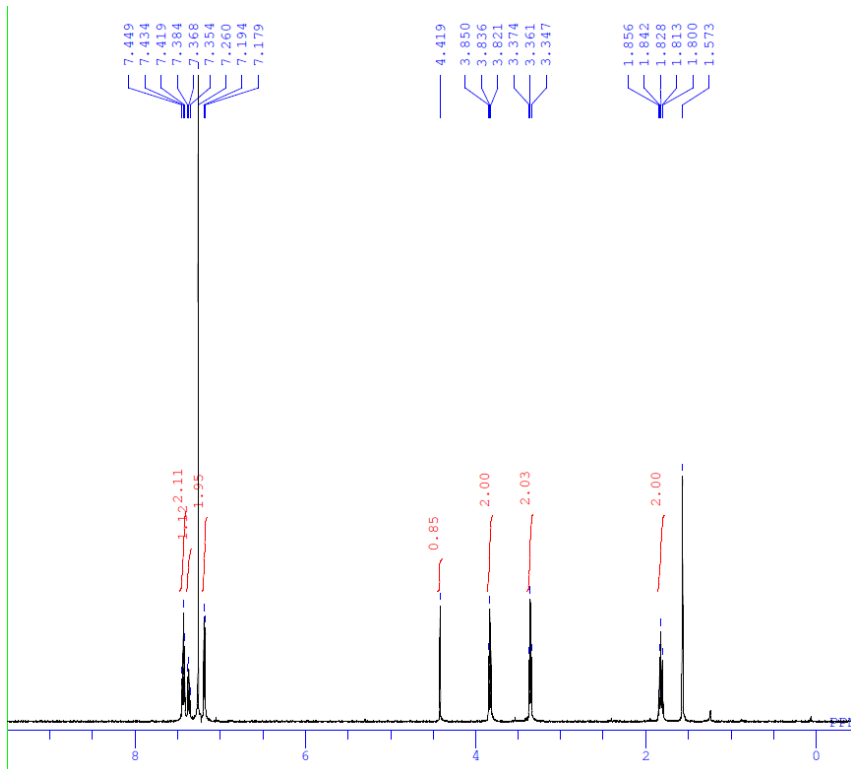
```

DFILE TY_09_037_02_proton-1-1.als
COMNT single_pulse
DATIM 2017-07-24 10:13:46
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 18.1 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 36
  
```

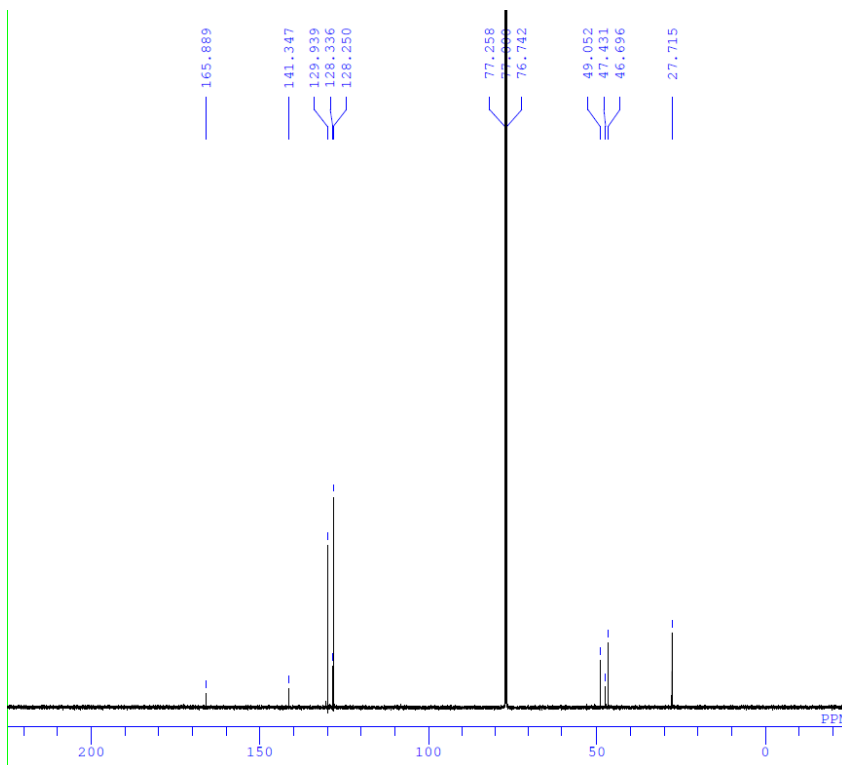
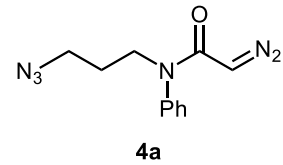


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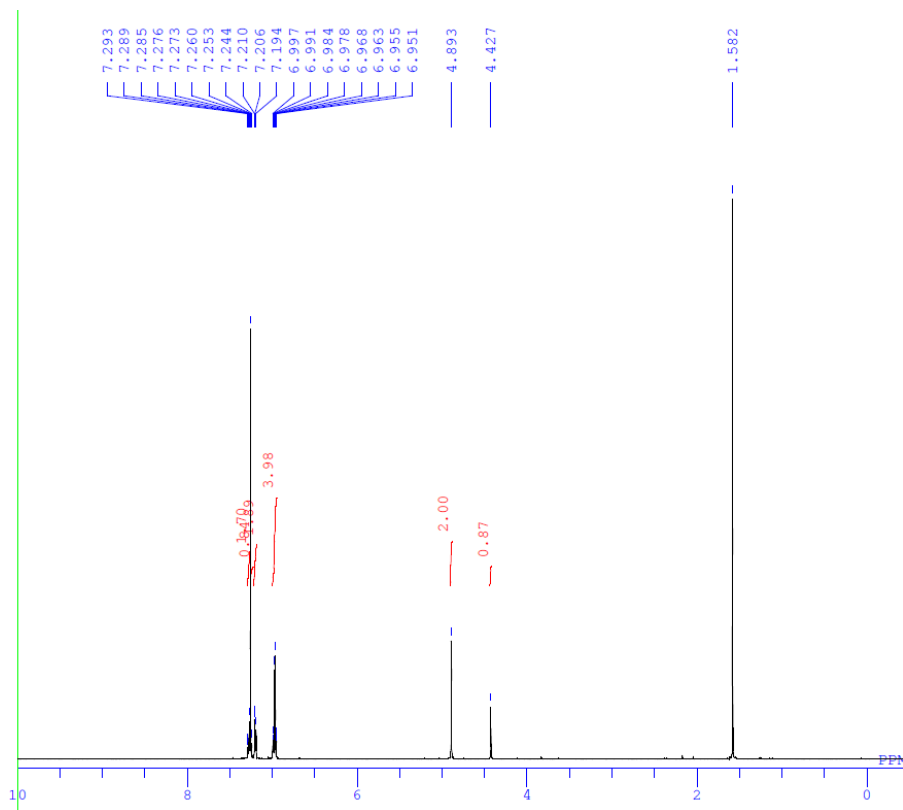
DFILE TY_09_037_02_carbon-1-1.als
COMNT single_pulse decoupled gated
DATIM 2017-07-24 10:15:44
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 1260
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 18.6 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
```



DFILE TY_08_044_02_proton-1-1.als
 COMNT single_pulse
 DATIM 2016-12-27 20:03:58
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 14.8 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 48



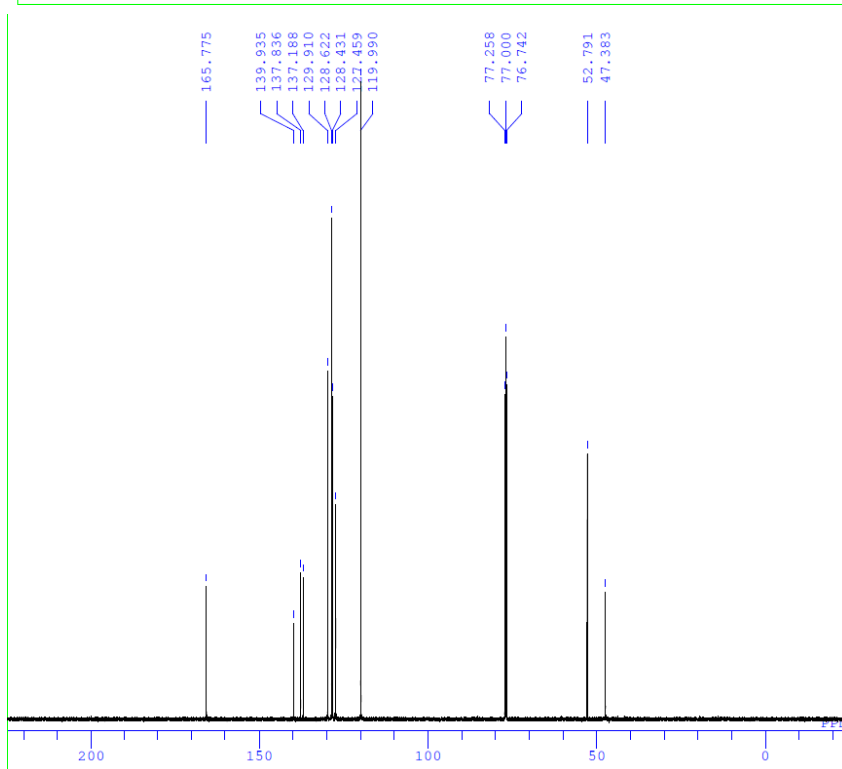
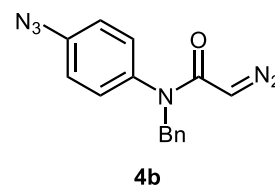
DFILE TY_07_088_02_carbon-1-1.als
 COMNT single_pulse decoupled gated
 DATIM 2016-10-08 00:07:30
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 7600
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 18.8 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60



```

DFILE TY_09_056_05-1-1.als
COMNT diazo-azide?
DATIM 2017-08-18 17:15:26
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 18.2 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 48

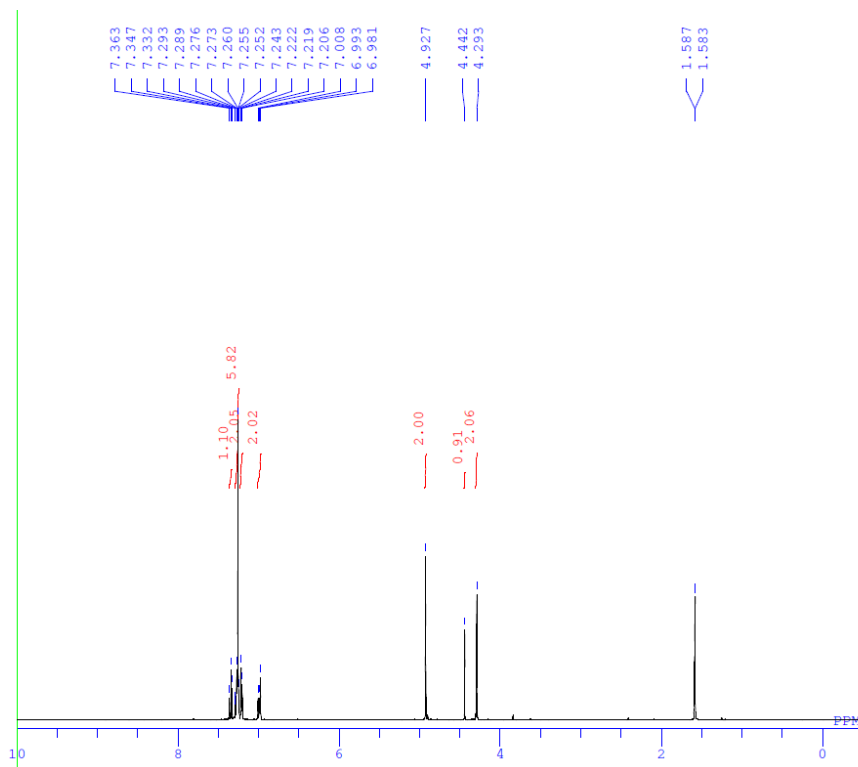
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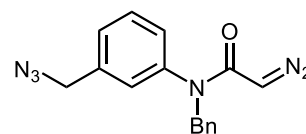
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DFILE TY_09_056_05_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2017-08-19 10:46:46
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 1780
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 18.4 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60

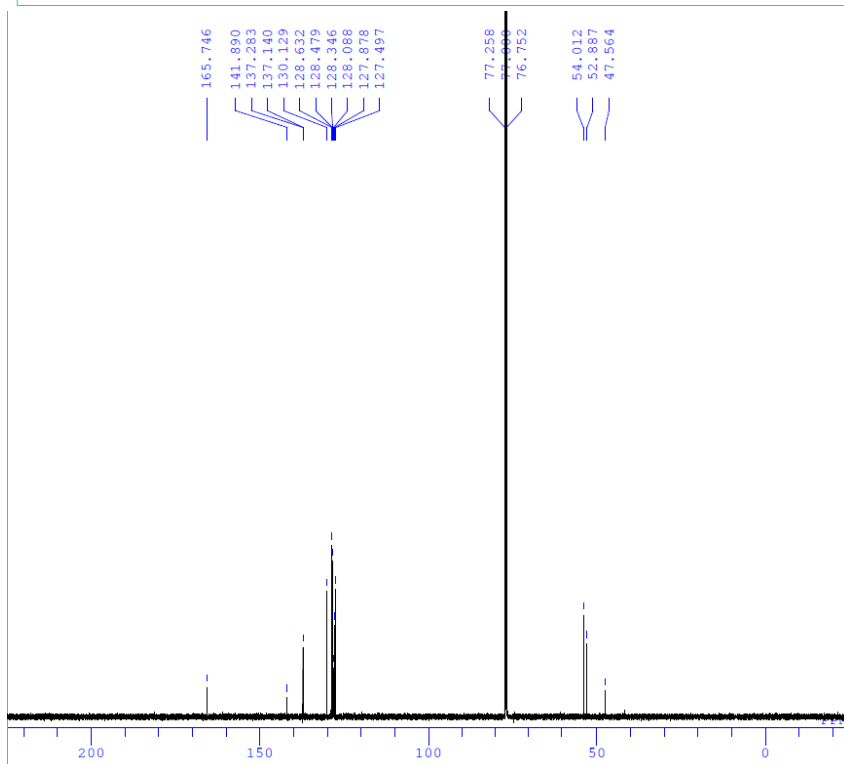
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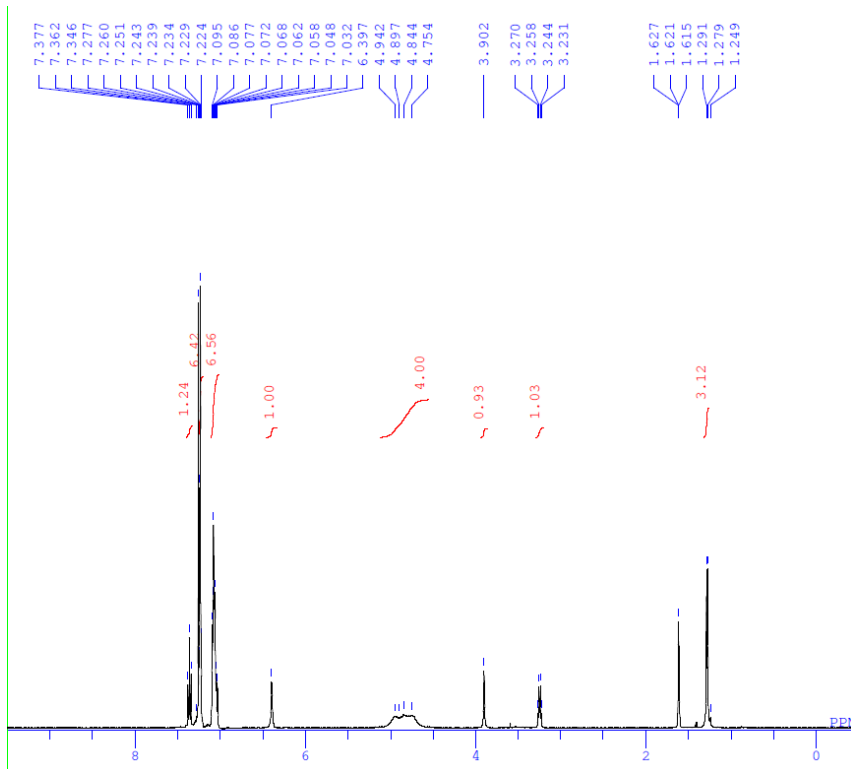
DFILE TY_09_123_02_proton-1-1.als
 COMNT single_pulse
 DATIM 2017-10-23 23:11:42
 OBNUC 1H
 EXMOD proton.jxp
 OBFRQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 16.8 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 46



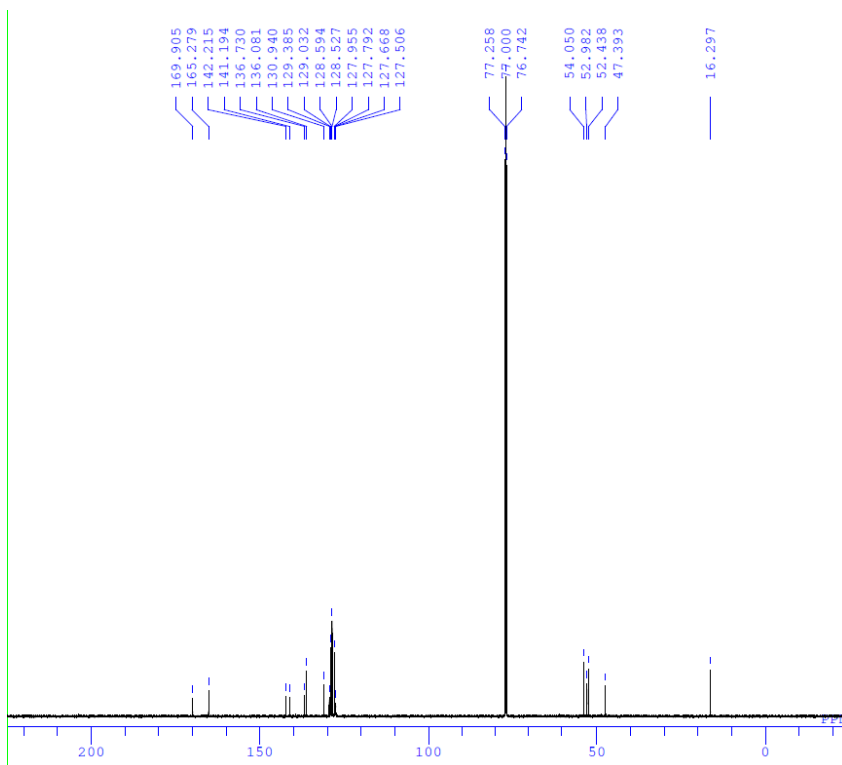
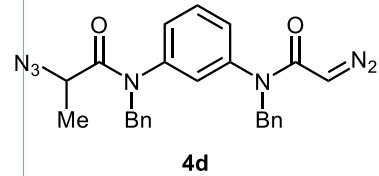
4c



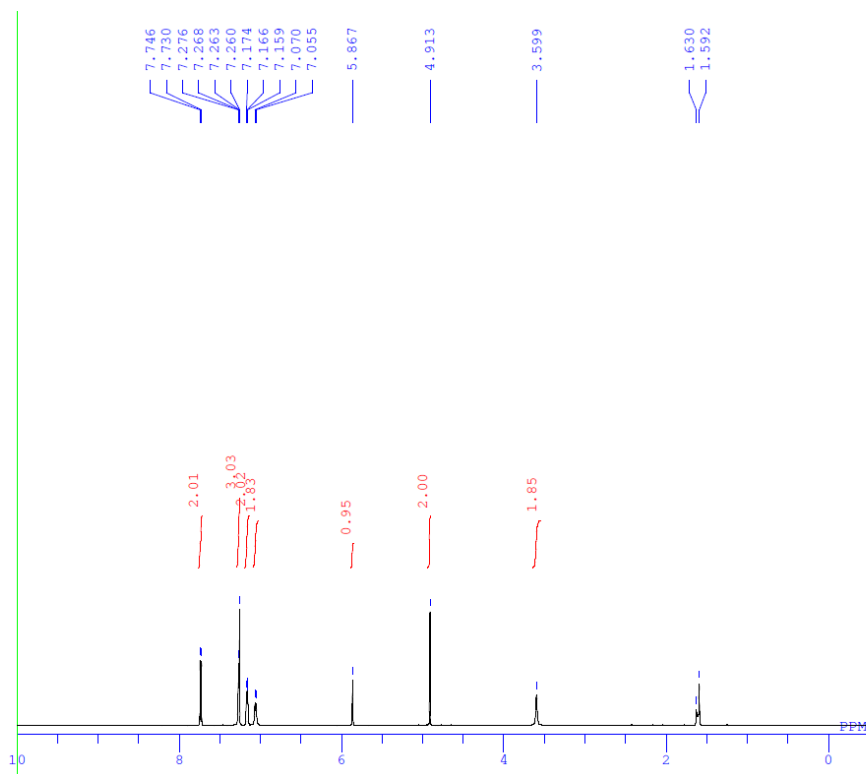
DFILE TY_09_123_02_carbon-1-1.als
 COMNT single_pulse decoupled gated
 DATIM 2017-10-23 23:13:21
 OBNUC 13C
 EXMOD carbon.jxp
 OBFRQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 8460
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 17.8 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60



DFILE TY_09_121_04_proton-1-1.als
 COMNT single_pulse
 DATIM 2017-10-24 23:12:57
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 17.9 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 40



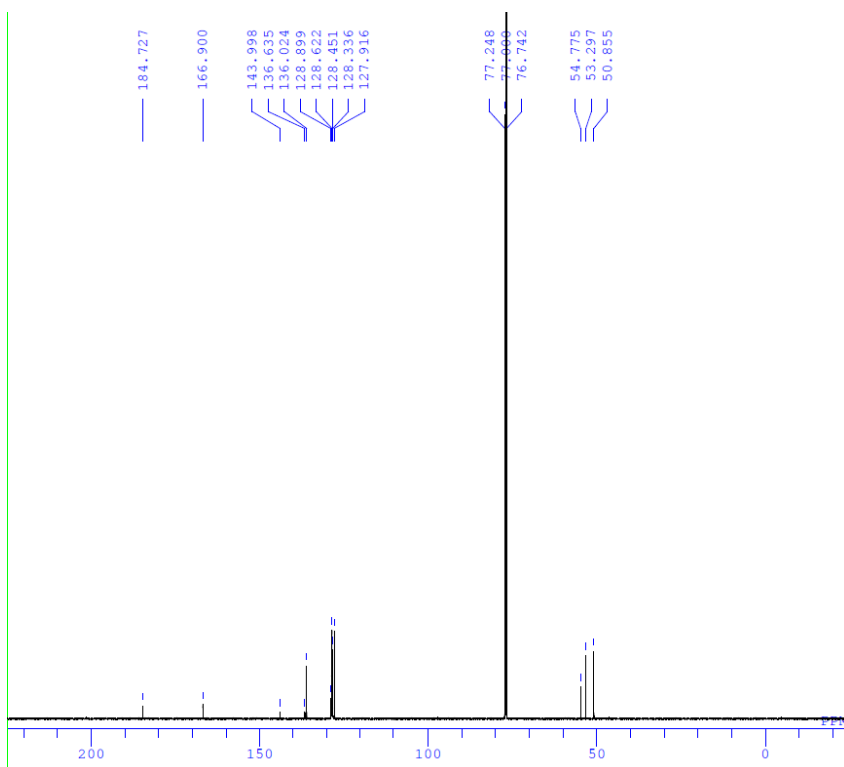
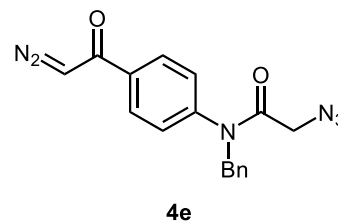
DFILE TY_09_121_04_carbon-1-1.als
 COMNT single pulse decoupled gated
 DATIM 2017-10-24 23:14:28
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 8860
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 19.2 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60



```

DFILE TY09_055_02_proton-1-1.als
COMNT single_pulse
DATIM 2017-08-06 14:51:11
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 19.6 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 44

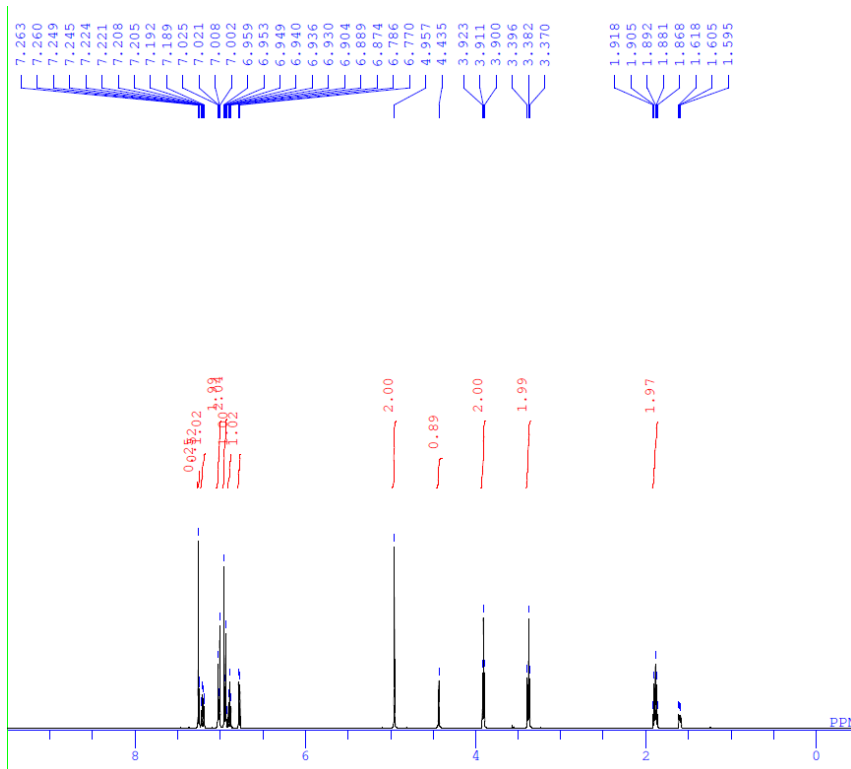
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```

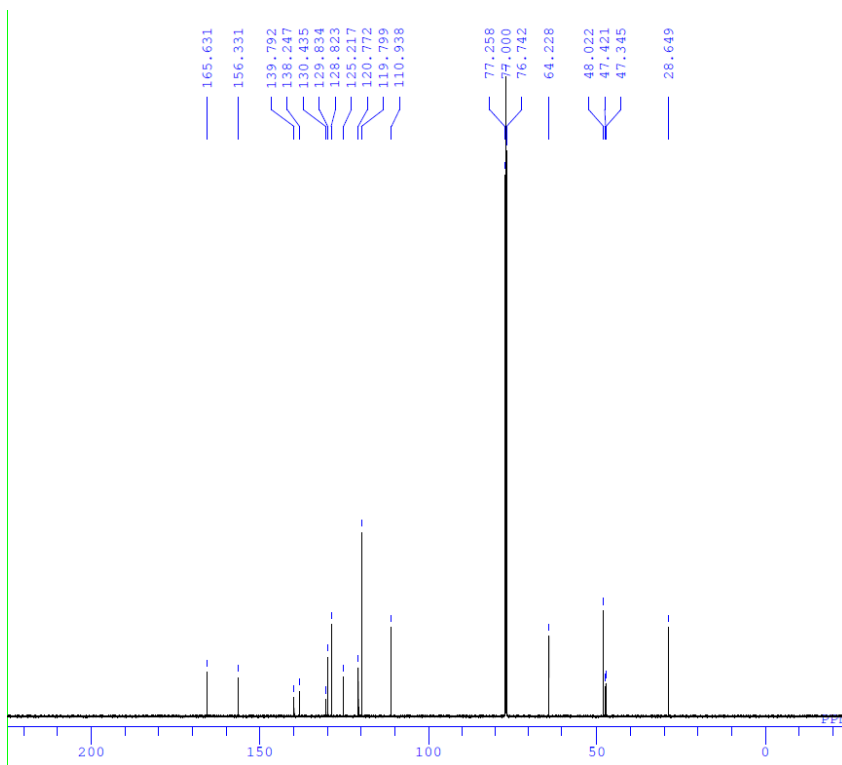
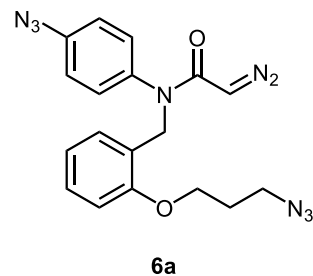
DFILE TY_09_055_02_2_carbon-1-1.als
COMNT single_pulse decoupled gated
DATIM 2017-08-17 23:05:07
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 3438
ACQTM 0.8336 sec
PD 10.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 17.9 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60

```



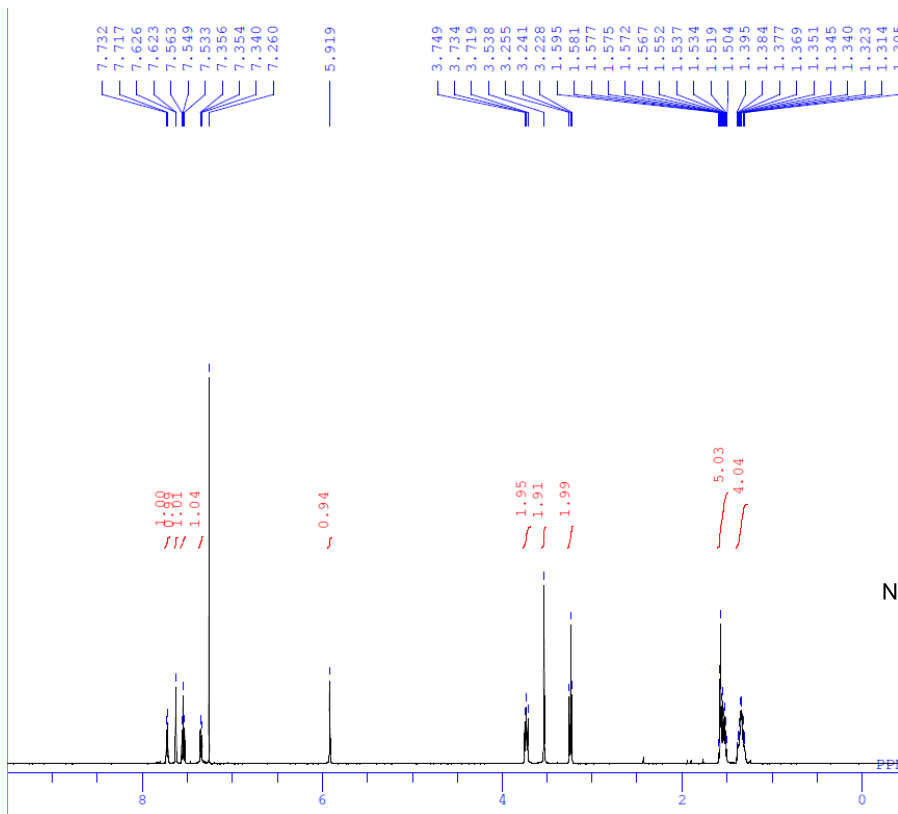
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DFILE TY_10_042_02_proton-1-1.als
COMNT single_pulse
DATIM 2018-01-10 23:09:05
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 17.2 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 44
  
```



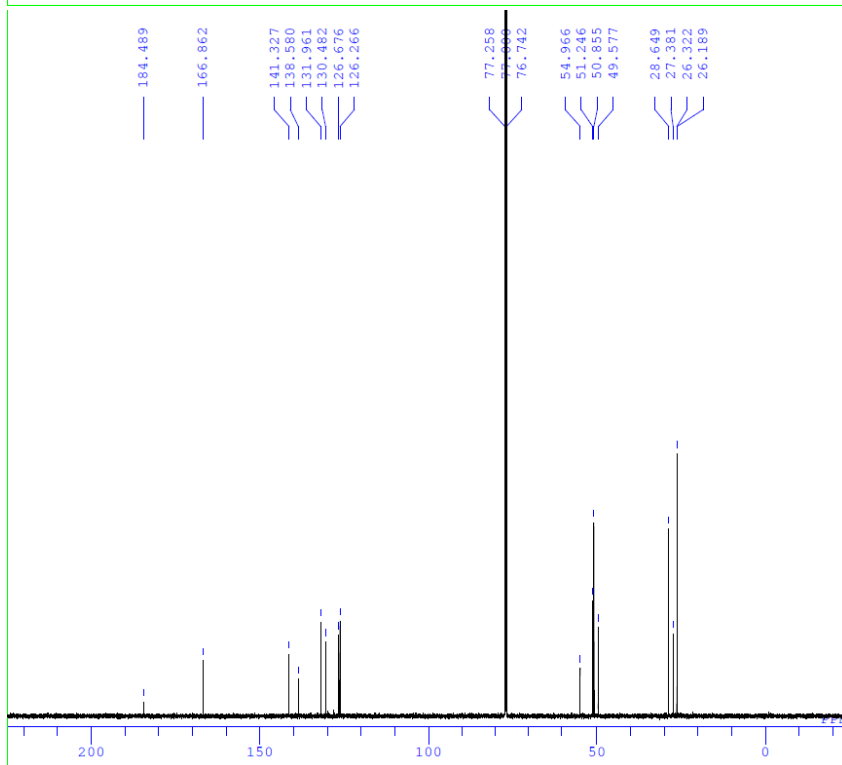
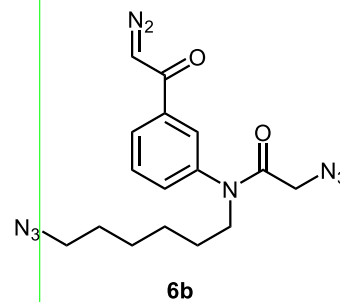
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DFILE TY_10_042_02_carbon-1-1.als
COMNT single_pulse decoupled gated
DATIM 2018-01-10 23:10:36
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 9000
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 18.2 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
```



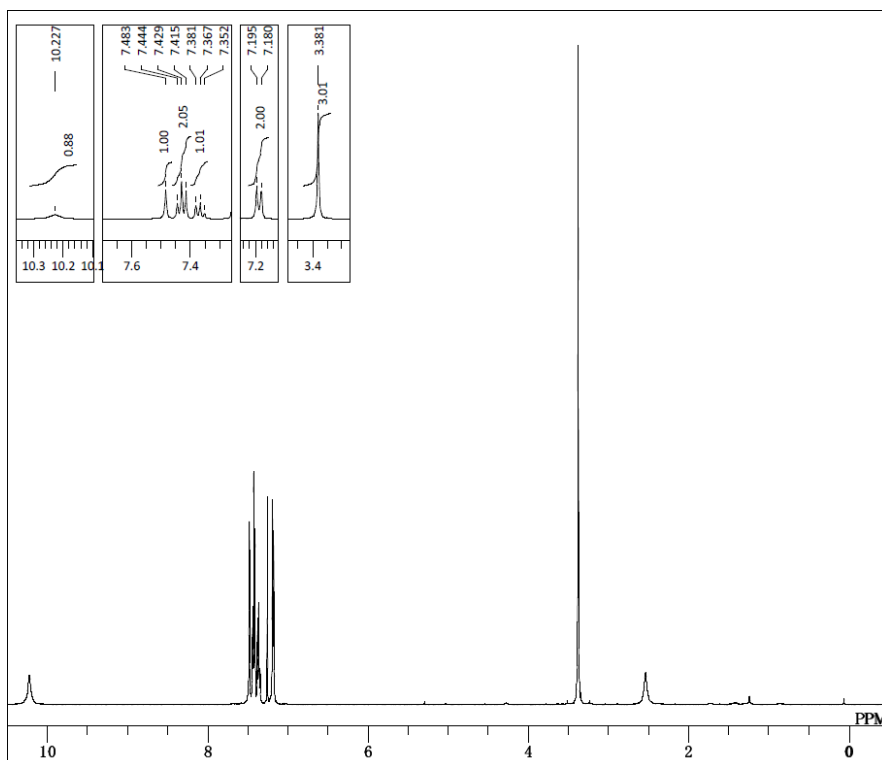
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DFILE TY_09_136_03-1-1.als
COMNT diazo-diazide
DATIM 2017-11-06 14:24:51
OBNUC 1H
EXMOD proton.jxp
OBFREQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 17.4 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 44
  
```

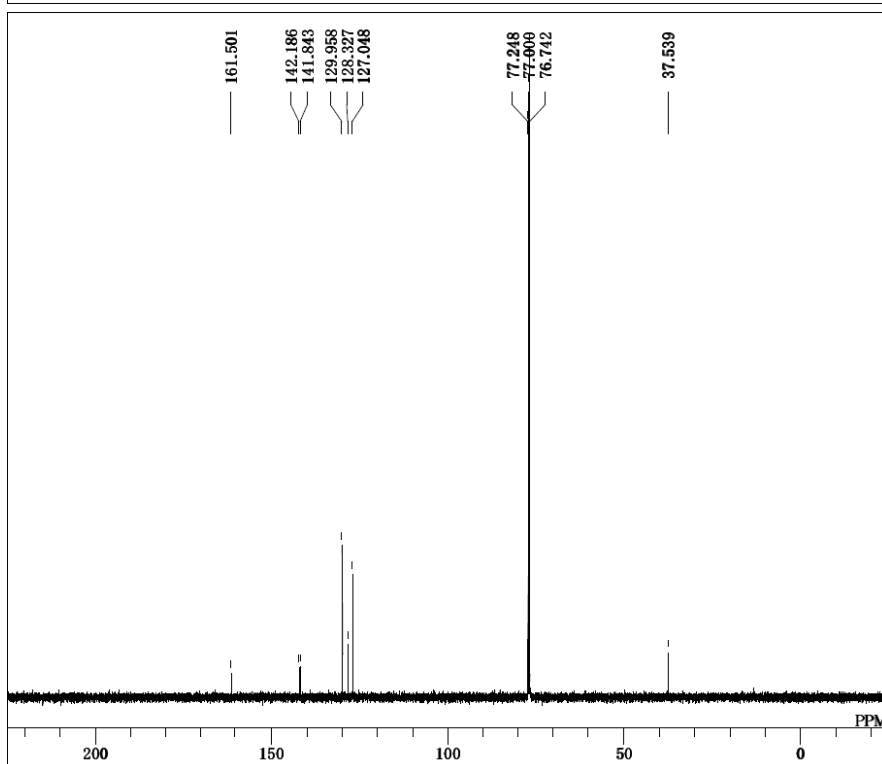
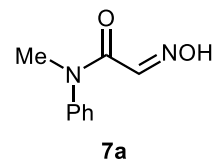


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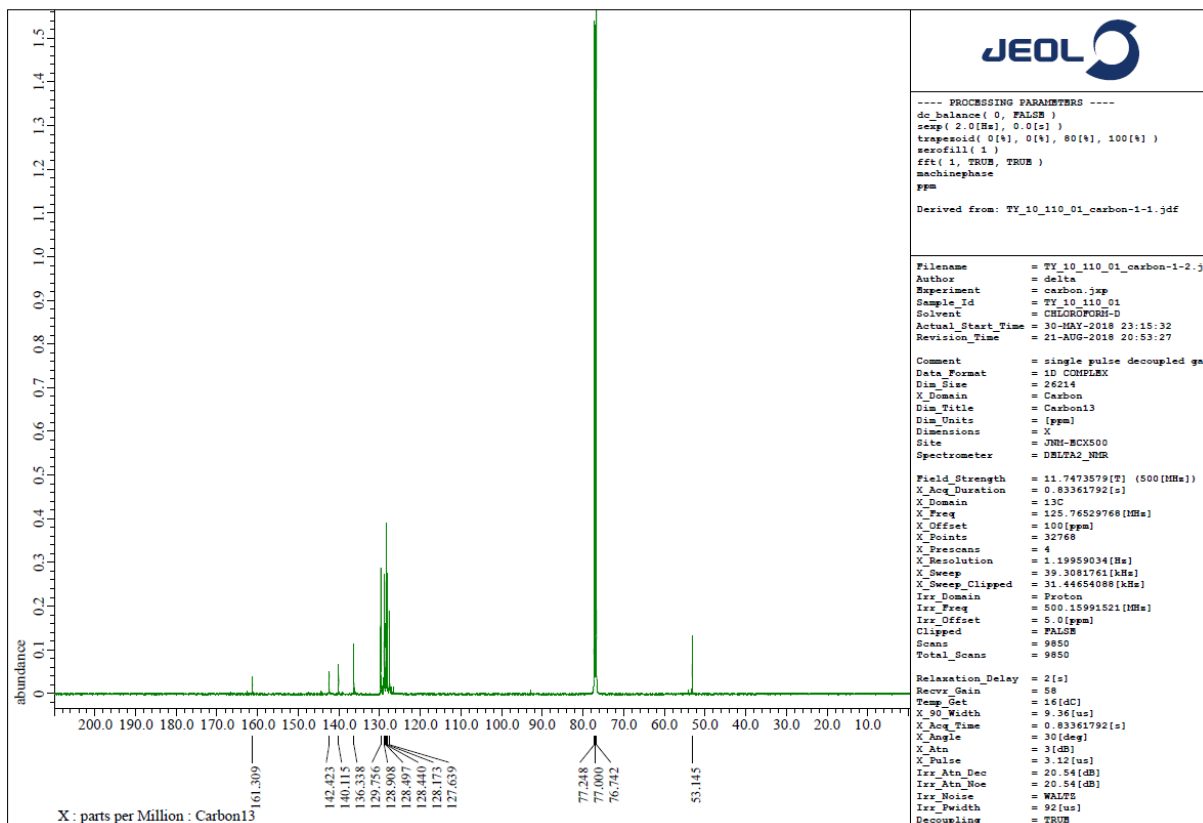
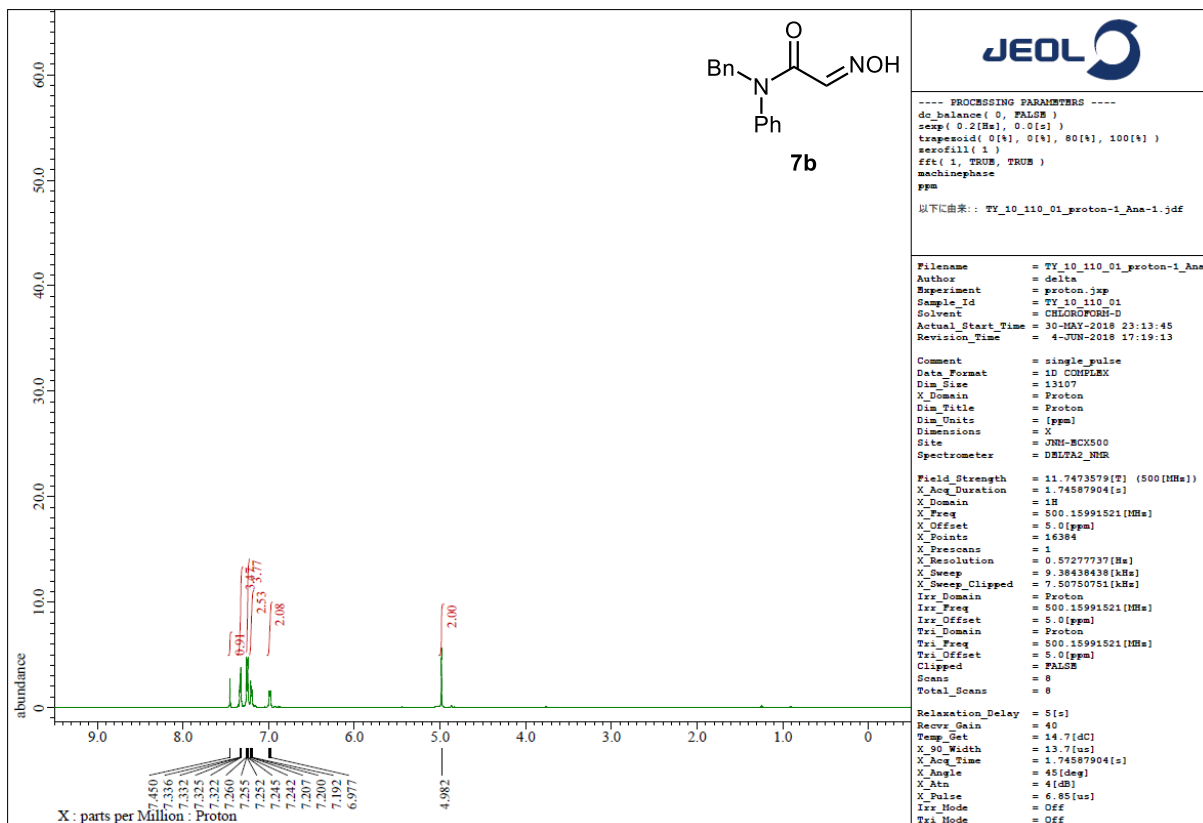
DFILE TY_09_136_01_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2017-10-30 23:16:35
OBNUC 13C
EXMOD carbon.jxp
OBFREQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 8920
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 19.6 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
```

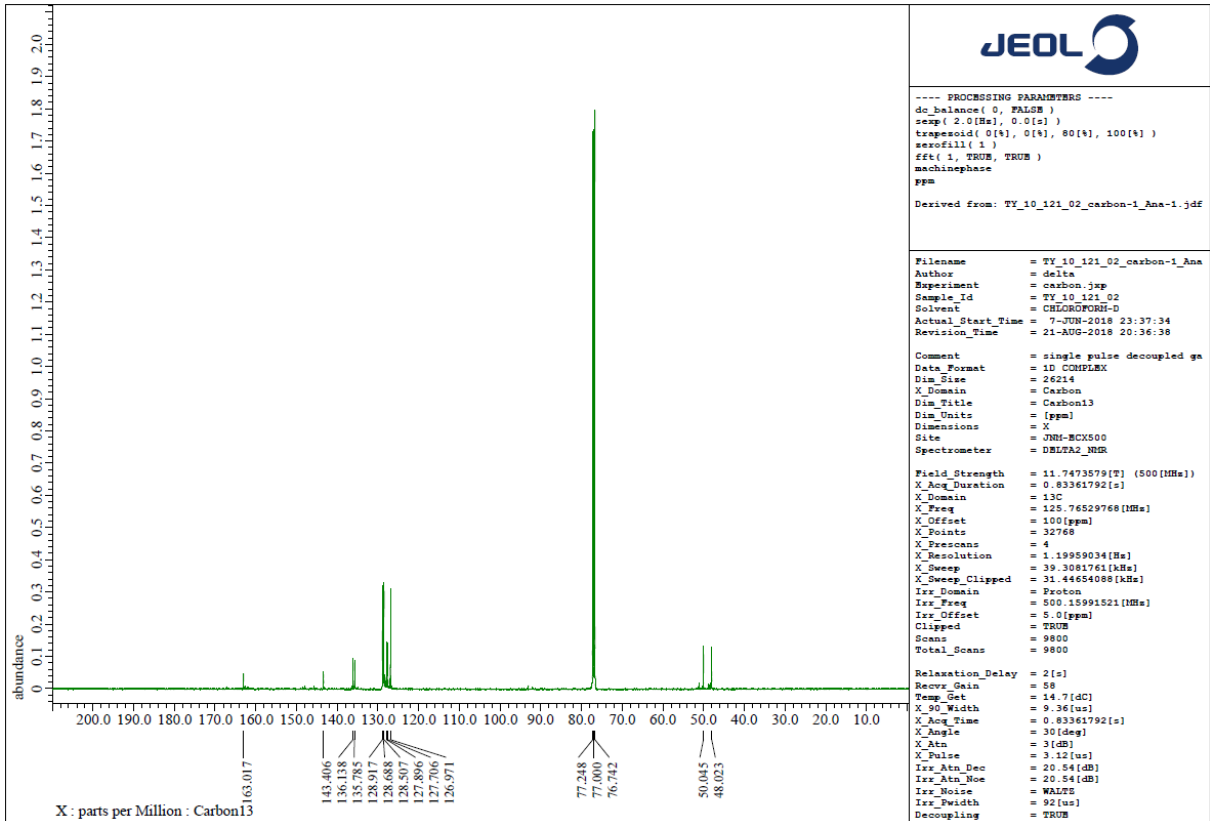
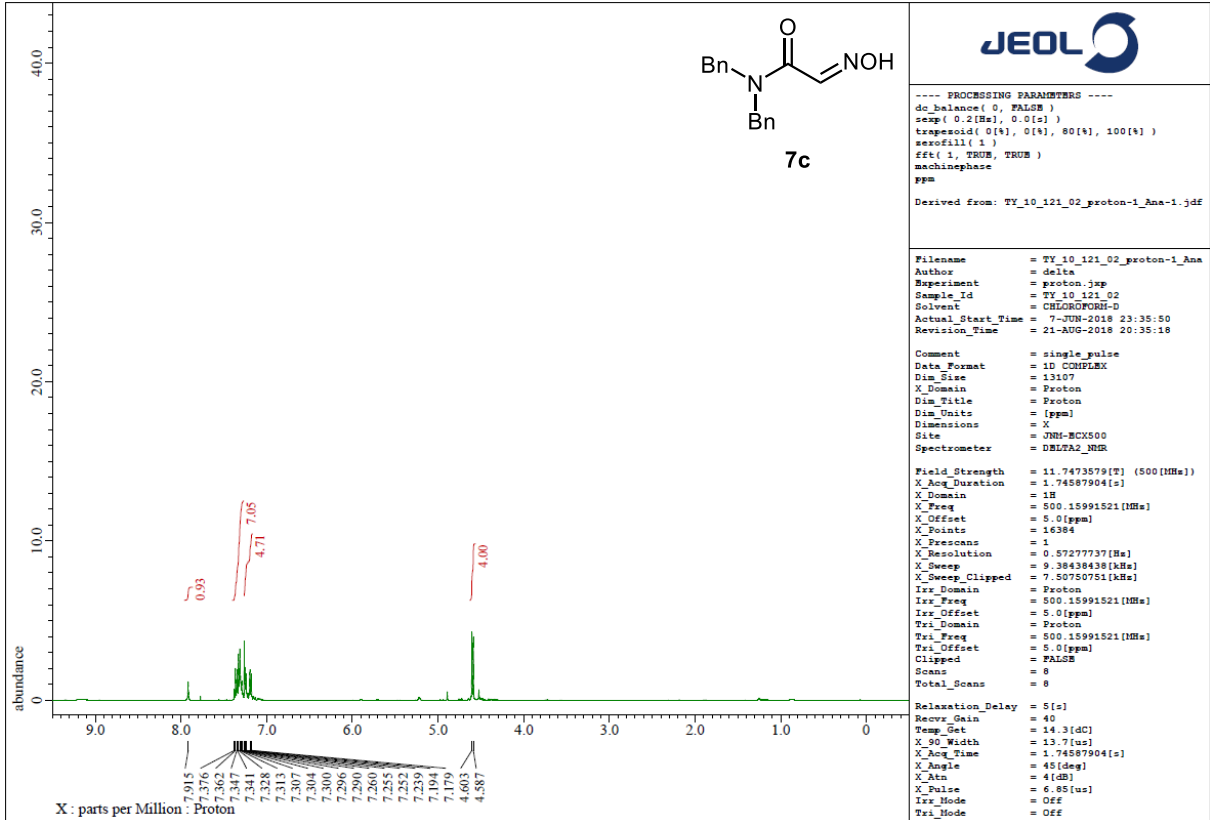


