이학석사학위논문

Transition Metal-Catalyzed Oxygenative α-Addition and β-Alkylation of Terminal Alkynes

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CONTENTS

ABSTRACT

Described in this dissertation is the development of the transition metal-catalyzed cyclization and oxygenative nucleophilic addition of terminal alkynes which gives cyclopentane and cyclohexane carboxylic acid derivatives as products. Using terminal alkynes tethered with electrophiles such as alkyl halides, aldehydes, imines, and Michael acceptors, the reaction can be carried out with a broad range of nucleophiles such as alcohols and amines in the presence of a suitable base, oxidant and rhodium catalyst. The proposed mechanism involves the formation of a disubstituted metal vinylidene intermediate via β-alkylation followed by transfer oxygenation to form a metalloketene which then undergoes nucleophilic addition. This transformation can provide diverse ester and amide products while forming a 5- and 6-membered ring moiety.

Keyword: Disubstituted rhodium vinylidene, Metalloketene, β-Alkylation, Oxygenative α-addition, 5-Membered ring synthesis, Carbonyl synthesis

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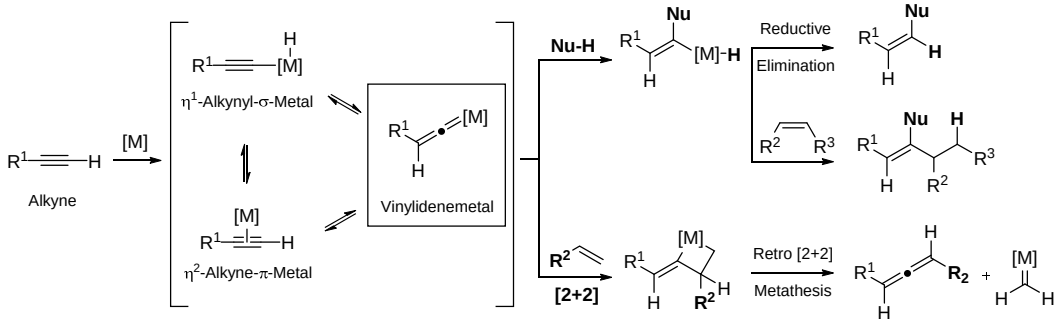
INTRODUCTION

Many strategies to prepare different functional groups from alkynes by transition metal catalysis have been studied in the modern synthetic organic chemistry. Among them, the use of transition metal vinylidene-mediated catalysis has emerged as one of the most powerful methods for alkyne functionalization.[1] Metal vinylidene intermediates have been observed to participate in various chemical reactions such as nucleophilic addition, [2+2] cycloaddition, and 6π-electrocyclization, providing substituted alkenes and allenes (Scheme 1).

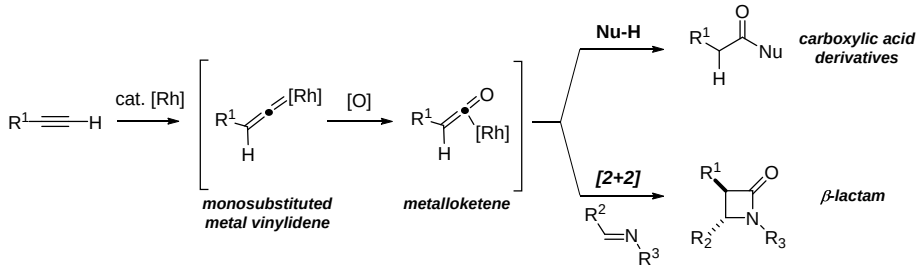


Scheme 1. Transition Metal Vinylidene-Mediated Catalysis.

Interestingly, catalytic processes based on oxidation of the metal-bound unsaturated carbene (i.e. metal vinylidene) has been slow to evolve, whereas a variety of catalytic methods have been developed making use of these reactivities observed with vinylidenemetals.

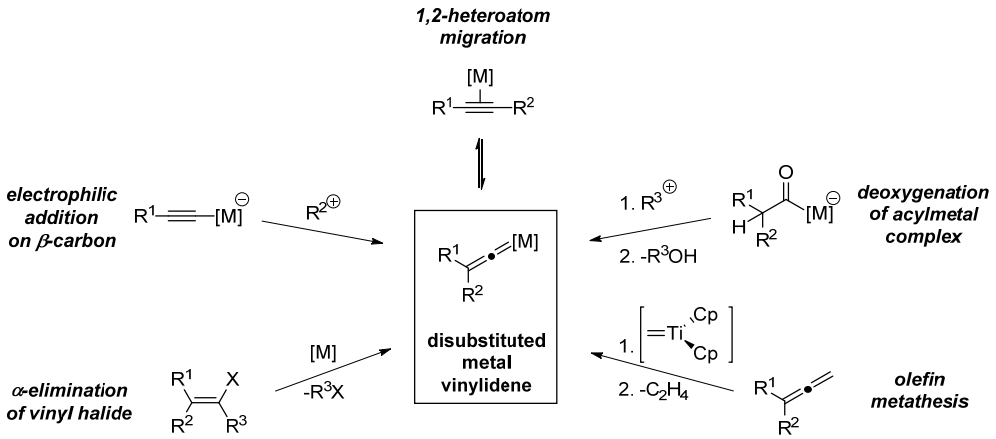
We recently found out that ketene intermediates can also be prepared by oxygenation of monosubstituted metal vinylidene species (Scheme 2). We reported a rhodium-catalyzed oxygenative nucleophilic addition and oxygenative [2+2] cycloaddition of terminal alkynes that furnishes carboxylic acid derivatives and *β*-

lactam products.[2] The proposed mechanism involves the formation of a monosubstituted metal vinylidene intermediate followed by transfer oxygenation to form a metalloketene which then undergoes nucleophilic addition and [2+2] cycloaddition .



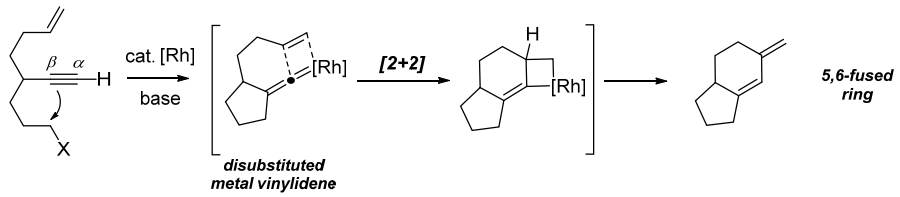
Scheme 2. Rhodium-Catalyzed Oxygenative Nucleophilic Addition/ [2+2] Cyclo-addition of Terminal Alkynes.

In the beginning of the study, our initial effort was focused on direct observation of a metalloketene intermediate for elucidating the reaction mechanism. Because monosubstituted ketenes turned out to be reactive and unstable, however, we decided to synthesize disubstituted ketenes, whose isolation was envisaged to be easier than that of monosubstituted ones.



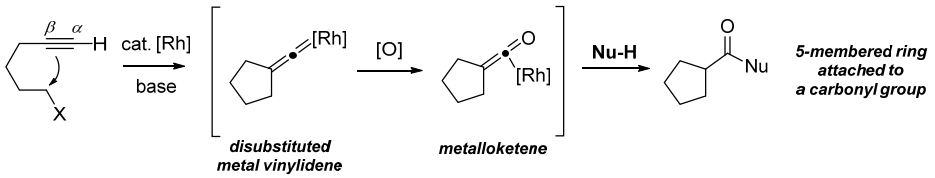
Scheme 3. Preparation of *β,β*-Disubstituted Metal Vinylidenes.

Expectedly, many methods used for generation of monosubstituted metal vinylidenes have been extended for the synthesis of disubstituted metal vinylidenes. For example, *β,β*-disubstituted metal vinylidenes can be prepared by 1,2-heteroatom migration of internal alkynes,[3] electrophilic addition of metal acetylides,[4] *α*-elimination of vinyl metal species,[5] deoxygenation of acylmetal complexes,[6] and allene metathesis of metal carbenes[7] (Scheme 3). In a similar manner to the cases of monosubstituted metal vinylidenes, disubstituted metal vinylidenes also participate in chemical reactions such as [2+2] cycloaddition and 6π-electrocyclization. However, it is important to note that *β,β*-disubstituted metal vinylidenes have been studied primarily in stoichiometric contexts, and applications in catalysis are rarely known.[8]



Scheme 4. Rhodium-Catalyzed Tandem Cylization of Terminal Alkynes via *β*-Alkylation and [2+2] Cycloaddition.