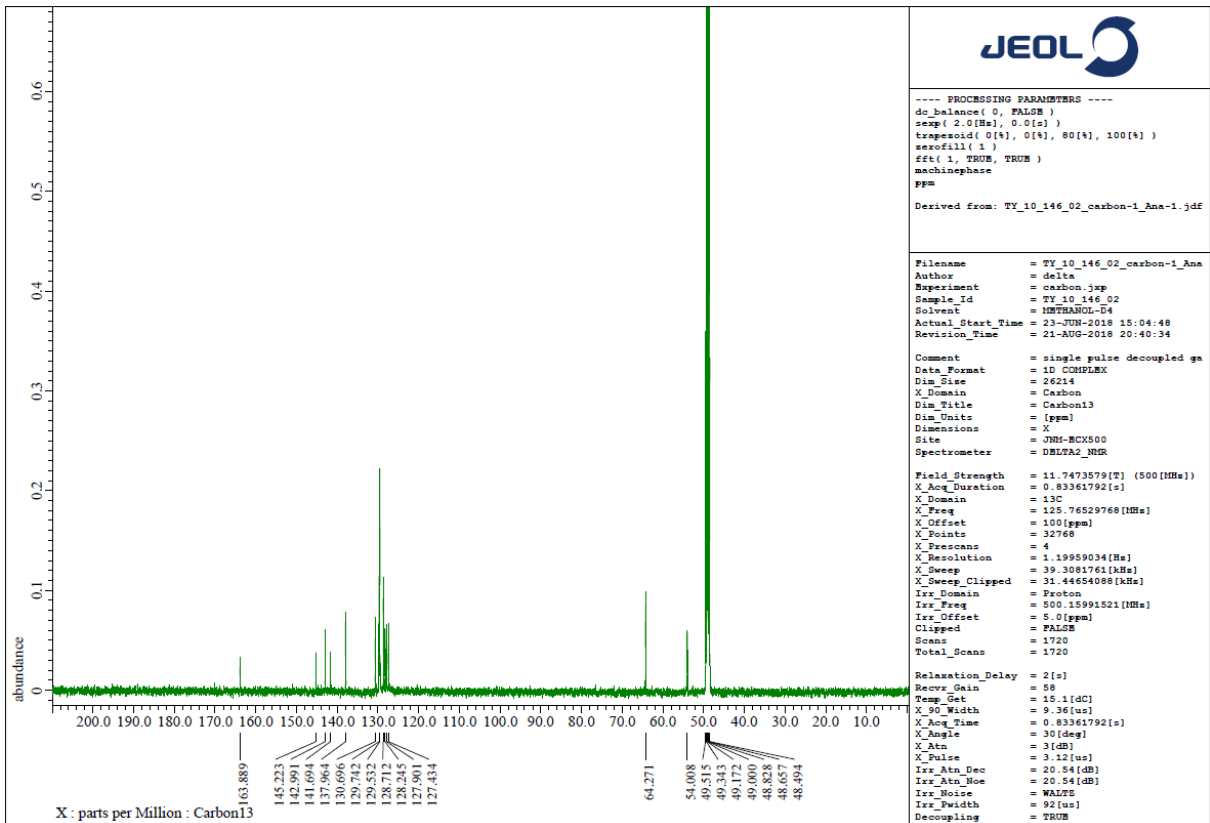
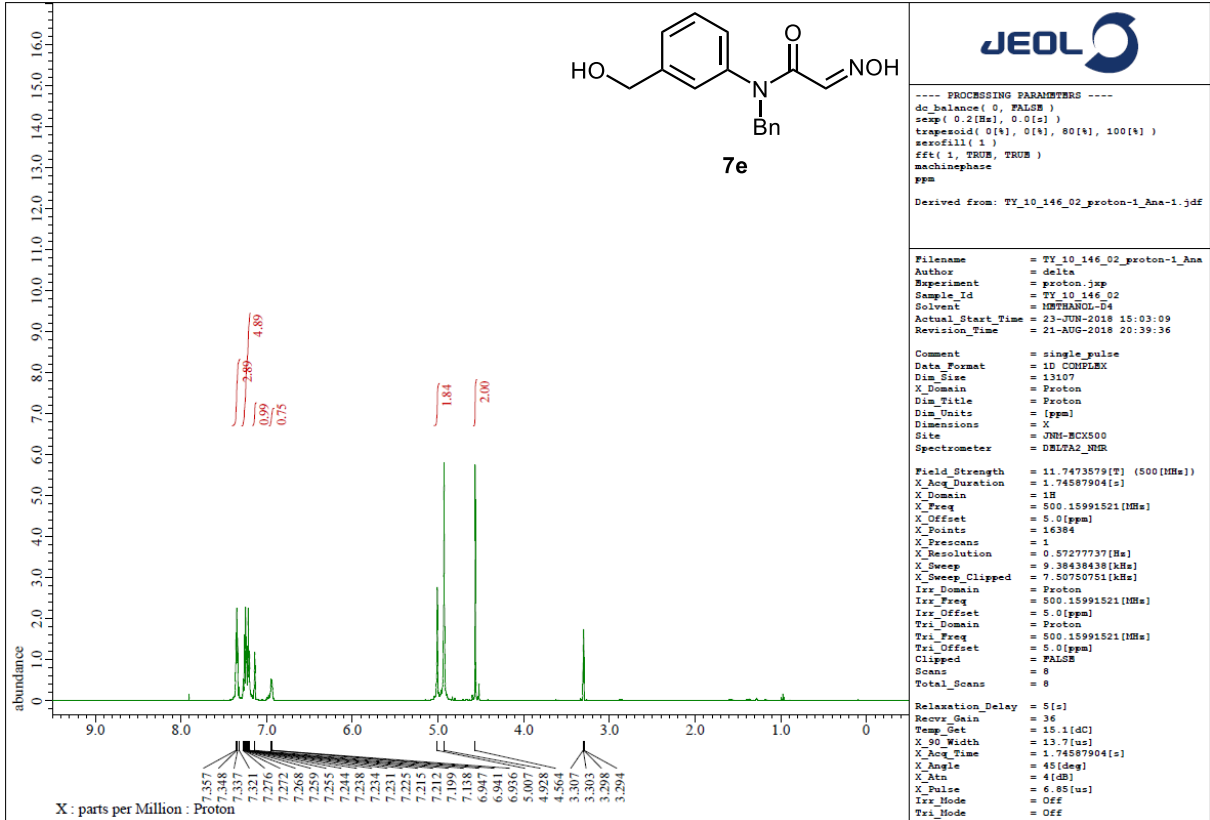
DFILE TU-02-037-2 170614_proton-1-
 COMNT single_pulse
 DATIM 2017-06-14 19:32:21
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 13.7 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 42

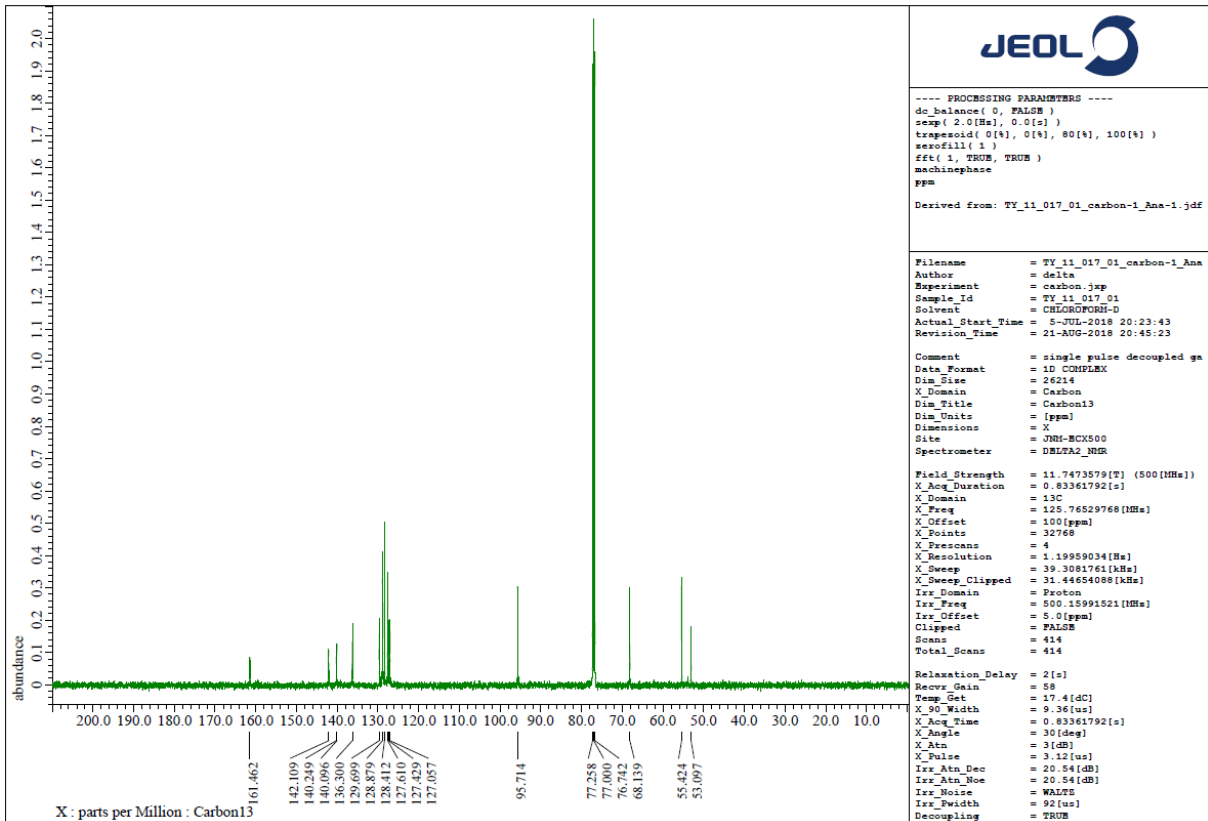
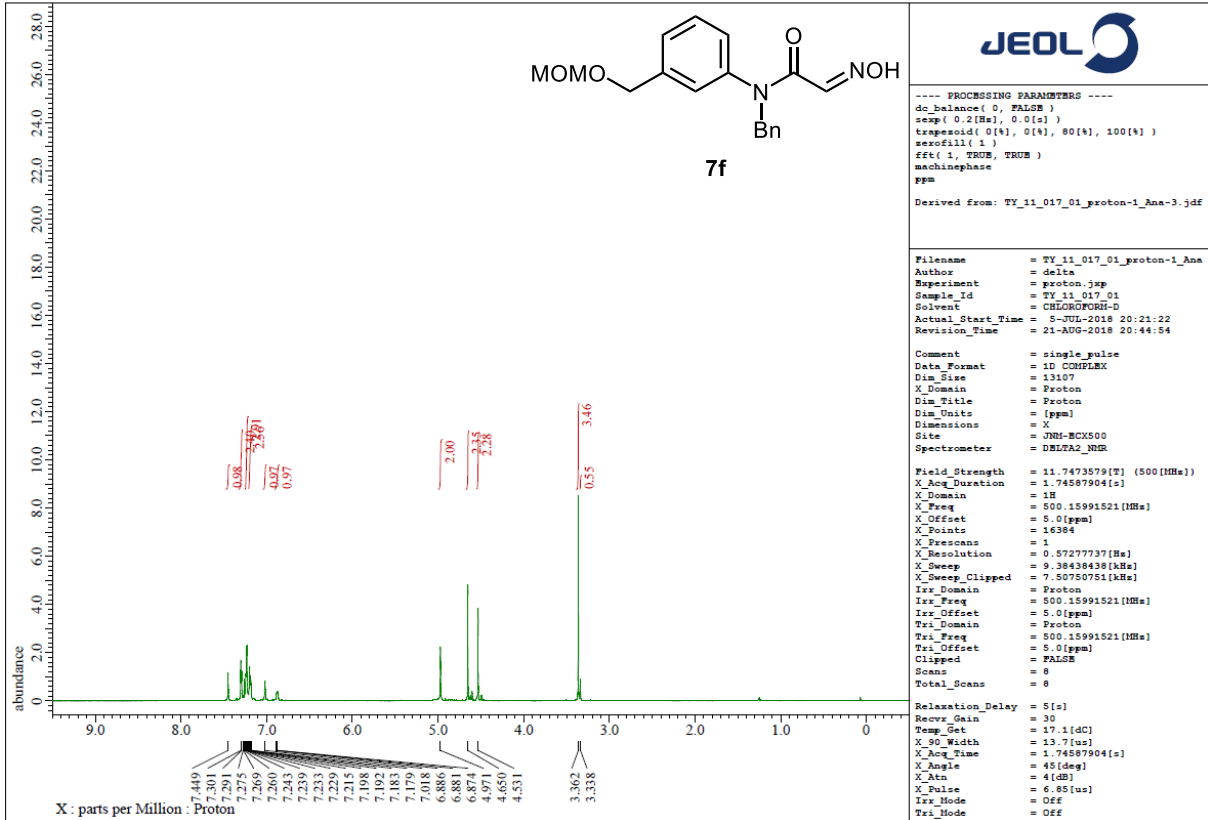


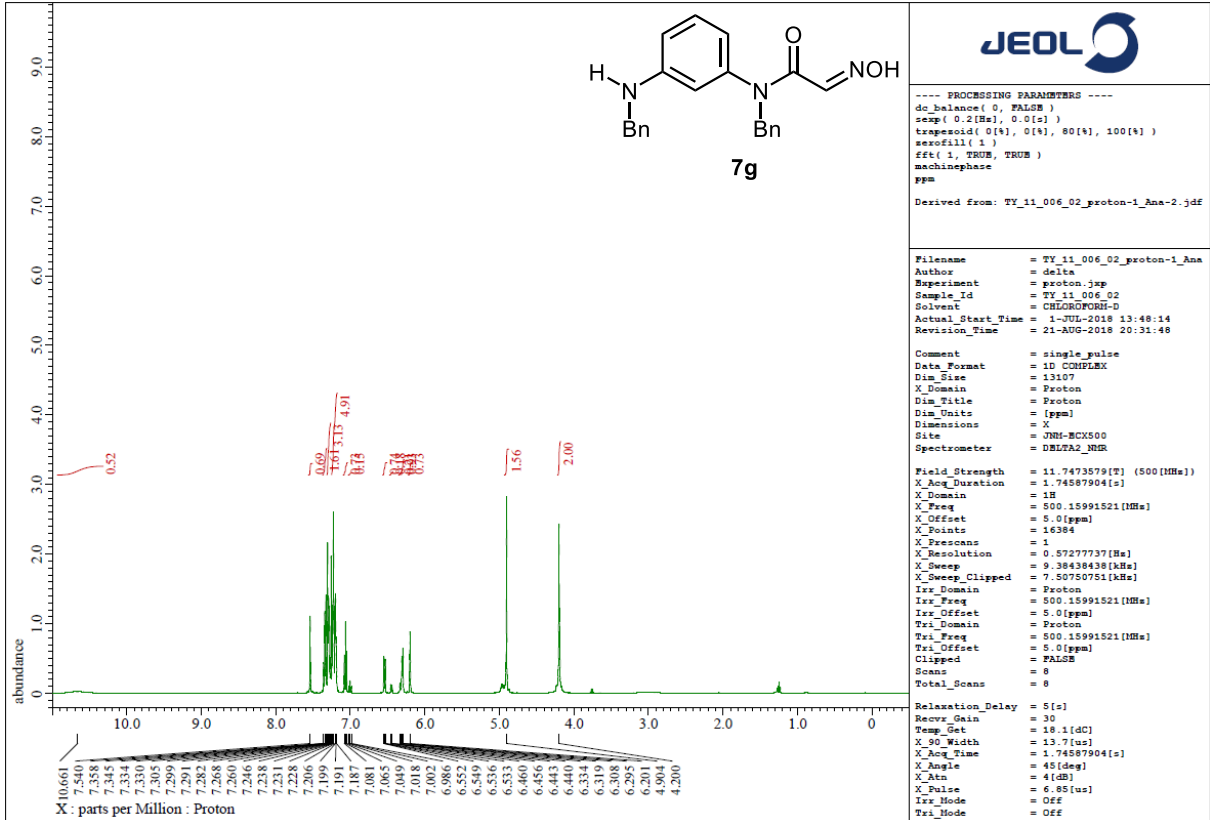
DFILE TU-02-037-2 170614_carbon-1-
 COMNT single_pulse decoupled gated NO
 DATIM 2017-06-14 19:33:45
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 512
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 13.7 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60











JEOL

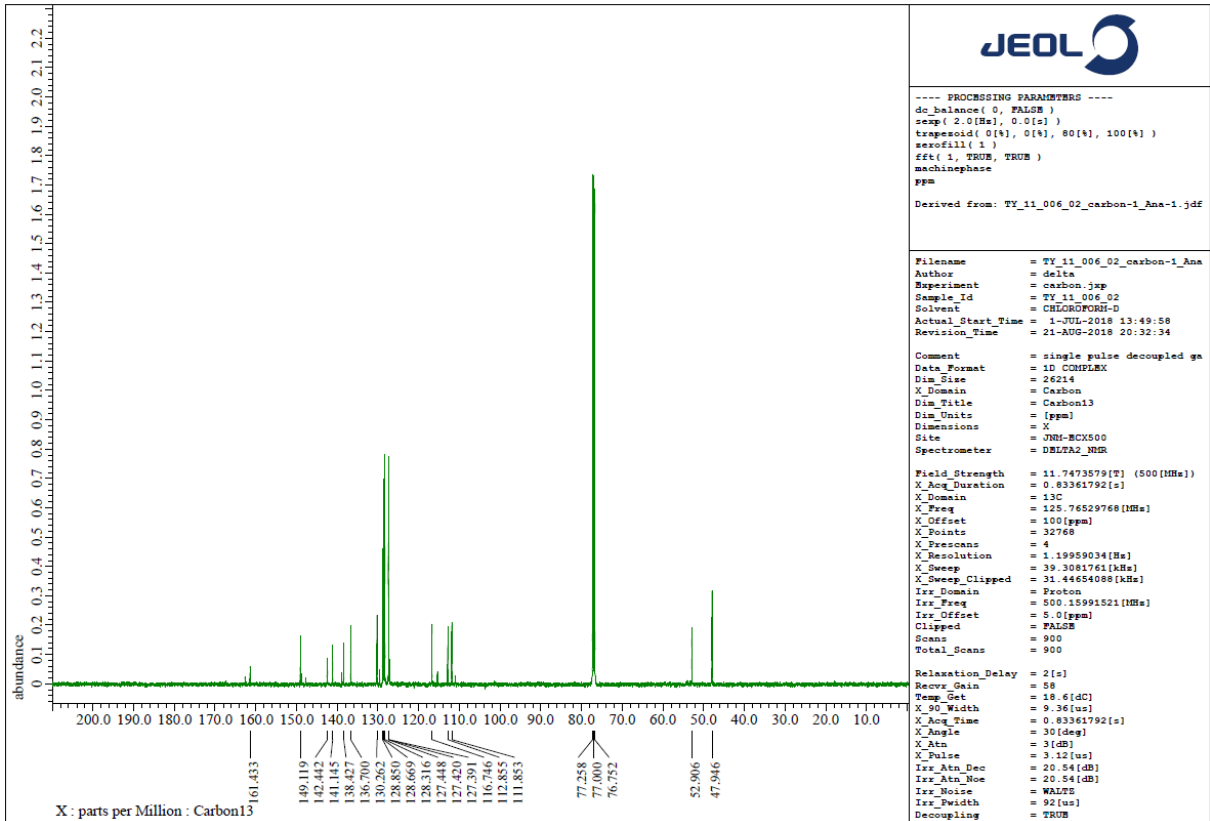
---- PROCESSING PARAMETERS ----
 dc_balance(0, FALSE)
 exp(0.2[Hz], 0.0[us])
 trapezoid(0[us], 0[us], 80[us], 100[us])
 zerofill(1)
 fft(1, TRUE, TRUE)
 machinephase
 ppm
 Derived from: TY_11_006_02_proton-1_Ana-2.jdf

Filename = TY_11_006_02_proton-1_Ana
 Author = delta
 Experiment = proton.jsp
 Sample_Id = TY_11_006_02
 Solvent = CDCl3/DMSO-D
 Actual_Start_Time = 1-JUL-2018 13:48:14
 Revision_Time = 21-AUG-2018 20:31:48

Comment = single_pulse
 Data_Format = 1D COMPLEX
 Dim_Size = 13107
 X_Domain = Proton
 Dim_File = Proton
 Dim_Units = [ppm]
 Dimensions = X
 Site = JNM-MCX500
 Spectrometer = DBLFA2_NMR

Field_Strength = 11.74735799[T] (500[MHz])
 X_Acq_Duration = 1.74587904[s]
 X_Domain = 1H
 X_Freq = 500.15991521[MHz]
 X_Offset = 5.0[ppm]
 X_Points = 15384
 X_Prescans = 1
 X_Resolution = 0.57277737[Hz]
 X_Sweep = 9.38438438[kHz]
 X_Sweep_Clippped = 7.50760751[kHz]
 Irv_Domain = Proton
 Irv_Freq = 500.15991521[MHz]
 Irv_Offset = 5.0[ppm]
 Tri_Domain = Proton
 Tri_Freq = 500.15991521[MHz]
 Tri_Offset = 5.0[ppm]
 Clipped = FALSE
 Scans = 8
 Total_Scans = 8

Relaxation_Delay = 5[s]
 Recv_Gain = 30
 Temp_Get = 18.1[dc]
 X_90_Width = 13.7[us]
 X_Acq_Time = 1.74587904[s]
 X_Angle = 45[deg]
 X_Atn = 4[db]
 X_Pulse = 6.85[us]
 Irv_Mode = Off
 Tri_Mode = Off



JEOL

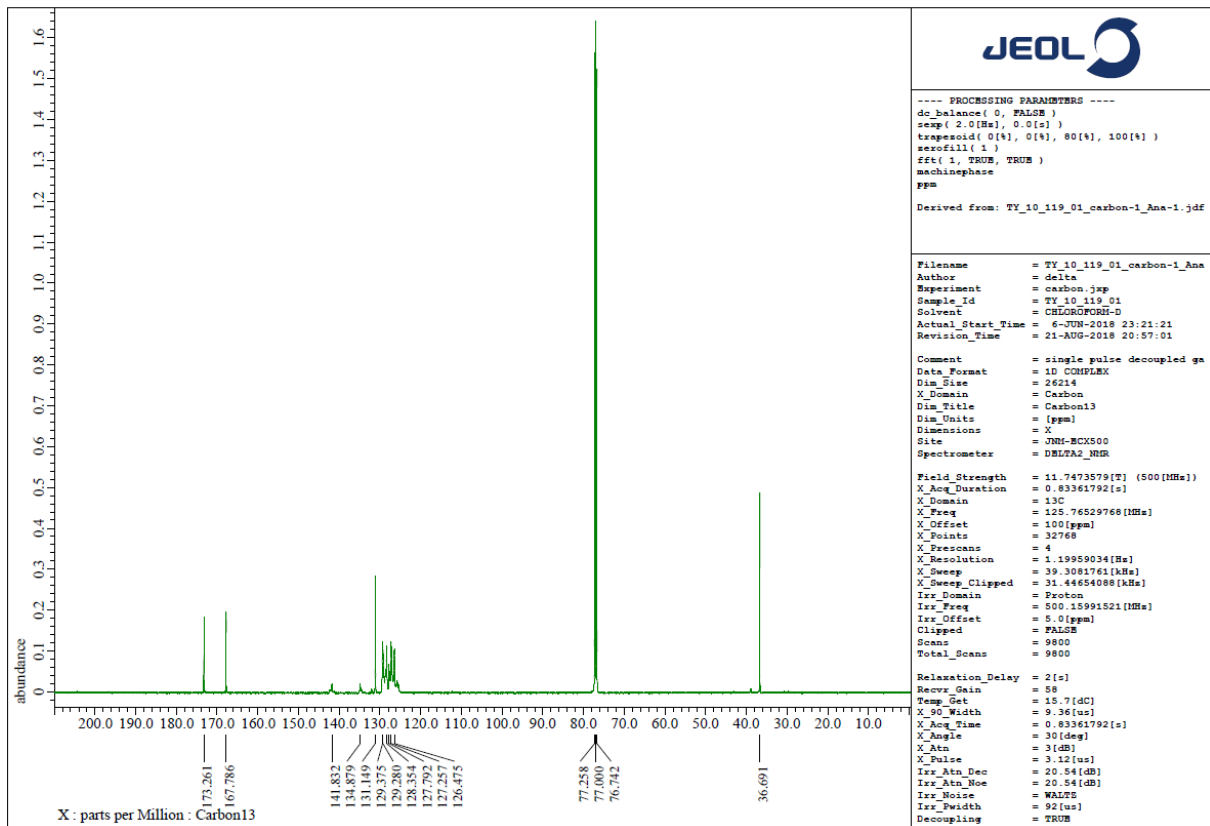
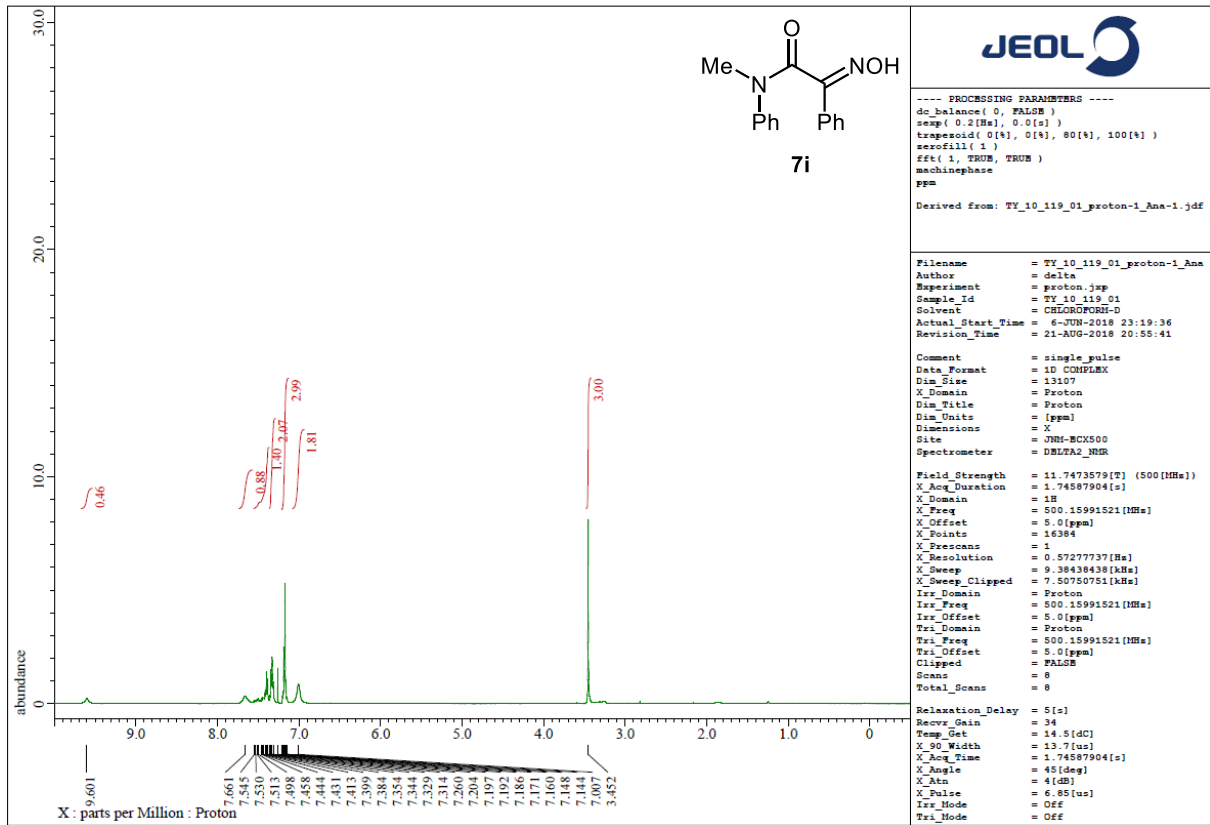
---- PROCESSING PARAMETERS ----
 dc_balance(0, FALSE)
 exp(2.0[Hz], 0.0[us])
 trapezoid(0[us], 0[us], 80[us], 100[us])
 zerofill(1)
 fft(1, TRUE, TRUE)
 machinephase
 ppm
 Derived from: TY_11_006_02_carbon-1_Ana-1.jdf

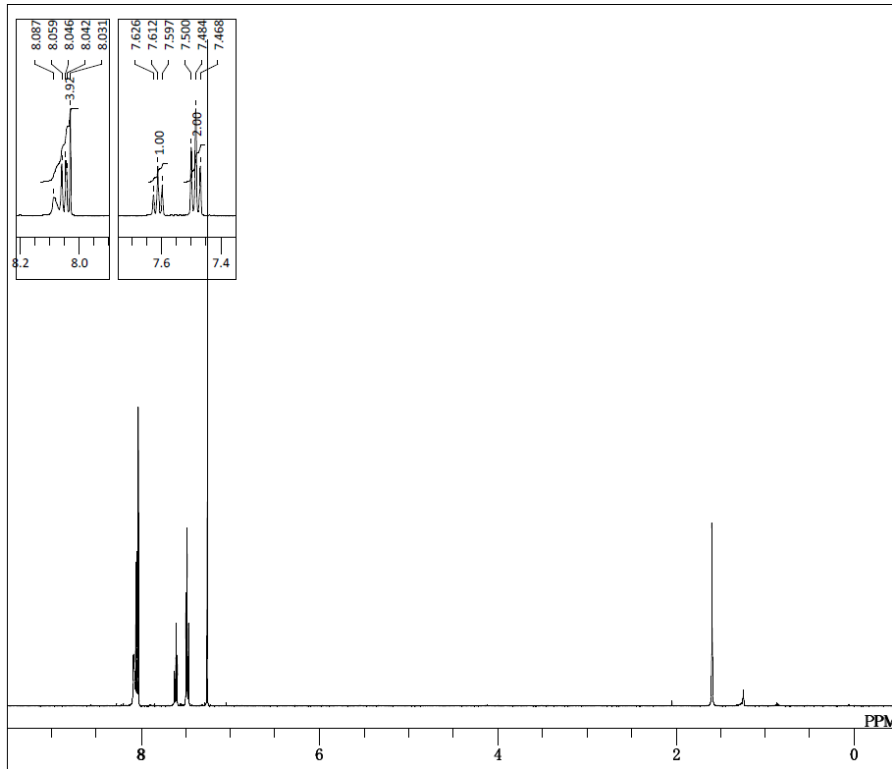
Filename = TY_11_006_02_carbon-1_Ana
 Author = delta
 Experiment = carbon.jsp
 Sample_Id = TY_11_006_02
 Solvent = CDCl3/DMSO-D
 Actual_Start_Time = 1-JUL-2018 13:49:58
 Revision_Time = 21-AUG-2018 20:32:34

Comment = single_pulse decoupled ga
 Data_Format = 1D COMPLEX
 Dim_Size = 26214
 X_Domain = Carbon
 Dim_File = Carbon13
 Dim_Units = [ppm]
 Dimensions = X
 Site = JNM-MCX500
 Spectrometer = DBLFA2_NMR

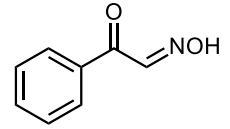
Field_Strength = 11.74735799[T] (500[MHz])
 X_Acq_Duration = 0.83361792[s]
 X_Domain = 13C
 X_Freq = 125.76529768[MHz]
 X_Offset = 100[ppm]
 X_Points = 32769
 X_Prescans = 4
 X_Resolution = 1.19959034[Hz]
 X_Sweep = 39.3081761[MHz]
 X_Sweep_Clippped = 31.44654088[kHz]
 Irv_Domain = Proton
 Irv_Freq = 500.15991521[MHz]
 Irv_Offset = 5.0[ppm]
 Clipped = FALSE
 Scans = 900
 Total_Scans = 900

Relaxation_Delay = 2[s]
 Recv_Gain = 58
 Temp_Get = 18.6[dc]
 X_90_Width = 9.36[us]
 X_Acq_Time = 0.83361792[s]
 X_Angle = 30[deg]
 X_Atn = 3[db]
 X_Pulse = 3.12[us]
 Irv_Atn_Dec = 20.54[db]
 Irv_Atn_Noce = 20.54[db]
 Irv_Boice = WALTZ
 Irv_Pwidth = 92[us]
 Decoupling = TRUM

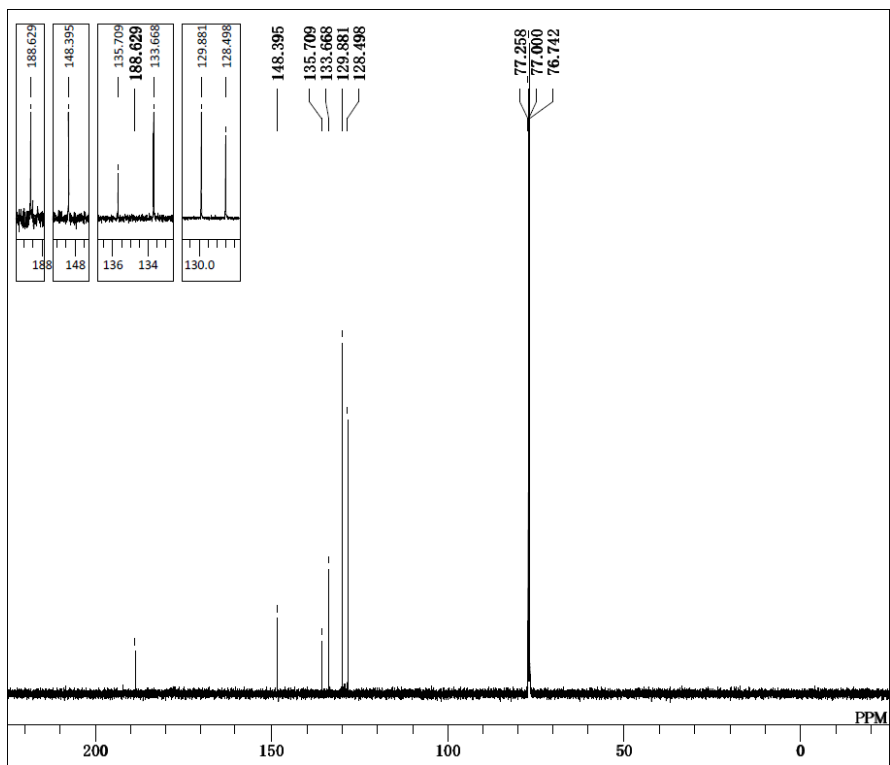




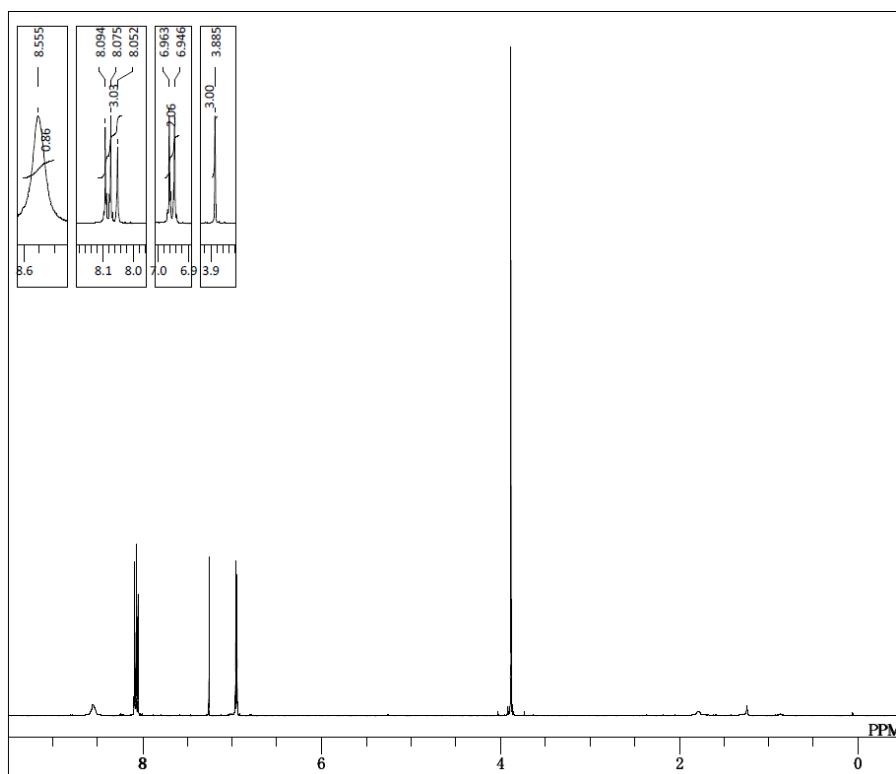
DFILE TU-02-069-3.proton-1-1.als
 COMNT single pulse
 DATIM 2017-09-08 17:08:28
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 15.2 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 48



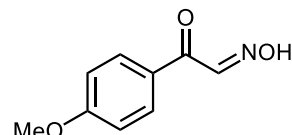
7j



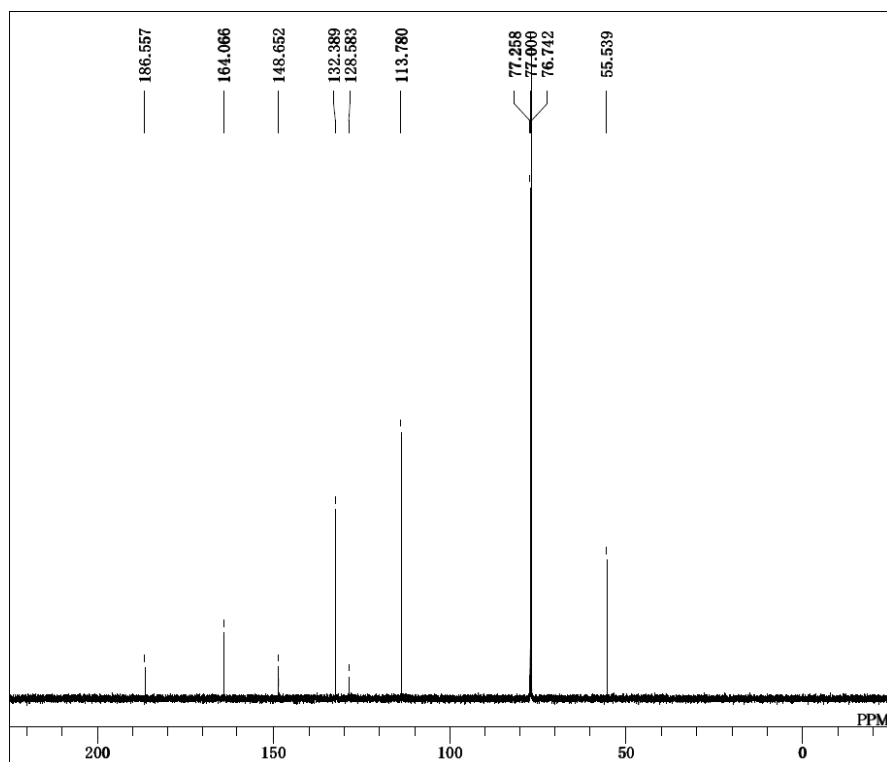
DFILE TU-01-oxime-2 161226_carbon-
 COMNT single pulse decoupled gated NO
 DATIM 2016-12-26 13:22:55
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 512
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 14.9 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 56



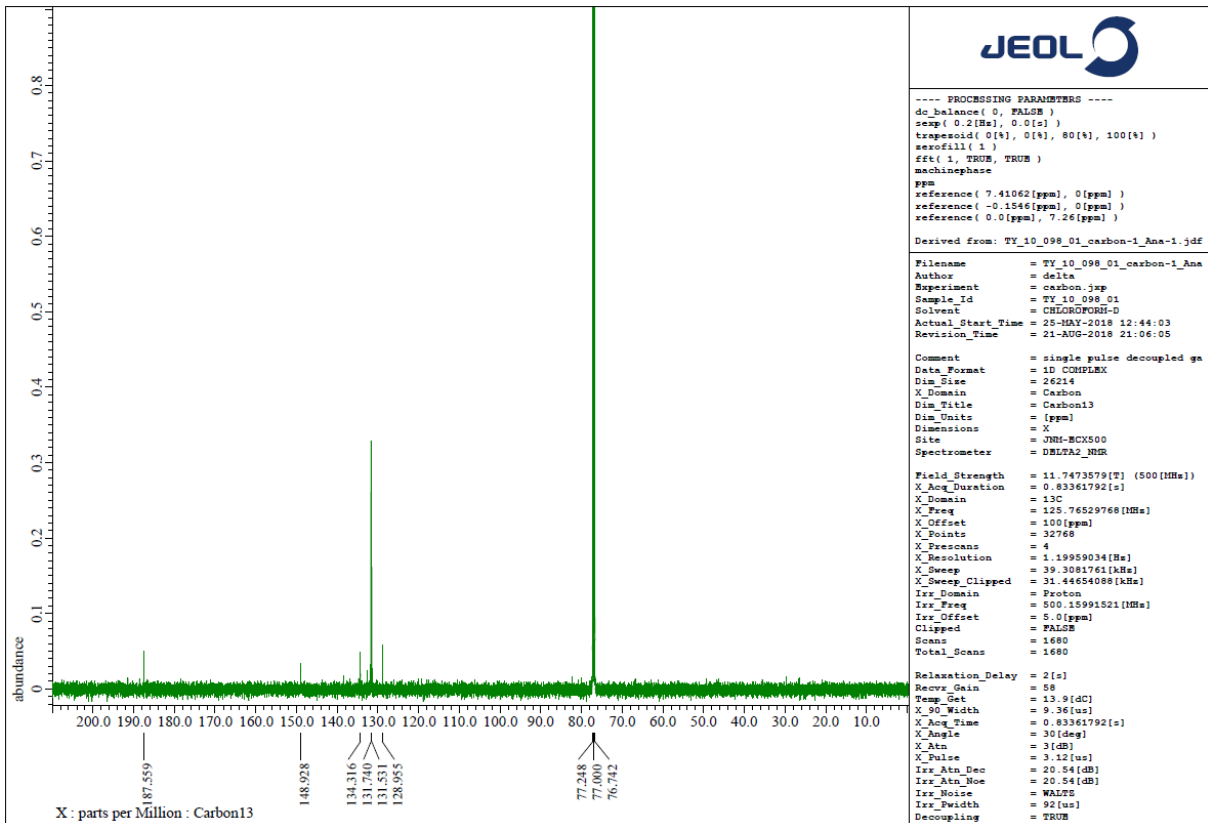
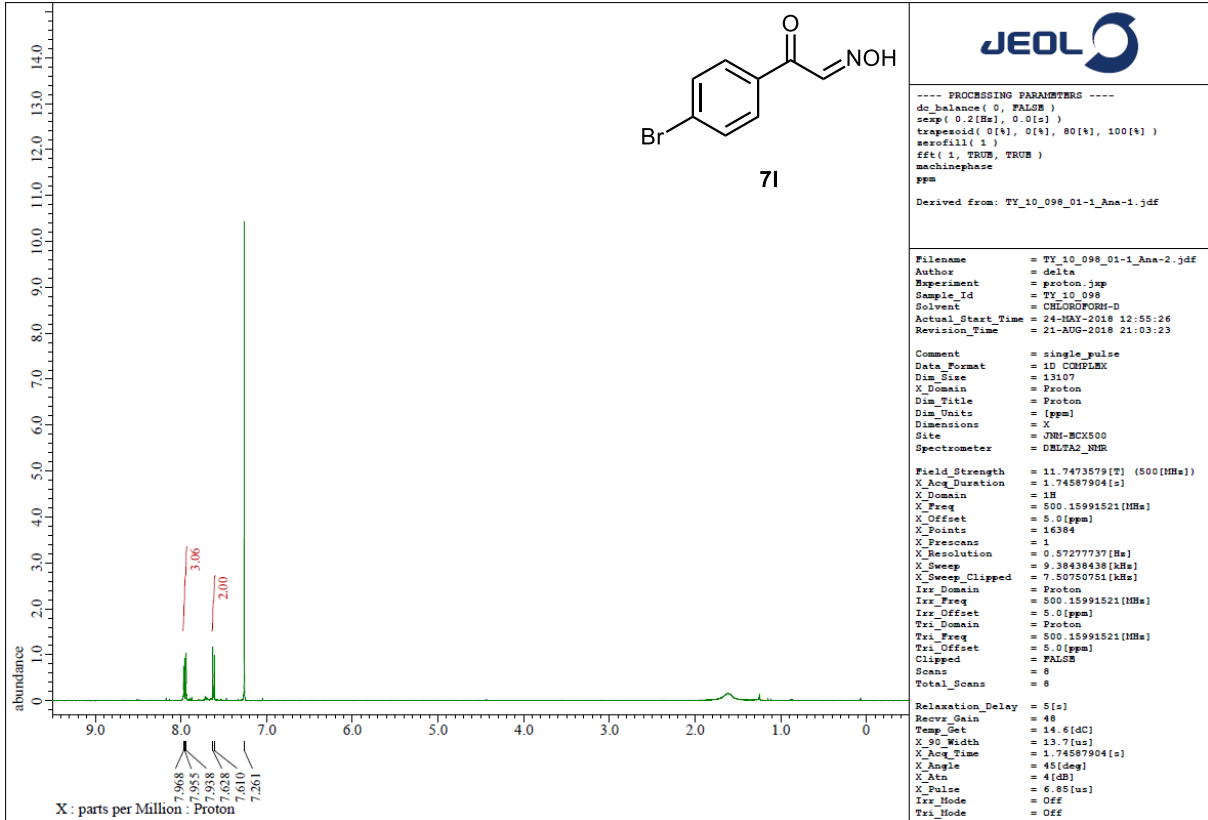
DFILE TU-02-146-2_proton-1-1.jdf
 COMNT single pulse
 DATIM 2018-03-10 23:05:24
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 16384
 FREQU 9384.38 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 14.2 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 42

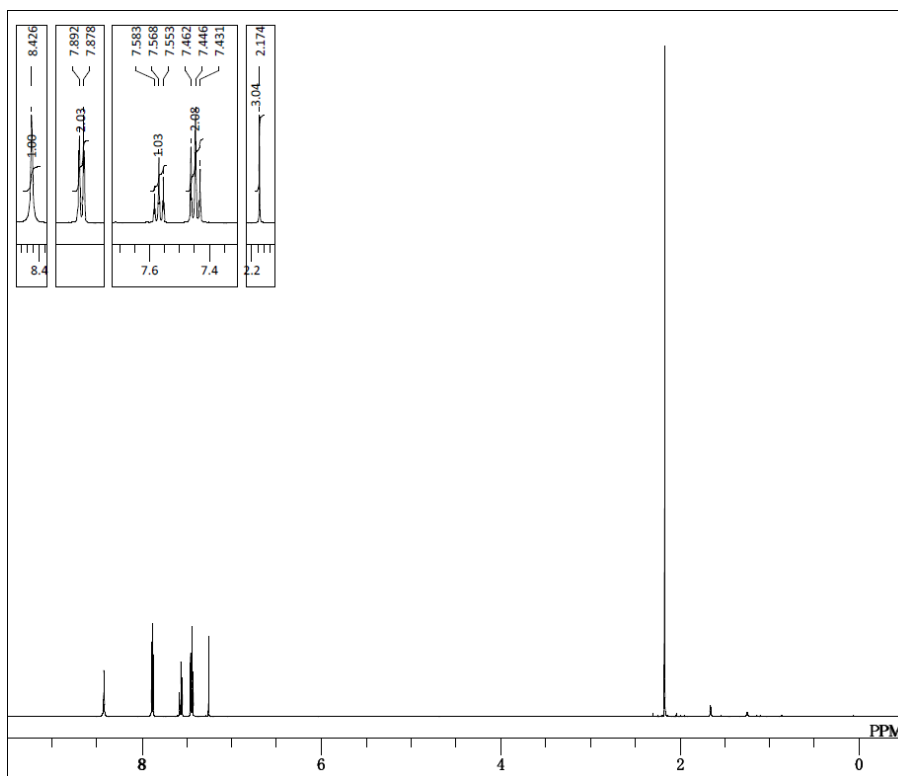


7k

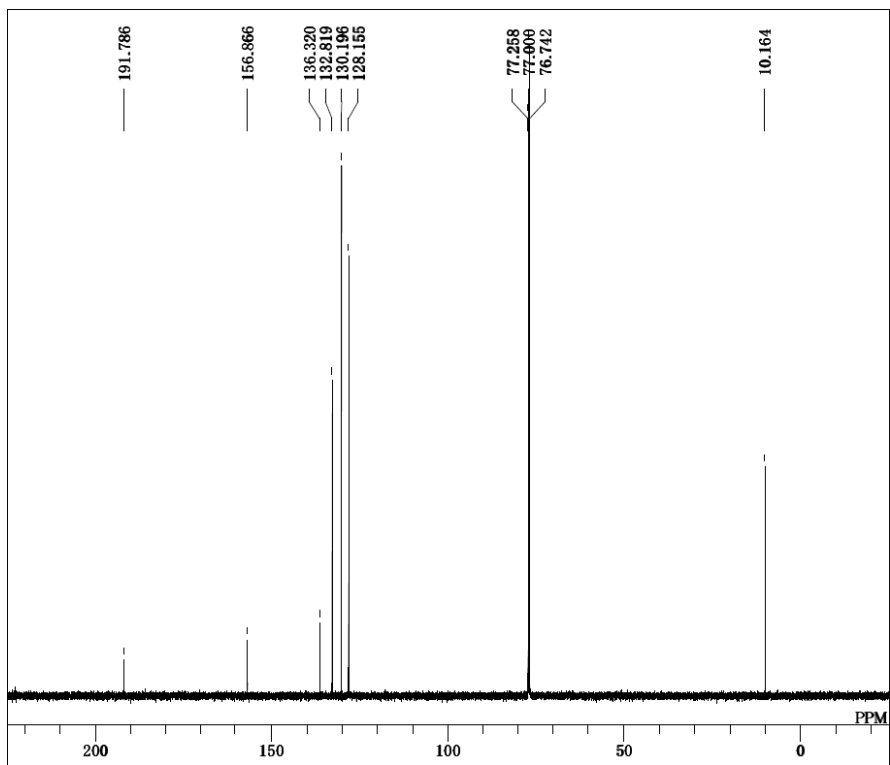
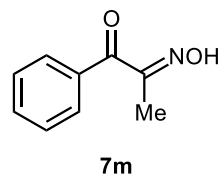


DFILE TU-02-146-2_carbon-1-1.jdf
 COMNT single pulse decoupled gated NO
 DATIM 2018-03-10 23:07:33
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 32767
 FREQU 39308.18 Hz
 SCANS 512
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 14.4 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 58

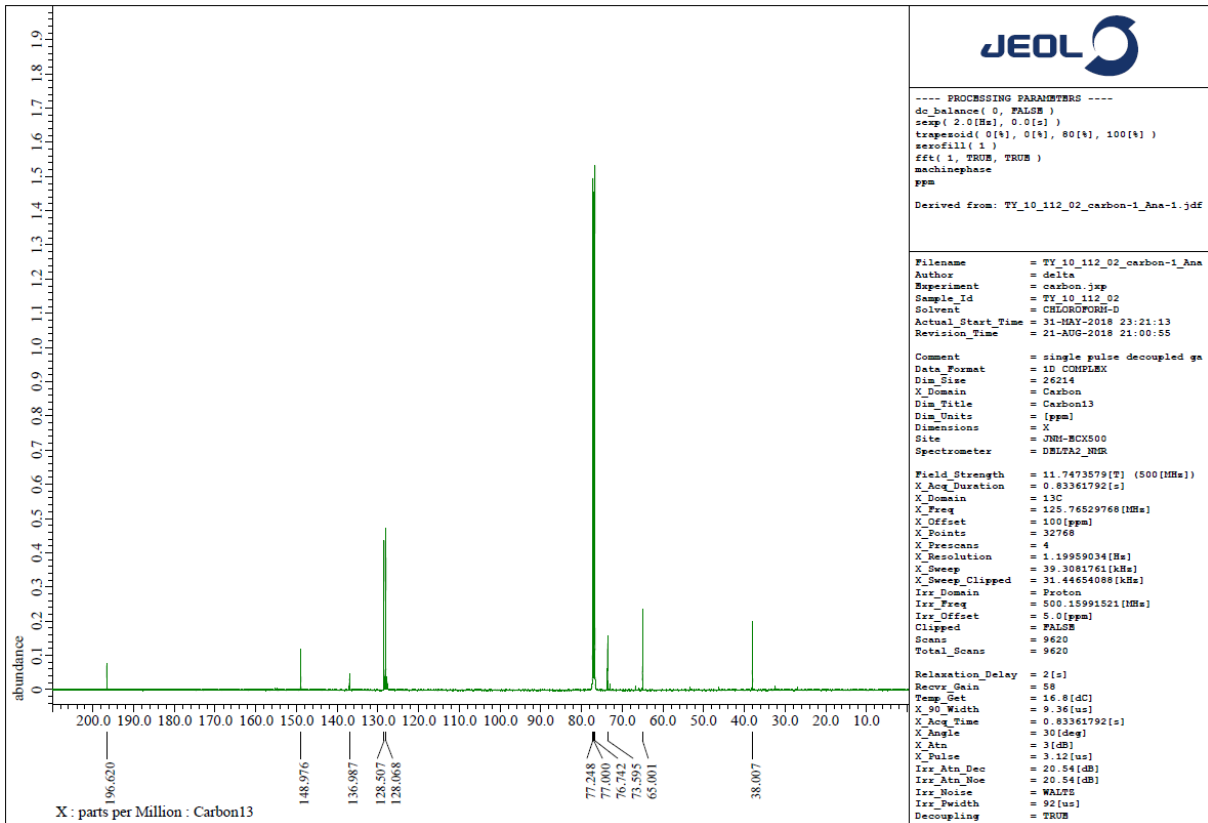
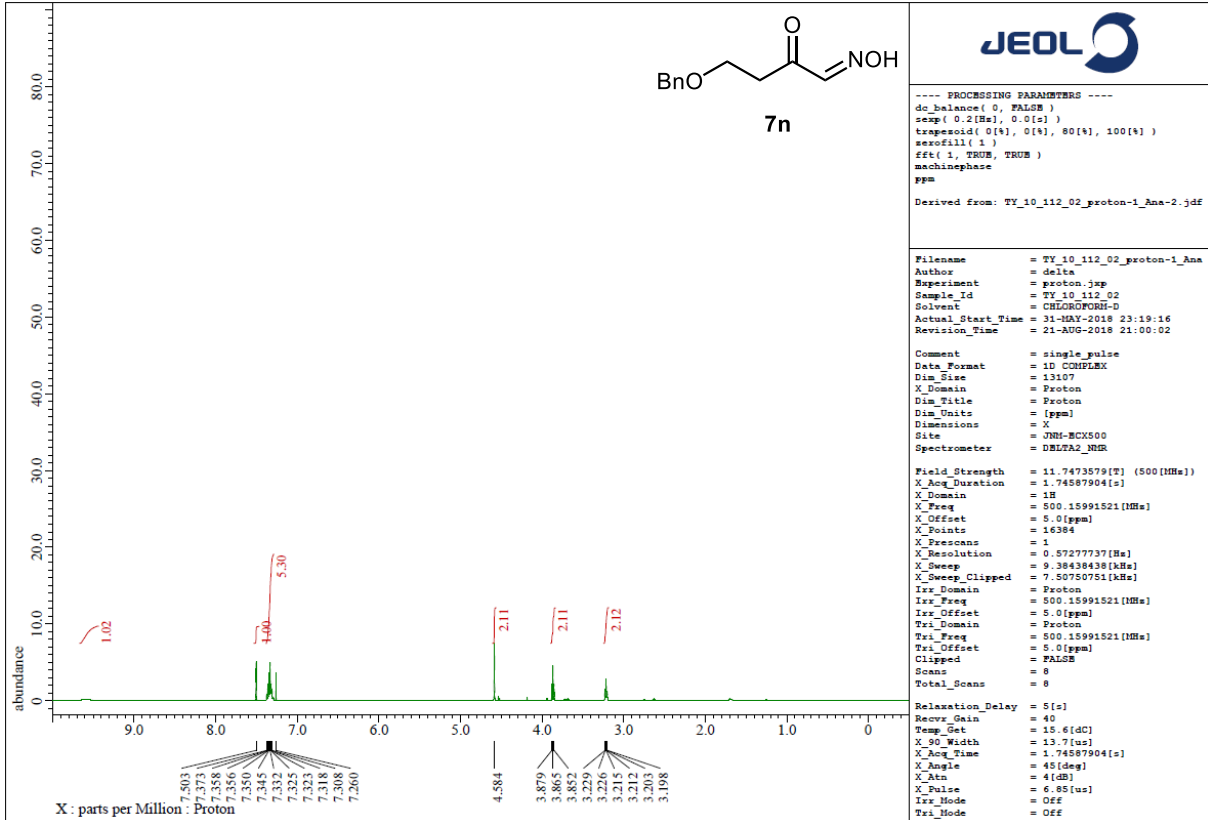


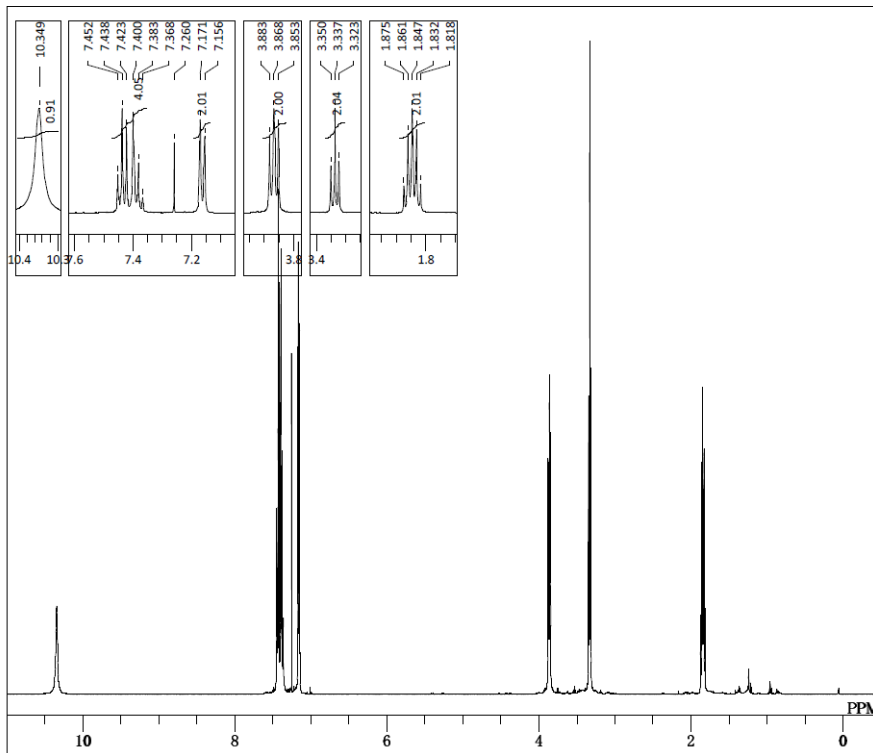


DFILE TU-02-133-2_proton-1-1.als
 COMNT single pulse
 DATIM 2018-01-22 16:15:54
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 16.4 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 42

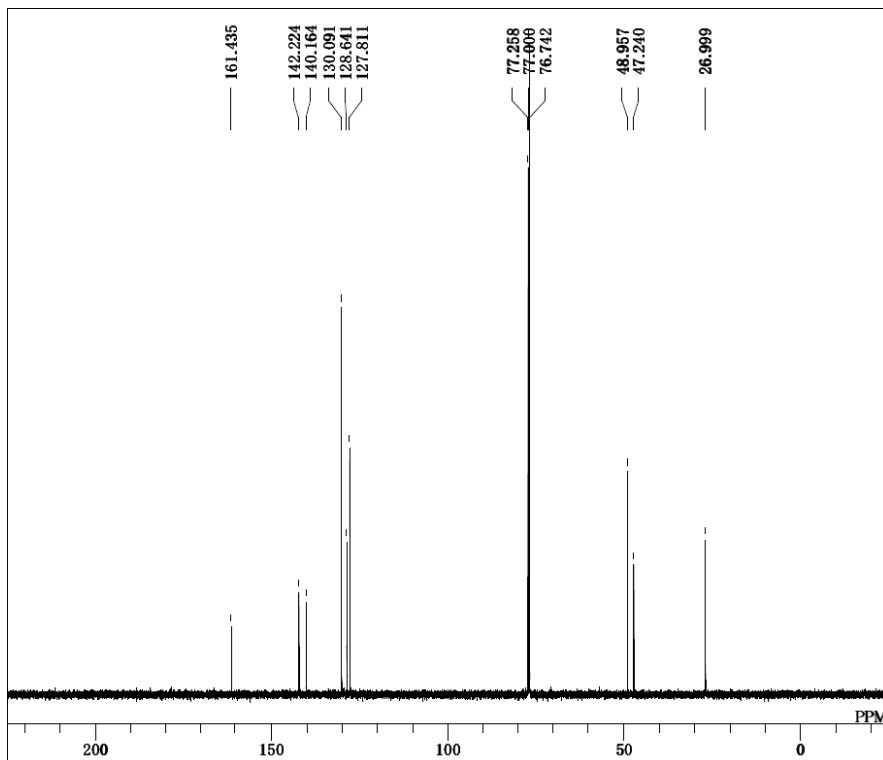
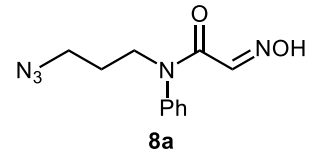


DFILE TU-02-133-2 180122_carbon-1-
 COMNT single pulse decoupled gated NO
 DATIM 2018-01-22 17:27:53
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 512
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 16.9 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60

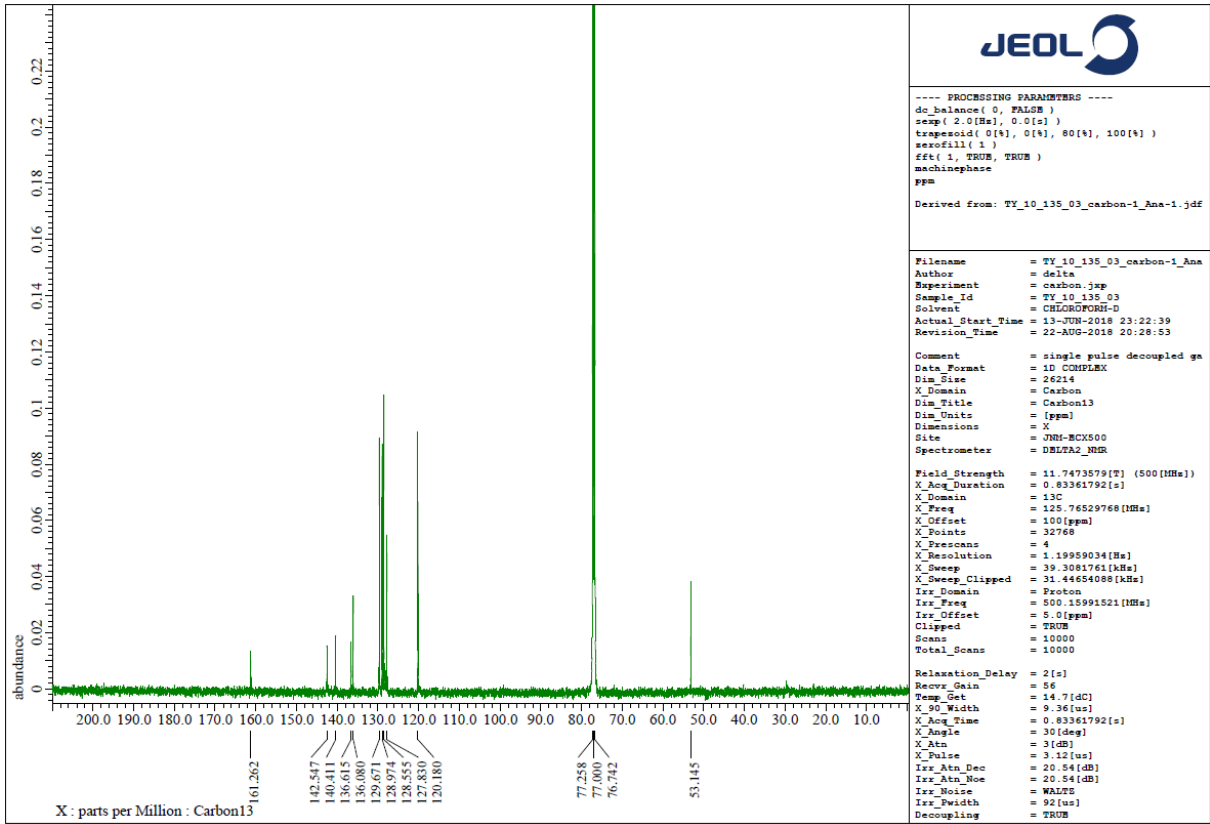
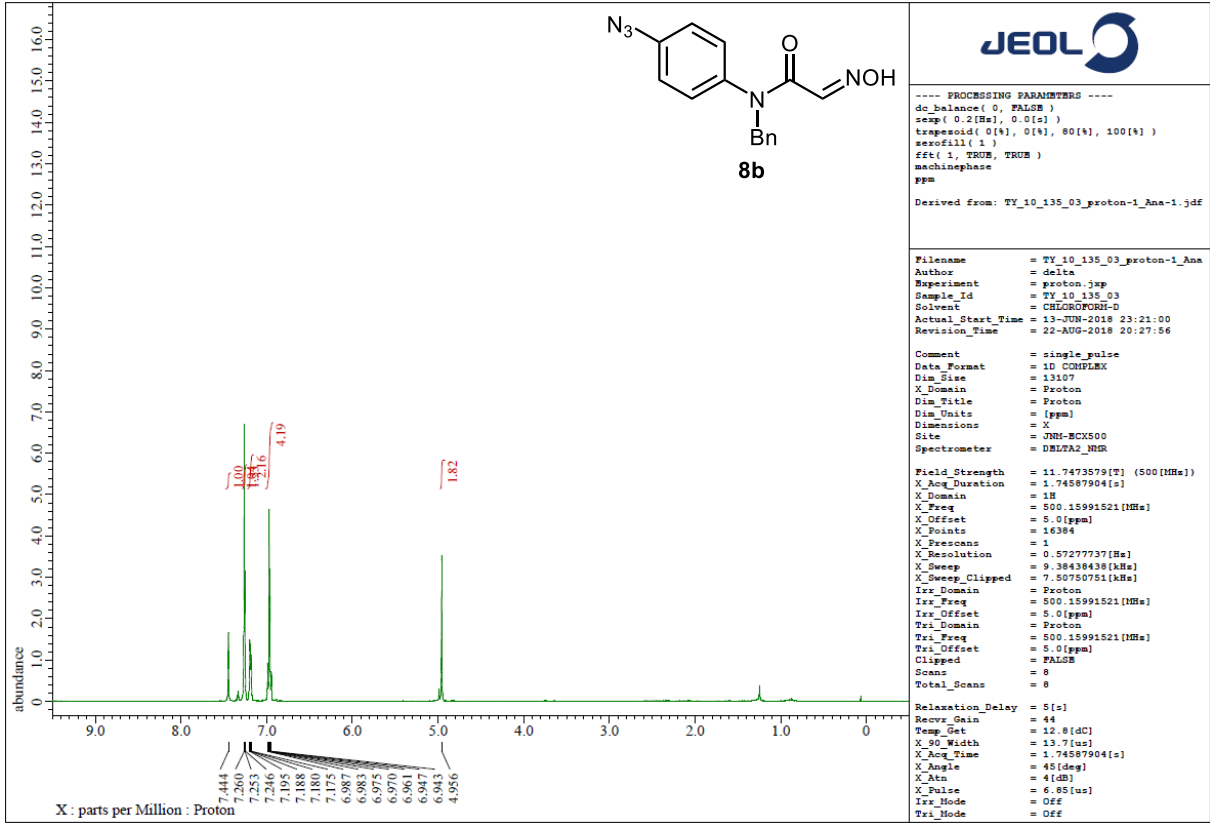


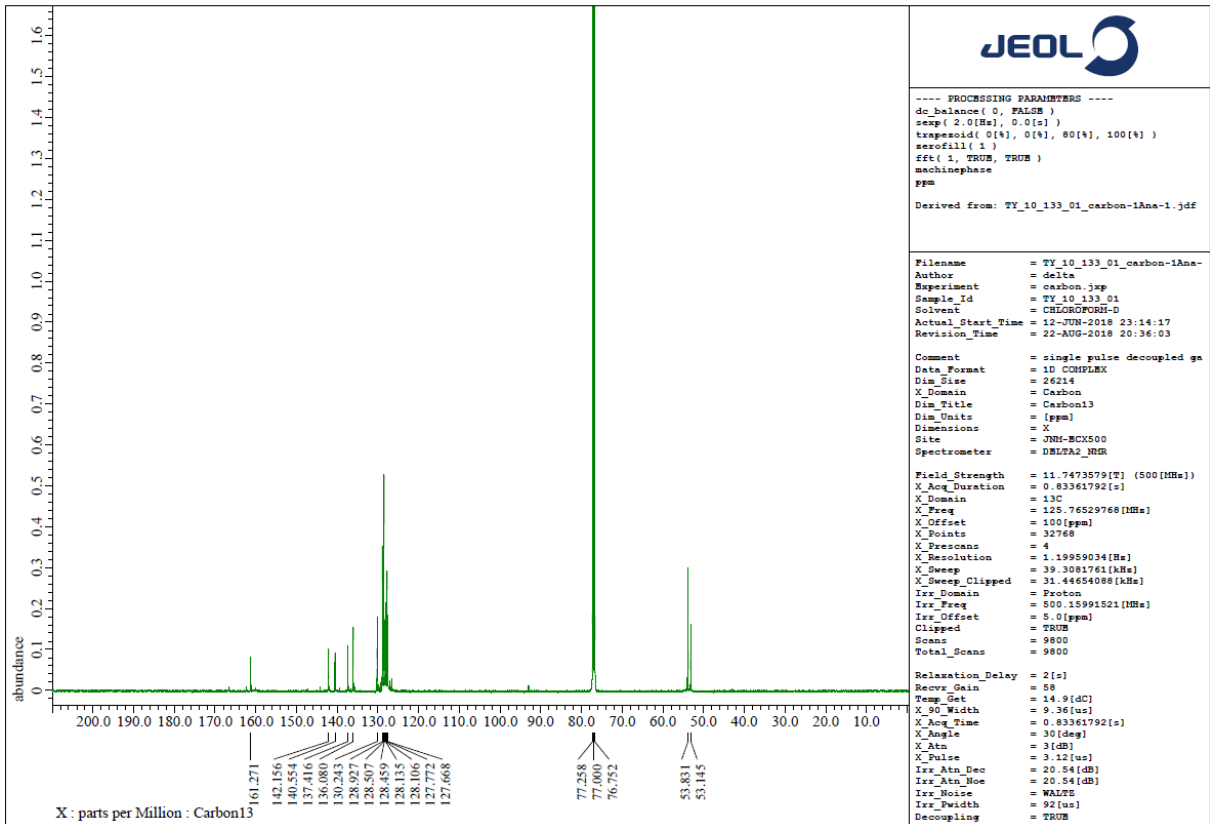
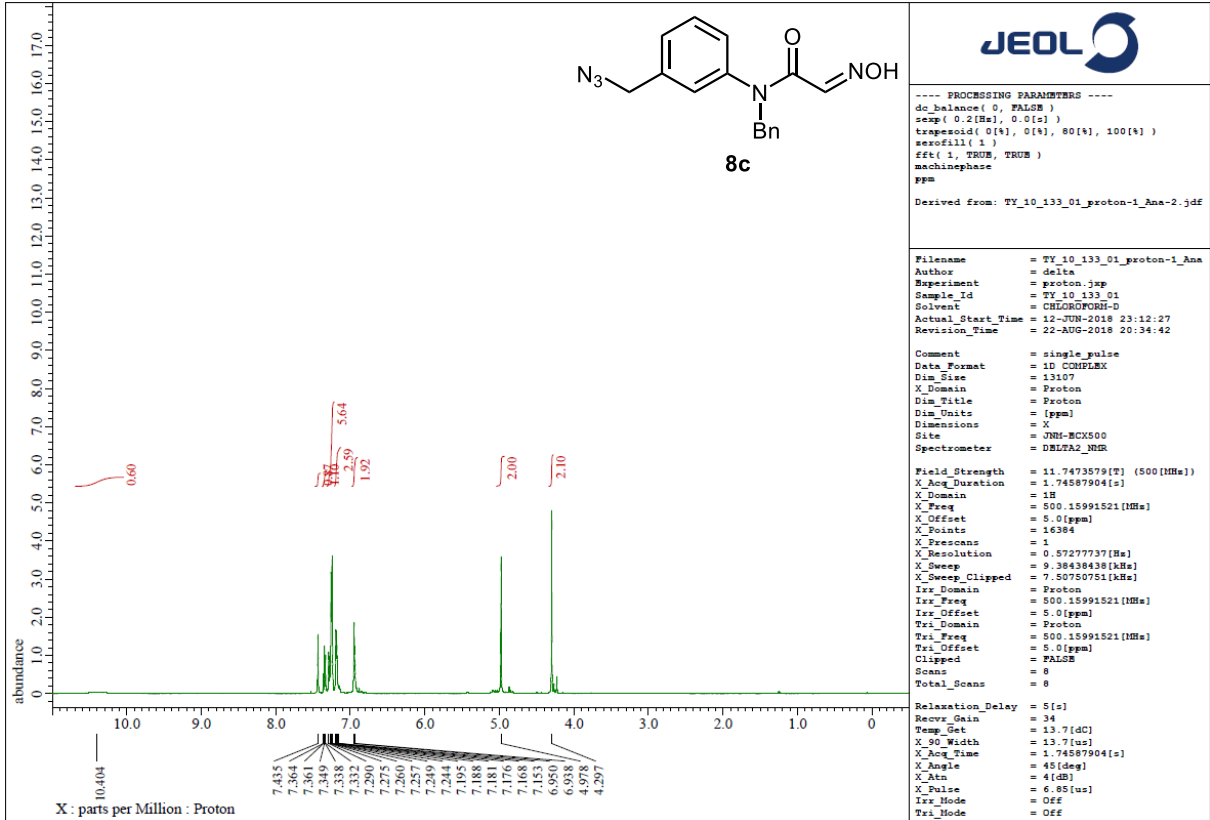


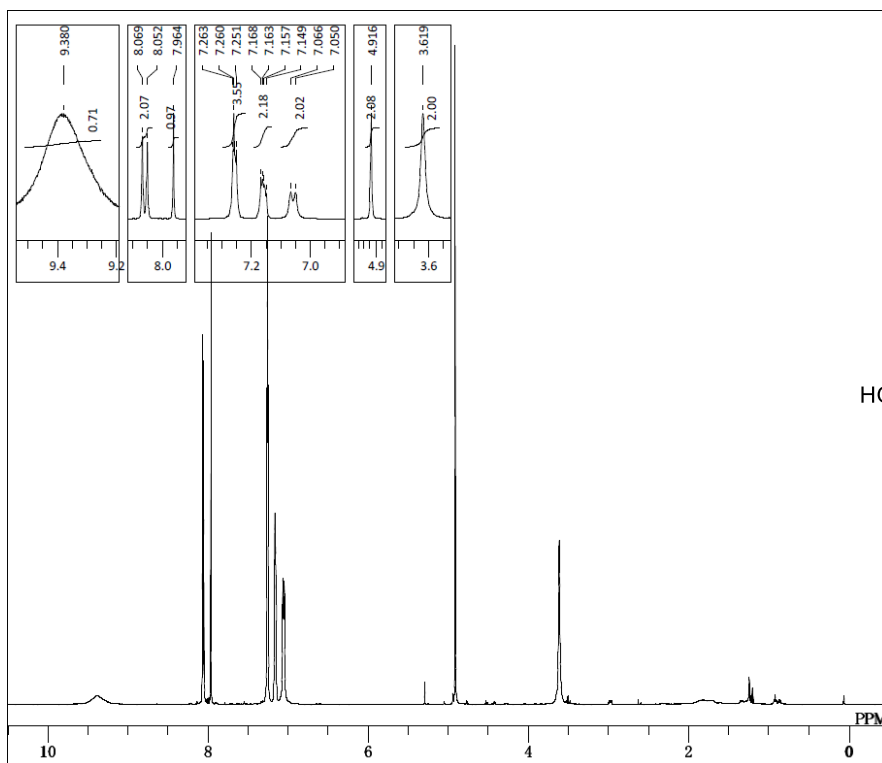
DFILE TU-01-147-2 170126_proton-1-
 COMNT single_pulse
 DATIM 2017-01-26 13:50:37
 OBNUC 1H
 EXMOD proton.jxp
 OBFRQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 17.7 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 34



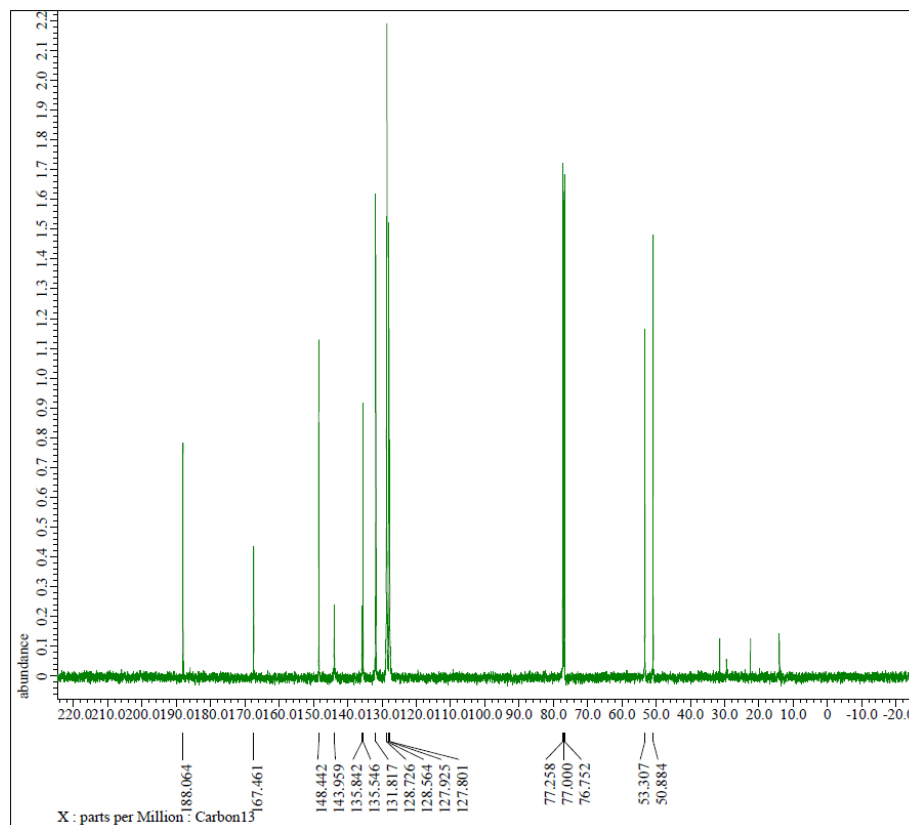
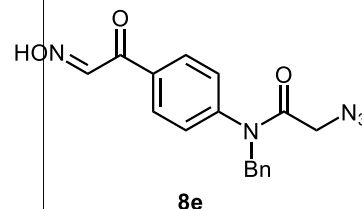
DFILE TU-01-147-2 170126_carbon-1-
 COMNT single_pulse decoupled gated NO
 DATIM 2017-01-26 13:52:28
 OBNUC 13C
 EXMOD carbon.jxp
 OBFRQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 512
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 18.2 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60







DFILE TU-02-045-2 170707_proton-1
 COMNT single_pulse
 DATIM 2017-07-07 13:16:27
 OBNUC 1H
 EXMOD proton.jxp
 OBFRQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 17.3 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 38



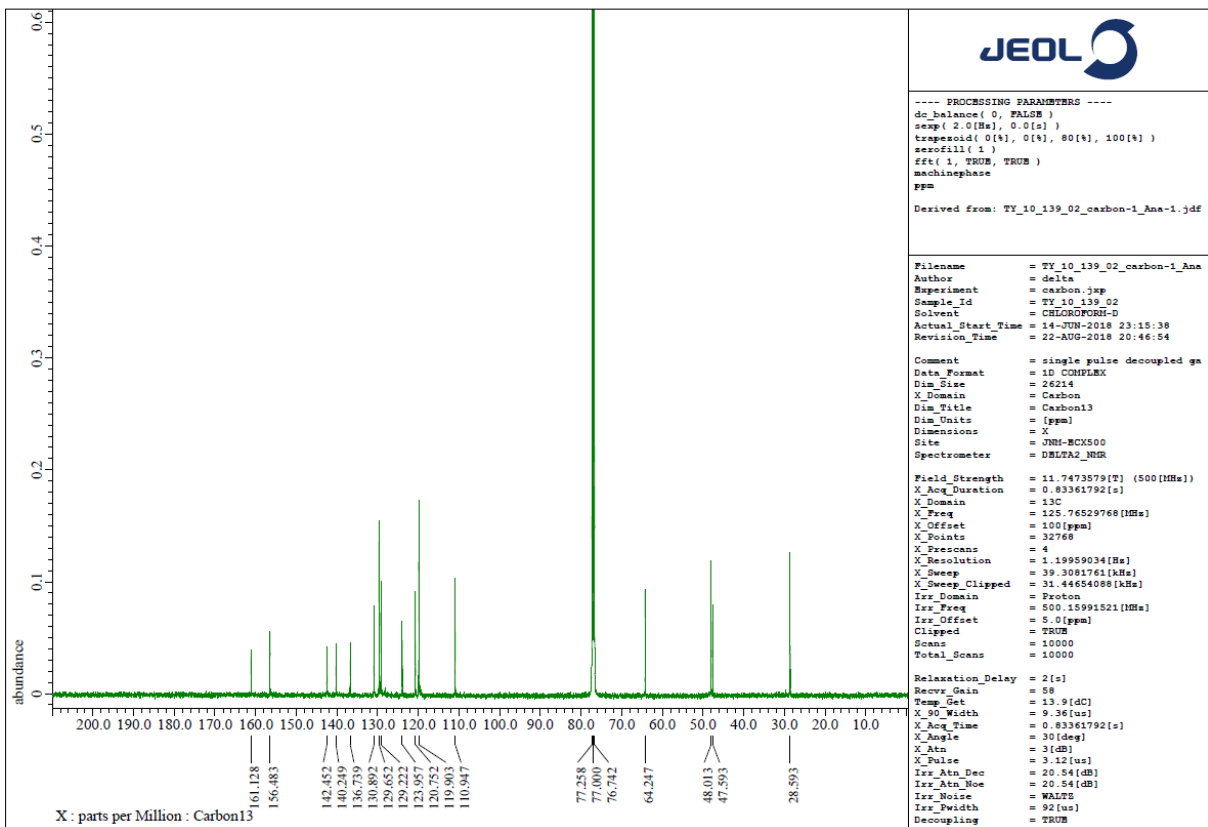
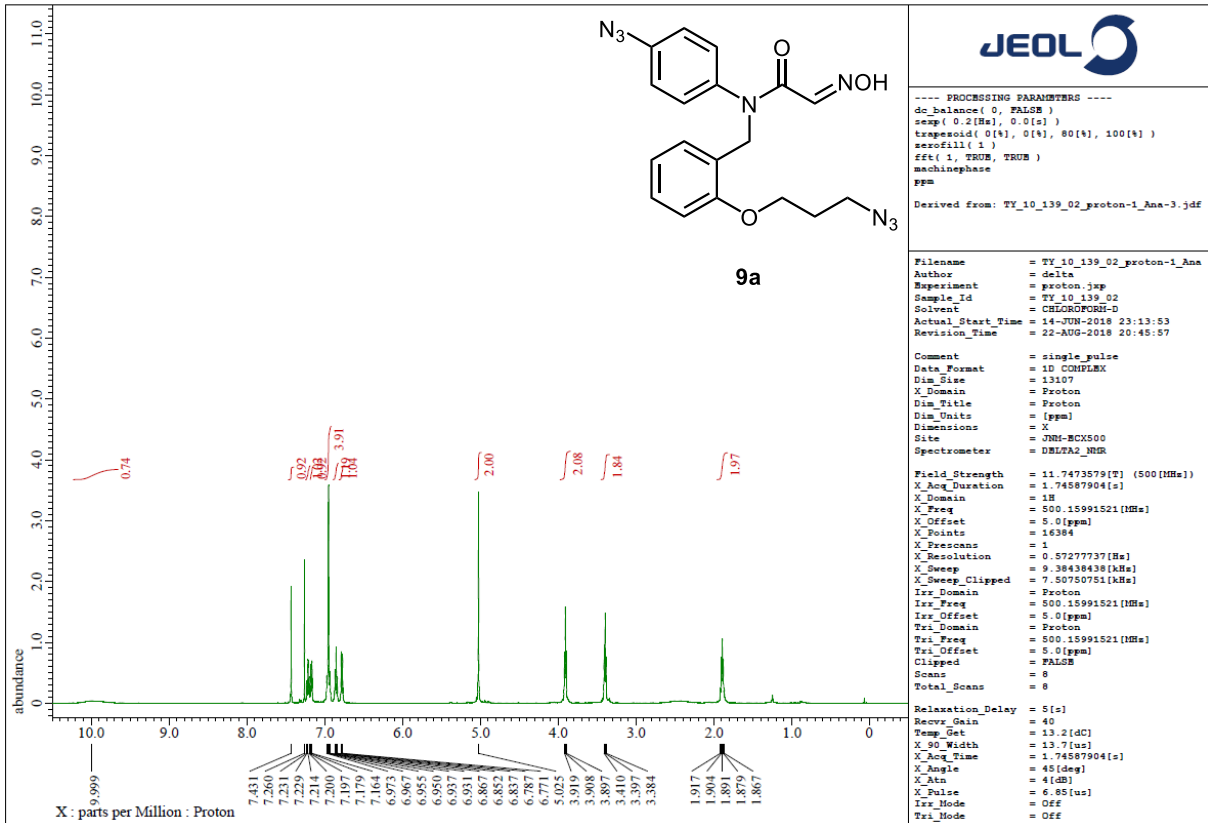
JEOL
 Solutions for Innovation

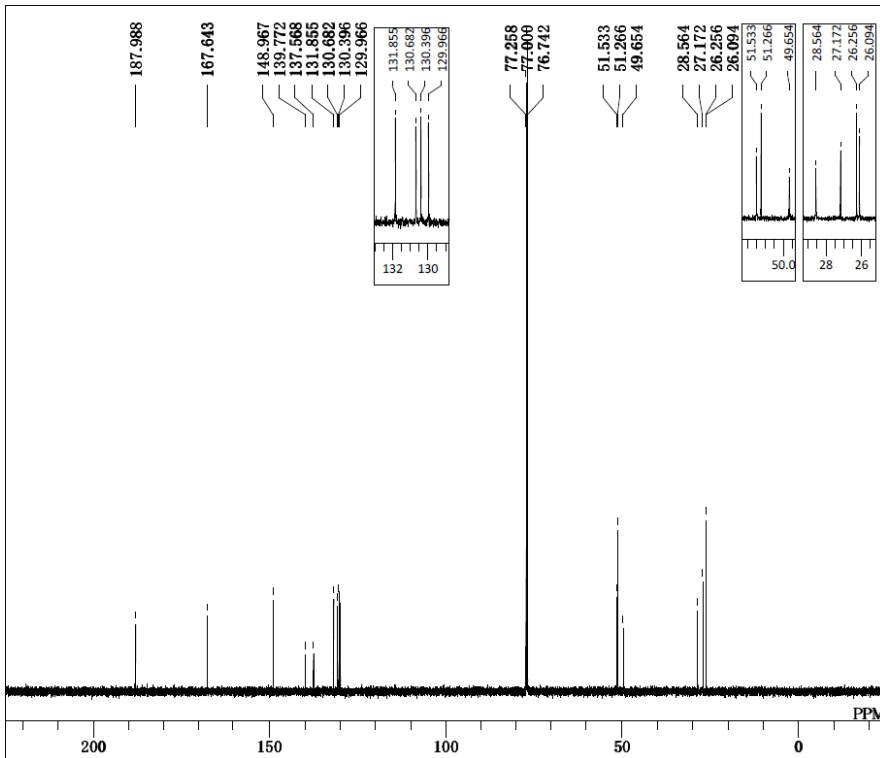
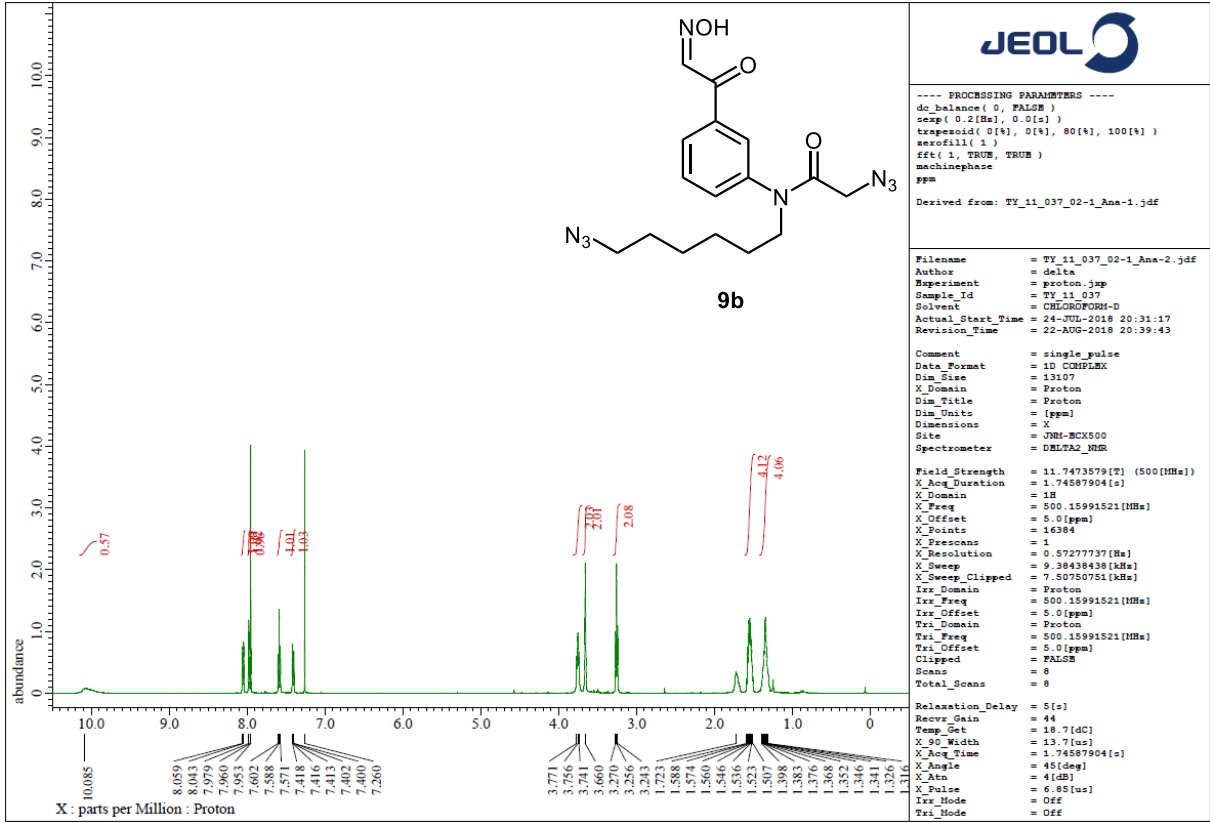
Filename = TU-02-145-2 180310_carbon-
 Author = delta
 Experiment = carbon_3pp
 Sample_Id = TU-02-145-2 180310
 Solvent = CHLOROFORM-D
 Creation_Time = 10-MAR-2018 20:20:31
 Revision_Time = 1-NOV-2018 15:17:50
 Current_Time = 1-NOV-2018 15:18:19

Comment = single pulse decoupled gat
 Data_Format = ID COMPLEX
 Dia_Size = 26214
 Dia_Title = Carbon13
 Dia_Units = [ppm]
 Dimensions = X
 Site = JNM-MCX500
 Spectrometer = DELTA2_NMR

Field_Strength = 11.7473579[T] (500[MHz])
 X_Acq_Duration = 0.83361792[s]
 X_Domain = 13C
 X_Freq = 125.76529768[MHz]
 X_Offset = 100[ppm]
 X_Points = 32768
 X_Prescans = 4
 X_Resolution = 1.19959034[Hz]
 X_Sweep = 39.3081761[kHz]
 X_Sweep_Clipped = 31.44654088[kHz]
 Ix1_Domain = Proton
 Ix1_Freq = 500.15991521[MHz]
 Ix1_Offset = 5.0[ppm]
 Clipped = FALSE
 Scans = 129
 Total_Scans = 129

Relaxation_Delay = 2[s]
 Recvry_Gain = 60
 Temp_Get = 13.4[dC]
 X_90_Width = 9.36[us]
 X_Acq_Time = 0.83361792[s]
 X_Angle = 30[deg]
 X_Attn = 3[dB]
 X_Pulse = 3.12[us]
 Ix1_Atn_Dec = 20.54[dB]
 Ix1_Atn_Noise = 20.54[dB]
 Ix1_Noise = WALZE
 Ix1_Pwidth = 92[us]
 Decoupling = TRUB
 Initial_Wait = 2[s]
 Noe = TRUB
 Noe_Time = 2[s]
 Repetition_Time = 2.83361792[s]

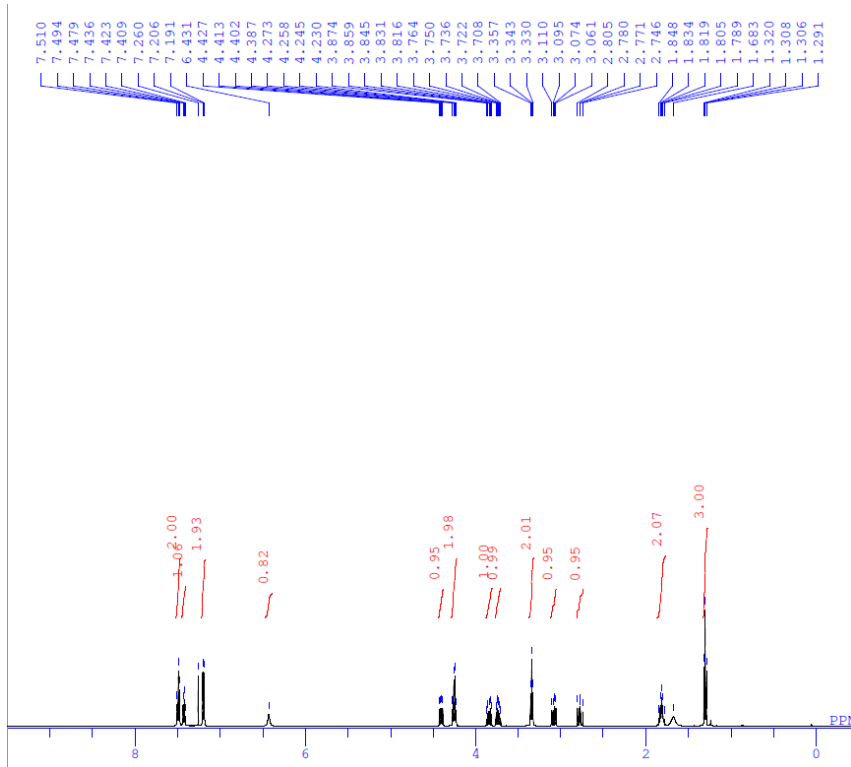




```

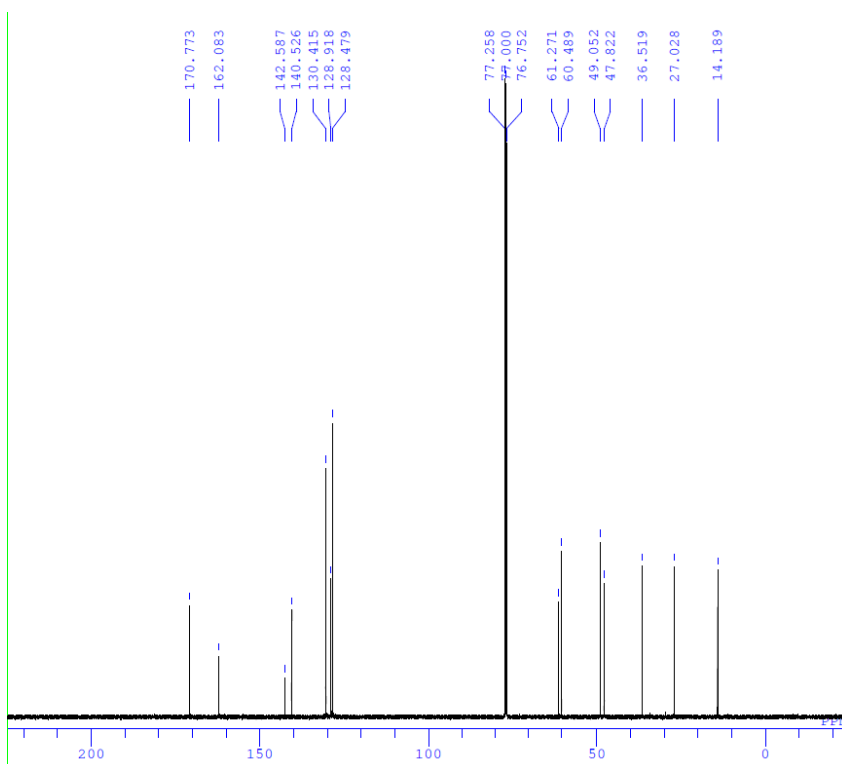
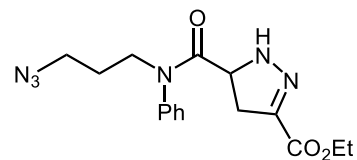
DFILE TU-02-092-5 180308_carbon-1-
COMNT single pulse decoupled gated NO
DATIM 2018-03-08 12:12:47
OBNUC 13C
OBXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 32767
FREQU 39308.18 Hz
SCANS 366
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IH 1H
CTEMP 15.3 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60

```



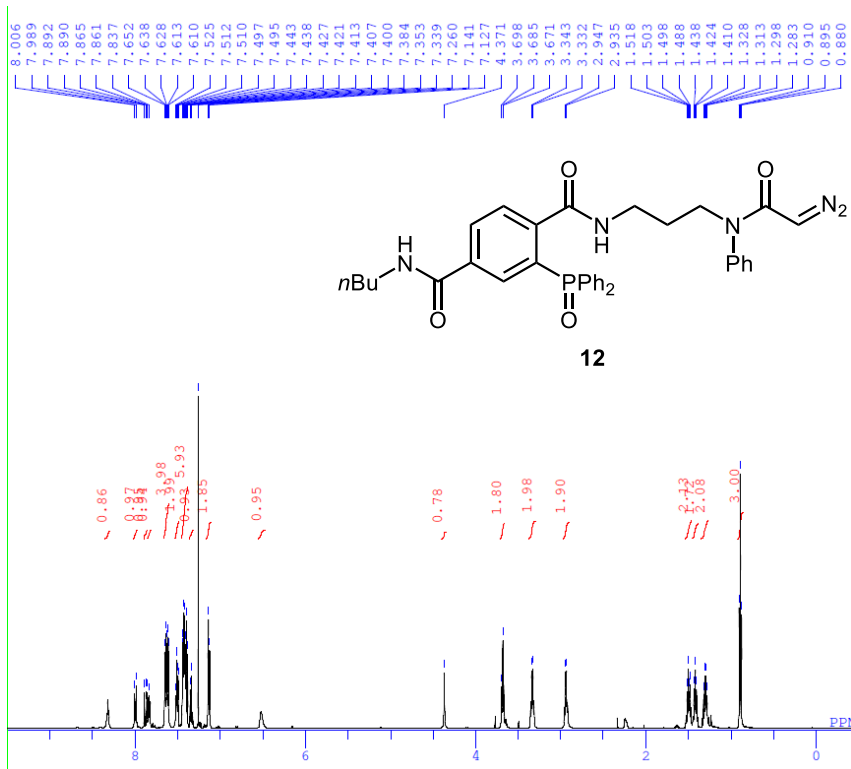
```

DFILE TY_09_064_01_proton-1-1.als
COMNT single_pulse
DATIM 2017-08-23 23:08:18
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 18.4 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 38
  