Among the few known examples, a tandem process that integrates the *β*-alkylation of metal alkynyls and a turnover of disubstituted metal vinylidene was developed in our group taking advantage of the potential of transition metal vinylidene complexes to mediate catalysis (Scheme 4).[9] This process enables multiple carbon-carbon bond formations to occur at both *α*- and *β*-positions of alkynes in one synthetic operation. This result in fact represents the first use of disubstituted metal vinylidenes for catalytic transformation.



Scheme 5. Rhodium-Catalyzed Oxygenative α-Addition and β-Alkylation of Terminal Alkynes.

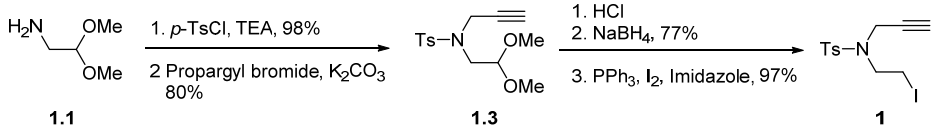
Given the feasibility of vinylidene oxidation under rhodium catalysis, we envisioned that oxidative nucleophilic addition reaction could be coupled with the catalytic formation of disubstituted metal vinylidenes, giving rise to 5-membered ring structures attached to a carbonyl group from terminal alkynes under mild conditions. This process would allow the introduction of one carbon-carbon bond and two carbon-heteroatom bonds via single catalysis.

RESULTS AND DISCUSSION

1. Reaction Discovery and Optimization

1.1 Preparation of a Model Substrate

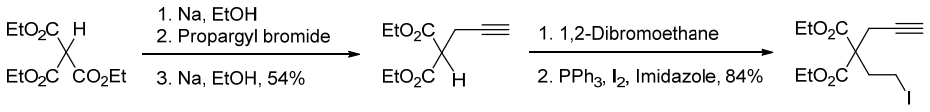
N-tosyl-tethered iodoalkyne **1** was readily synthesized from simple building blocks, amino acetal compound **1.1** and propargyl bromide, through a sequence shown in Scheme 6. Tosylation and propargylation of amino acetal **1.1** established the skeleton of the model substrate **1.3** in good yield, and the resulting acetal **1.3** was hydrolyzed under acidic conditions to give aldehyde, which was then converted to the corresponding alcohol via reduction. Subsequently, the alcohol intermediate was transformed to iodide **1** by iodination.



1.1 **1.3** **1**

Scheme 6. Synthesis of *N*-Tosyl-Tethered Iodoalkyne.

Iodoalkyne **2** was prepared in five steps from triethyl methanetricarboxylate **2.1** as illustrated in Scheme 7. First, sodium triethyl methanetricarboxylate was isolated as white flowing powder in a solution of sodium ethoxide. After then, propargylation and decarboxylation gave the desired propargyl malonate **2.3**, which subsequently underwent alkylation and iodination to form iodoalkyne **2**.

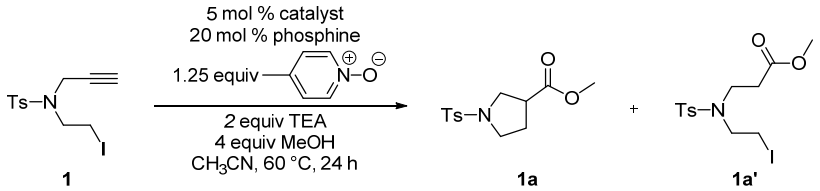


2.1 **2.3** **2**

Scheme 7. Synthesis of Diethyl Malonate-Tethered Iodoalkyne.

1.2 Reaction Optimization

Table 1. Screening of Catalysts and Ligands[a]



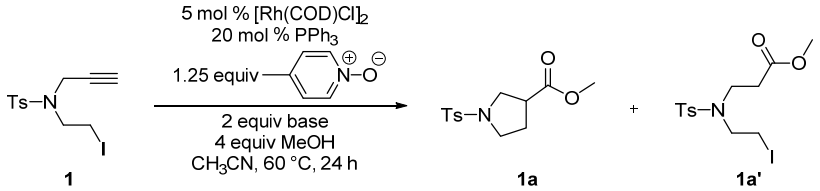
Entry	Catalyst	Ligand	**1a**[b](%)	**1a'**[b](%)
1	-	-	-	-
2[c],[d]	$CpRu(PPh_3)_2Cl$	-	9	2
3[e]	$[Ru(p\text{-}cymene)Cl]_2$	PPh_3	6	4
4[c],[f]	$TpRu(PPh_3)_2Cl$	-	-	-
5[c]	$Rh(PPh_3)_3Cl$	-	58	10
6	$[Rh(C_2H_4)Cl]_2$	PPh_3	59	7
7	$[Rh(OH)(COD)]_2$	PPh_3	61	9
8	$[Rh(COD)Cl]_2$	PPh_3	67	9
9	$[Rh(COD)Cl]_2$	$P(4\text{-}MeO\text{-}C_6H_4)_3$	61	11
10	$[Rh(COD)Cl]_2$	$P(4\text{-}F\text{-}C_6H_4)_3$	59	7
11[g]	$[Rh(COD)Cl]_2$	PPh_3	55 (75)[j]	7 (5)[j]
12[h],[i]	$[Rh(COD)Cl]_2$	PPh_3	21 (42)[j]	4 (trace)[j]