```



```

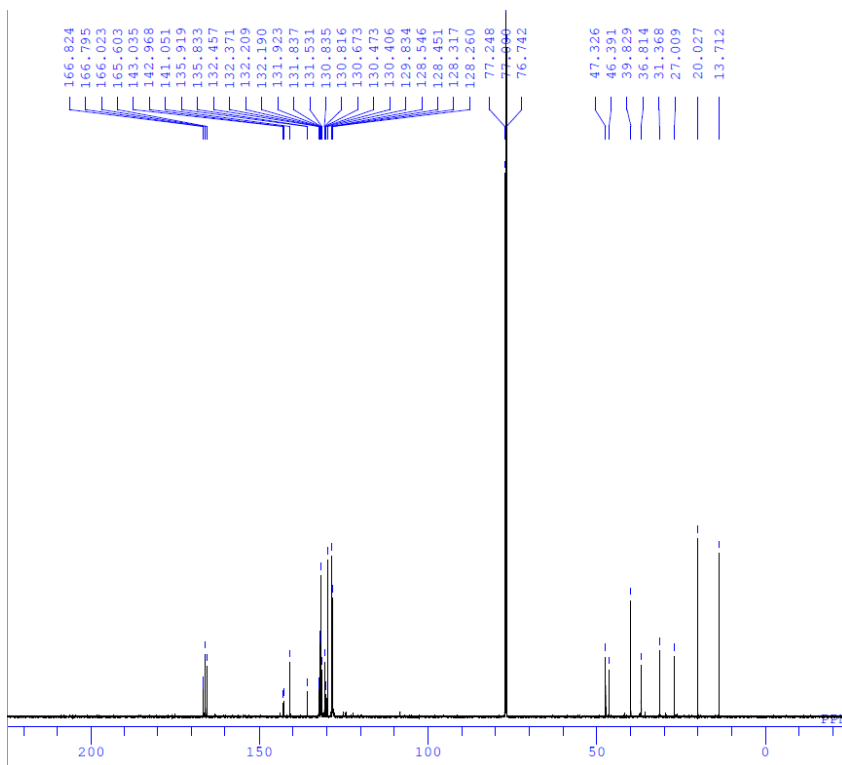
DFILE TY_09_064_01_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2017-08-23 23:10:02
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 8880
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 18.4 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
```



```

DFILE TY_09_095_04_proton-1-1.als
COMNT single_pulse
DATIM 2018-02-14 23:16:20
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 14.8 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 34

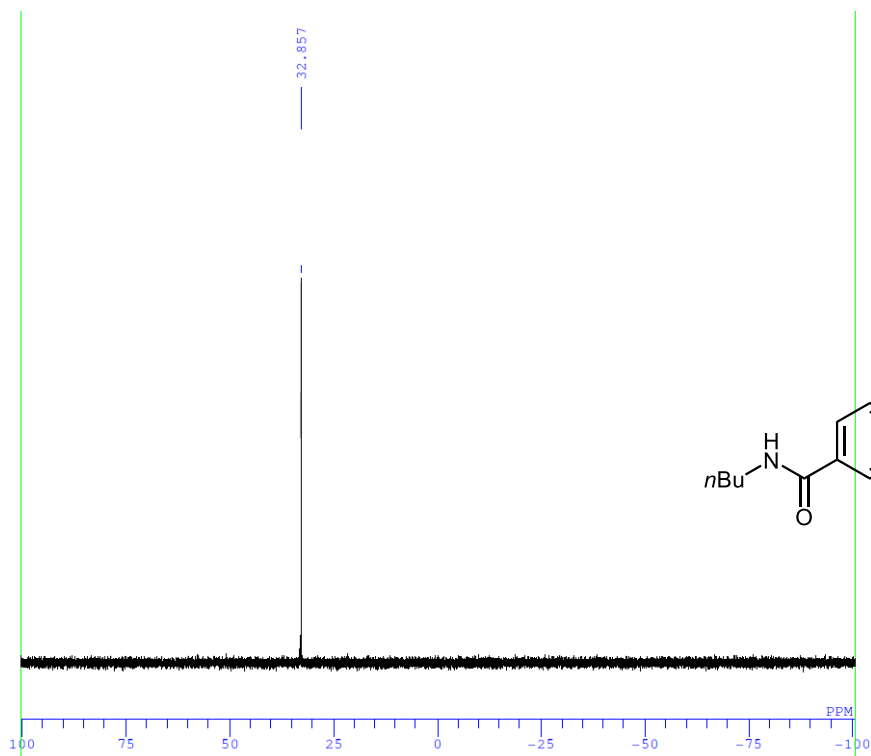
```



```

DFILE TY_09_095_04_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2018-02-14 23:18:56
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 8900
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 16.0 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 58

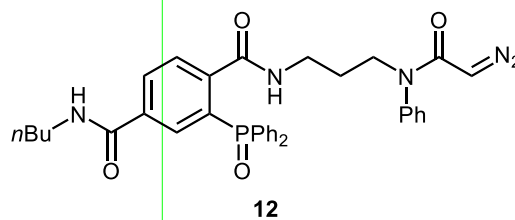
```

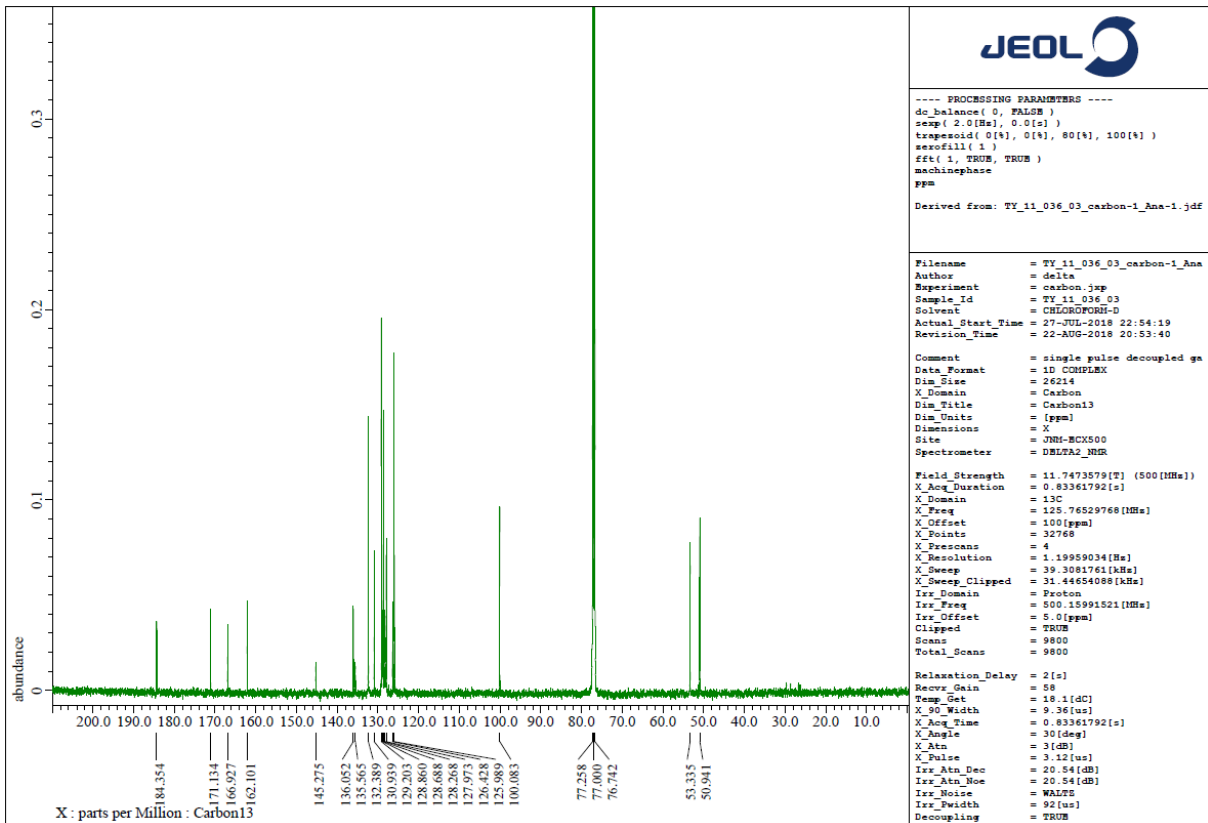
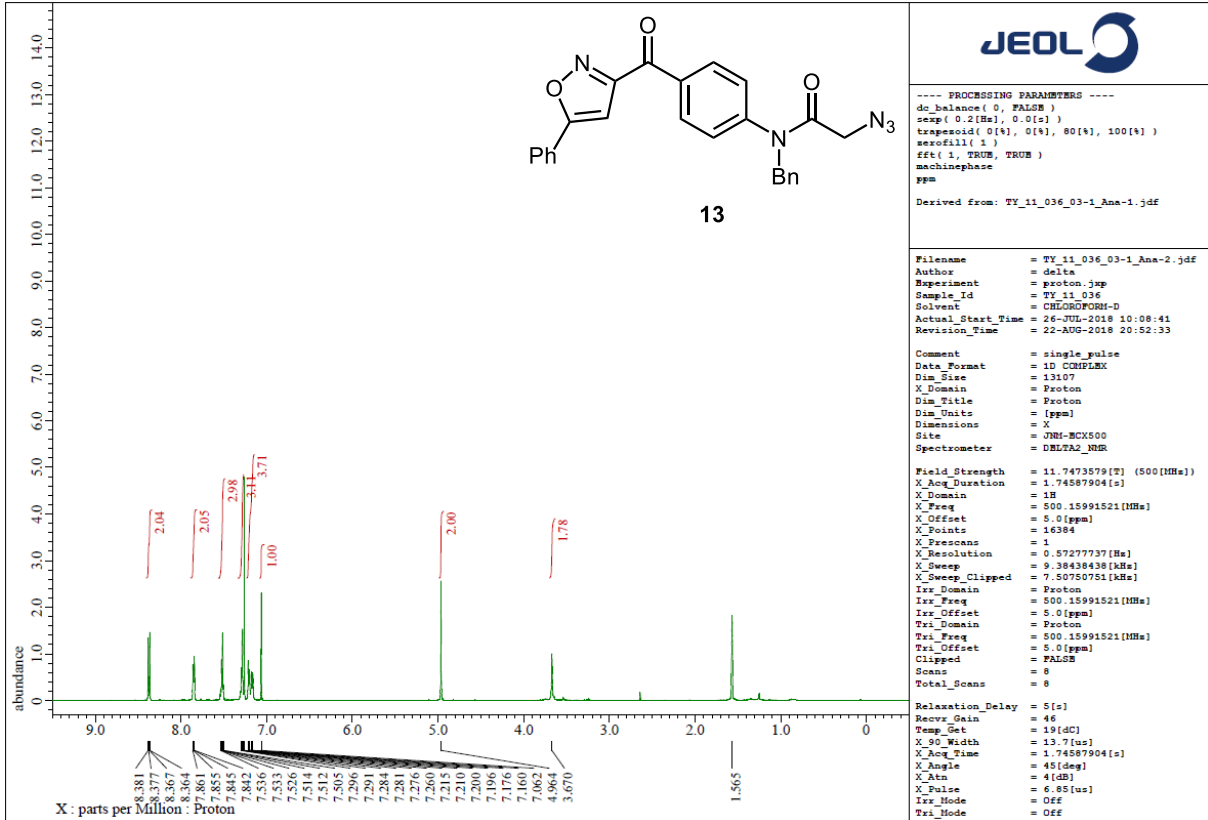



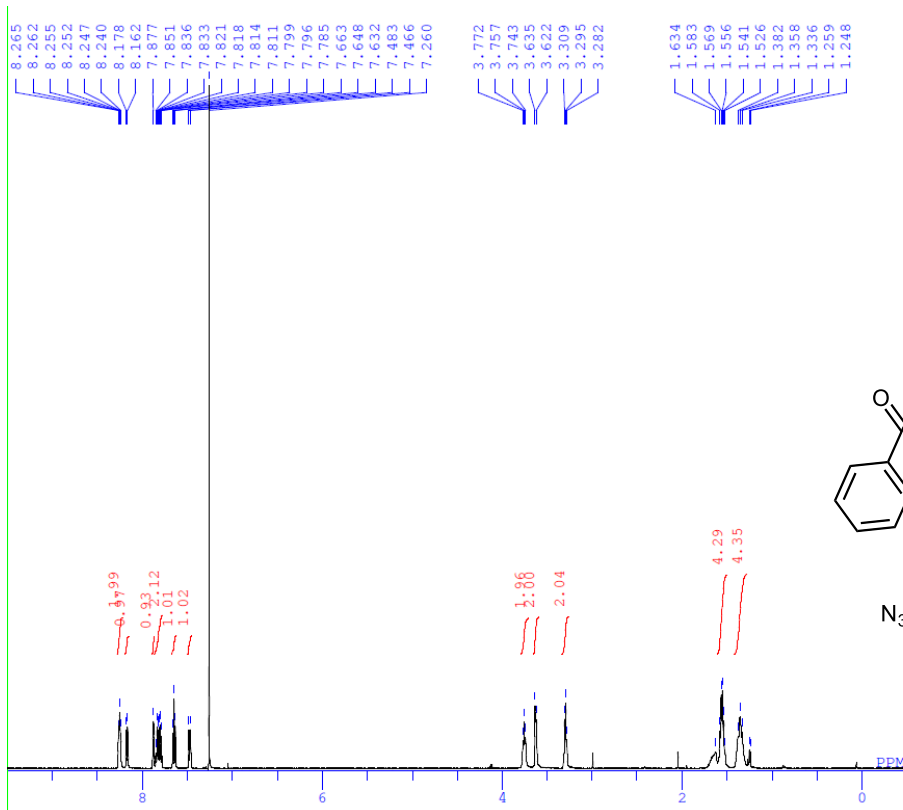
```

DFILE TY_09_095_04_phosphorus-1-1.
COMNT single pulse decoupled gated
DATIM 2018-02-22 15:57:34
OBNUC 31P
EXMOD carbon.jxp
OBFREQ 202.46 MHz
OBSET 8.31 KHz
OBFIN 0.75 Hz
POINT 26214
FREQU 40650.41 Hz
SCANS 10
ACQTM 0.6449 sec
PD 2.0000 sec
PW1 3.88 usec
IRNUC 1H
CTEMP 15.1 c
SLVNT C6D6
EXREF 0.00 ppm
BF 0.10 Hz
RGAIN 58

```

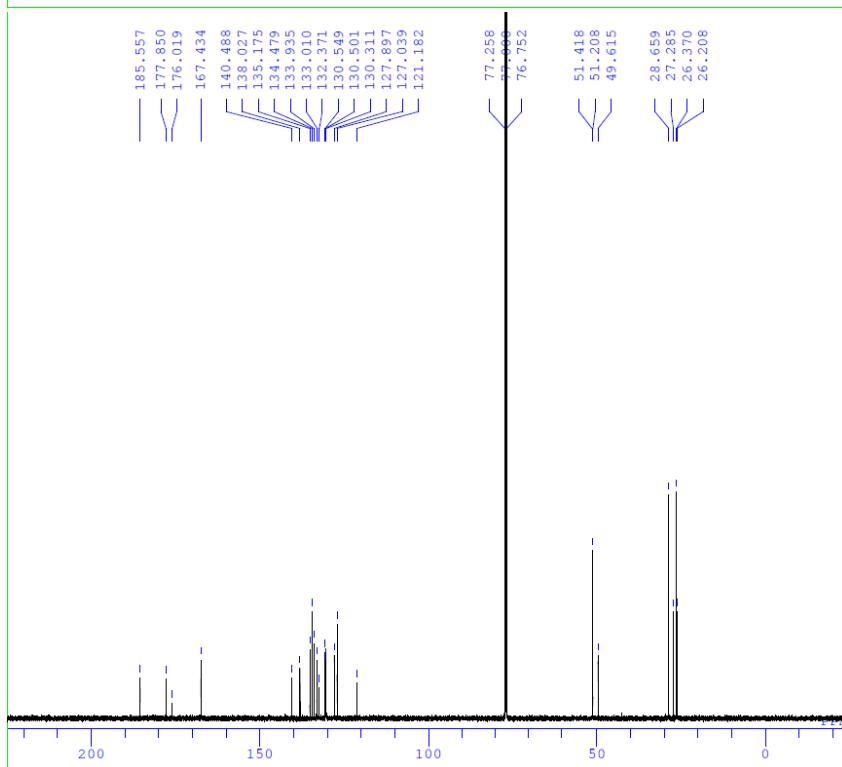
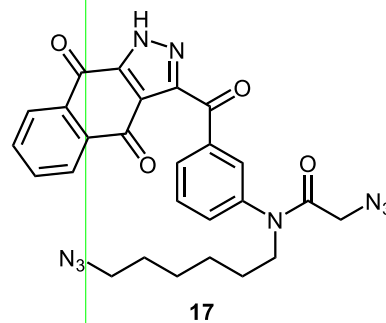






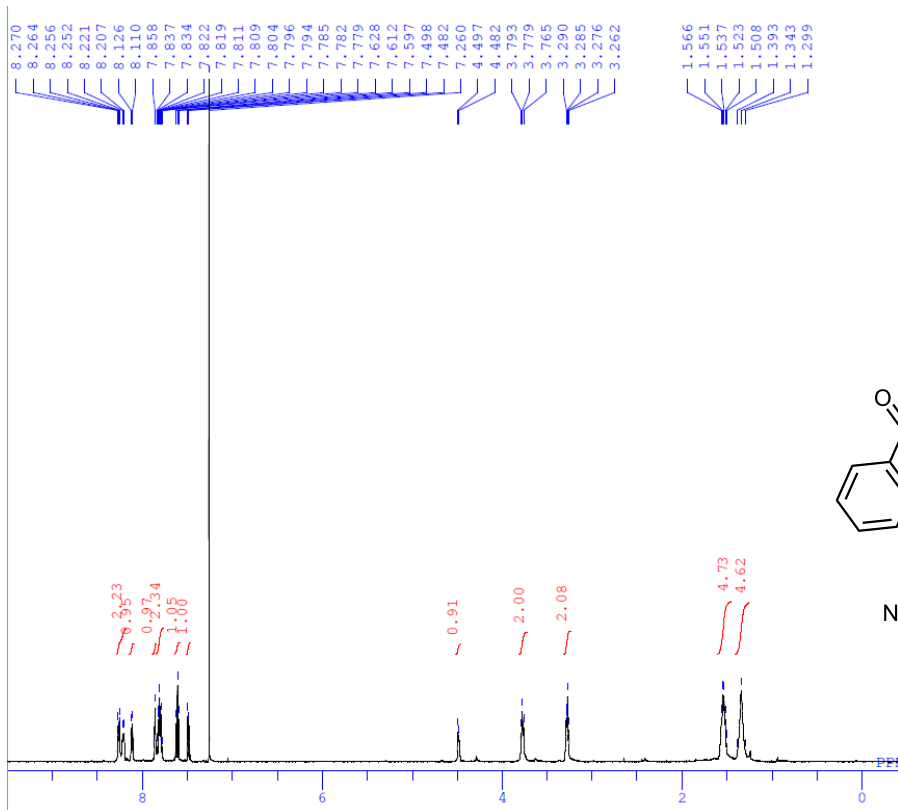
```

DFILE TY_10_033_01-1-1.als
COMNT desired
DATIM 2017-12-14 15:44:38
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 18.6 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 46
  
```



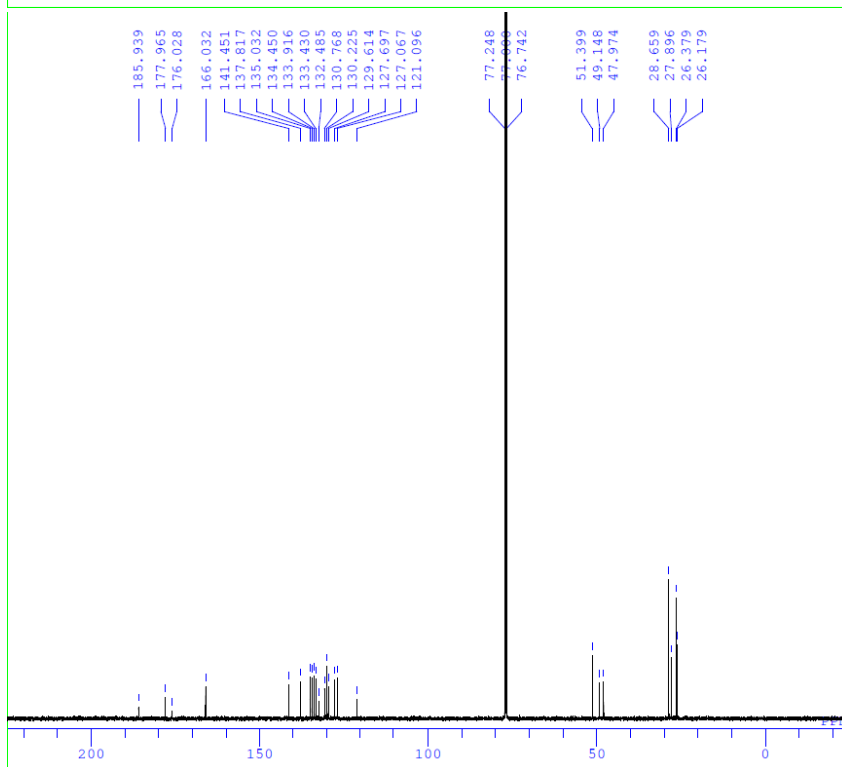
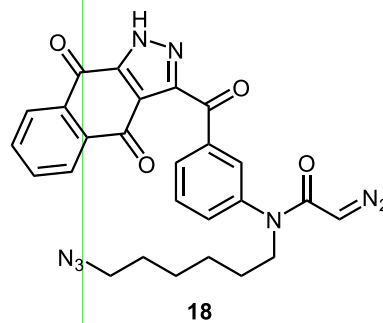
```

DFILE TY_10_033_01_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2017-12-18 23:19:47
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 8680
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 19.9 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
```



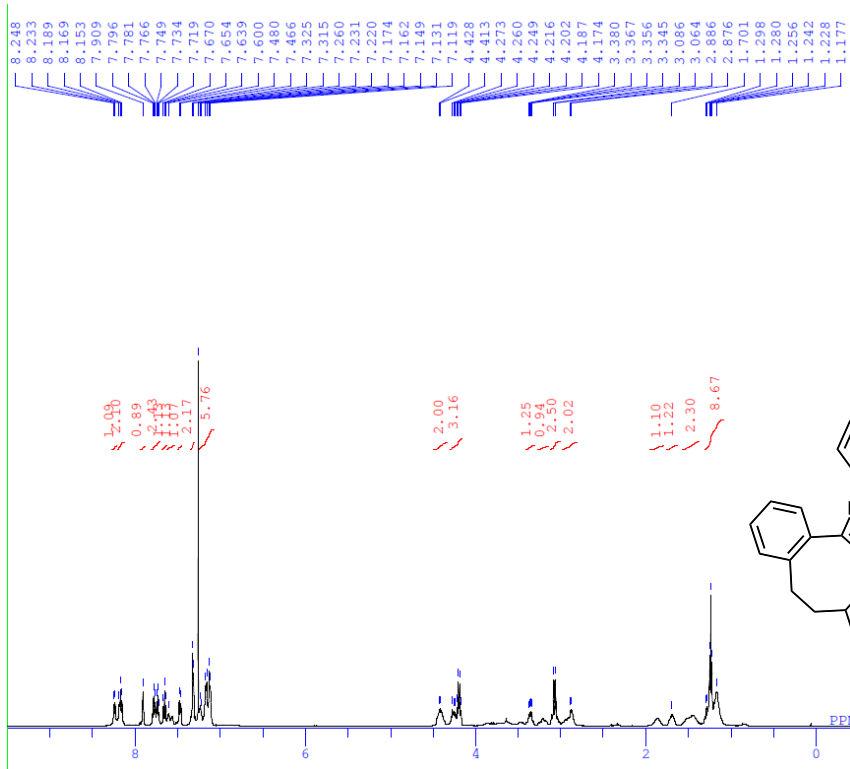
```

DFILE TY_10_051_01-1-1.als
COMNT diazo
DATIM 2018-02-01 21:17:19
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 17.6 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 46
  
```

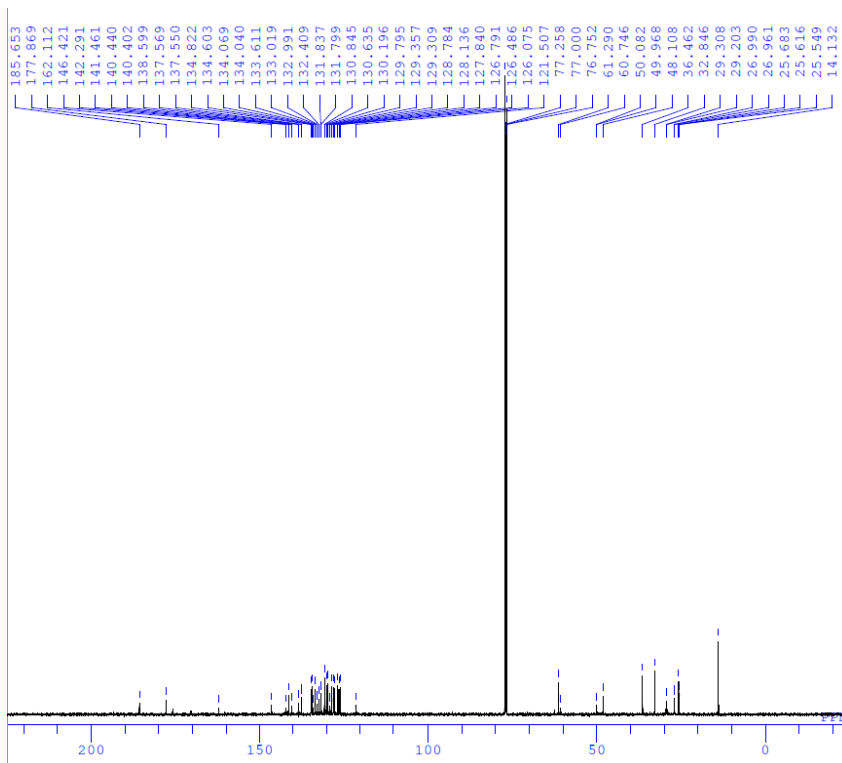
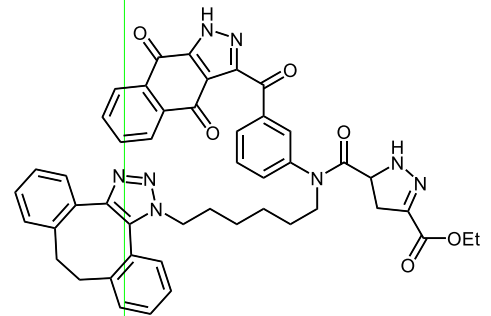


```

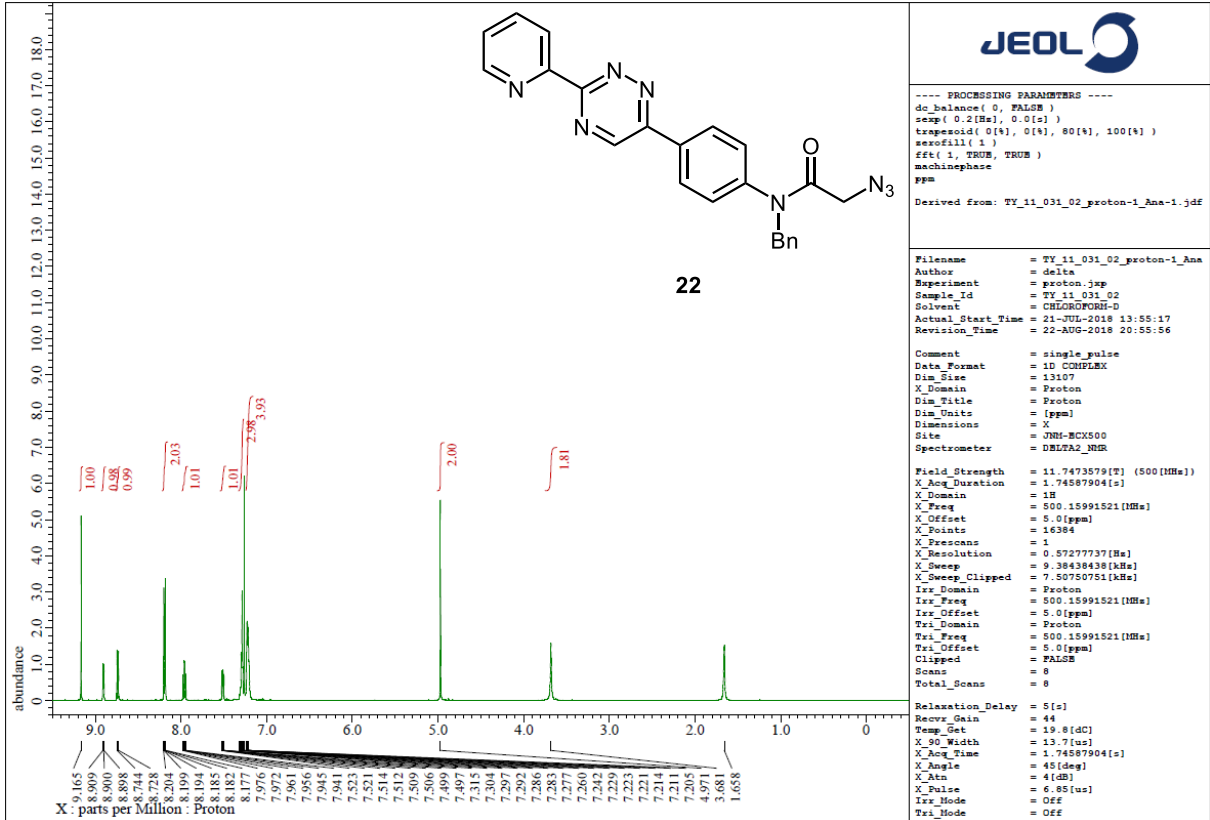
DFILE TY_10_051_01_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2018-02-05 23:15:43
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 8860
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 18.9 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 58
  
```



DFILE TY_10_061_02_proton-1-1.als
COMNT single_pulse
DATIM 2018-04-06 23:22:52
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 16.5 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 30



DFILE TY_10_061_02_carbon-1-1.als
COMNT single_pulse decoupled gated
DATIM 2018-04-06 23:24:27
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 8900
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 18.2 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60



JEOL

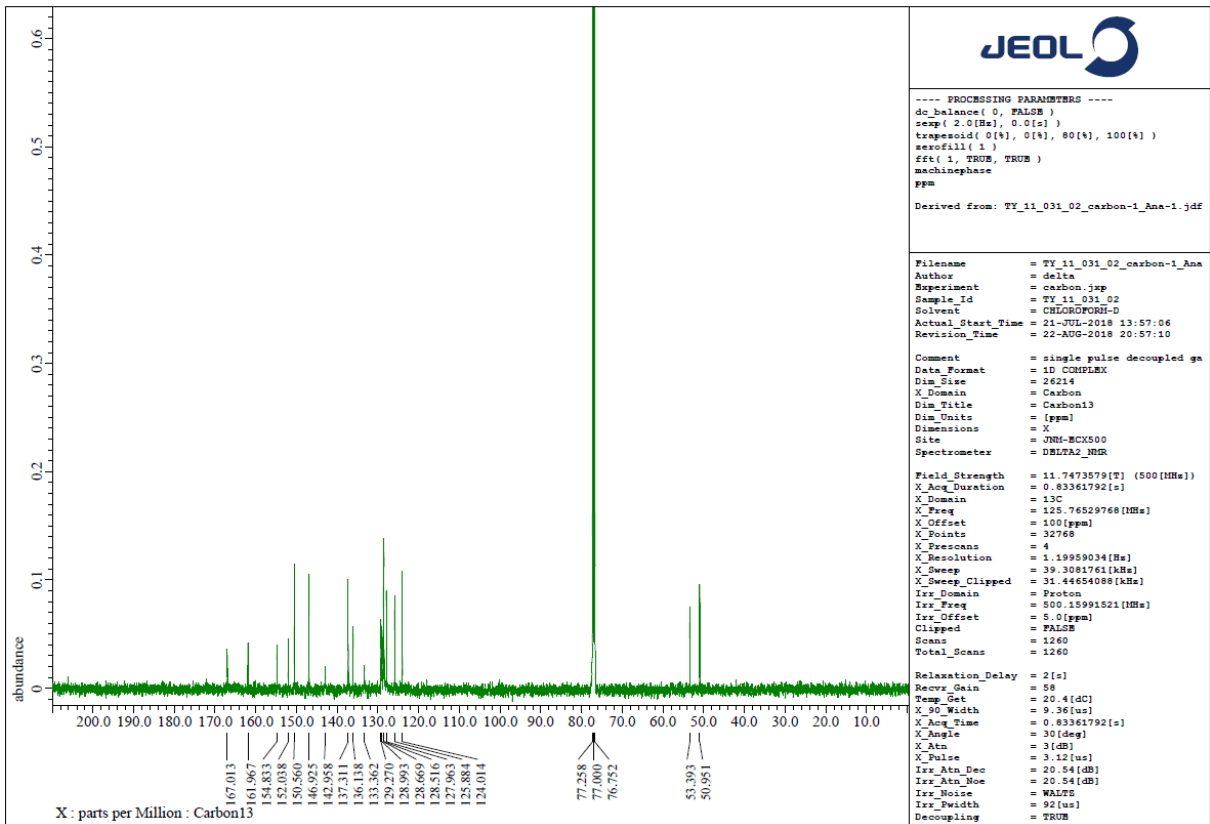
---- PROCESSING PARAMETERS ----
 dc_balance(0, FALSE)
 secp(0.2[Hz], 0.0[s])
 trapenoid(0[1], 0[1], 80[1], 100[1])
 zerofill(1)
 fft(1, TRUE, TRUE)
 machinephase
 ppm
 Derived from: TY_11_031_02_proton-1_Ana-1.jdf

Filename = TY_11_031_02_proton-1_Ana
 Author = delta
 Experiment = proton.jxp
 Sample_Id = TY_11_031_02
 Solvent = CHLOROFORM-D
 Actual_Start_Time = 21-JUL-2018 13:55:17
 Revision_Time = 22-AUG-2018 20:55:56

Comment = single_pulse
 Data_Format = 1D COMPLEX
 Dim_Size = 13107
 X_Domain = Proton
 Dim_File = Proton
 Dim_Units = [ppm]
 Dimensions = X
 Site = JNM-EX500
 Spectrometer = DELTA2_NMR

Field_Strength = 11.7473579[Hz] (500[MHz])
 X_Acq_Duration = 1.74587904[s]
 X_Domain = 1H
 X_Freq = 500.15991521[MHz]
 X_Offset = 5.0[ppm]
 X_Points = 16384
 X_Prescans = 1
 X_Resolution = 0.57277737[Hz]
 X_Sweep = 9.38438438[kHz]
 X_Sweep_Clippped = 7.50769751[kHz]
 Ixv_Domain = Proton
 Ixv_Freq = 500.15991521[MHz]
 Ixv_Offset = 5.0[ppm]
 Tx1_Domain = Proton
 Tx1_Freq = 500.15991521[MHz]
 Tx1_Offset = 5.0[ppm]
 Clipped = FALSE
 Scans = 8
 Total_Scans = 8

Relaxation_Delay = 5[s]
 Recvr_Gain = 44
 Temp_Get = 19.8[dC]
 X_90_Width = 13.7[us]
 X_Acq_Time = 1.74587904[s]
 X_Angle = 45[deg]
 X_Atn = 4[dB]
 X_Pulse = 6.85[us]
 Ixv_Mode = Off
 Tx1_Mode = Off



JEOL

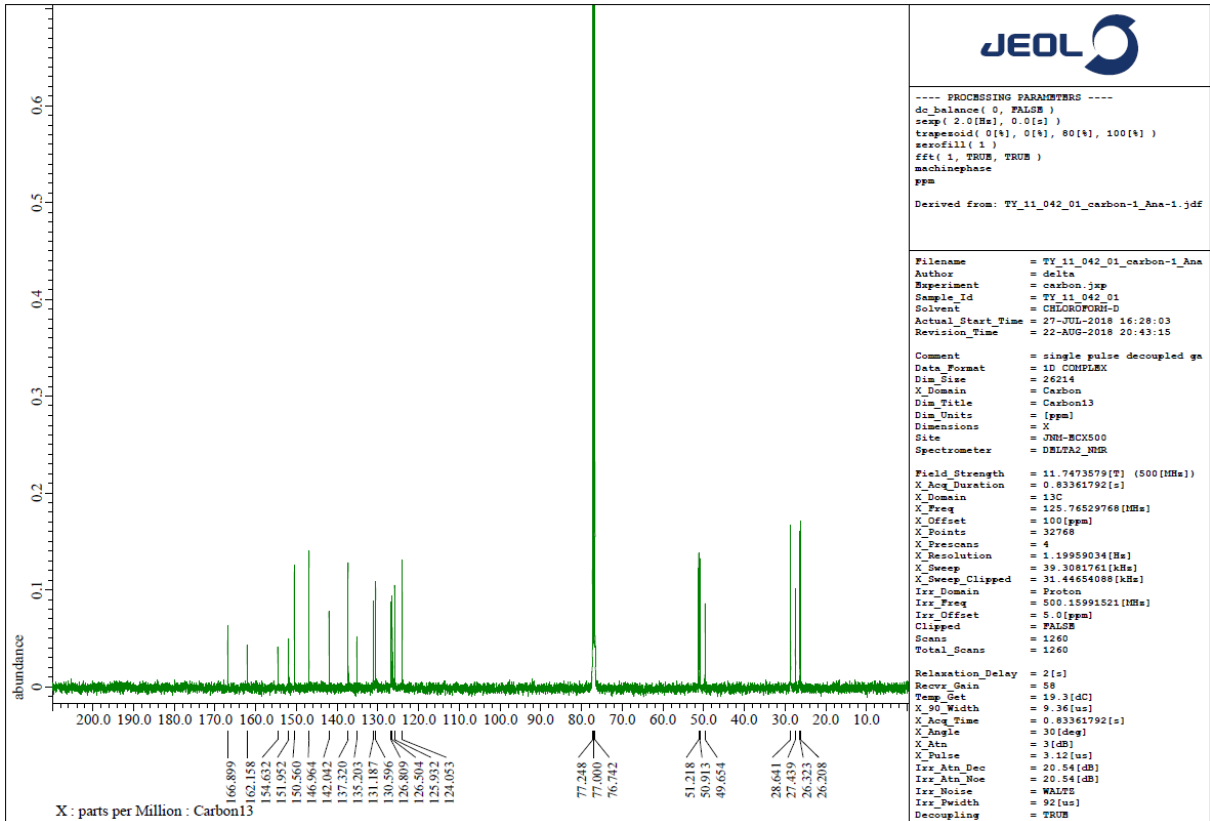
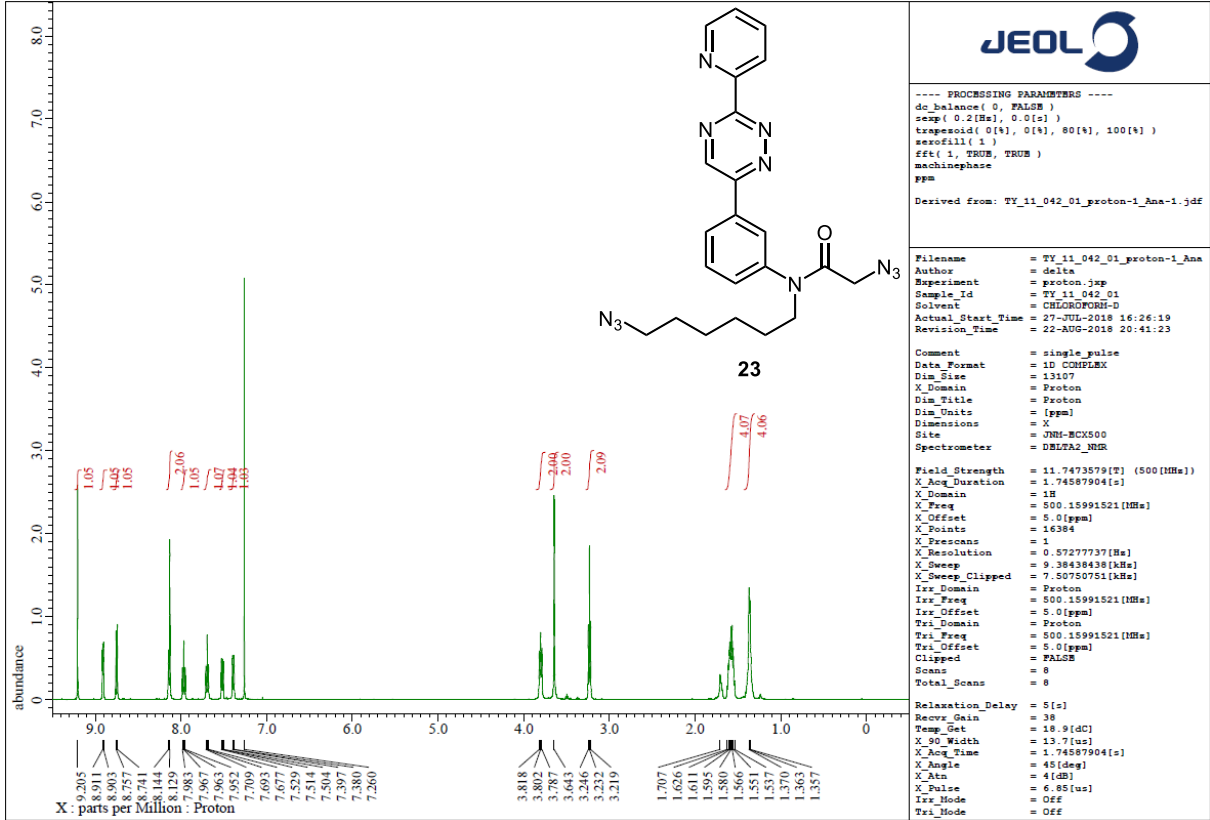
---- PROCESSING PARAMETERS ----
 dc_balance(0, FALSE)
 secp(2.0[Hz], 0.0[s])
 trapenoid(0[1], 0[1], 80[1], 100[1])
 zerofill(1)
 fft(1, TRUE, TRUE)
 machinephase
 ppm
 Derived from: TY_11_031_02_carbon-1_Ana-1.jdf

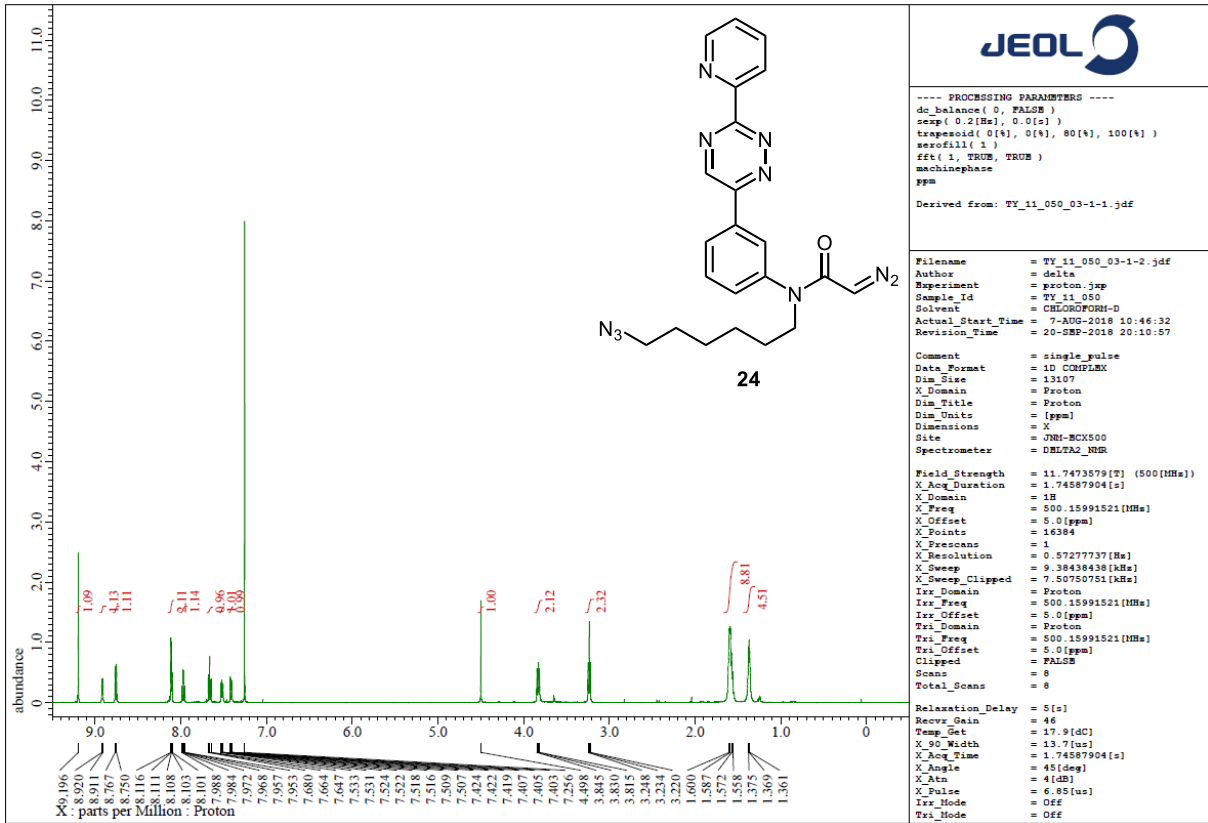
Filename = TY_11_031_02_carbon-1_Ana
 Author = delta
 Experiment = carbon.jxp
 Sample_Id = TY_11_031_02
 Solvent = CHLOROFORM-D
 Actual_Start_Time = 21-JUL-2018 13:57:06
 Revision_Time = 22-AUG-2018 20:57:10

Comment = single_pulse decoupled ga
 Data_Format = 1D COMPLEX
 Dim_Size = 26214
 X_Domain = Carbon
 Dim_File = Carbon13
 Dim_Units = [ppm]
 Dimensions = X
 Site = JNM-EX500
 Spectrometer = DELTA2_NMR

Field_Strength = 11.7473579[Hz] (500[MHz])
 X_Acq_Duration = 0.83361792[s]
 X_Domain = 13C
 X_Freq = 125.76529768[MHz]
 X_Offset = 100[ppm]
 X_Points = 32768
 X_Prescans = 4
 X_Resolution = 1.19959034[Hz]
 X_Sweep = 39.3081761[kHz]
 X_Sweep_Clippped = 31.49654088[kHz]
 Ixv_Domain = Proton
 Ixv_Freq = 500.15991521[MHz]
 Ixv_Offset = 5.0[ppm]
 Clipped = FALSE
 Scans = 1260
 Total_Scans = 1260

Relaxation_Delay = 2[s]
 Recvr_Gain = 58
 Temp_Get = 20.4[dC]
 X_90_Width = 9.36[us]
 X_Acq_Time = 0.83361792[s]
 X_Angle = 30[deg]
 X_Atn = 3[dB]
 X_Pulse = 3.12[us]
 Ixv_Atn_Dec = 20.54[dB]
 Ixv_Atn_Noc = 20.54[dB]
 Ixv_Mode = WALTZ
 Ixv_Width = 92[us]
 Decoupling = TRUB





JEOL

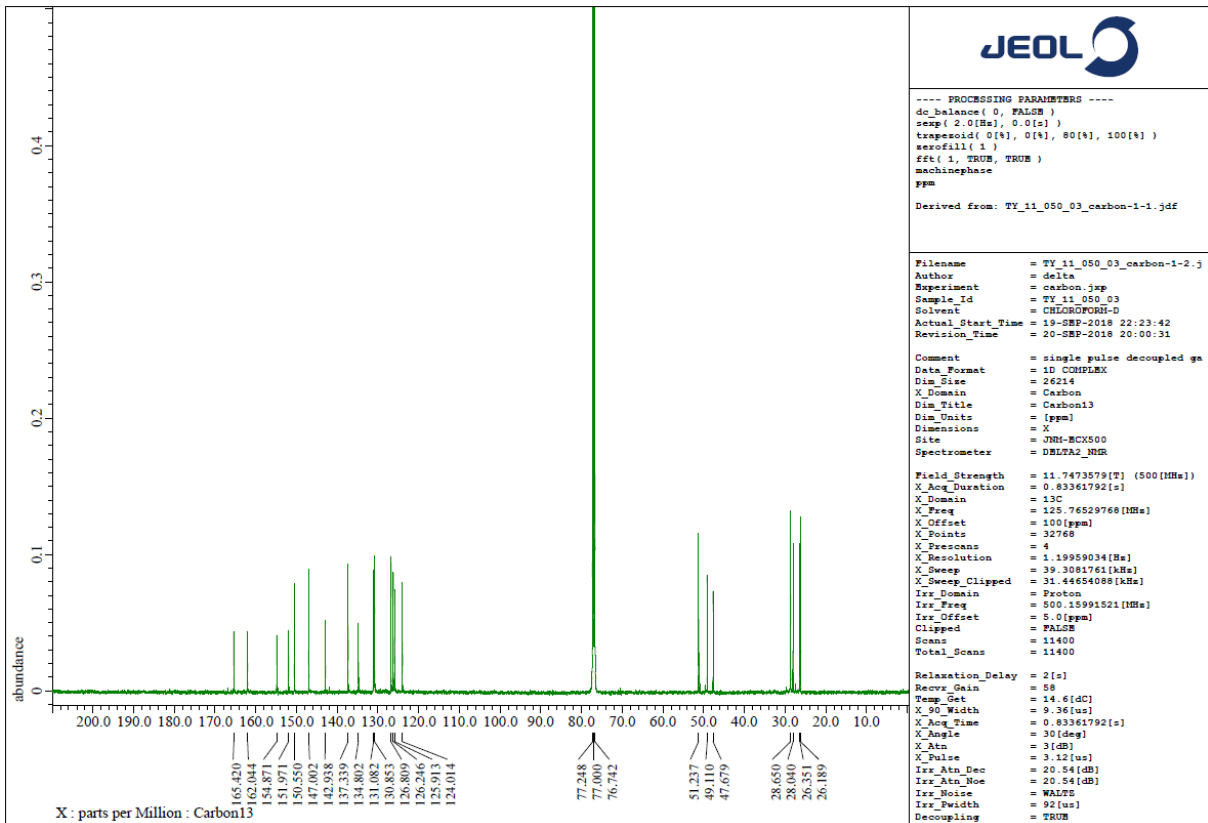
---- PROCESSING PARAMETERS ----
 dc_balance(0, FALSE)
 smp(0.2[Hz], 0.0[us])
 trapzoid(0[us], 0[us], 80[us], 100[us])
 zerofill(1)
 fft(1, TRUE, TRUE)
 machinephase
 ppm
 Derived from: TY_11_050_03-1-1.jdf

Filename = TY_11_050_03-1-2.jdf
 Author = delta
 Experiment = proton.jsp
 Sample_Id = TY_11_050
 Solvent = CHLOROFORM-D
 Actual_Start_Time = 7-SEP-2018 10:46:32
 Revision_Time = 20-SEP-2018 20:10:57

Comment = single_pulse
 Data_Format = 1D COMPLEX
 Dim_Size = 13107
 X_Domain = Proton
 Dim_Title = Proton
 Dim_Units = [ppm]
 Dimensions = X
 Site = JNM-EX500
 Spectrometer = DELTA2_NMR

Field_Strength = 11.7473579[Hz] (500[MHz])
 X_Acq_Duration = 1.74587904[s]
 X_Domain = 1H
 X_Freq = 500.15991521[MHz]
 X_Offset = 5.0[ppm]
 X_Points = 16384
 X_Prescans = 1
 X_Resolution = 0.57277737[Hz]
 X_Sweep = 9.38438438[kHz]
 X_Sweep_Clipped = 1.74587904[s]
 Ix_Domain = Proton
 Ix_Freq = 500.15991521[MHz]
 Ix_Offset = 5.0[ppm]
 Tx_Domain = Proton
 Tx_Freq = 500.15991521[MHz]
 Tx_Offset = 5.0[ppm]
 Clipped = FALSE
 Scans = 8
 Total_Scans = 8

Relaxation_Delay = 5[s]
 Recv_Gain = 46
 Temp_Get = 17.9[deg]
 X_90_Width = 13.7[us]
 X_Acq_Time = 1.74587904[s]
 X_Angle = 45[deg]
 X_Pulse = 4[us]
 X_Pulse = 6.85[us]
 Ix_Mode = Off
 Tx_Mode = Off



JEOL

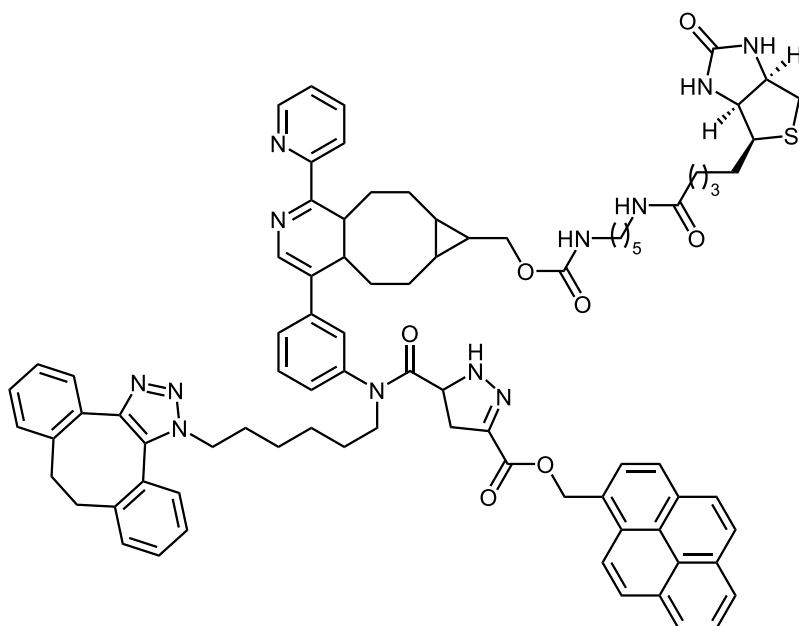
---- PROCESSING PARAMETERS ----
 dc_balance(0, FALSE)
 smp(2.0[Hz], 0.0[us])
 trapzoid(0[us], 0[us], 80[us], 100[us])
 zerofill(1)
 fft(1, TRUE, TRUE)
 machinephase
 ppm
 Derived from: TY_11_050_03_carbon-1-1.jdf

Filename = TY_11_050_03_carbon-1-2.j
 Author = delta
 Experiment = carbon.jsp
 Sample_Id = TY_11_050_03
 Solvent = CHLOROFORM-D
 Actual_Start_Time = 19-SEP-2018 22:23:42
 Revision_Time = 20-SEP-2018 20:00:31

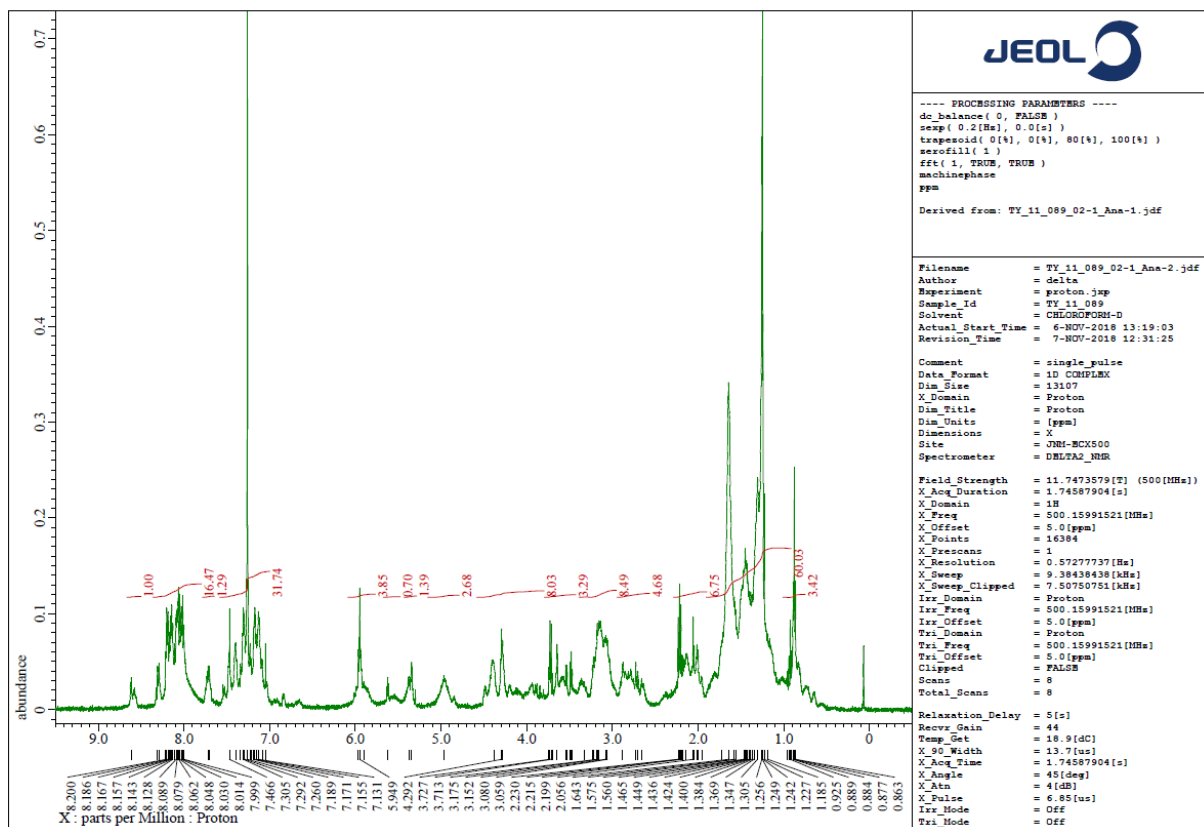
Comment = single pulse decoupled ga
 Data_Format = 1D COMPLEX
 Dim_Size = 26214
 X_Domain = Carbon
 Dim_Title = Carbon13
 Dim_Units = [ppm]
 Dimensions = X
 Site = JNM-EX500
 Spectrometer = DELTA2_NMR

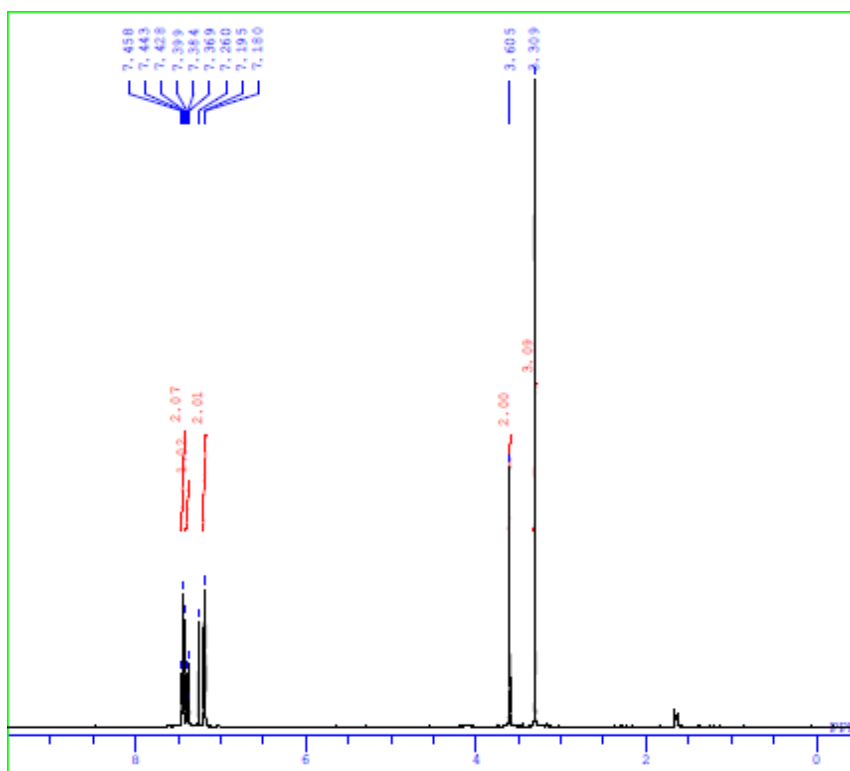
Field_Strength = 11.7473579[Hz] (500[MHz])
 X_Acq_Duration = 0.83361792[s]
 X_Domain = 13C
 X_Freq = 125.76529768[MHz]
 X_Offset = 100[ppm]
 X_Points = 32768
 X_Prescans = 4
 X_Resolution = 1.19959034[Hz]
 X_Sweep = 39.3081761[MHz]
 X_Sweep_Clipped = 31.44654088[kHz]
 Ix_Domain = Proton
 Ix_Freq = 500.15991521[MHz]
 Ix_Offset = 5.0[ppm]
 Clipped = FALSE
 Scans = 11400
 Total_Scans = 11400

Relaxation_Delay = 2[s]
 Recv_Gain = 58
 Temp_Get = 14.6[deg]
 X_90_Width = 9.36[us]
 X_Acq_Time = 0.83361792[s]
 X_Angle = 30[deg]
 X_Pulse = 3[us]
 X_Pulse = 3.12[us]
 Ix_Atn_Dec = 20.54[db]
 Ix_Atn_Noise = 20.54[db]
 Ix_Voice = WALTZ
 Ix_Width = 92[us]
 Decoupling = TRUE

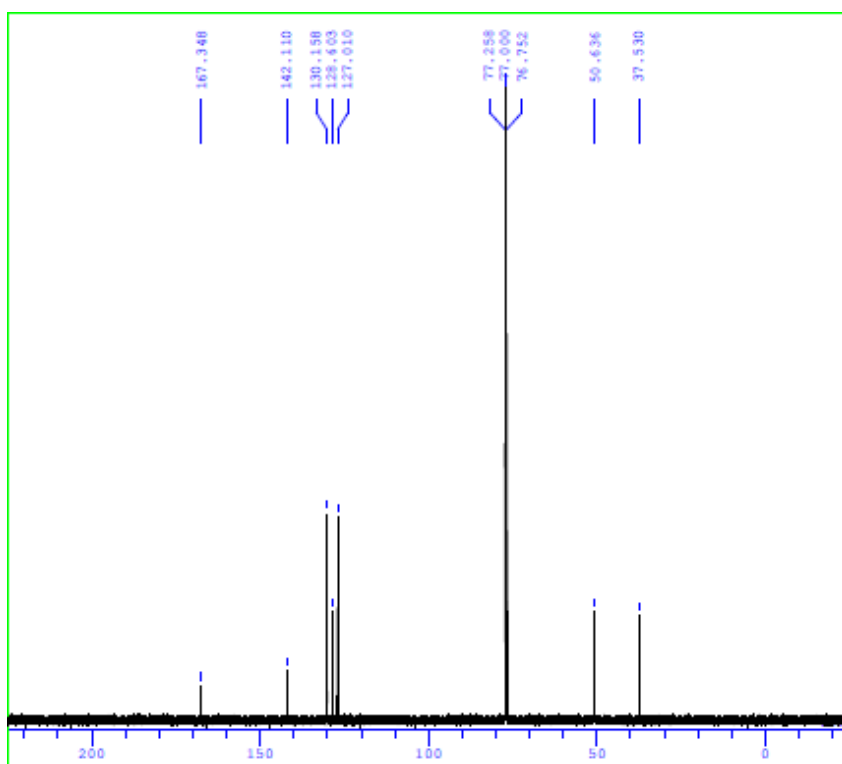
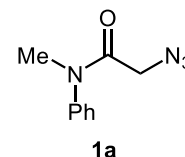


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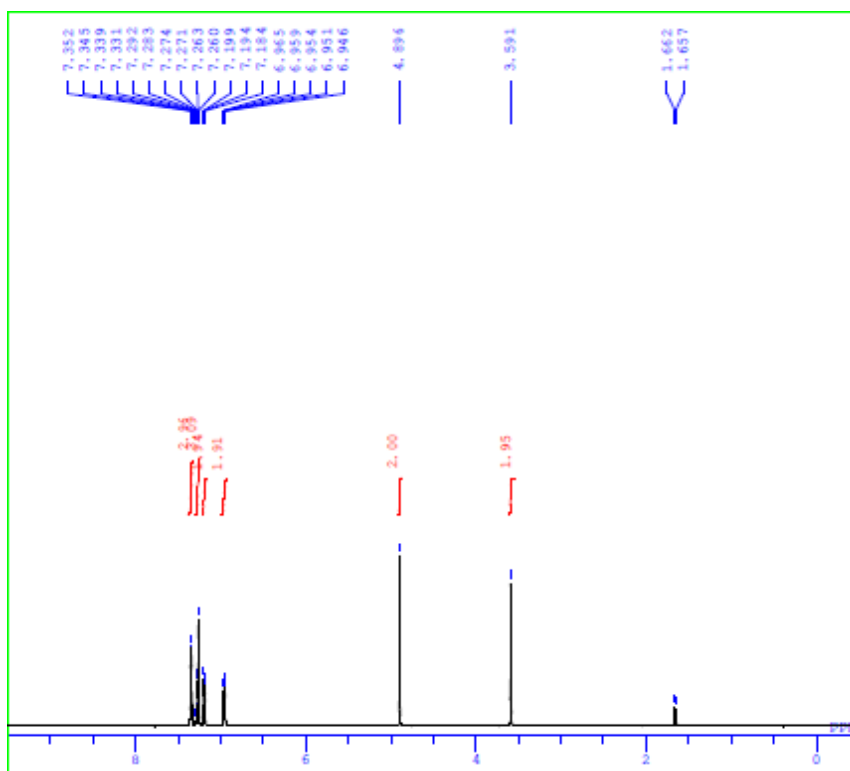




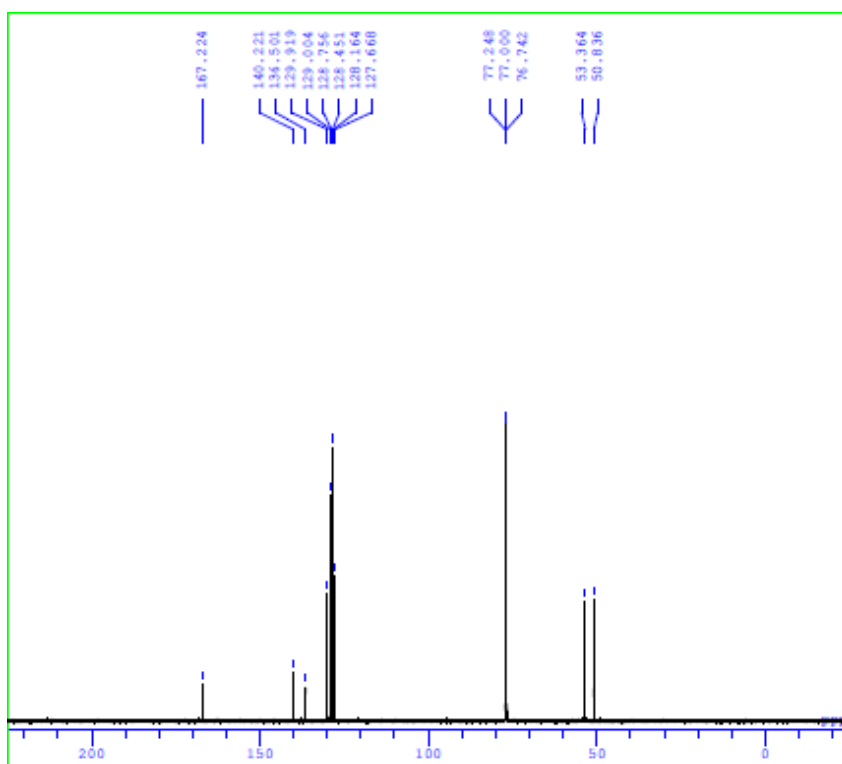
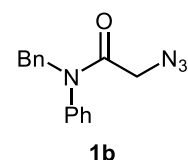
DFILE TY_07_048_02_proton-1-1.als
COMNT single_pulse
DATIM 2016-09-24 15:10:01
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PM1 6.85 usec
IRNUC 1H
CTEMP 18.7 c
SLVNT CDCl₃
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 40



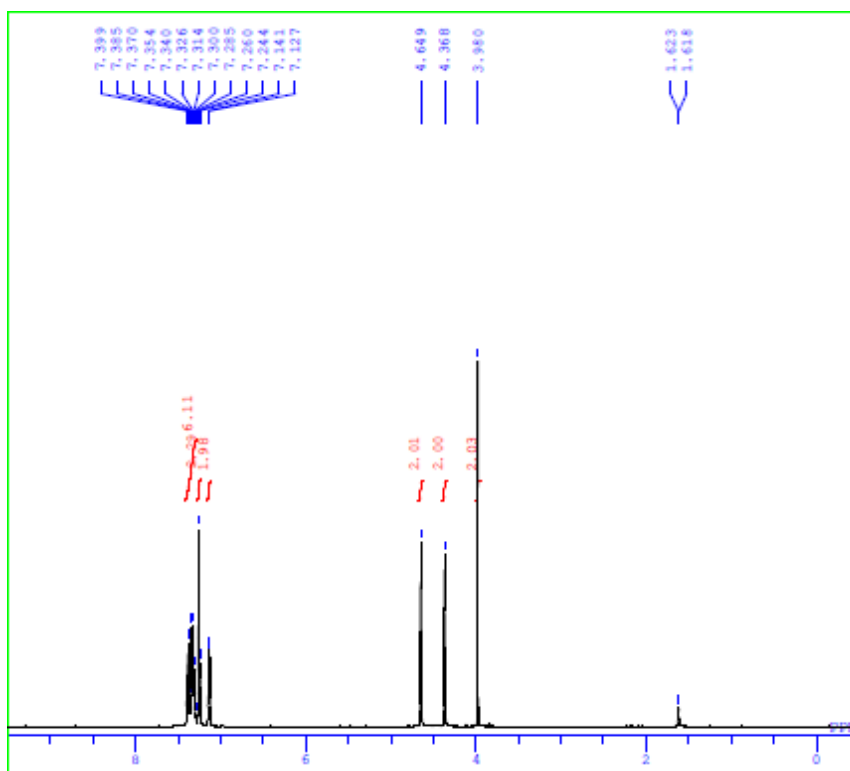
DFILE TY_07_048_02_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2016-09-24 15:11:50
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 620
ACQTM 0.8336 sec
PD 2.0000 sec
PM1 3.12 usec
IRNUC 1H
CTEMP 19.0 c
SLVNT CDCl₃
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60



DFILE TY_08_137_01_proton-1-1.als
 COMNT single_pulse
 DATIM 2017-07-01 10:05:41
 OBNUC 1H
 EXMOD proton.jxp
 OBFRQ 500.16 MHz
 OBSST 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PM1 6.85 usec
 IRNUC 1H
 CTEMP 16.8 c
 SLVNT CDCl3
 EXREF 7.26 ppm
 HF 0.10 Hz
 RGAIN 36

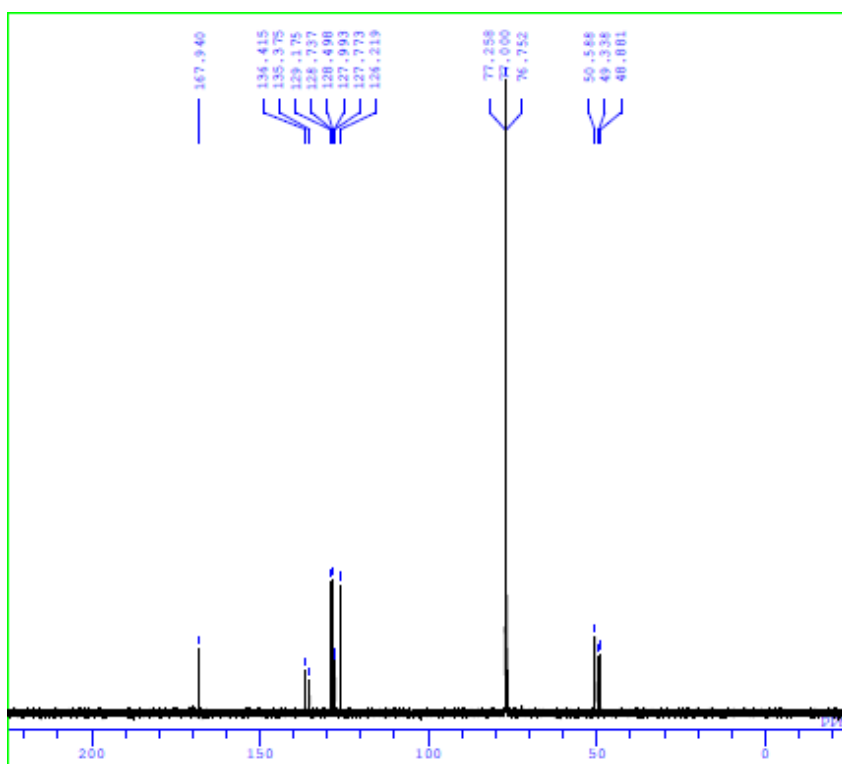
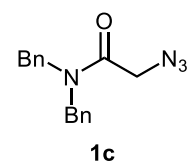


DFILE TY_08_137_01_carbon-1-1.als
 COMNT single pulse decoupled gated
 DATIM 2017-07-01 10:07:16
 OBNUC 13C
 EXMOD carbon.jxp
 OBFRQ 125.77 MHz
 OBSST 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 1260
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PM1 3.12 usec
 IRNUC 1H
 CTEMP 17.4 c
 SLVNT CDCl3
 EXREF 77.00 ppm
 HF 0.10 Hz
 RGAIN 60



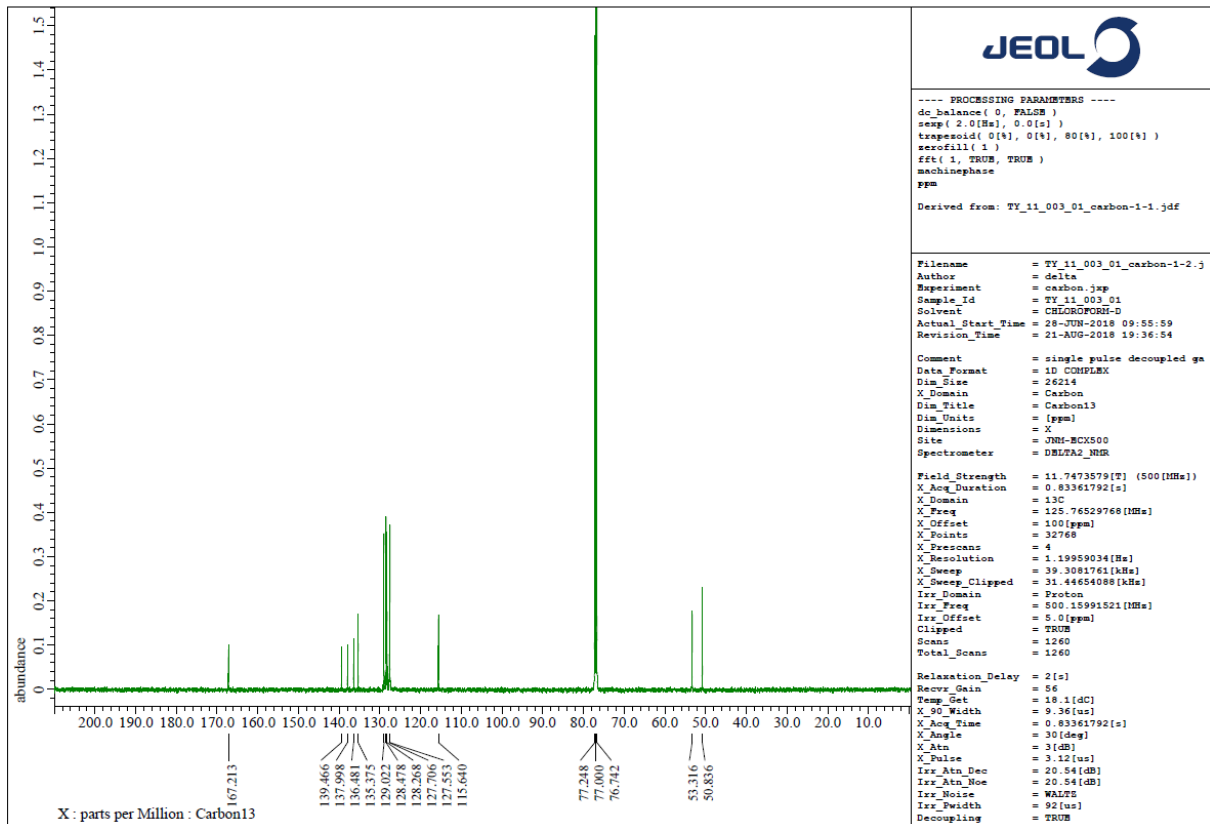
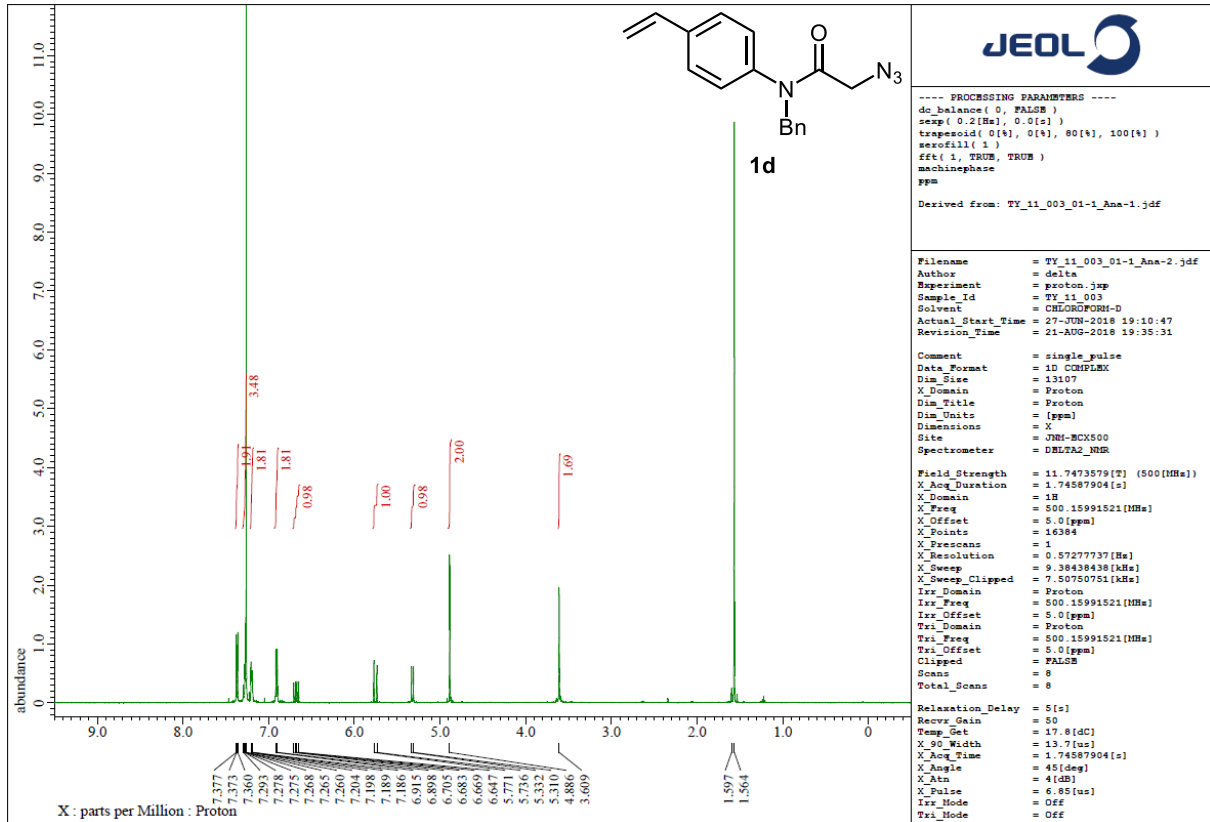
```

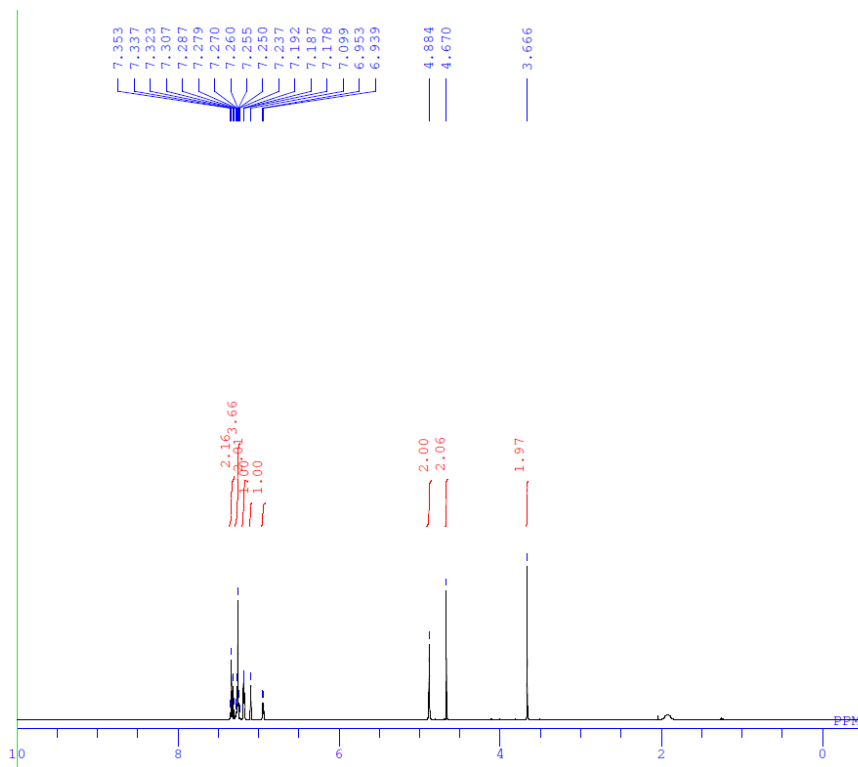
DFILE TY_07_106_02_proton-1-1.a1s
COMNT single_pulse
DATIM 2016-10-18 14:58:27
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PM1 6.85 usec
IRNUC 1H
CTEMP 18.2 c
SLVNT CDCl3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 38
  
```



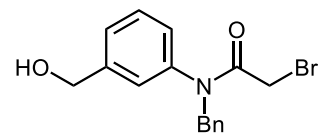
```

DFILE TY_07_106_02_carbon-1-1.a1s
COMNT single_pulse decoupled gated
DATIM 2016-10-18 15:00:36
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 620
ACQTM 0.8336 sec
PD 2.0000 sec
PM1 3.12 usec
IRNUC 1H
CTEMP 19.1 c
SLVNT CDCl3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 56
  
```

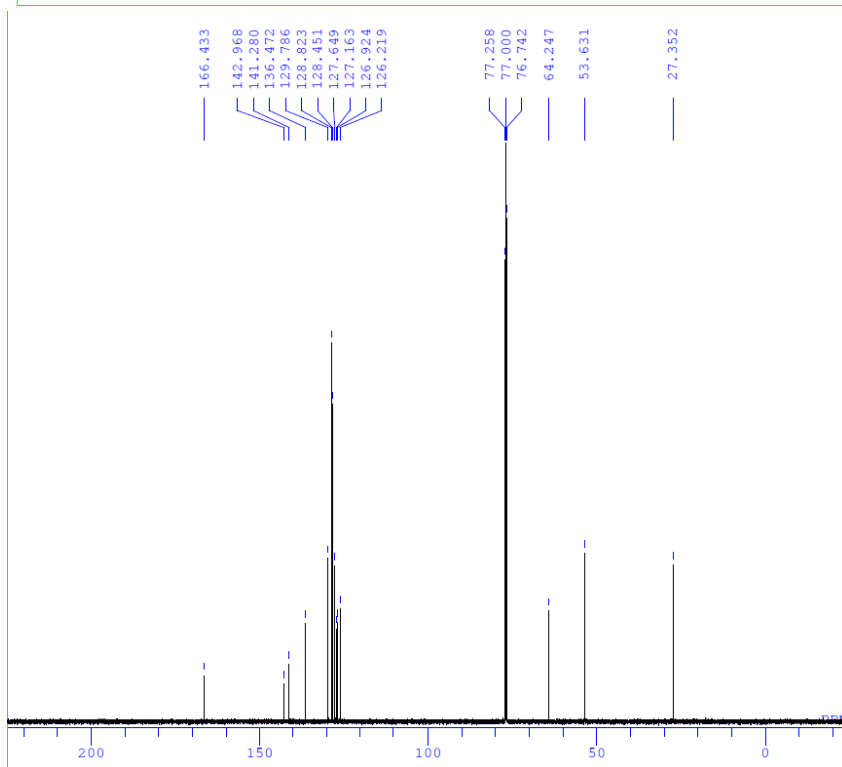




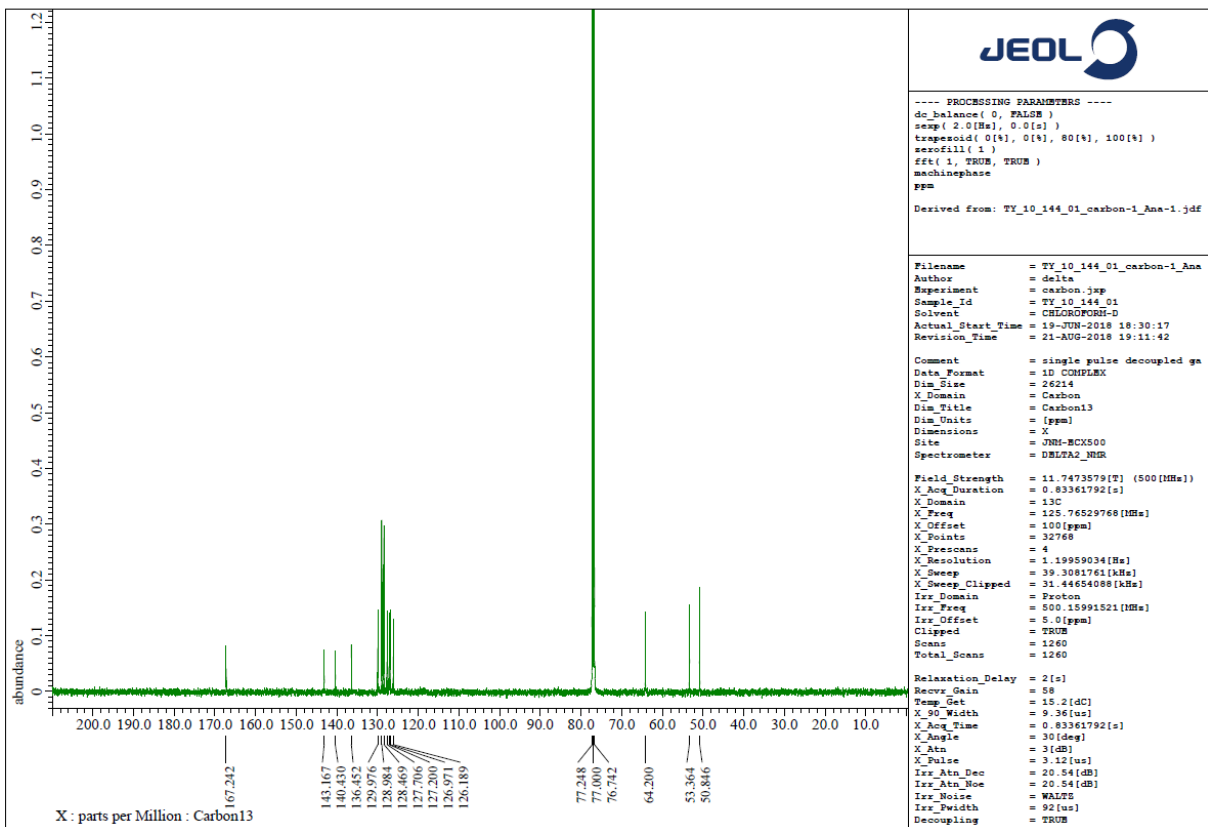
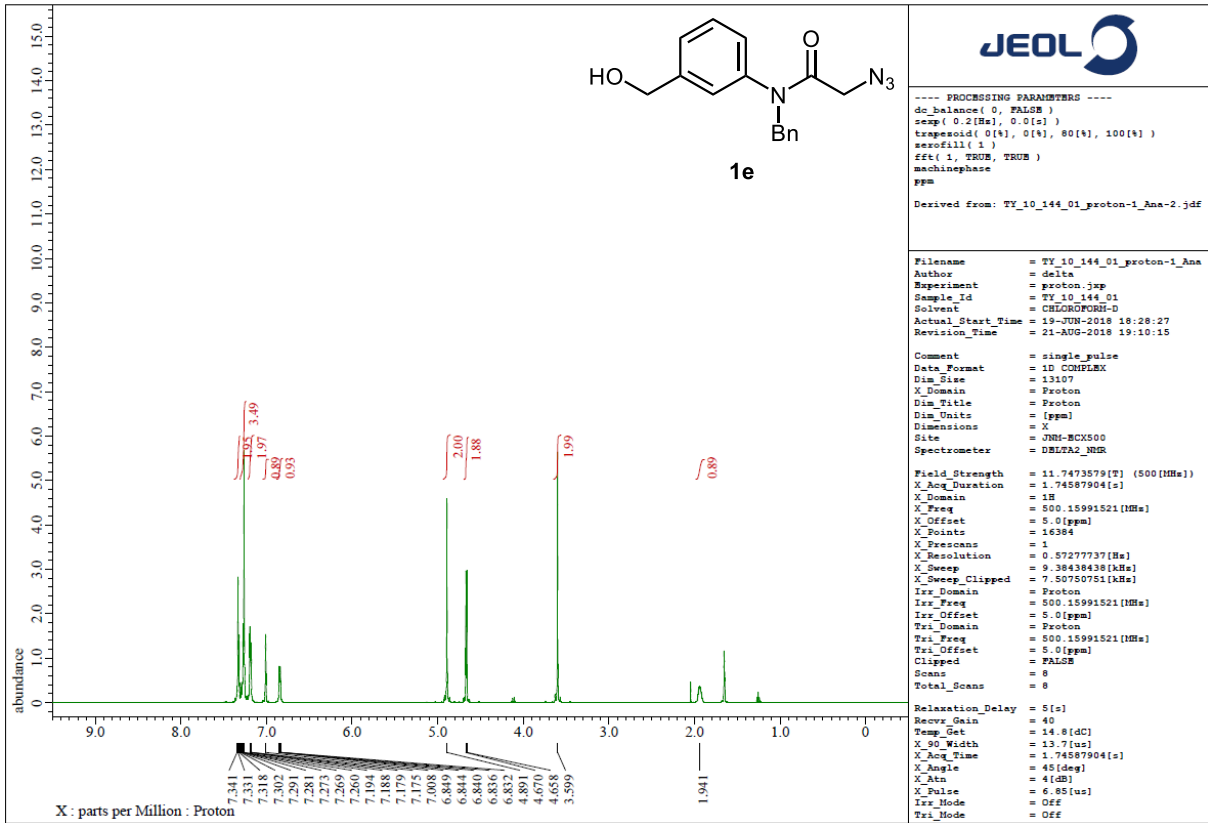
DFILE TY_09_099_01_proton-1-1.als
 COMNT single_pulse
 DATIM 2017-09-30 11:55:25
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 14.2 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 38

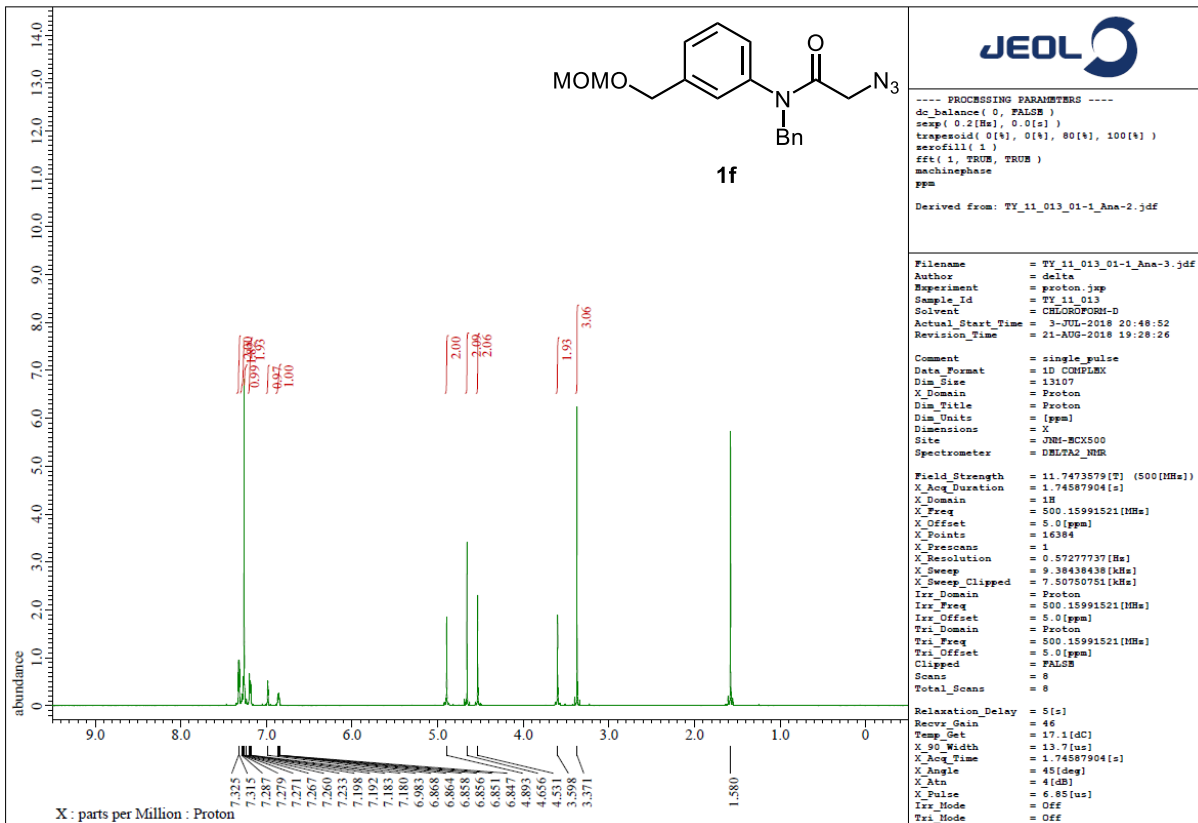


1e-1



DFILE TY_09_099_01_carbon-1-1.als
 COMNT single pulse decoupled gated
 DATIM 2017-09-30 11:57:05
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 1680
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 14.2 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 58





JEOL

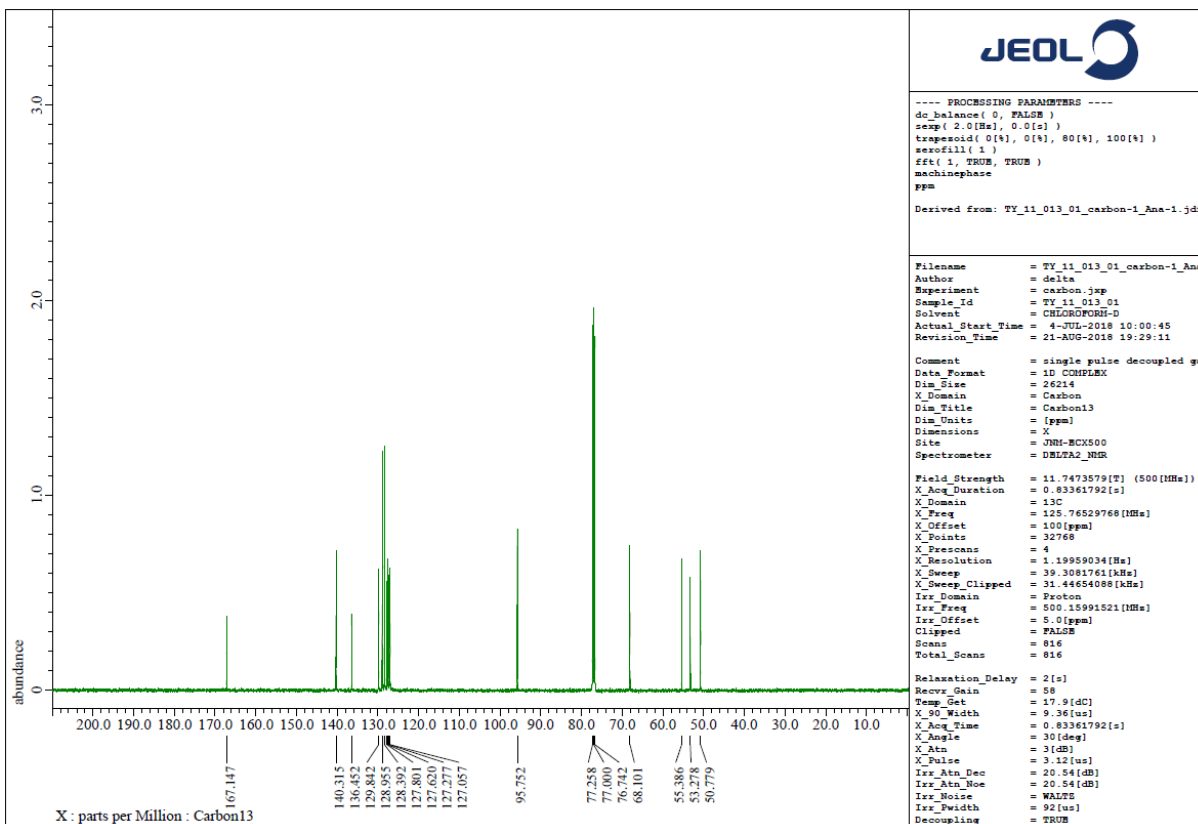
----- PROCESSING PARAMETERS -----
 dc_balance(0, FALSE)
 smp(0.2[Hz], 0.0[s])
 trapezoid(0[1], 0[1], 80[4], 100[4])
 zeroFill(1)
 fft(1, TRUE, TRUE)
 machinephase
 ppm
 Derived from: TY_11_013_01-1_Ana-2.jdf

Filename = TY_11_013_01-1_Ana-3.jdf
 Author = delta
 Experiment = proton.jsp
 Sample_Id = TY_11_013
 Solvent = CHLOROFORM-D
 Actual_Start_Time = 3-JUL-2018 20:48:52
 Revision_Time = 21-AUG-2018 19:28:26

Comment = single pulse
 Data_Format = 1D COMPLEX
 Dim_Size = 13107
 X_Domain = Proton
 Dim_Title = Proton
 Dim_Units = [ppm]
 Dimensions = X
 Site = JNM-EX500
 Spectrometer = DELTA2_NMR

Field_Strength = 11.7473579[T] (500[MHz])
 X_Acq_Duration = 1.74587904[s]
 X_Domain = 18
 X_Freq = 500.15991521[MHz]
 X_Offset = 5.0[ppm]
 X_Points = 16384
 X_Prescans = 1
 X_Resolution = 0.57277737[Hz]
 X_Sweep = 9.38438438[kHz]
 X_Sweep_Clipped = 7.50750751[kHz]
 Ixv_Domain = Proton
 Ixv_Freq = 500.15991521[MHz]
 Ixv_Offset = 5.0[ppm]
 Txv_Domain = Proton
 Txv_Freq = 500.15991521[MHz]
 Txv_Offset = 5.0[ppm]
 Clipped = FALSE
 Scans = 8
 Total_Scans = 8

Relaxation_Delay = 5[s]
 Recv_Gain = 46
 Temp_Get = 17.1[dC]
 X_90_Width = 13.7[us]
 X_Acq_Time = 1.74587904[s]
 X_Angle = 45[deg]
 X_Atn = 4[dB]
 X_Pulse = 6.85[us]
 Ixv_Mode = Off
 Txv_Mode = Off



JEOL

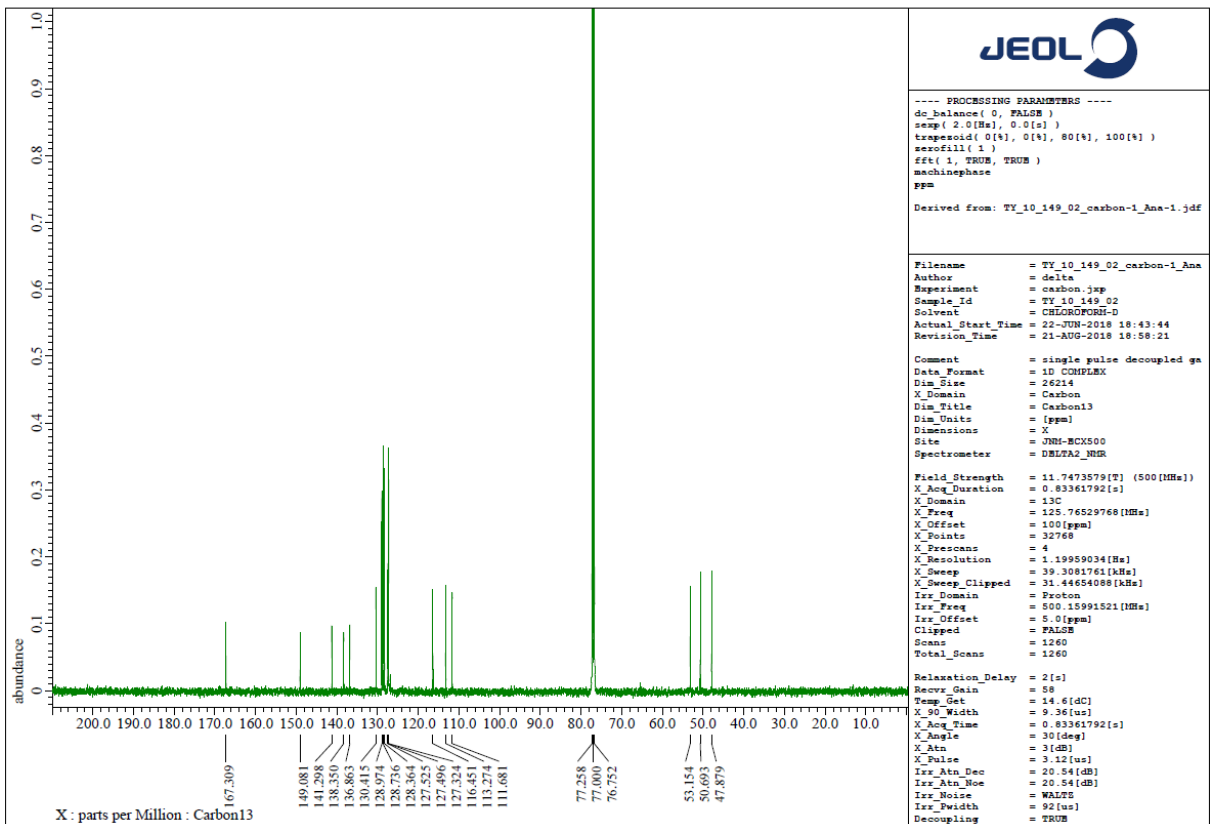
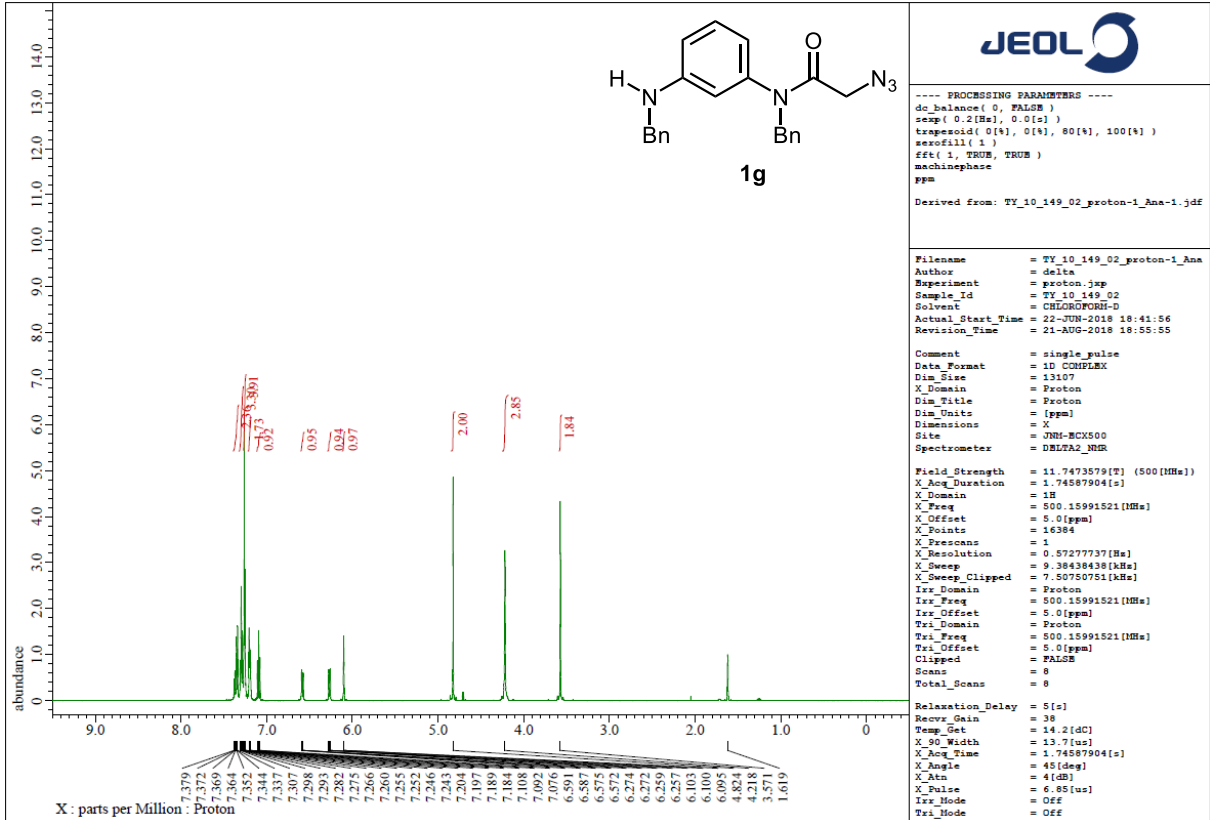
----- PROCESSING PARAMETERS -----
 dc_balance(0, FALSE)
 smp(2.0[Hz], 0.0[s])
 trapezoid(0[1], 0[1], 80[4], 100[4])
 zeroFill(1)
 fft(1, TRUE, TRUE)
 machinephase
 ppm
 Derived from: TY_11_013_01_carbon-1_Ana-1.jdf

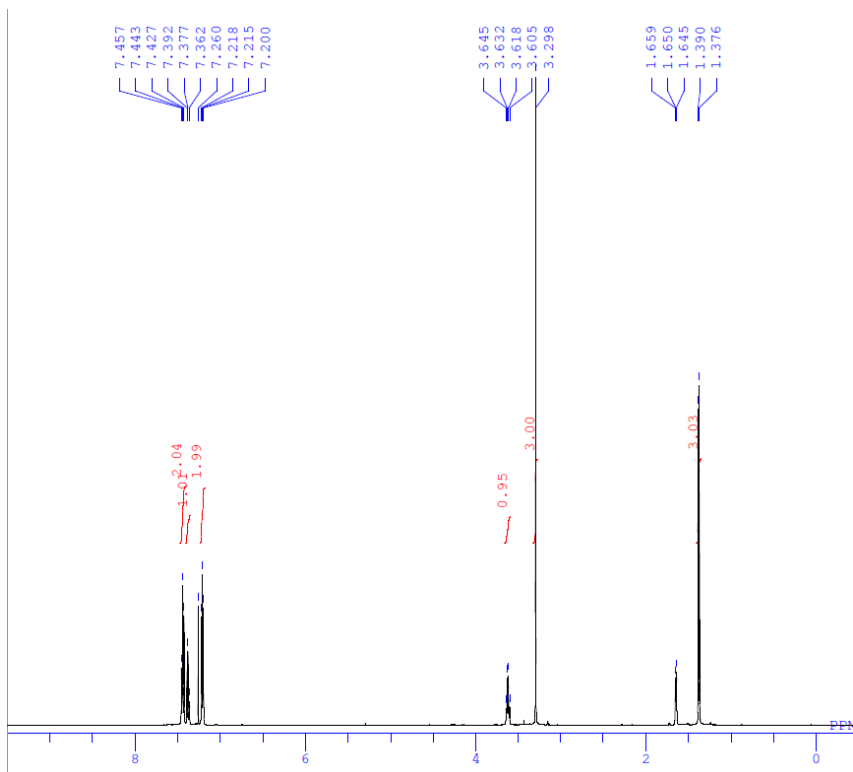
Filename = TY_11_013_01_carbon-1_Ana
 Author = delta
 Experiment = carbon.jsp
 Sample_Id = TY_11_013_01
 Solvent = CHLOROFORM-D
 Actual_Start_Time = 4-JUL-2018 10:00:45
 Revision_Time = 21-AUG-2018 19:29:11

Comment = single pulse decoupled ga
 Data_Format = 1D COMPLEX
 Dim_Size = 26214
 X_Domain = Carbon
 Dim_Title = Carbon13
 Dim_Units = [ppm]
 Dimensions = X
 Site = JNM-EX500
 Spectrometer = DELTA2_NMR

Field_Strength = 11.7473579[T] (500[MHz])
 X_Acq_Duration = 0.83361792[s]
 X_Domain = 13C
 X_Freq = 125.76529768[MHz]
 X_Offset = 100[ppm]
 X_Points = 32768
 X_Prescans = 4
 X_Resolution = 1.19959034[Hz]
 X_Sweep = 39.3081761[kHz]
 X_Sweep_Clipped = 31.44654088[kHz]
 Ixv_Domain = Proton
 Ixv_Freq = 500.15991521[MHz]
 Ixv_Offset = 5.0[ppm]
 Clipped = FALSE
 Scans = 816
 Total_Scans = 816

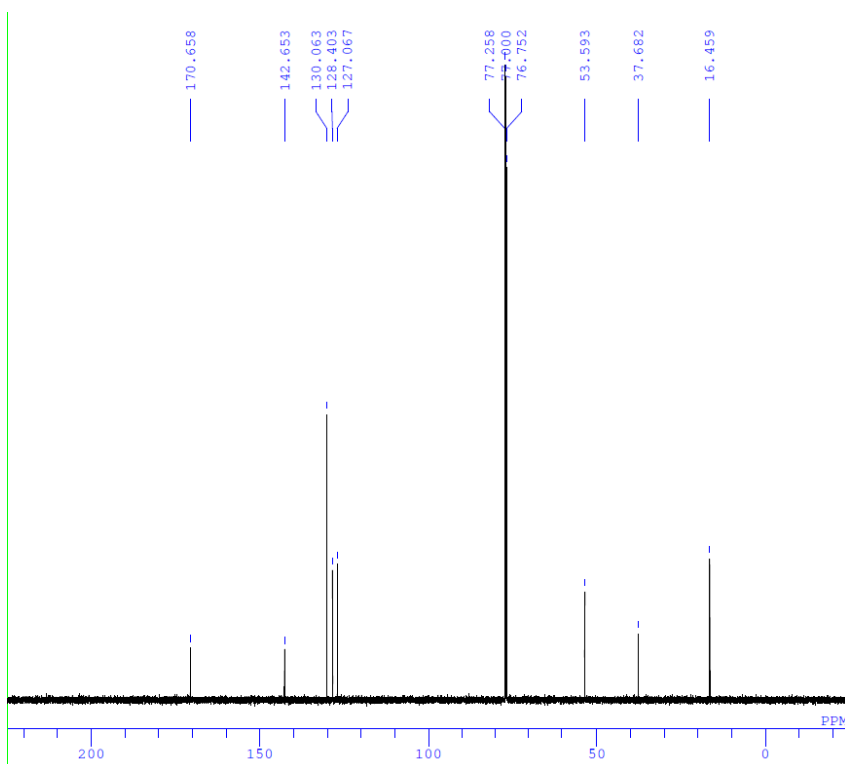
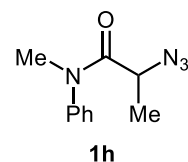
Relaxation_Delay = 2[s]
 Recv_Gain = 58
 Temp_Get = 17.9[dC]
 X_90_Width = 9.36[us]
 X_Acq_Time = 0.83361792[s]
 X_Angle = 30[deg]
 X_Atn = 3[dB]
 X_Pulse = 3.12[us]
 Ixv_Atn_Dec = 20.54[dB]
 Ixv_Atn_Noise = 20.54[dB]
 Ixv_Noise = WALTZ
 Ixv_Width = 92[us]
 Decoupling = TRUM





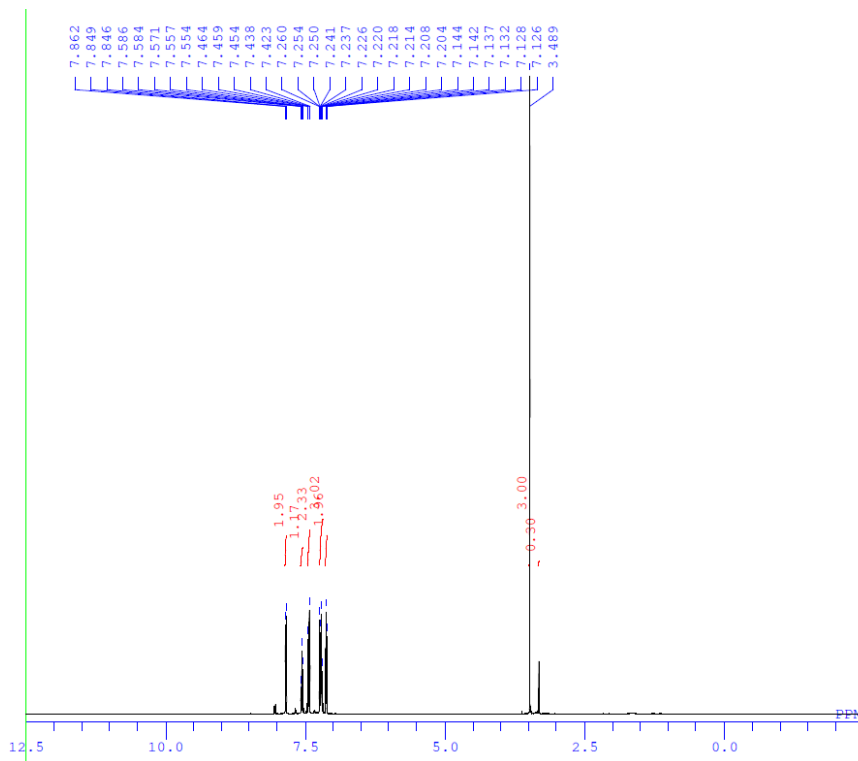
```

DFILE TY_07_020_02_proton-1-1.als
COMNT single_pulse
DATIM 2016-09-27 20:12:32
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 18.6 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 40
  
```



```

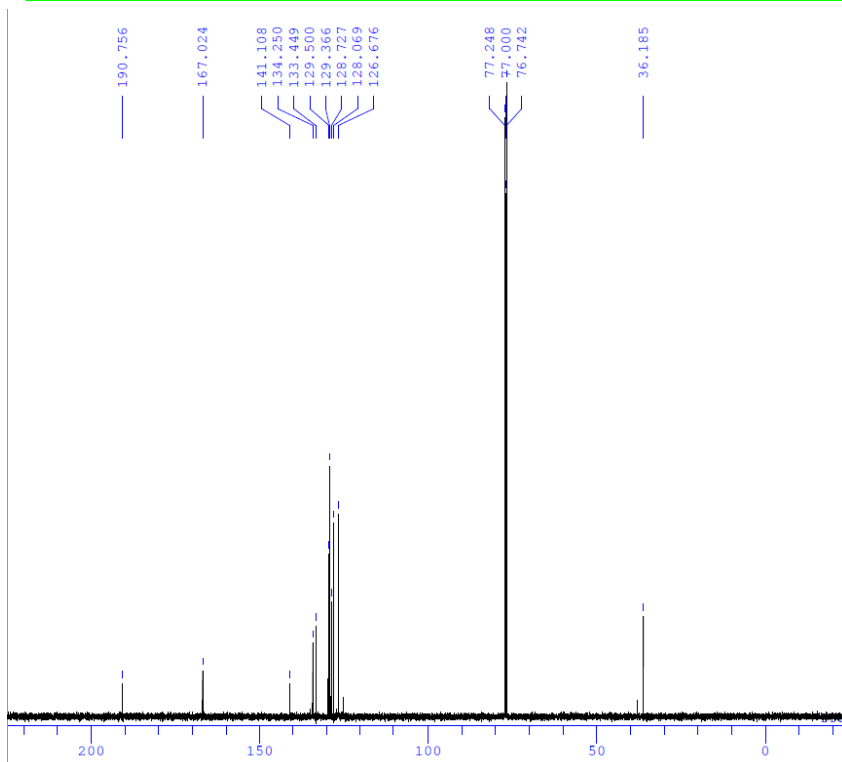
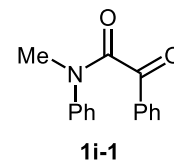
DFILE TY_07_020_02_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2016-09-27 20:14:15
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 620
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 19.0 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 58
  
```



```

DFILE TY_07_097_02_proton-1-1.als
COMNT single_pulse
DATIM 2016-10-13 19:17:49
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 17.7 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 38

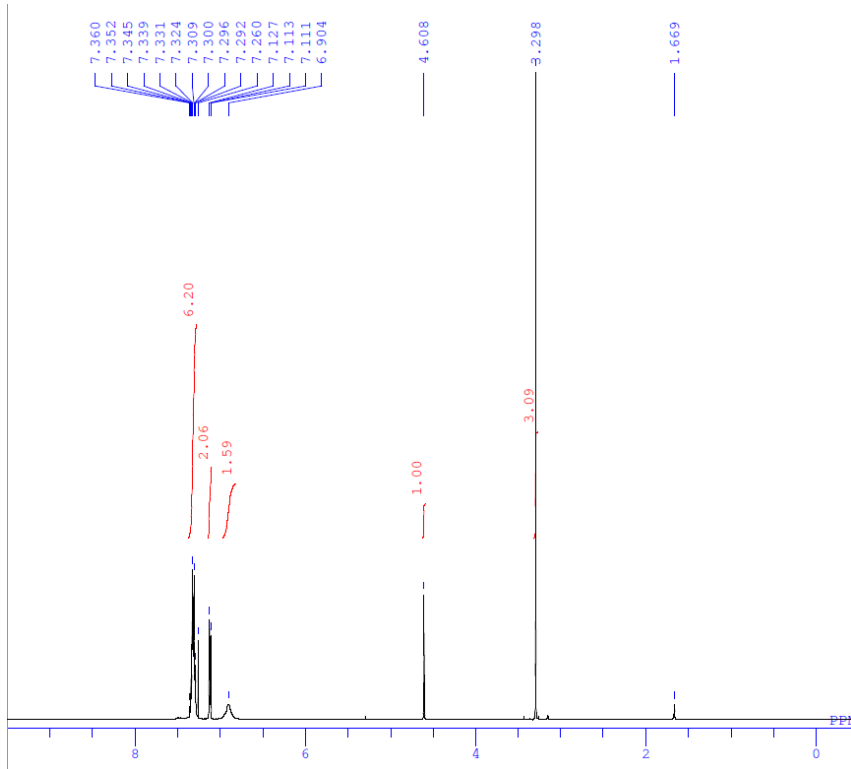
```



```

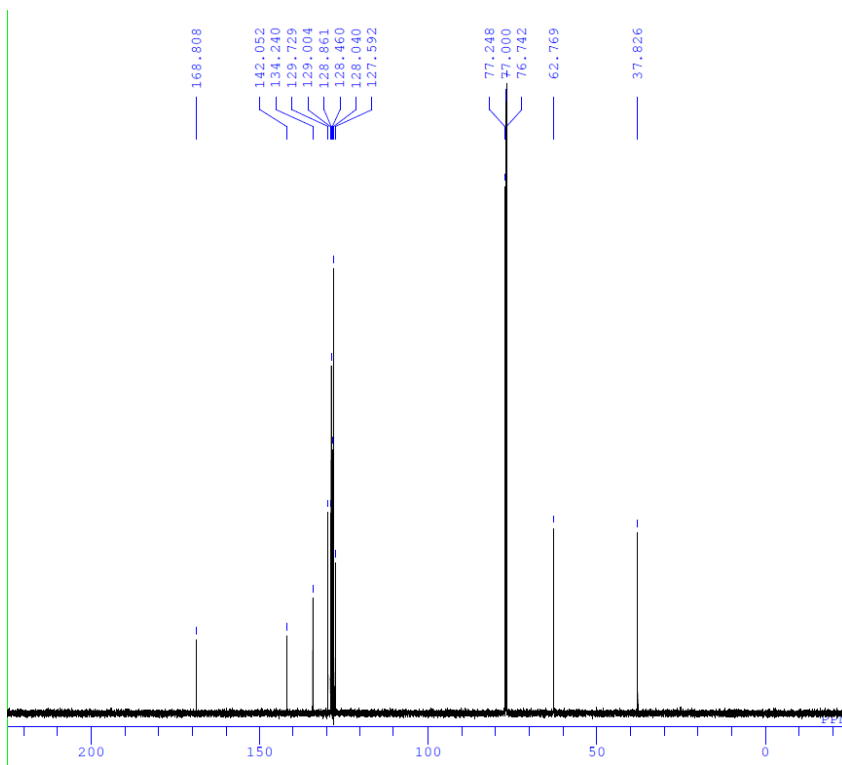
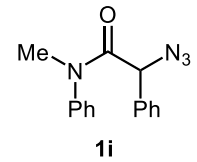
DFILE TY_07_097_02_carbon-1-1.als
COMNT single_pulse decoupled gated
DATIM 2016-10-13 19:19:53
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 620
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 17.4 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 56

```



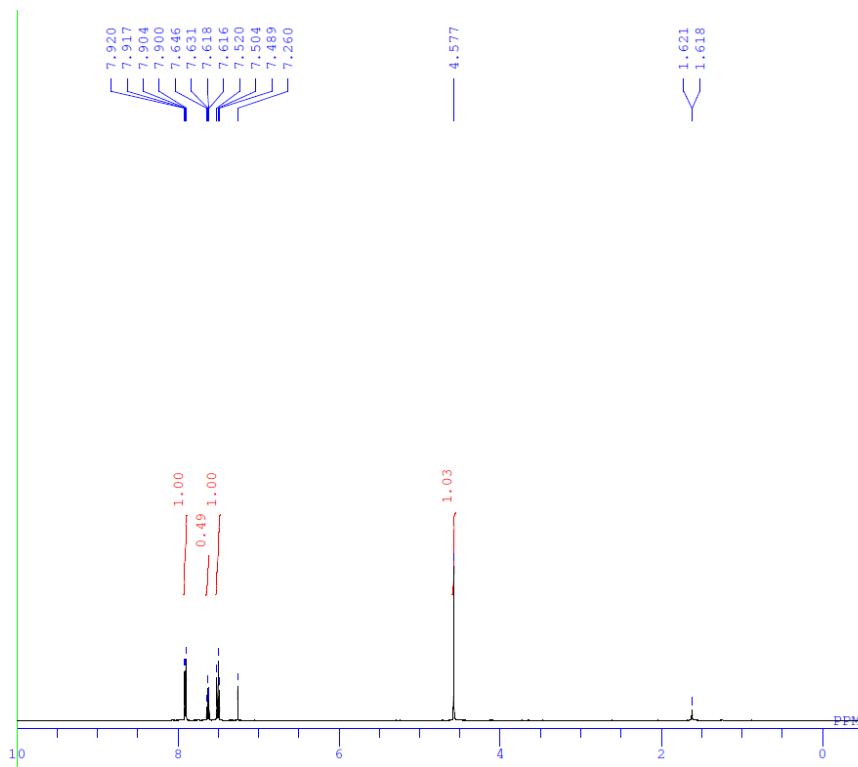
```

DFILE TY_08_026_02_proton-1-1.als
COMNT single_pulse
DATIM 2016-12-09 20:16:58
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 14.5 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 36
  
```



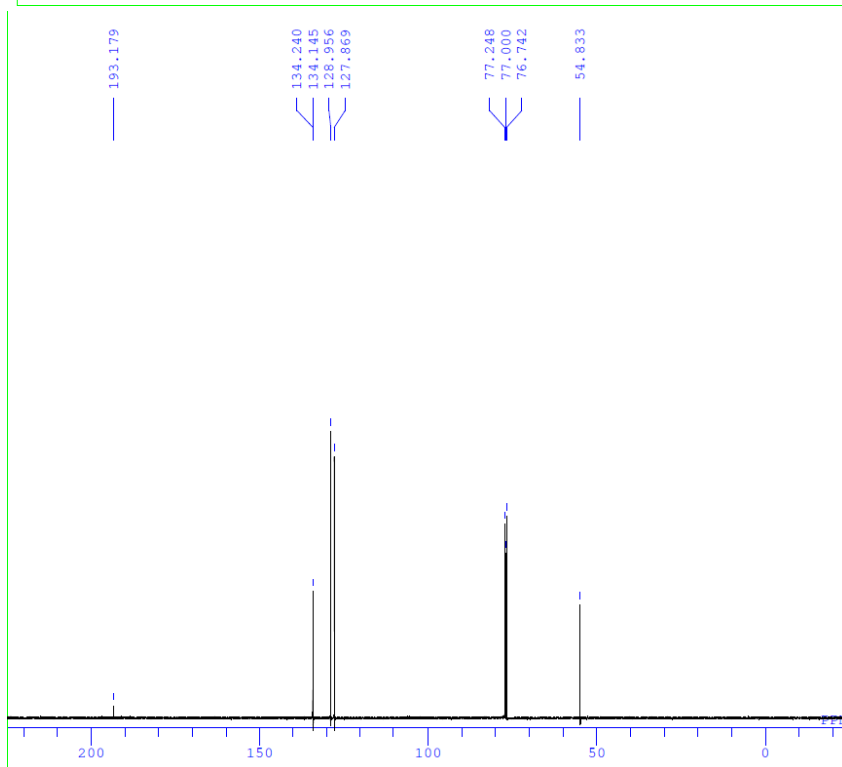
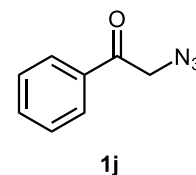
```

DFILE TY_08_026_02_carbon-1-1.als
COMNT single_pulse decoupled gated
DATIM 2016-12-09 20:21:10
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 620
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 15.3 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
```



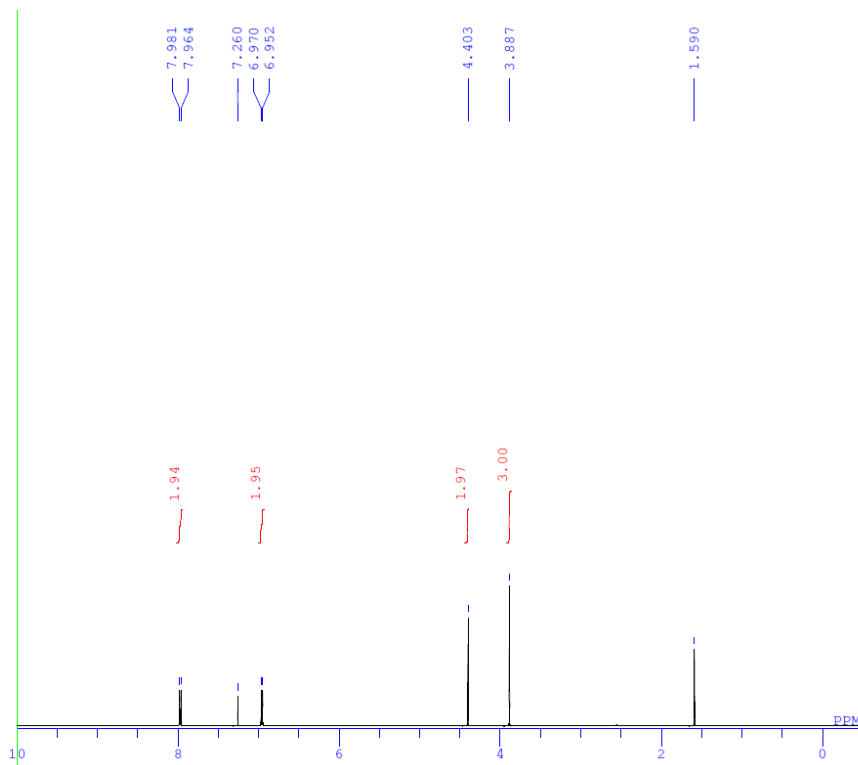
```

DFILE TY_08_069_00_proton-1-1.als
COMNT single_pulse
DATIM 2017-05-25 20:13:05
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 13.5 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 40
  
```

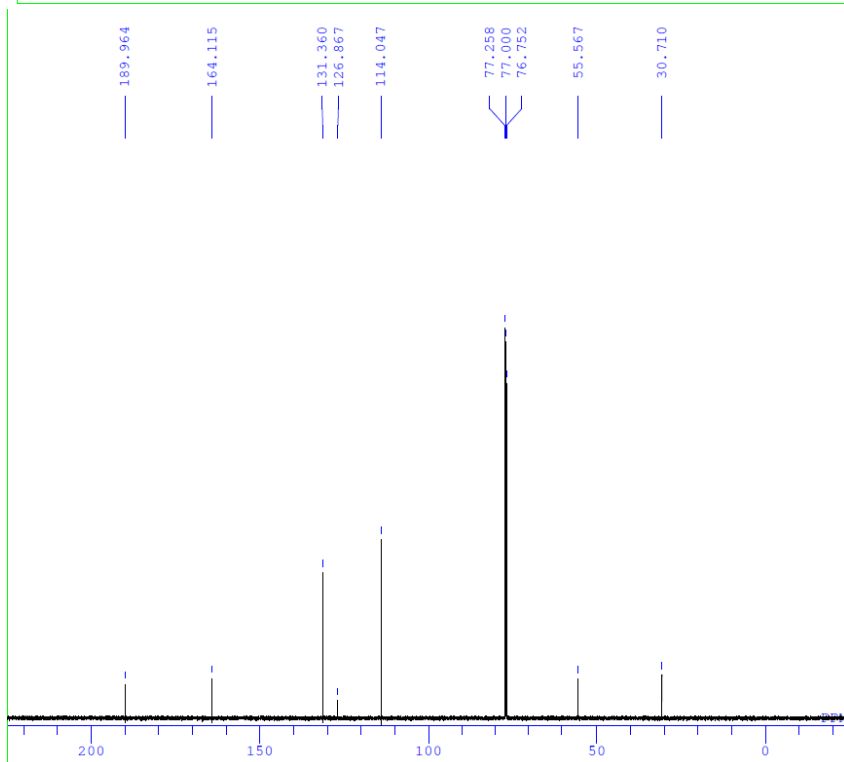
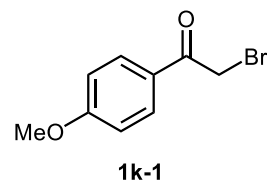


```

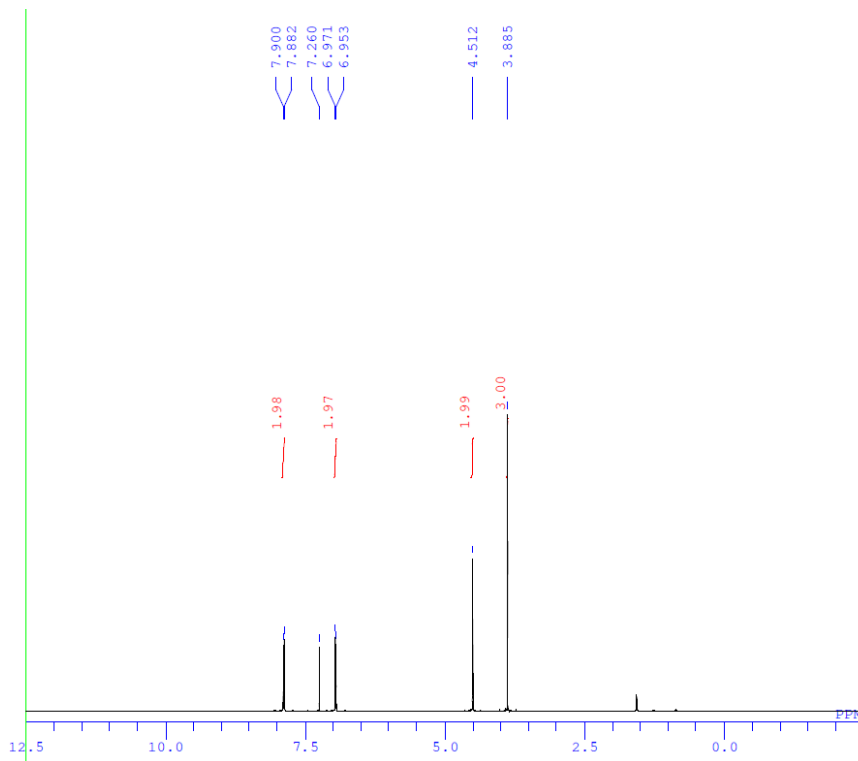
DFILE TY_08_069_00_carbon-1-1.als
COMNT single_pulse decoupled gated
DATIM 2017-05-25 20:15:17
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 840
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 14.0 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
```



DFILE TY_09_020_01_proton-1-1.als
 COMNT single_pulse
 DATIM 2017-07-14 16:17:33
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 18.8 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 44



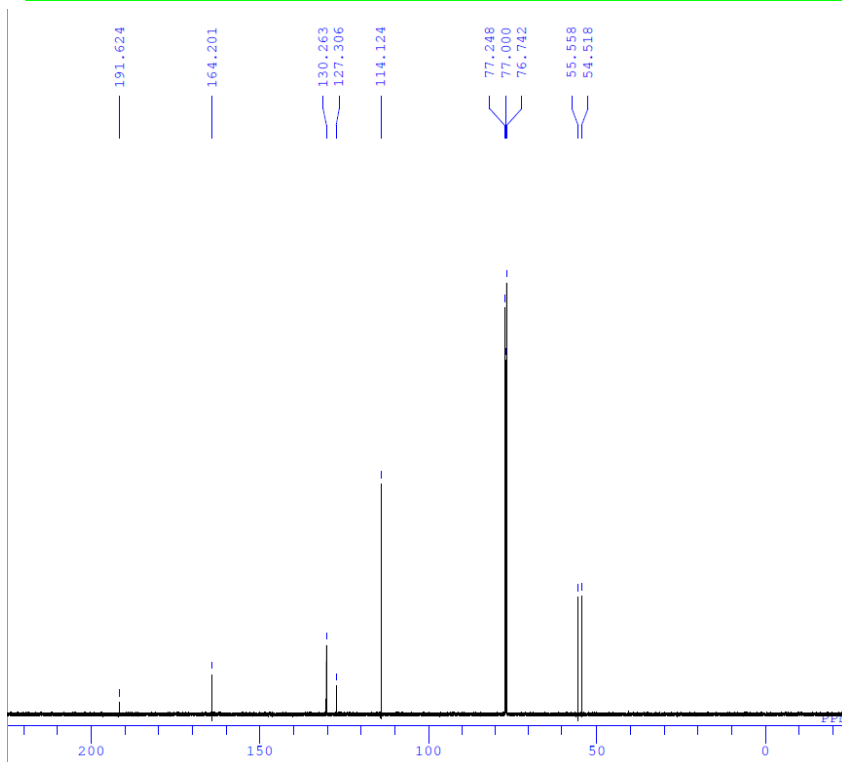
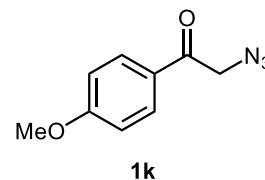
DFILE TY_09_020_01_carbon-1-1.als
 COMNT single_pulse decoupled gated
 DATIM 2017-07-14 16:19:06
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 1260
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 19.0 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60



```

DFILE TY_09_022_01_proton-1-1.als
COMNT single_pulse
DATIM 2017-07-19 09:54:13
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 17.7 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 46

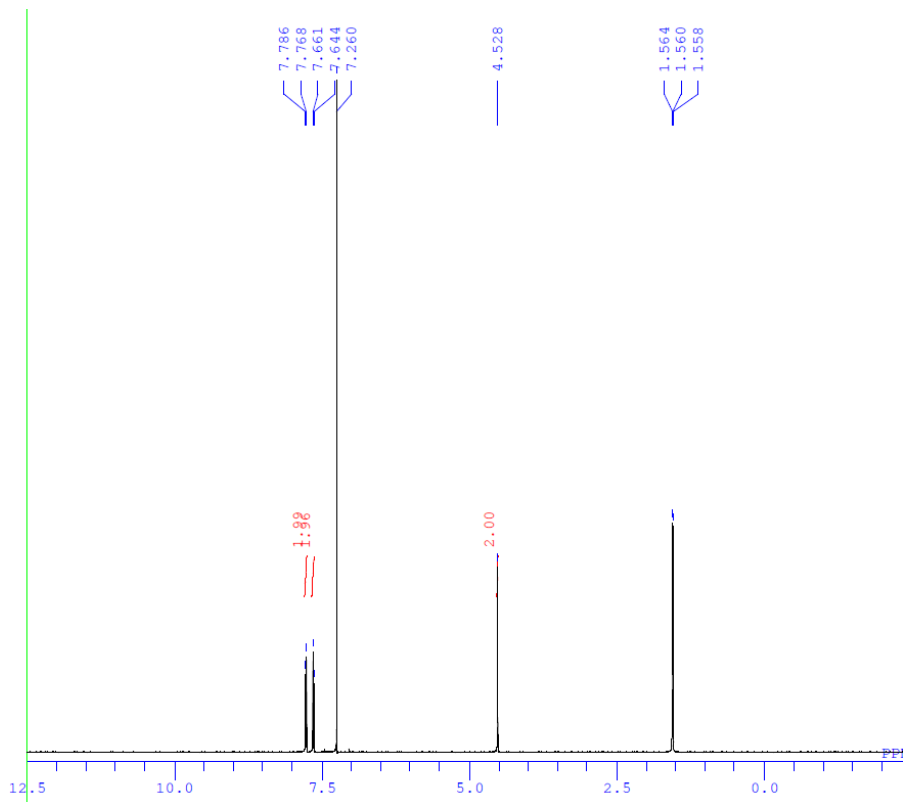
```



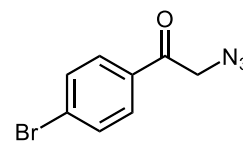
```

DFILE TY_09_022_01_carbon-1-1.als
COMNT single_pulse decoupled gated
DATIM 2017-07-19 09:56:02
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 1680
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 18.5 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60

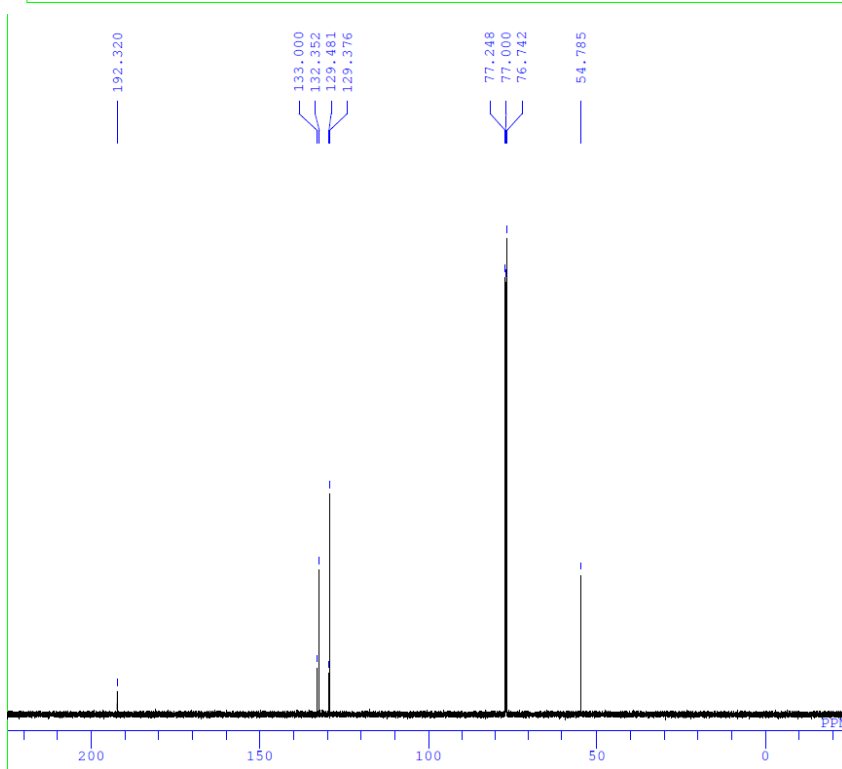
```



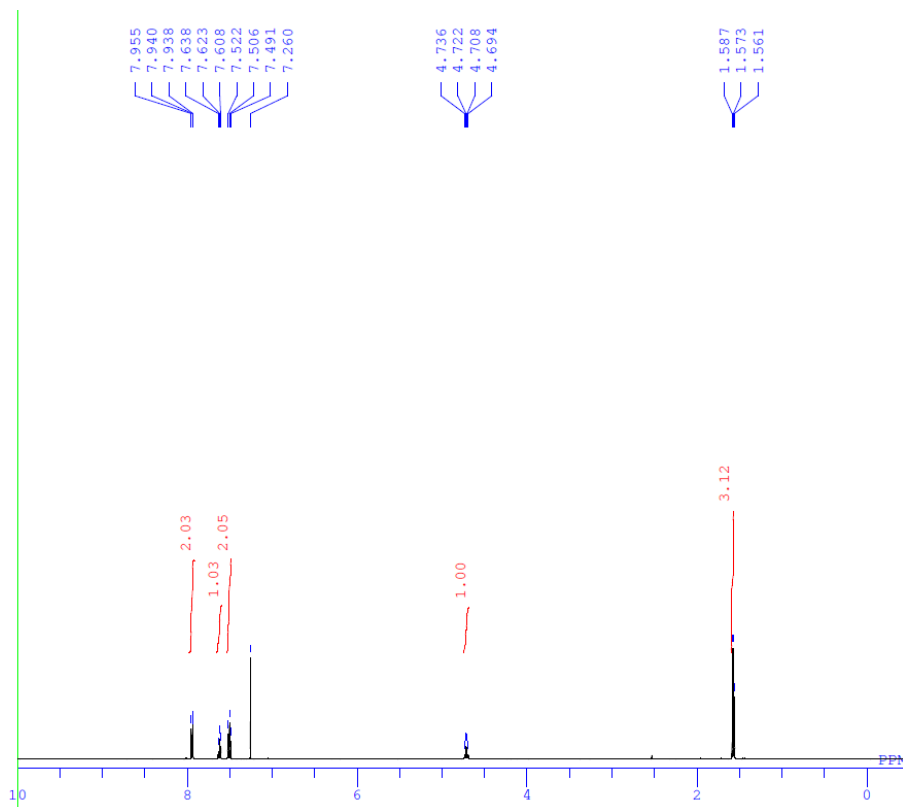
DFILE TY_09_048_01-1-1.als
 COMNT azide
 DATIM 2017-08-01 16:34:23
 OBNUC 1H
 EXMOD proton.jxp
 OBFRQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 19.0 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 50



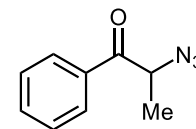
11



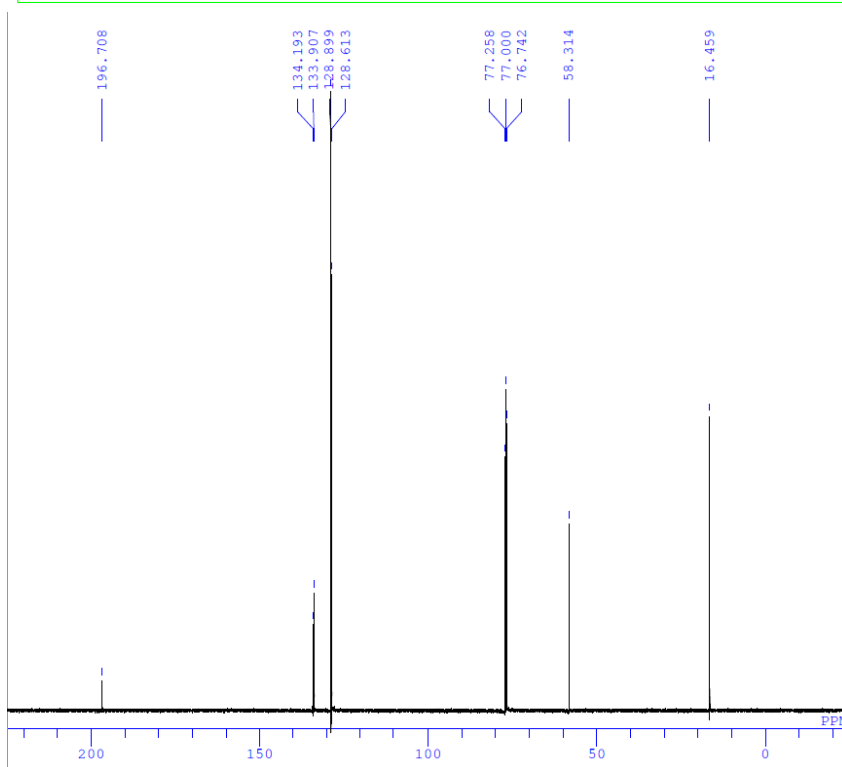
DFILE TY_09_048_01_carbon-1-1.als
 COMNT single pulse decoupled gated
 DATIM 2017-08-01 17:44:57
 OBNUC 13C
 EXMOD carbon.jxp
 OBFRQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 1360
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 19.0 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60



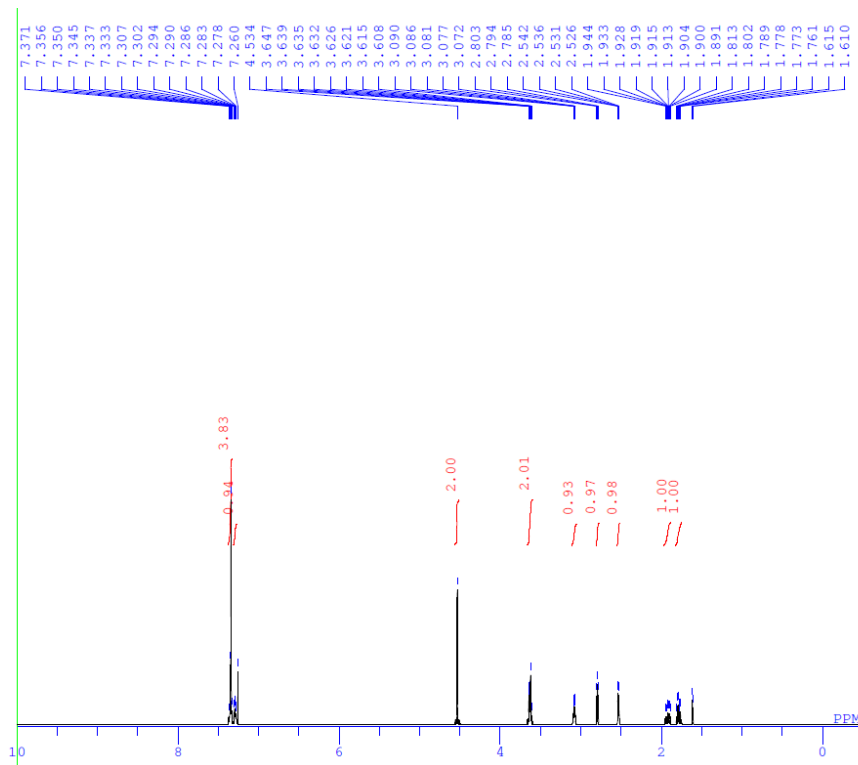
DFILE TY_09_033_03-1-1.als
 COMNT azide
 DATIM 2017-07-20 13:55:45
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 18.5 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 48



1m

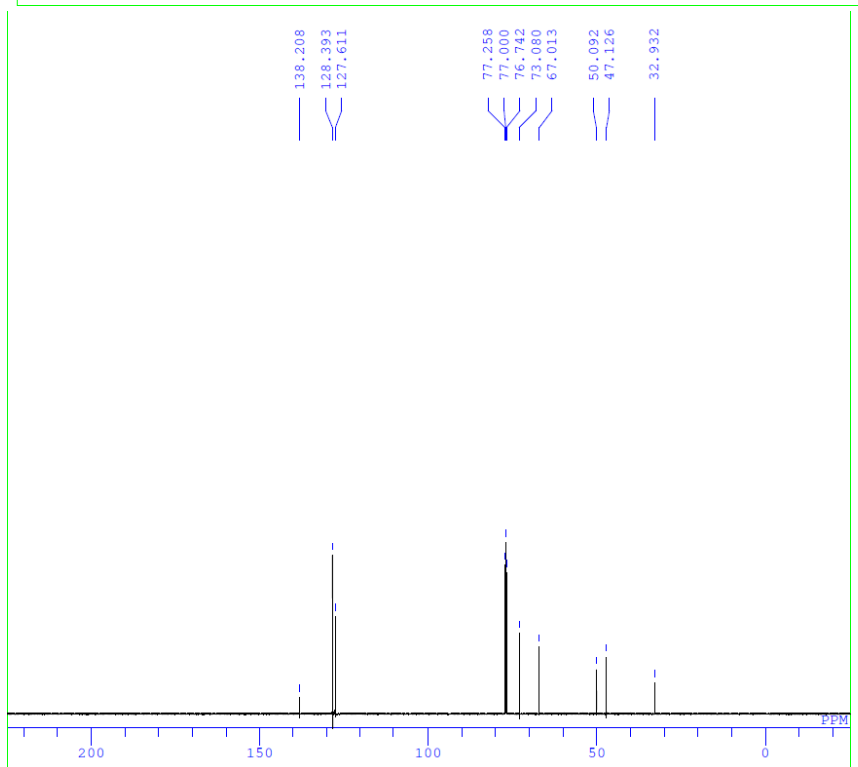
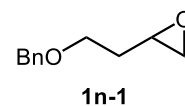


DFILE TY_09_033_03_carbon-1-1.als
 COMNT single pulse decoupled gated
 DATIM 2017-07-20 14:16:28
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 1260
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 19.2 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60



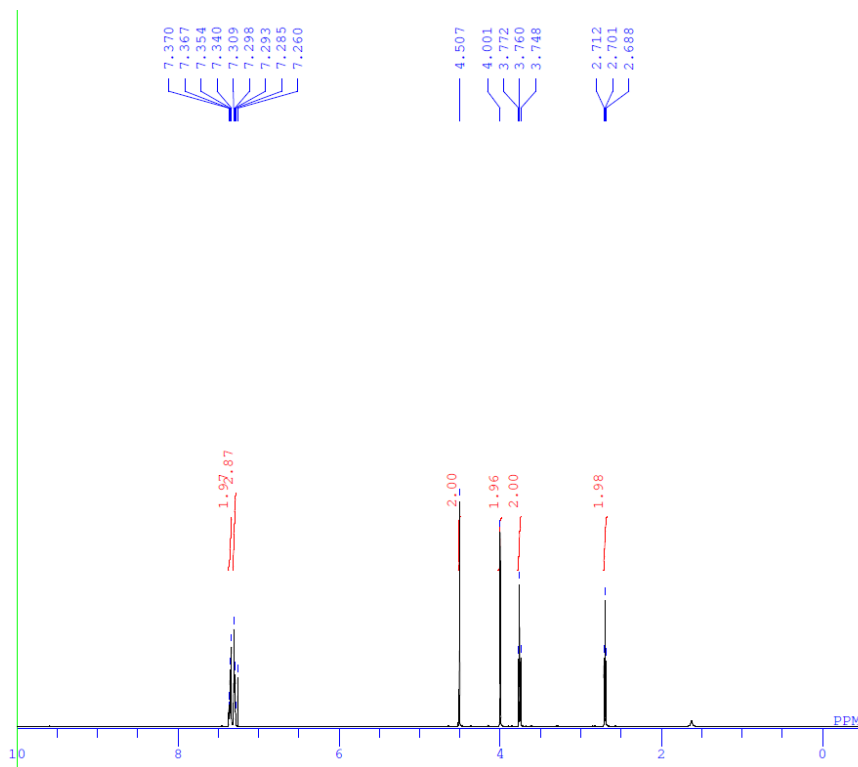
```

DFILE TY_08_094_01_proton-1-1.als
COMNT single_pulse
DATIM 2017-06-08 10:26:51
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 16.3 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 38
  
```



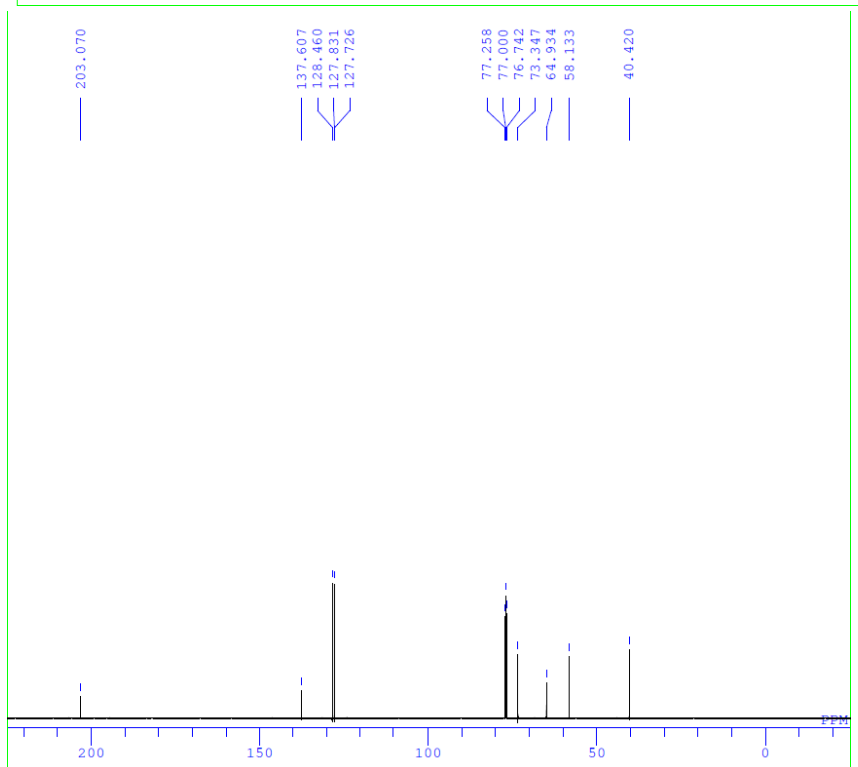
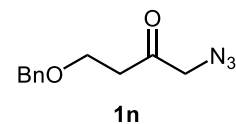
```

DFILE TY_08_094_01_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2017-06-08 10:29:07
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 1260
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 16.6 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
```



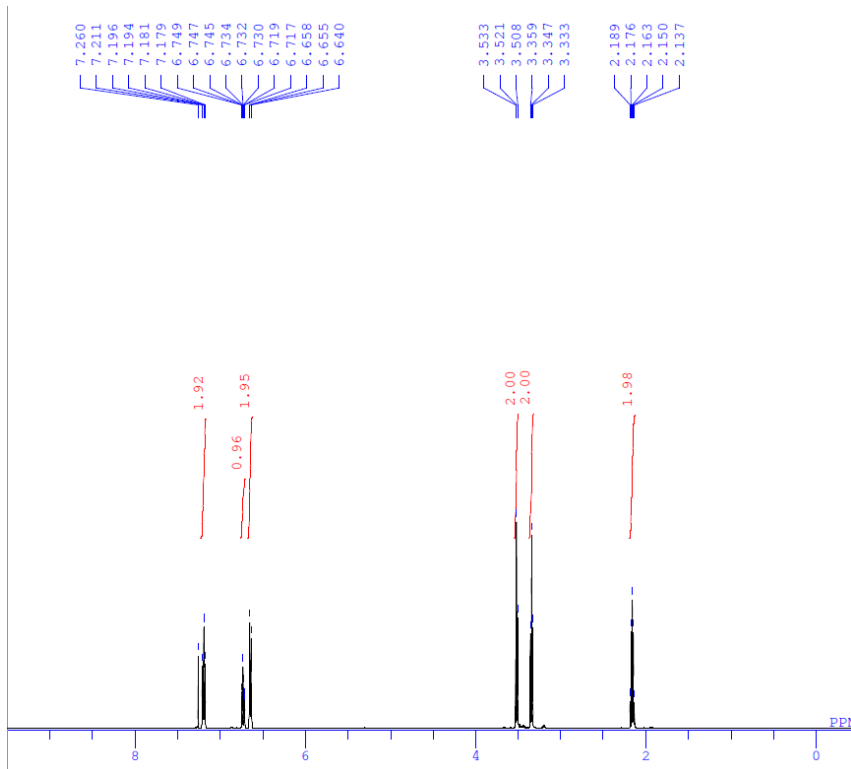
```

DFILE TY_08_110_01_proton-1-1.als
COMNT single_pulse
DATIM 2017-06-16 10:02:48
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 13.1 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 38
  
```



```

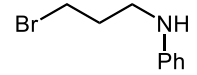
DFILE TY_08_110_01_carbon-1-1.als
COMNT single_pulse decoupled gated
DATIM 2017-06-16 10:04:47
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 1260
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 13.8 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
```



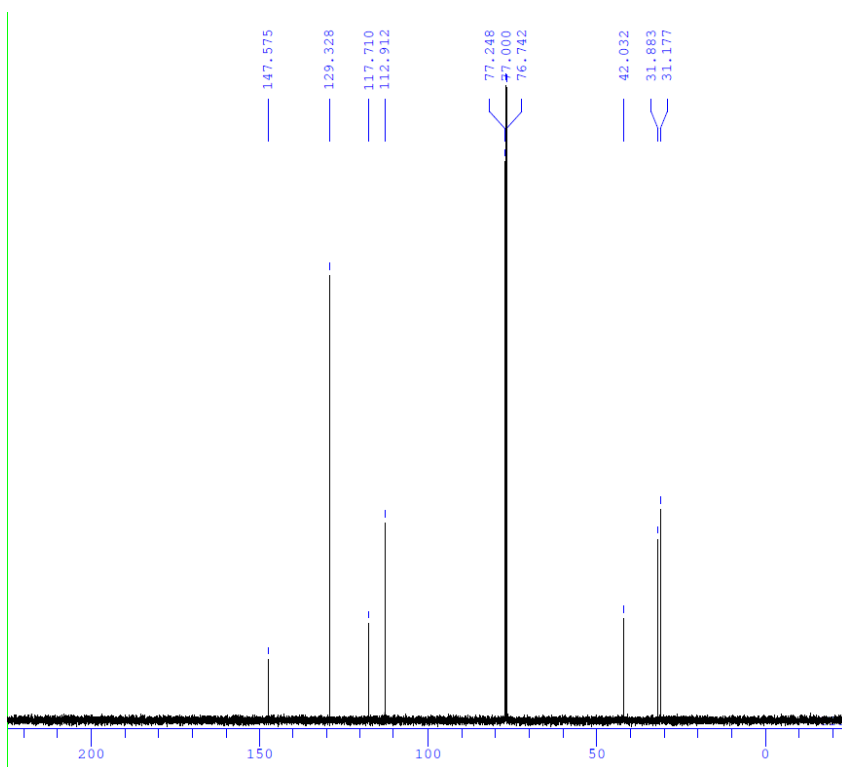
```

DFILE TY_07_067_03_proton-1-1.als
COMNT single_pulse
DATIM 2016-09-26 17:49:12
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 18.3 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 40

```



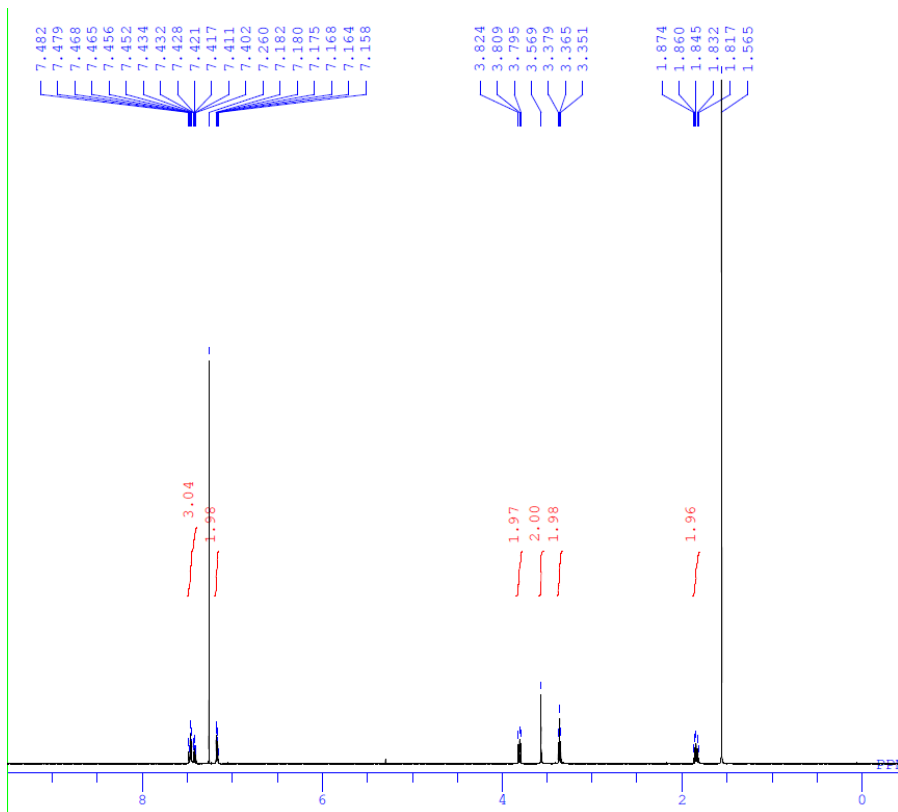
3a-1



```

DFILE TY_07_067_03_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2016-09-26 17:51:11
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 620
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 18.8 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 58

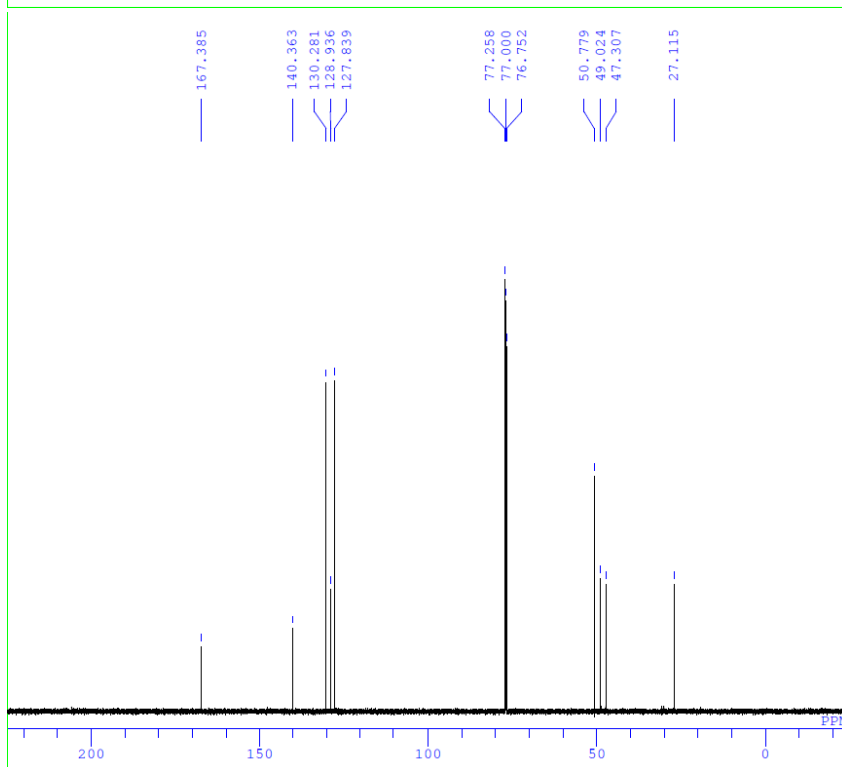
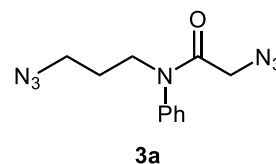
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```

DFILE TY_07_069_02-1-1.als
COMNT diazide
DATIM 2016-09-27 15:59:16
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 18.8 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 48

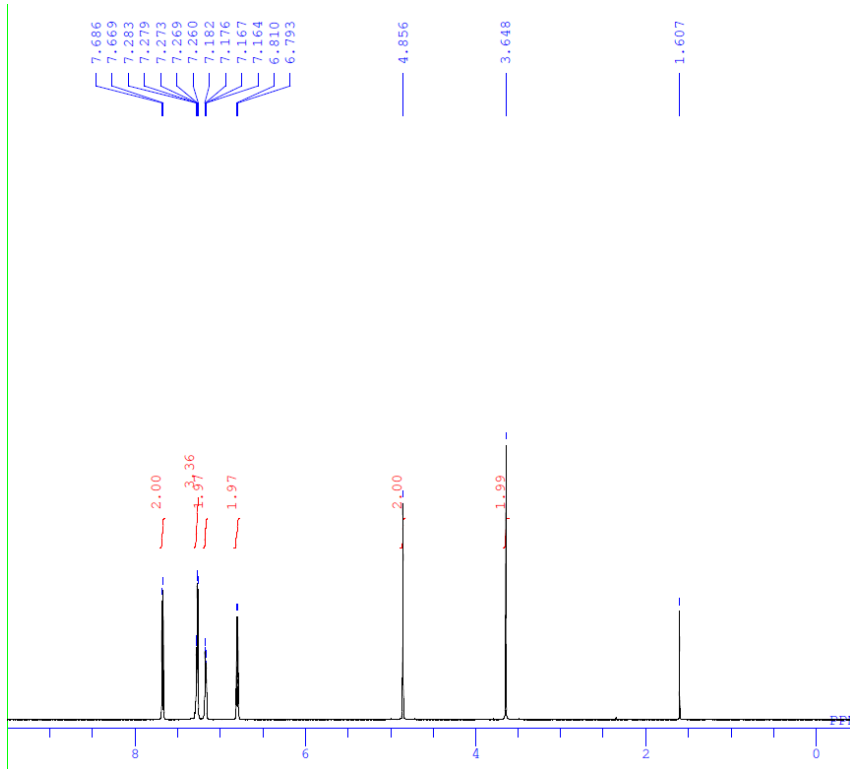
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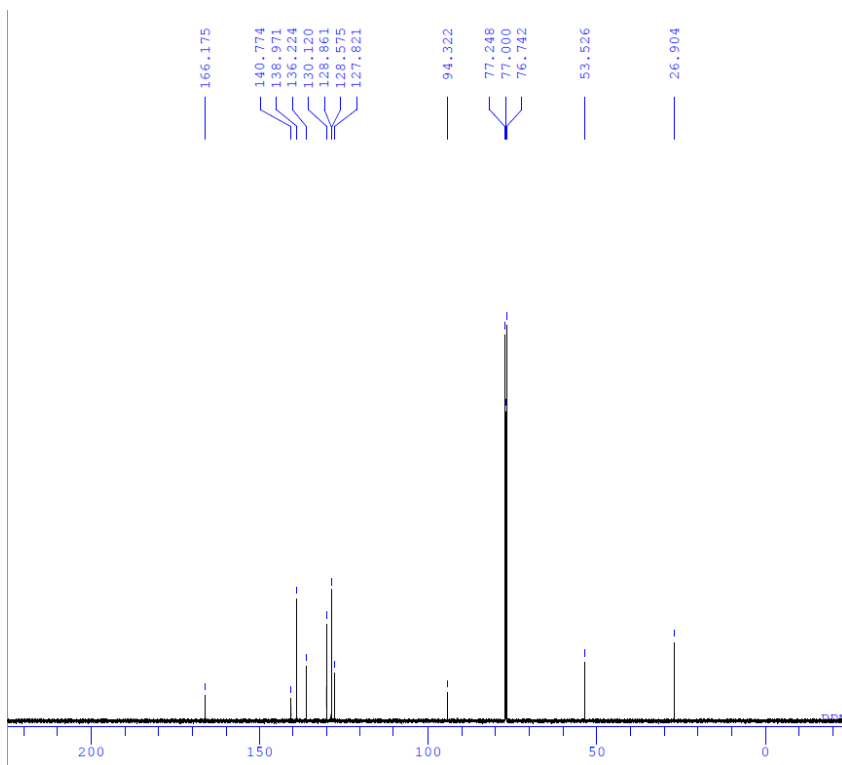
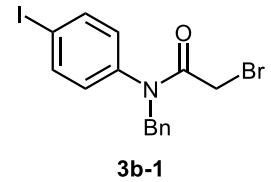
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DFILE TY_07_015_04_carbon-1-1.jdf
COMNT single pulse decoupled gated
DATIM 2016-09-21 18:22:35
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 32767
FREQU 39308.18 Hz
SCANS 620
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 18.9 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60

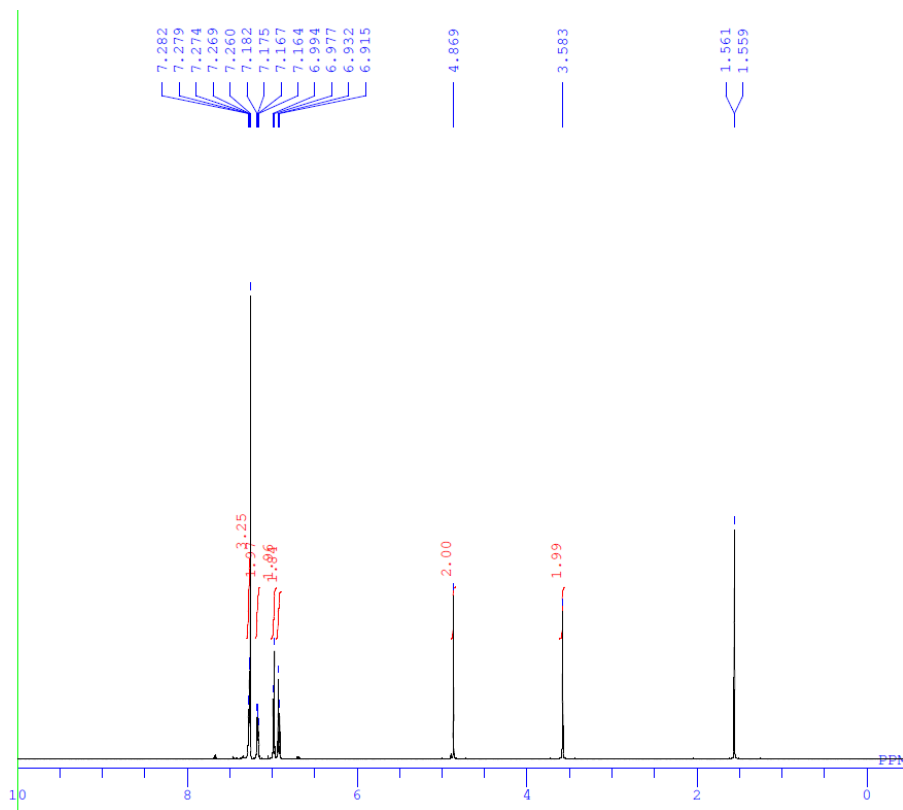
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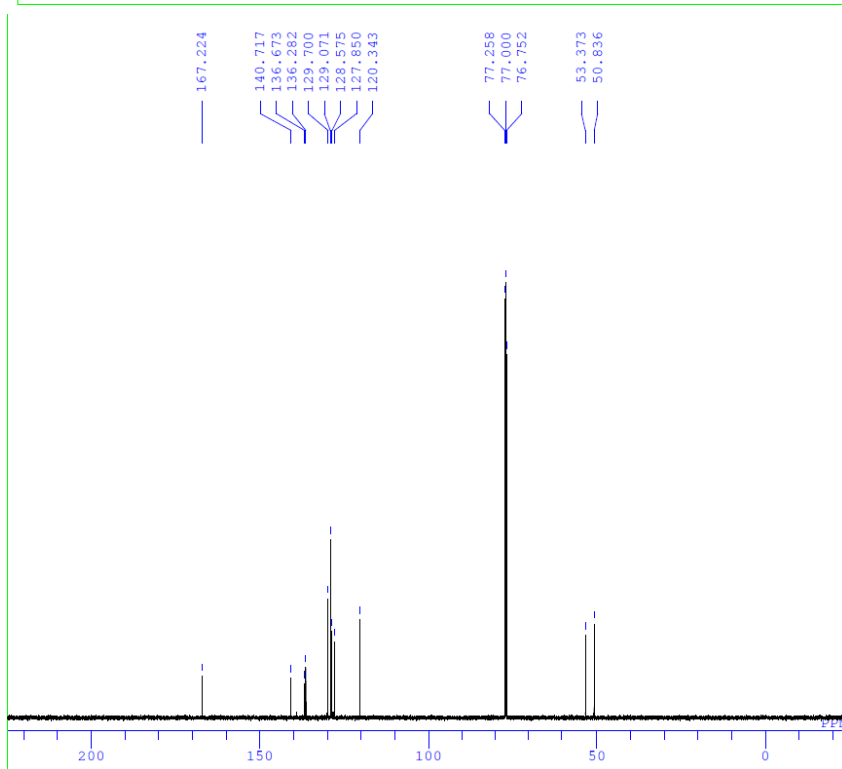
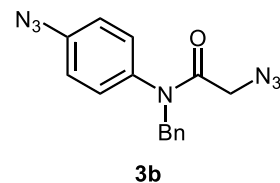
DFILE TY_09_041_01_proton-1-1.als
 COMNT single_pulse
 DATIM 2017-07-26 09:56:09
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 17.9 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 40



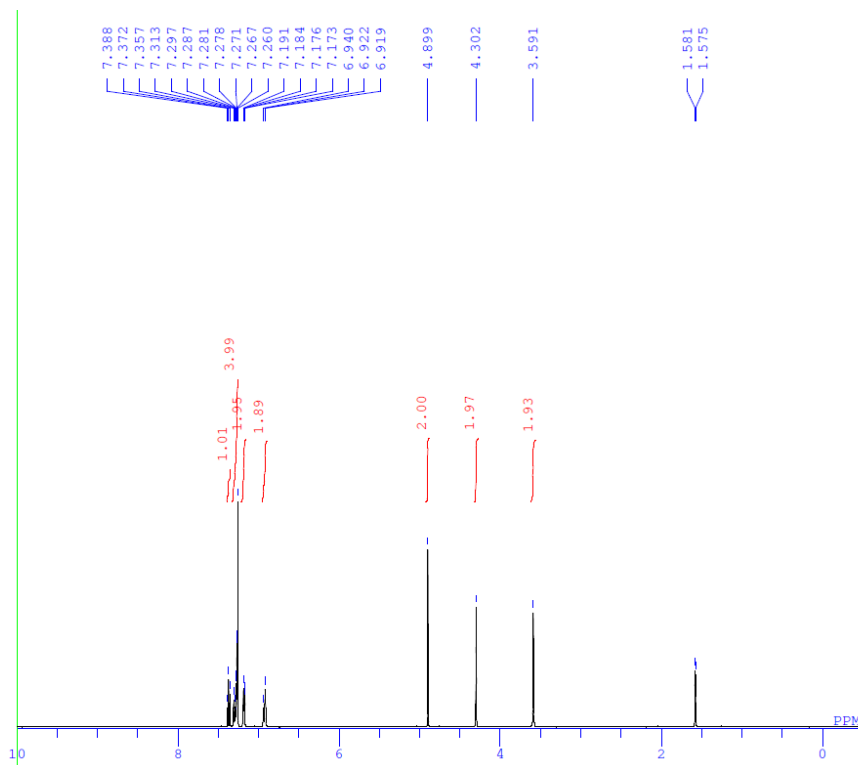
DFILE TY_09_041_01_carbon-1-1.als
 COMNT single_pulse decoupled gated
 DATIM 2017-07-26 10:01:44
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 1680
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 18.9 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60



DFILE TY_09_042_01-1-1.als
COMNT diazide
DATIM 2017-07-26 12:13:20
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 18.7 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 48



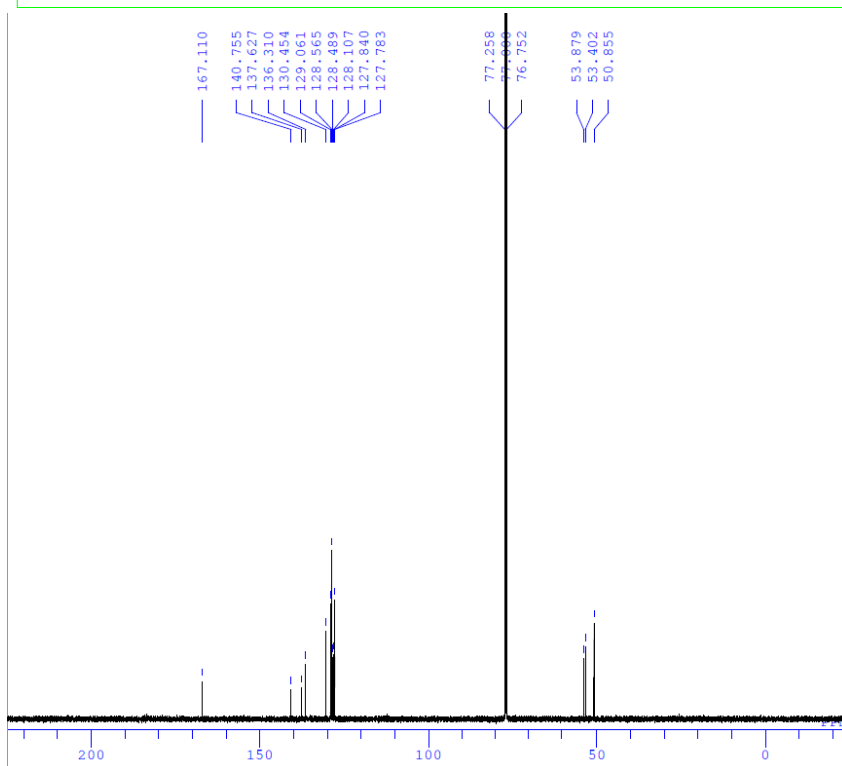
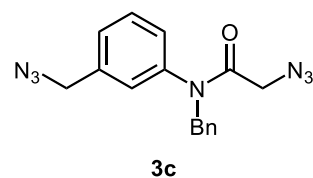
DFILE TY_09_042_01_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2017-07-27 09:55:36
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 1680
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 19.0 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60



```

DFILE TY_09_108_01_proton-1-1.als
COMNT single_pulse
DATIM 2017-10-17 23:17:24
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 18.4 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 44

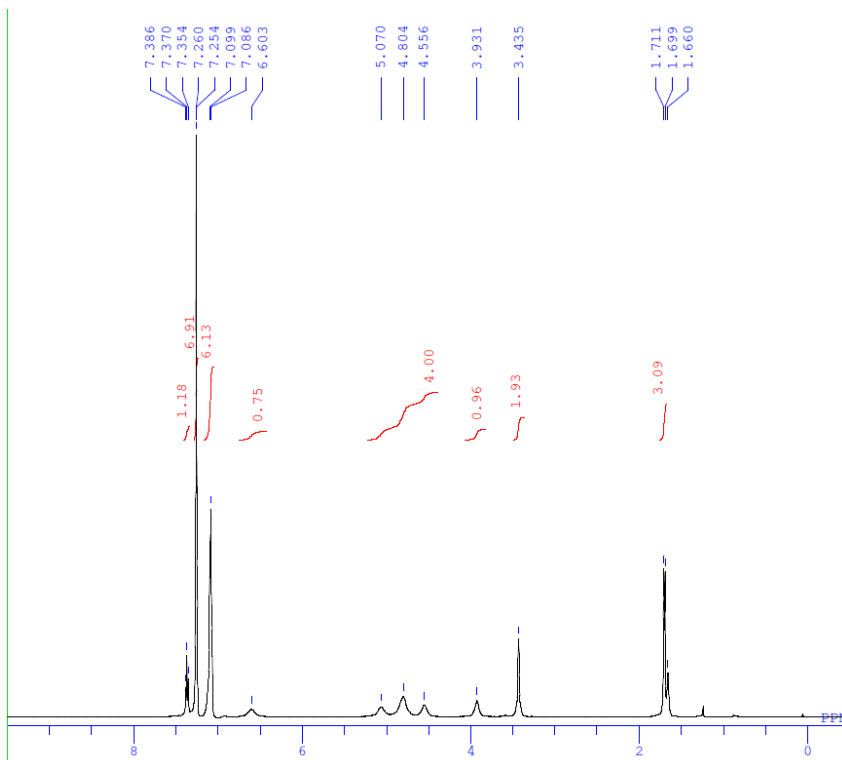
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```

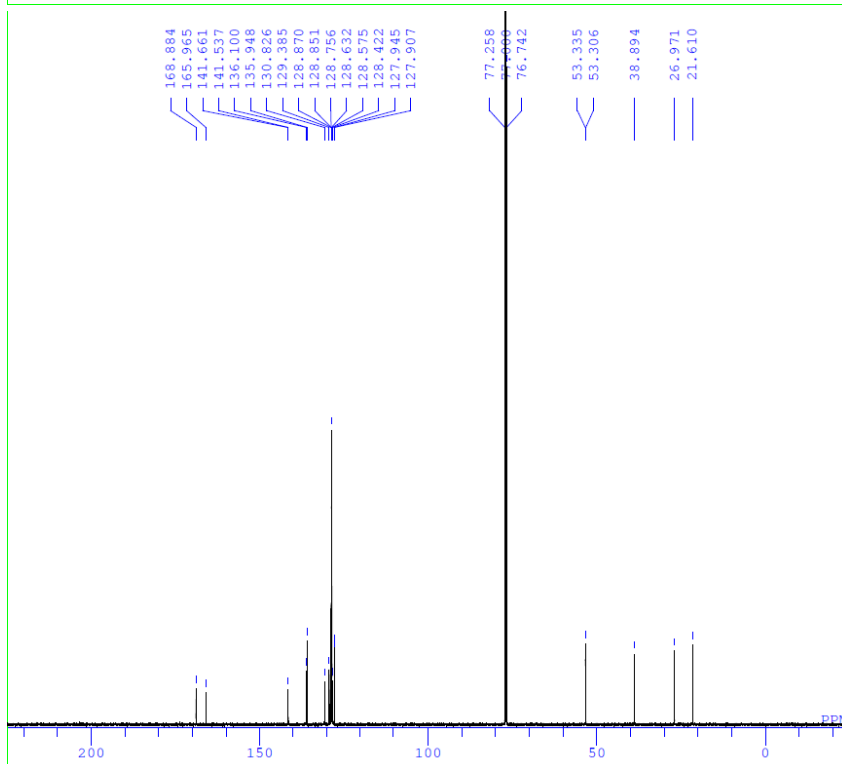
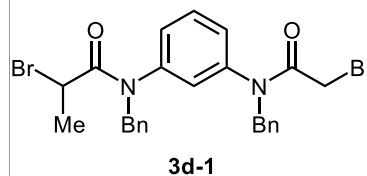
DFILE TY_09_108_01_carbon-1-1.als
COMNT single_pulse decoupled gated
DATIM 2017-10-17 23:19:05
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 8460
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 19.2 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60

```

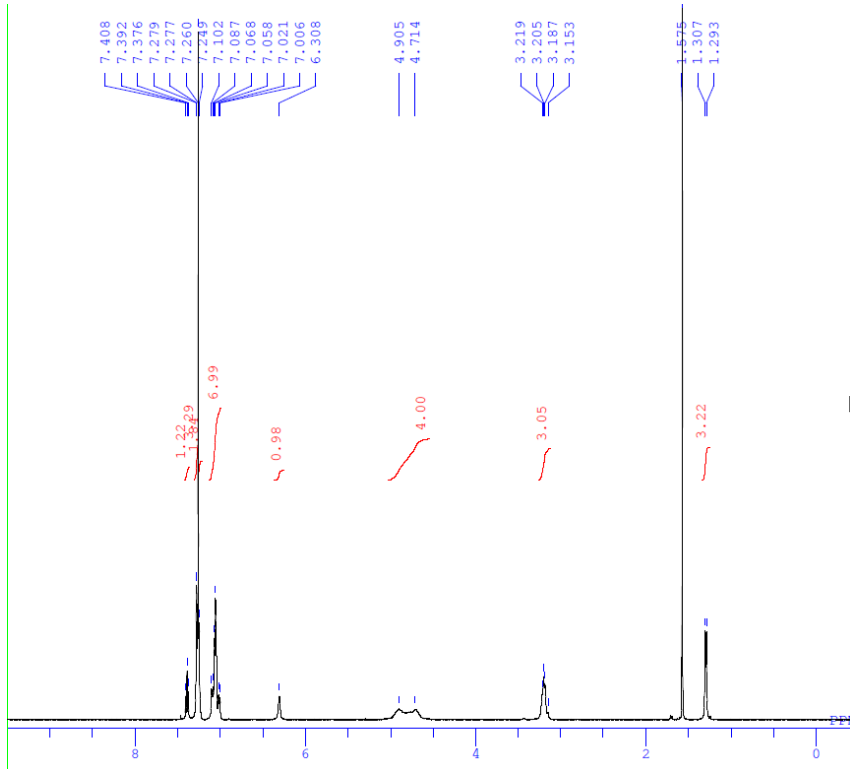
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DFILE TY_09_106_01_2_proton-1-1.als
COMNT single_pulse
DATIM 2017-10-11 23:19:13
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 14.9 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 38
  
```



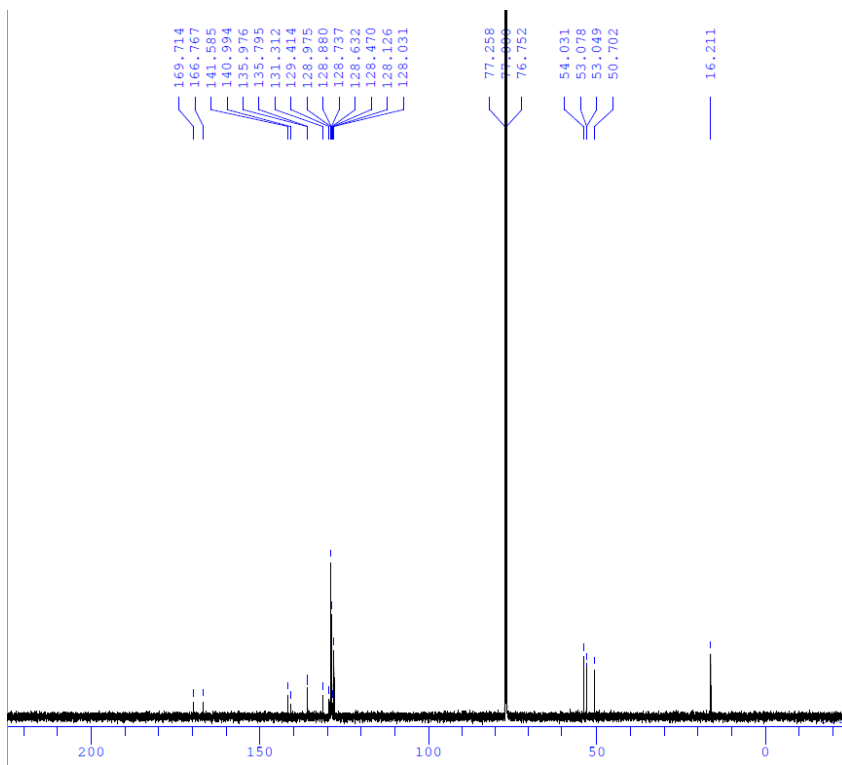
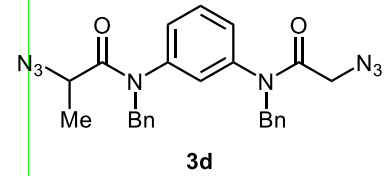
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DFILE TY_09_106_01_2_carbon-1-1.als
COMNT single_pulse decoupled gated
DATIM 2017-10-11 23:20:47
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 8840
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 14.6 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
```



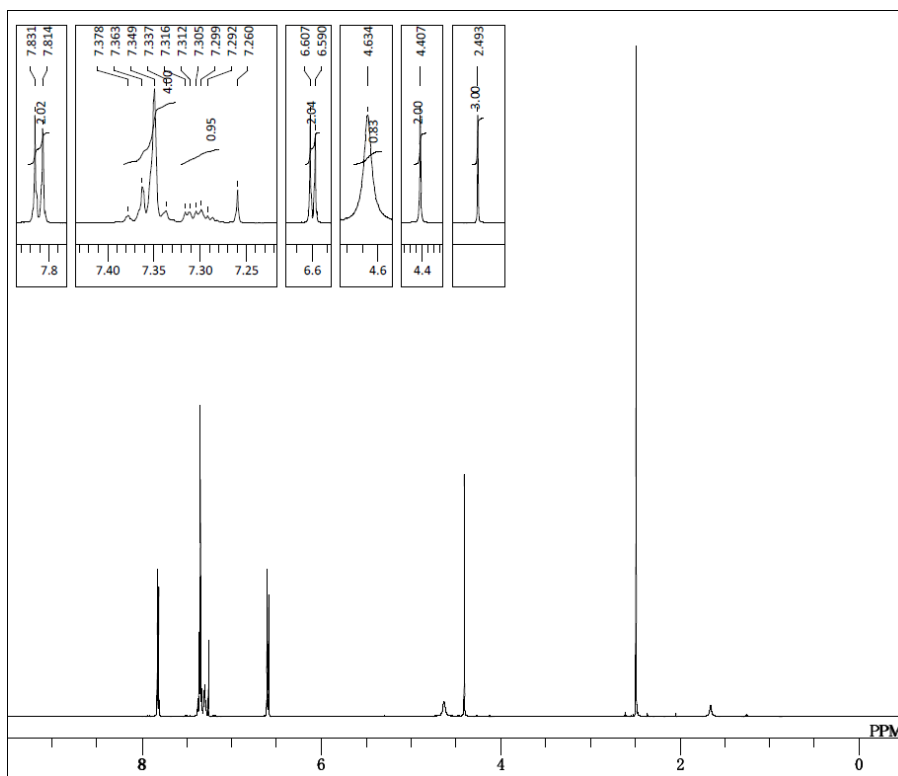
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DFILE TY_09_109_01_proton-1-1.als
COMNT single_pulse
DATIM 2017-10-18 23:11:59
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 17.3 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 46
  
```

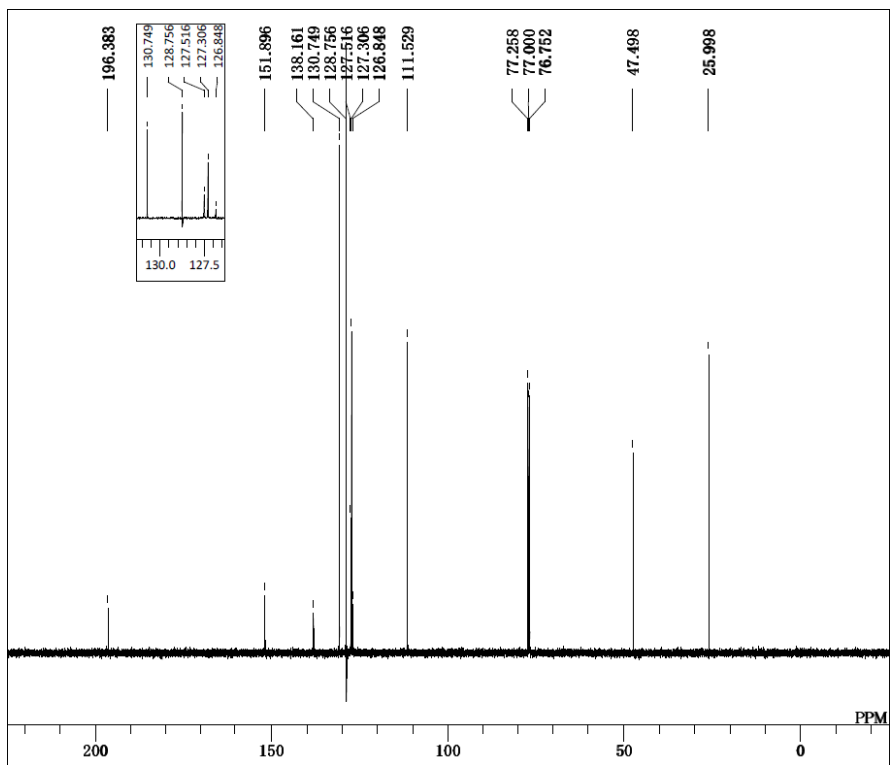
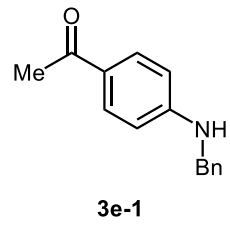


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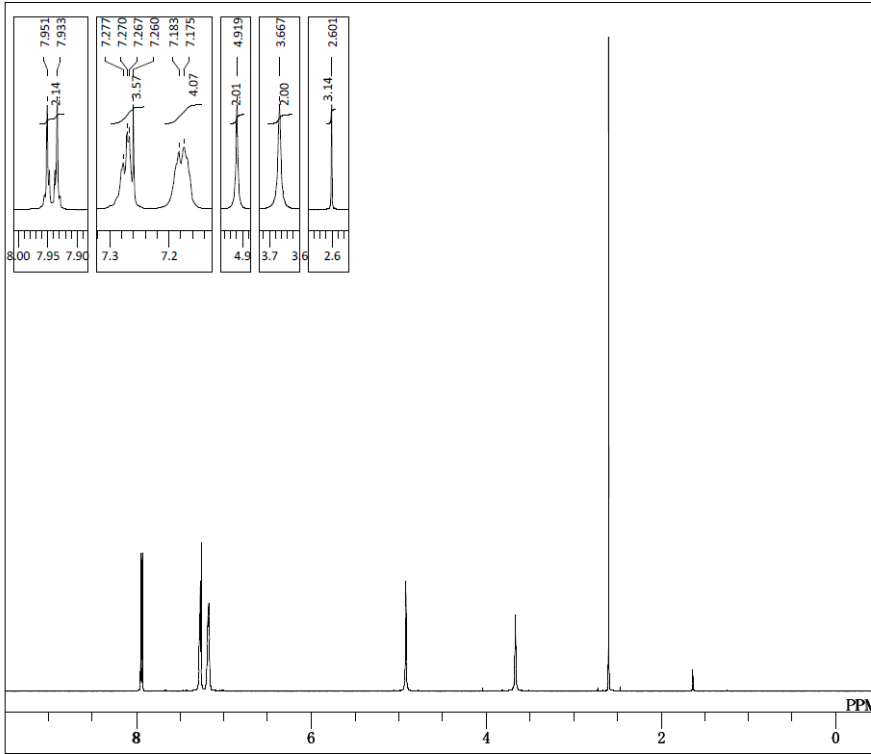
DFILE TY_09_109_01_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2017-10-18 23:13:37
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 8680
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 18.1 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
```



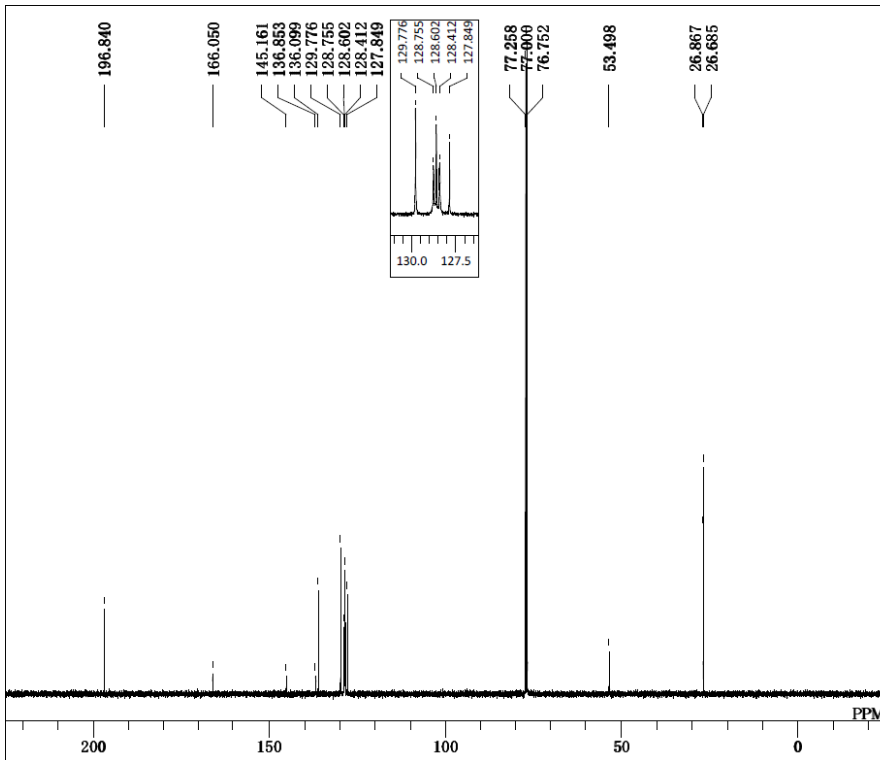
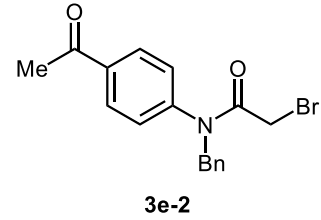
DFILE TU-02-057-1_proton-1-1.als
 COMNT single pulse
 DATIM 2017-08-04 11:09:13
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 17.9 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 38



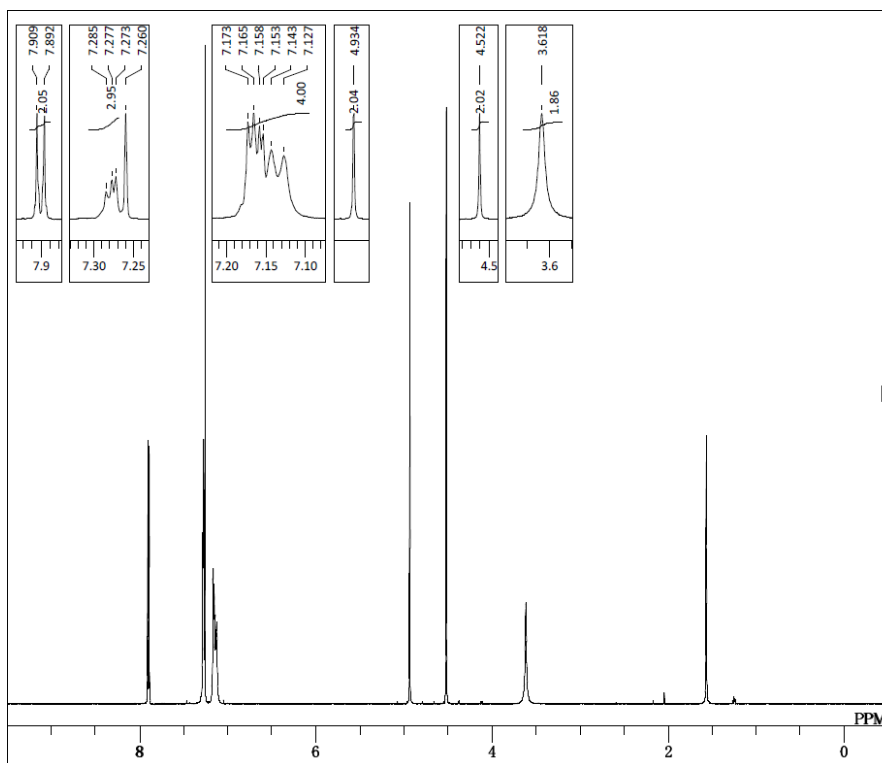
DFILE TU-02-057-1 170808_carbon-1-
 COMNT single pulse decoupled gated NO
 DATIM 2017-08-08 15:12:13
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 256
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 18.0 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60



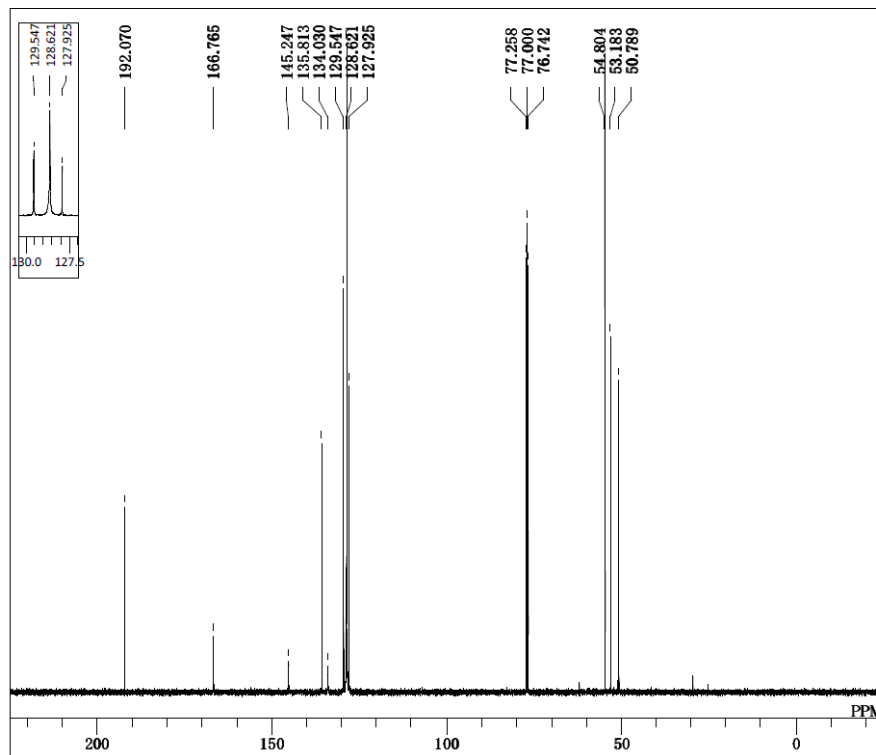
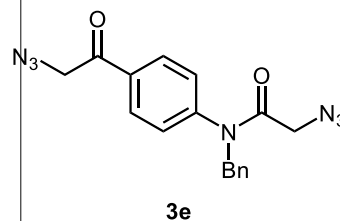
DFILE TU-02-060-3 180215_proton-1-
 COMNT single_pulse
 DATIM 2018-02-15 18:50:56
 OBNUC 1H
 EXMOD proton.jxp
 OBFRQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 15.0 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 40



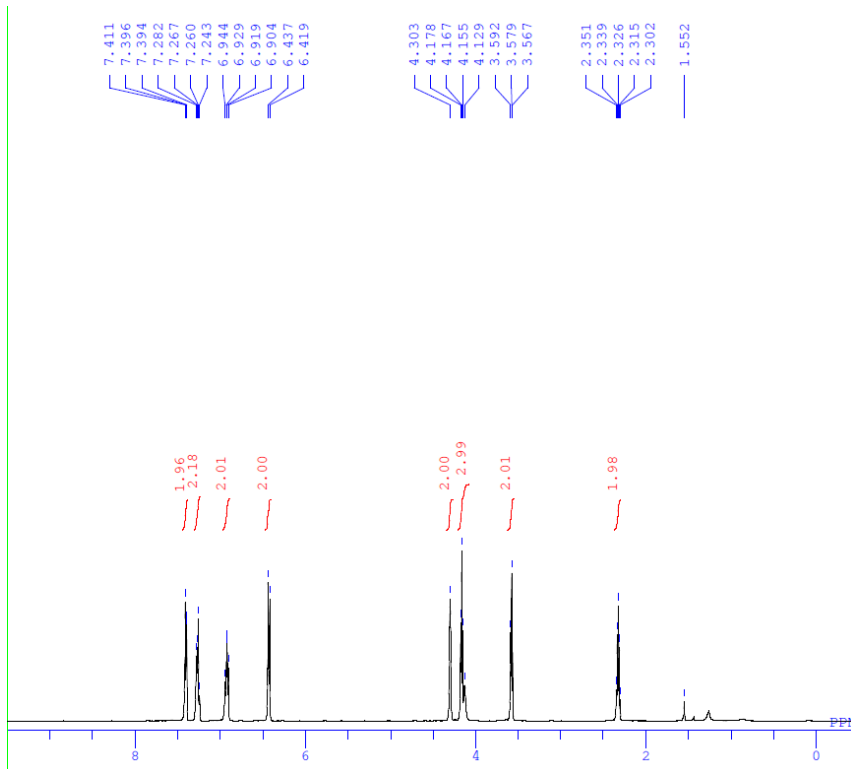
DFILE TU-02-060-3 180216_carbon-1-
 COMNT single_pulse decoupled gated NO
 DATIM 2018-02-16 20:29:26
 OBNUC 13C
 EXMOD carbon.jxp
 OBFRQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 32767
 FREQU 39308.18 Hz
 SCANS 1024
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 14.7 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60



DFILE TU-02-056-2 dry_proton-1-1.a
 COMNT single_pulse
 DATIM 2017-07-28 17:07:56
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 18.9 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 44

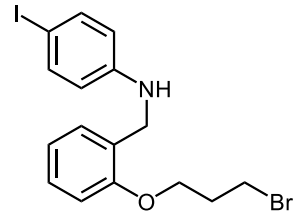


DFILE TU-02-055-2 170808_carbon-1-
 COMNT single_pulse decoupled gated NO
 DATIM 2017-08-08 19:59:57
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 32767
 FREQU 39308.18 Hz
 SCANS 1024
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 17.6 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60

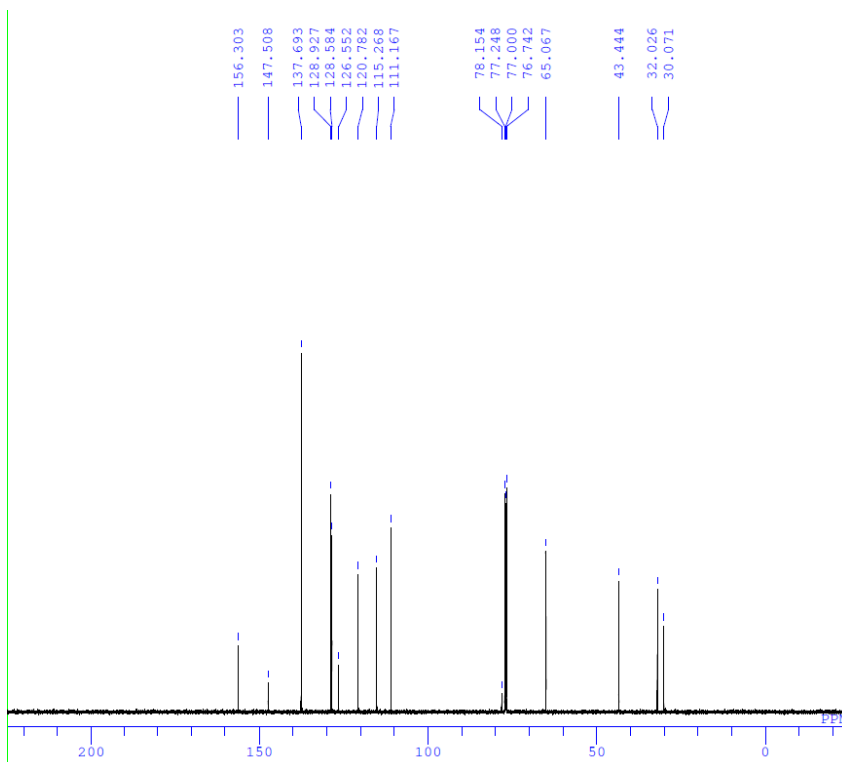


```

DFILE TY_10_029_01_proton-1-1.als
COMNT single_pulse
DATIM 2017-12-14 10:10:51
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 19.9 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 36
  
```

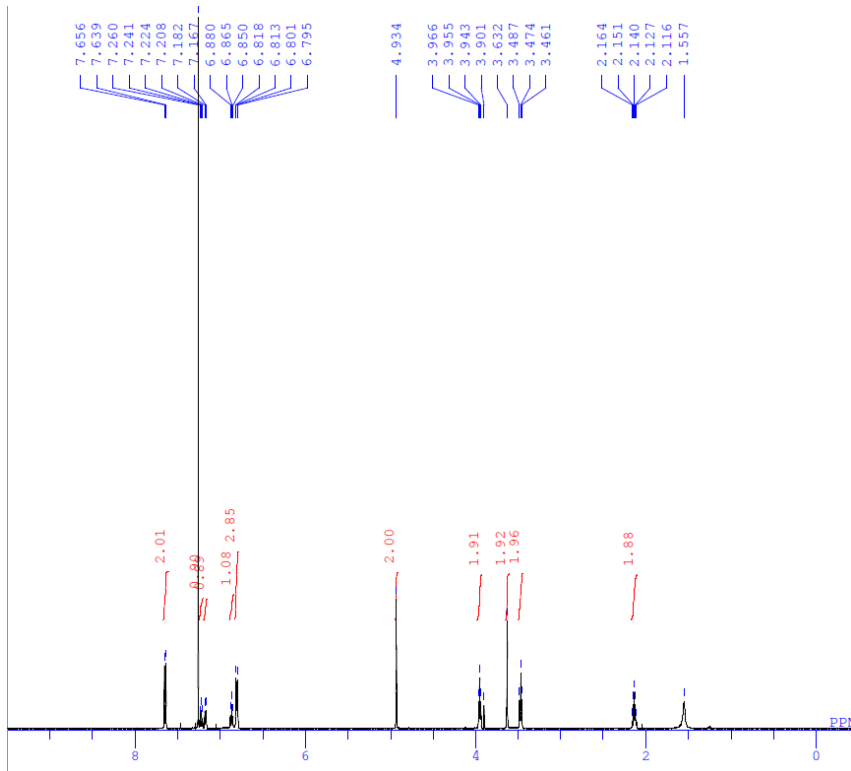


5a-1



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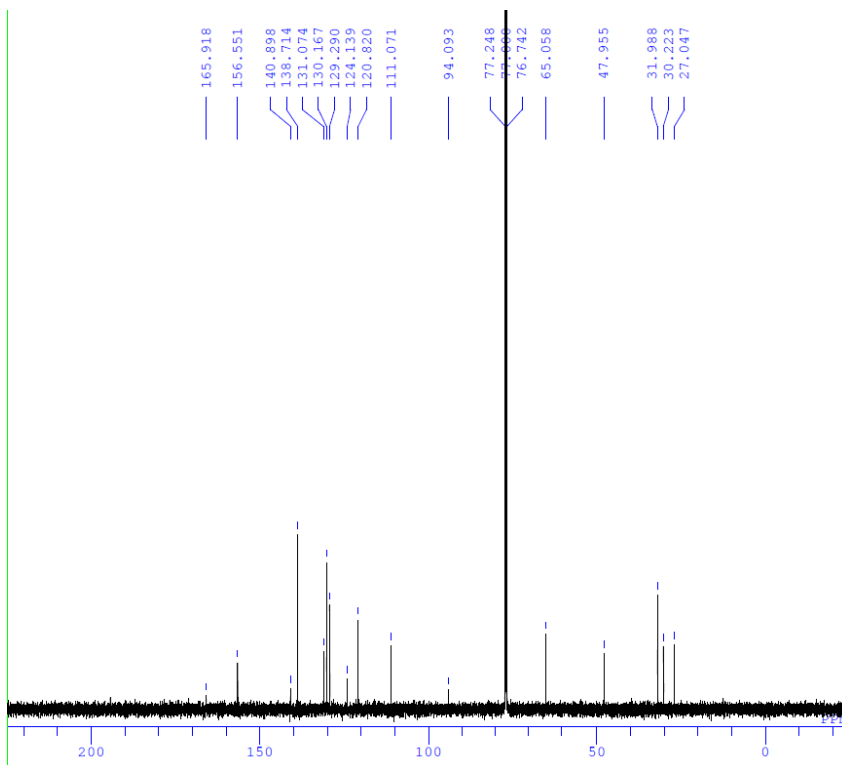
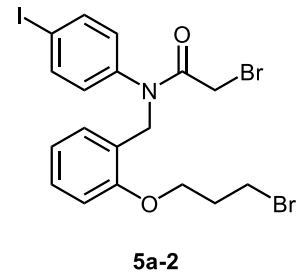
DFILE TY_10_029_01_2_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2018-02-13 15:52:32
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 1256
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 16.2 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60
  
```



```

DFILE TY_10_038_01_proton-1-1.als
COMNT single_pulse
DATIM 2017-12-21 00:50:35
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 18.4 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 50

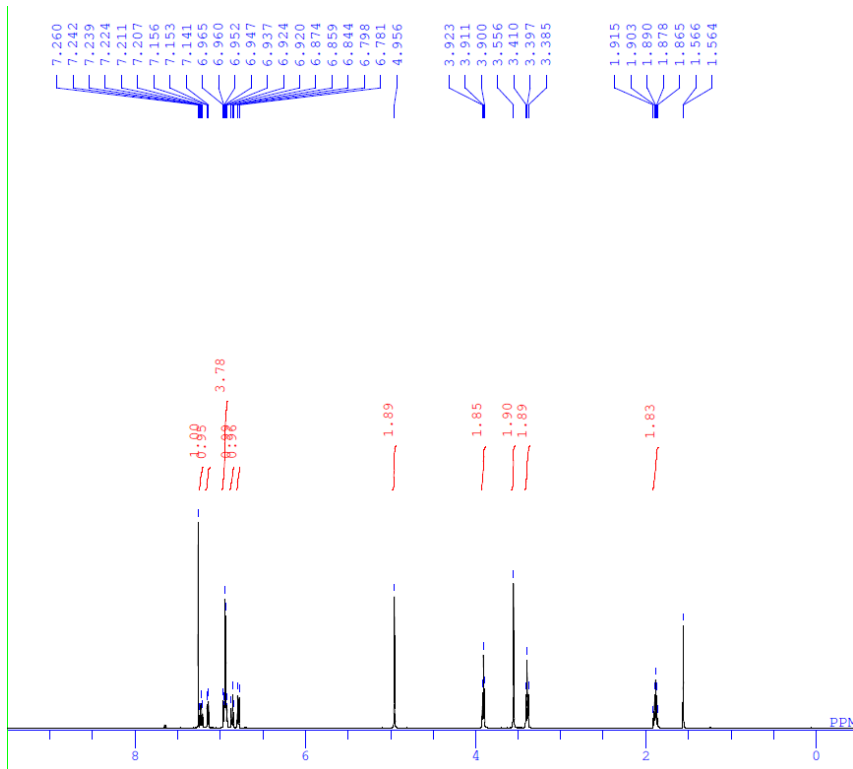
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```

DFILE TY_10_038_01_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2017-12-21 00:52:01
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 6980
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 19.7 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60

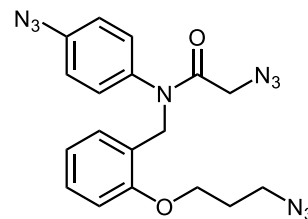
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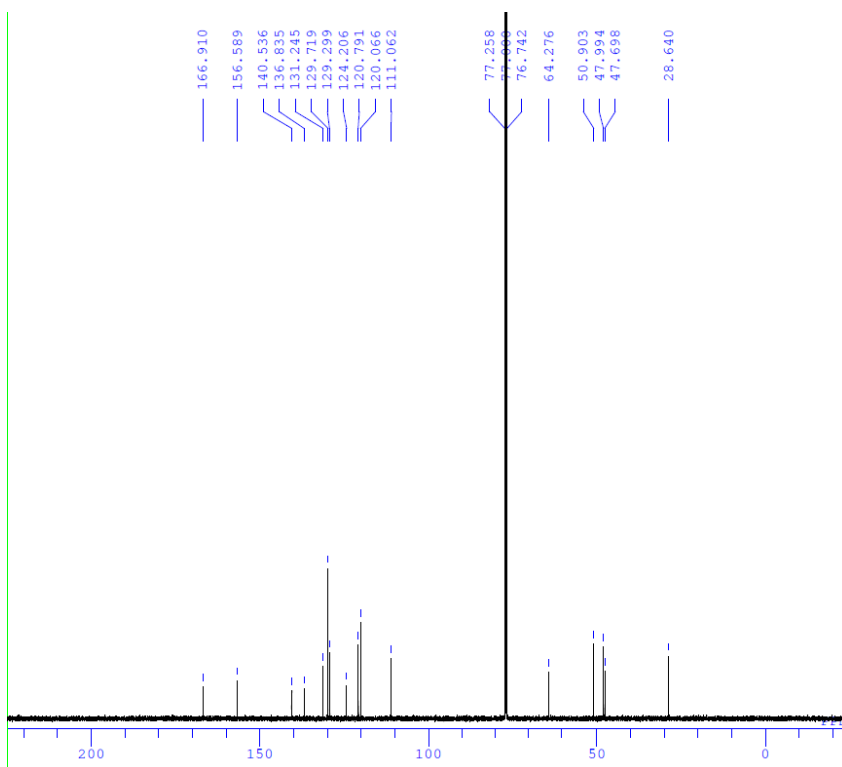
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DFILE TY_10_039_02_proton-1-1.als
COMNT single_pulse
DATIM 2017-12-21 23:12:23
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 18.5 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 48

```



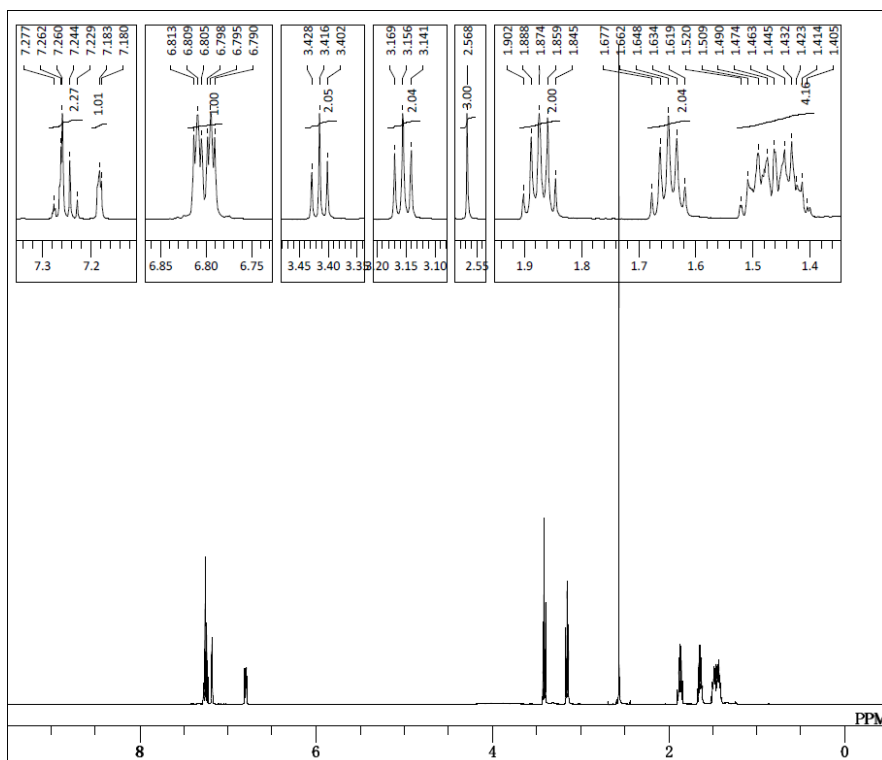
5a



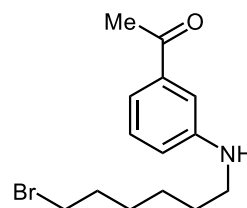
```

DFILE TY_10_039_02_carbon-1-1.als
COMNT single pulse decoupled gated
DATIM 2017-12-21 23:13:55
OBNUC 13C
EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 8920
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 19.7 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 50

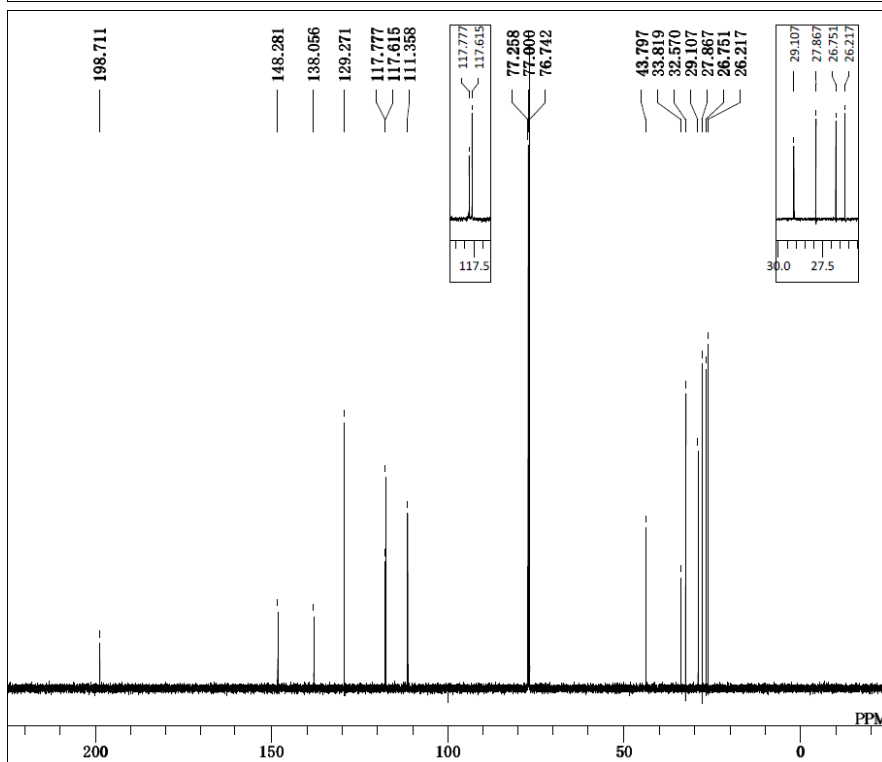
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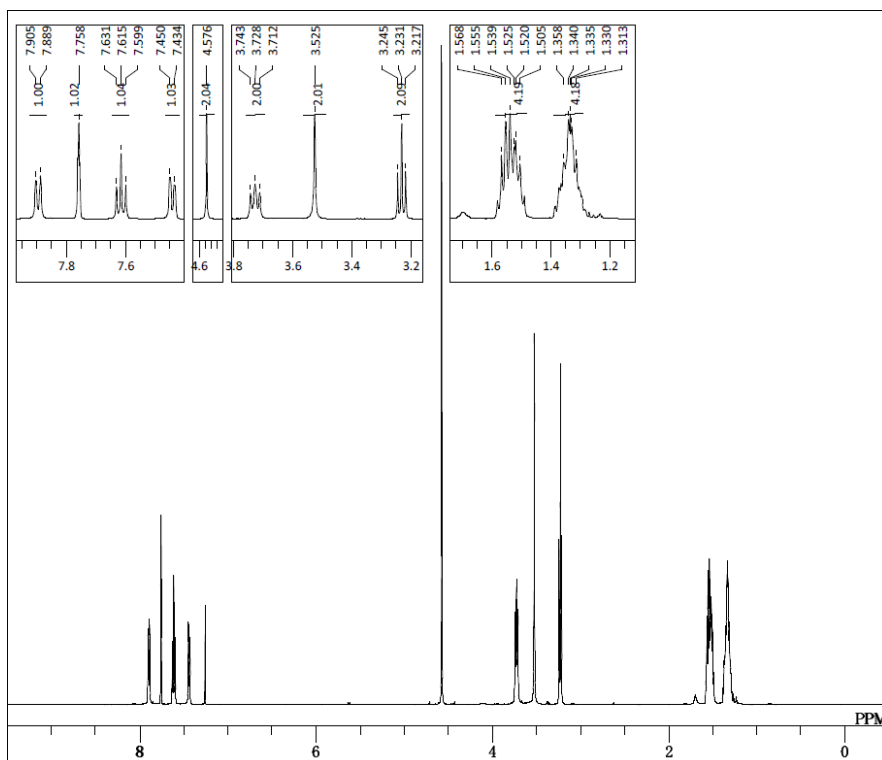
DFILE TU-02-080-2 180215_proton-1-
 COMNT single_pulse
 DATIM 2018-02-15 14:43:58
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 15.5 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 34



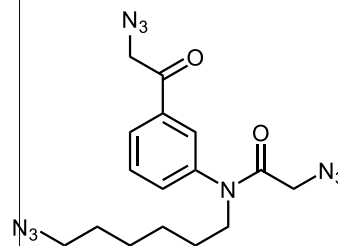
5b-1



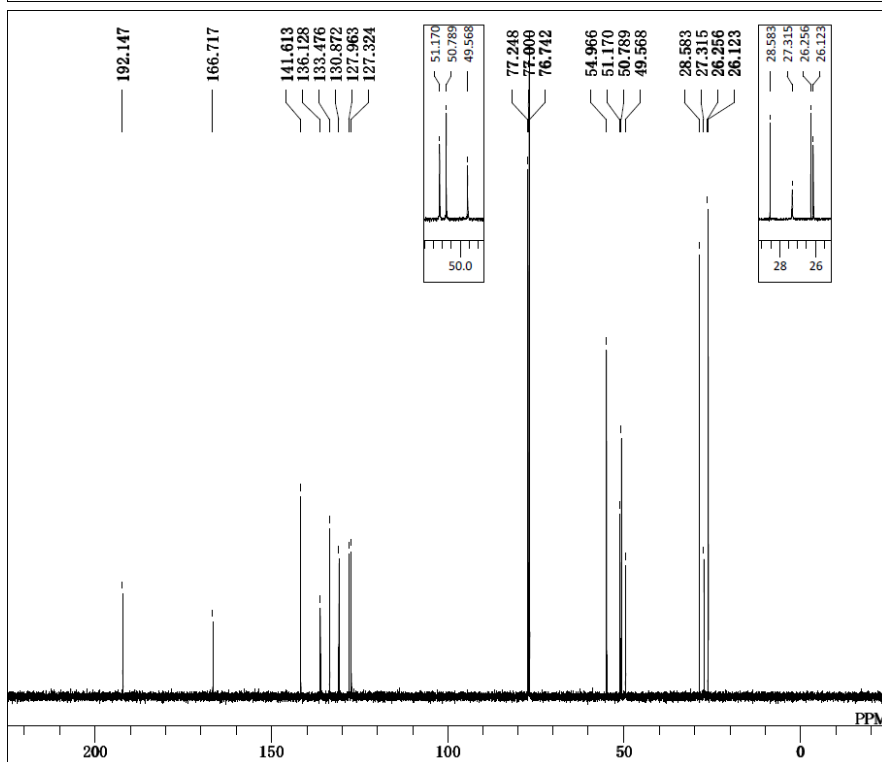
DFILE TU-02-080-2 180215_carbon-1-
 COMNT single pulse decoupled gated NO
 DATIM 2018-02-15 14:45:57
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 26214
 FREQU 31446.54 Hz
 SCANS 350
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 1H
 CTEMP 15.9 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 58



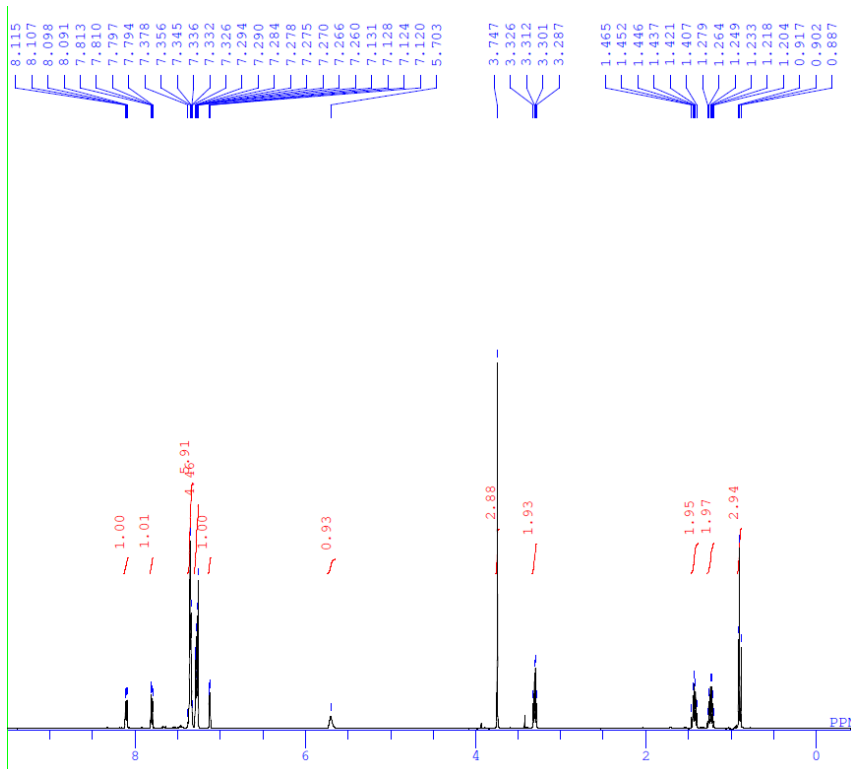
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 COMNT single_pulse
 DATIM 2017-10-13 14:28:29
 OBNUC 1H
 EXMOD proton.jxp
 OBFREQ 500.16 MHz
 OBSET 2.41 KHz
 OBFIN 6.01 Hz
 POINT 13107
 FREQU 7507.51 Hz
 SCANS 8
 ACQTM 1.7459 sec
 PD 5.0000 sec
 PW1 6.85 usec
 IRNUC 1H
 CTEMP 15.3 c
 SLVNT CDCL3
 EXREF 7.26 ppm
 BF 0.10 Hz
 RGAIN 32



5b



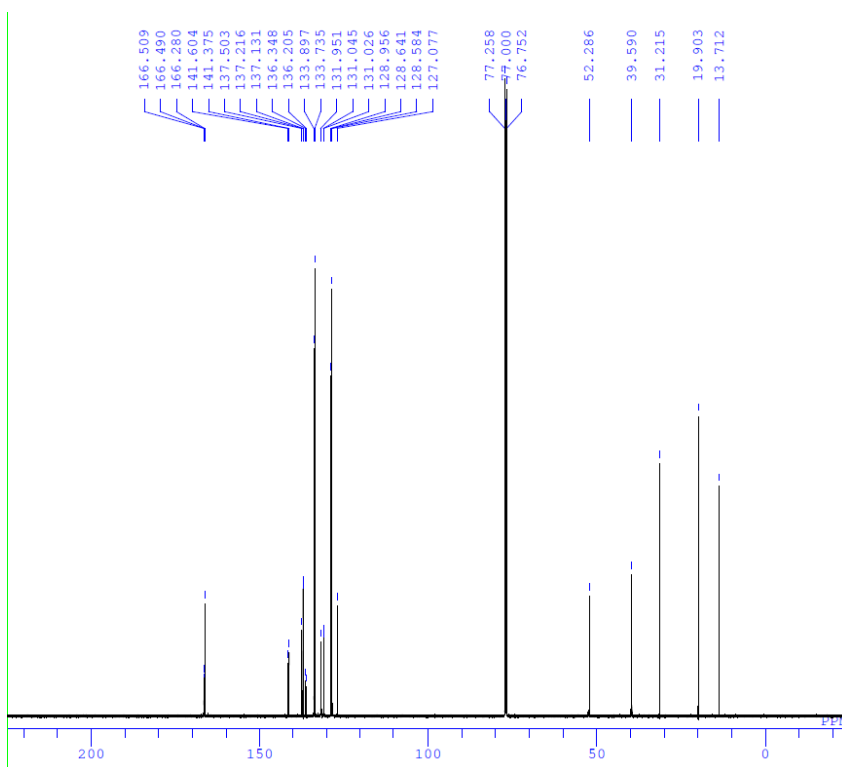
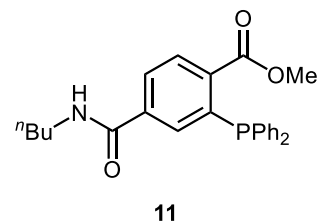
DFILE TU-02-087-2 171013_carbon-1
 COMNT single_pulse decoupled gated NO
 DATIM 2017-10-13 14:30:16
 OBNUC 13C
 EXMOD carbon.jxp
 OBFREQ 125.77 MHz
 OBSET 7.87 KHz
 OBFIN 4.21 Hz
 POINT 32767
 FREQU 39308.18 Hz
 SCANS 512
 ACQTM 0.8336 sec
 PD 2.0000 sec
 PW1 3.12 usec
 IRNUC 13C
 CTEMP 15.5 c
 SLVNT CDCL3
 EXREF 77.00 ppm
 BF 0.10 Hz
 RGAIN 60



```

DFILE TY_09_080_02_proton-1-1.als
COMNT single_pulse
DATIM 2018-02-20 23:12:14
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 13107
FREQU 7507.51 Hz
SCANS 8
ACQTM 1.7459 sec
PD 5.0000 sec
PW1 6.85 usec
IRNUC 1H
CTEMP 13.4 c
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.10 Hz
RGAIN 34

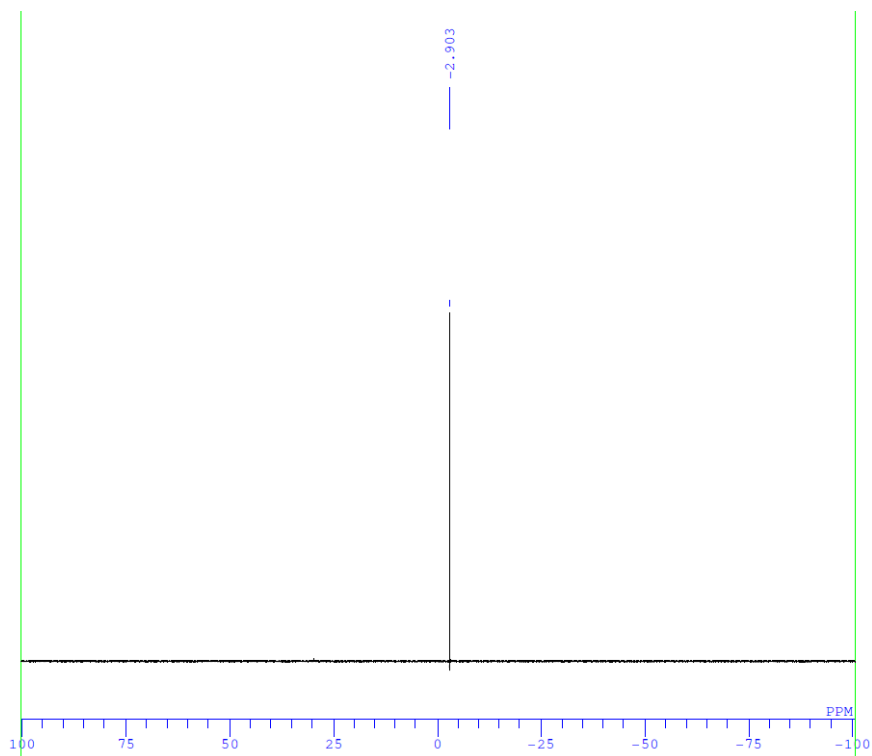
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EXMOD carbon.jxp
OBFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 26214
FREQU 31446.54 Hz
SCANS 9200
ACQTM 0.8336 sec
PD 2.0000 sec
PW1 3.12 usec
IRNUC 1H
CTEMP 15.2 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.10 Hz
RGAIN 60

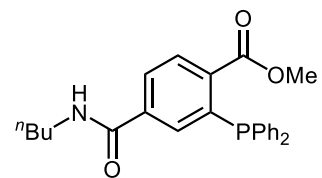
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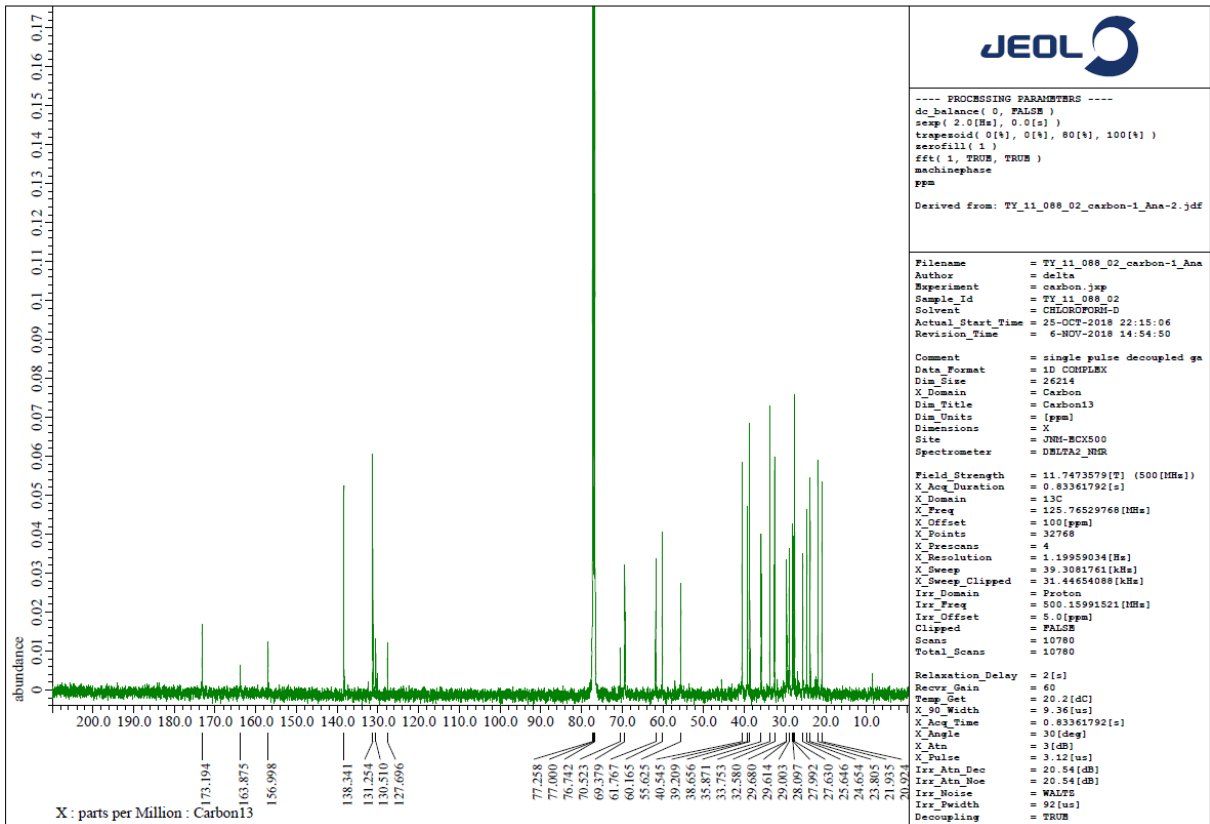
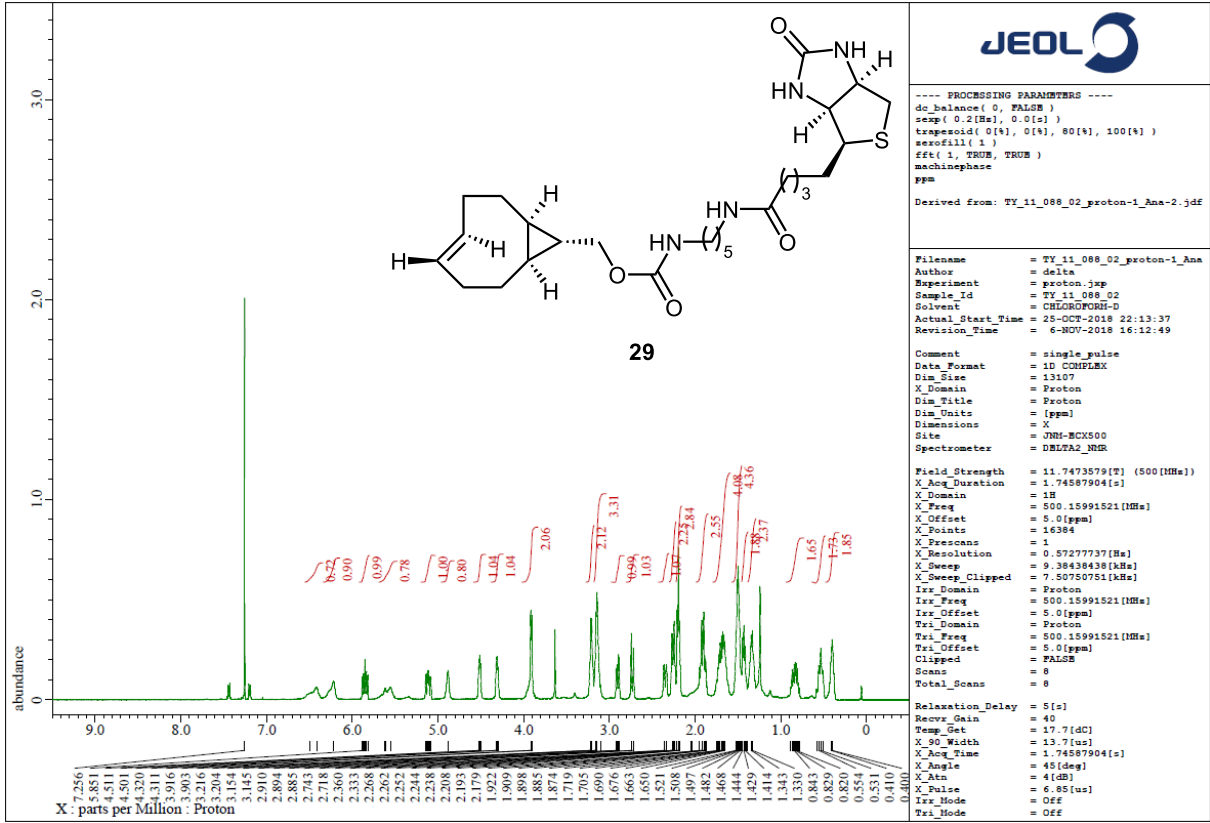
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DFILE TY_09_080_02_phosphorus-1-1.
COMNT single pulse decoupled gated
DATIM 2018-02-22 15:50:30
OBNUC 31P
EXMOD carbon.jxp
OBFRQ 202.46 MHz
OBSET 8.31 KHz
OBFIN 0.75 Hz
POINT 26214
FREQU 40650.41 Hz
SCANS 35
ACQTM 0.6449 sec
PD 2.0000 sec
PW1 3.88 usec
IRNUC 1H
CTEMP 15.2 c
SLVNT C6D6
EXREF 0.00 ppm
BF 0.10 Hz
RGAIN 56

```

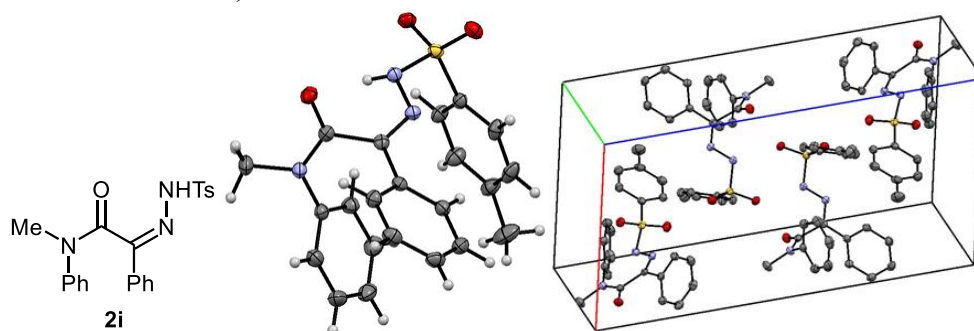


11



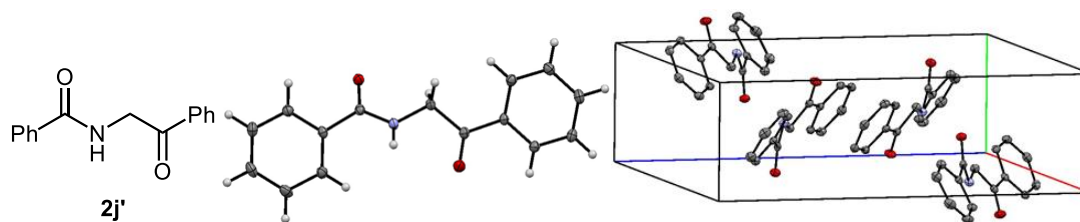
6-7 X-ray Crystallographic Analysis Information
(ORTEP thermal ellipsoids at 50% probability)

2i (CCDC No. 1839202)



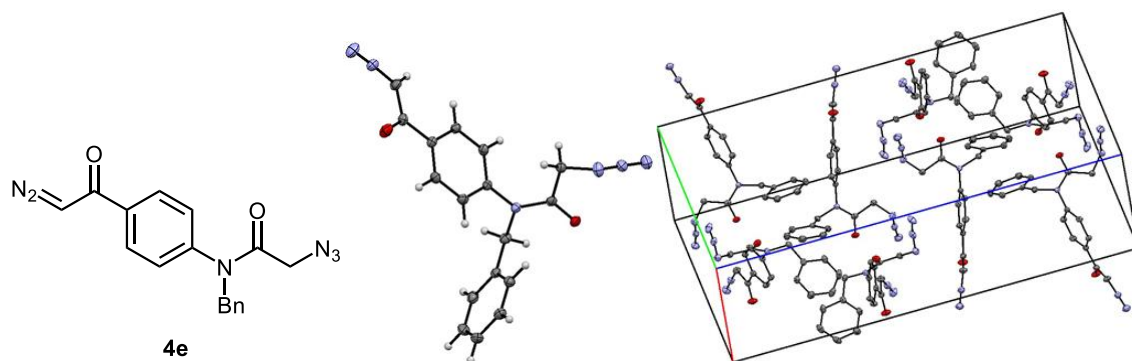
Empirical formula	C ₂₂ H ₂₁ N ₃ O ₃ S
Formula weight	407.49
Temperature	-150.0 ± 1 °C
Wavelength	MoK α (λ = 0.71075 Å)
Crystal system	monoclinic
Space group	P2 ₁ /c (#14)
Unit cell dimensions	a = 10.37797(19) Å b = 9.68067(18) Å β = 98.126(7) ° c = 20.4861(4) Å
Volume	V = 2037.48(7) Å ³
Z	4
Density (calculated)	1.328 g/cm ³
2 θ _{max}	55.0 °
Absorption coefficient μ for Mo-K α	1.873 cm ⁻¹
F(000)	856.00
Crystal size	0.120 × 0.090 × 0.020 mm
No. of reflection collected	Total: 33730 Unique: 4683 (R _{int} = 0.0325)
Transmission factor	min: 0.834, max: 0.996
Refinement method	Full-matrix least-squares on F ²
Goodness-of-fit on F ²	1.041
Final R indices [$I > 2\sigma(I)$]	R ₁ = 0.0380
R indices (all data)	R ₁ = 0.0463 wR ₂ = 0.0948
Largest diff. peak and hole	-0.35 and 0.45 e \cdot Å ⁻³

2j' (CCDC No. 1839204)

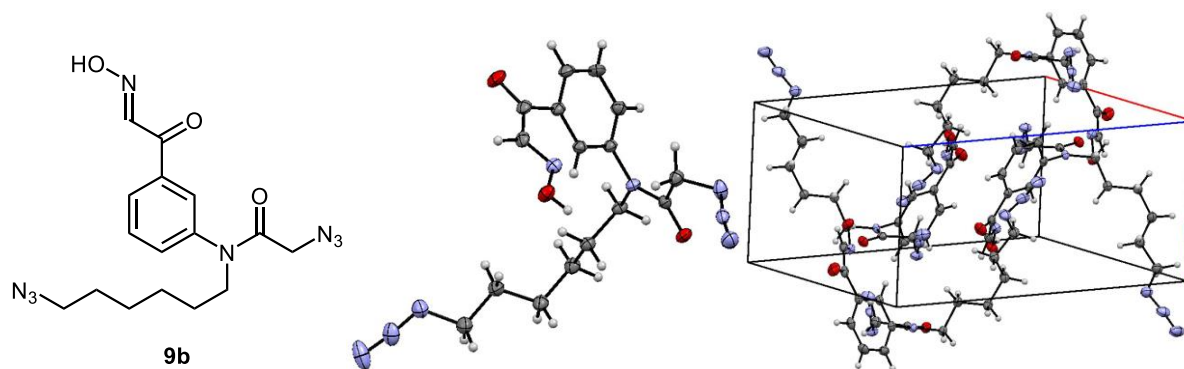


Empirical formula	C ₁₅ H ₁₃ NO ₂
Formula weight	239.27
Temperature	-170.0 ± 1 °C
Wavelength	MoKα (λ = 0.71075 Å)
Crystal system	monoclinic
Space group	P2 ₁ /c (#14)
Unit cell dimensions	a = 12.9092(4) Å b = 5.32654(15) Å β = 98.180(7) ° c = 17.0164(5) Å
Volume	V = 1158.17(6) Å ³
Z	4
Density (calculated)	1.372 g/cm ³
2θ _{max}	55.0 °
Absorption coefficient μ for Mo-Kα	0.915 cm ⁻¹
F(000)	504.00
Crystal size	0.200 × 0.130 × 0.060 mm
No. of reflection collected	Total: 10780 Unique: 2643 (R _{int} = 0.0160)
Transmission factor	min: 0.902, max: 0.995
Refinement method	Full-matrix least-squares on F ²
Goodness-of-fit on F ²	1.049
Final R indices [I > 2σ (I)]	R ₁ = 0.0361
R indices (all data)	R ₁ = 0.0397 wR ₂ = 0.0973
Largest diff. peak and hole	0.41 and -0.16 e ⁻ Å ⁻³

4e (CCDC No. 1839203)



Empirical formula	C ₁₇ H ₁₄ N ₆ O ₂
Formula weight	334.34
Temperature	-170.0 ± 1 °C
Wavelength	MoKα (λ = 0.71075 Å)
Crystal system	orthorhombic
Space group	Pbca (#61)
Unit cell dimensions	a = 8.17797(15) Å b = 14.6247(3) Å c = 27.2033(5) Å
Volume	V = 3253.52(10) Å ³
Z	8
Density (calculated)	1.365 g/cm ³
2θ _{max}	55.0 °
Absorption coefficient μ for Mo-Kα	0.951 cm ⁻¹
F(000)	1392.00
Crystal size	0.190 × 0.060 × 0.030 mm
No. of reflection collected	Total: 52120 Unique: 3740 (R _{int} = 0.0341)
Transmission factor	min: 0.890, max: 0.997
Refinement method	Full-matrix least-squares on F ²
Goodness-of-fit on F ²	1.034
Final R indices [I > 2σ (I)]	R ₁ = 0.0367
R indices (all data)	R ₁ = 0.0432 wR ₂ = 0.0897
Largest diff. peak and hole	-0.22 and 0.35 e ⁻ •Å ⁻³

9b (CCDC No. 1879115)

Empirical formula	C ₁₆ H ₂₀ N ₈ O ₃
Formula weight	372.39
Temperature	-150.0 °C
Wavelength	MoKα (λ = 0.71075 Å)
Crystal system	monoclinic
Space group	P2 ₁ /c (#14)
Unit cell dimensions	a = 13.5247(4) Å b = 7.64772(17) Å β = 97.938(7) ° c = 17.7480(5) Å
Volume	V = 1818.14(9) Å ³
Z	4
Density (calculated)	1.360 g/cm ³
2θ _{max}	50.7 °
Absorption coefficient μ for Mo-Kα	0.992 cm ⁻¹
F(000)	784.00
Crystal size	0.140 × 0.030 × 0.030 mm
No. of reflection collected	Total: 24512 Unique: 3334 (R _{int} = 0.0332)
Transmission factor	min: 0.836, max: 0.997
Refinement method	Full-matrix least-squares on F ²
Goodness-of-fit on F ²	1.046
Final R indices [I > 2σ (I)]	R ₁ = 0.0359
R indices (all data)	R ₁ = 0.0454 wR ₂ = 0.0822
Largest diff. peak and hole	-0.17 and 0.21 e ⁻ •Å ⁻³

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【論文】

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1. “Site-Selective Conversion of Azido Groups at Carbonyl α -Positions to Diazo Groups in Diazido and Triazido Compounds”
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