[a] All reactions were performed with 0.2 mmol of alkyne, 0.25 mmol of 4-methylpyridine *N*-oxide, 0.40 mmol of TEA, 0.8 mmol of MeOH, 5 mol % of catalyst and 20 mol % of ligand at 60 °C in CH_3CN. [b] Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] 10 mol % of catalyst was used. [d] Conversion was 22%. [e] Conversion was 89%. [f] Conversion was 57%. [g] 3 mol % of catalyst and 12 mol % of phosphine ligand were used. [h] 1 mol % of catalyst and 4 mol % of phosphine ligand were used. [i] Conversion was 85% for 48 h. [j] Values in parentheses are product yields when 6 equiv of TEA were used.

With model substrates **1** and **2** prepared, we first set out to examine the efficacy of the catalytic transformation of **1** to **1a**. We employed a set of metal complexes known to mediate catalysis via vinylidene formations to conduct a series of screening experiments (Table 1). As expected, no reaction took place in the catalyst-free conditions, which only employed a base and an oxidant

(entry 1). A first hint of the feasibility of the reaction came from the reaction using $CpRu(PPh_3)_2Cl$ catalysts that did produce the desired product **1a** but in very low yield (≤9%), while mostly returning unreacted **1** (entry 2). However, further screening with other ruthenium catalysts did not give improvement (entries 3 and 4). In contrast, in the presence of a rhodium catalyst, the starting material was completely consumed to give rise to **1a** in 58-61% yield (entries 5-7). Most rhodium catalysts showed good activity, among which $[Rh(COD)Cl]_2$ in combination with PPh_3 provided the best result (entry 8). A brief examination of phosphine ligands revealed that the electronic character of arylphosphine ligands might not be an important factor in this transformation (entries 8-10). The rhodium-catalyzed oxygenative addition reaction was less efficient when the catalyst loading was decreased to 3.0 mol %, which afforded **1a** in 55% yield (entry 11). When 1.0 mol % of rhodium catalyst was used, complete conversion was not observed even in 2 days while only 21% of the desired product **1a** was obtained from the reaction (entry 12). The catalyst half-life appeared to be quite short as more than 3.0 mol % of the rhodium catalyst was required for good conversion of these reactions. Further screening revealed that 10 mol % of rhodium catalyst could reduce the reaction times, but there were no significant differences in yields when 5.0 mol % catalysts were used. Therefore, the use of 5 mol % of $[Rh(COD)Cl]_2$ and 20 mol % of PPh_3 was determined to be an optimal catalytic system, which gave an yield of 67% (entry 8).

Table 2. Screening of Bases[a]



Entry	Base	**1a**[b](%)	**1a'**[b](%)
1	-	-	62
2[c]	Pyridine	6	53
3	*N*-Methylmorpholine	18	58
4	DBU	25	-
5	DABCO	46	19
6	DIPEA	54	12
7	TEA	66	13
8[d]	TEA	74	3
9[e]	TEA	75	2
10	Cs_2CO_3	25	-

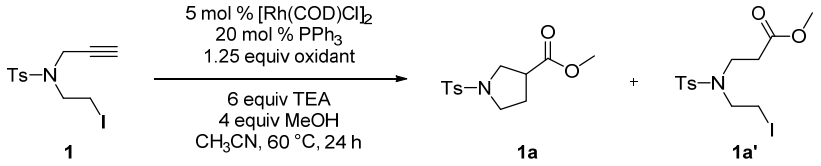
[a] All reactions were performed with 0.2 mmol of alkyne, 0.25 mmol of 4-methylpyridine *N*-oxide, 0.40 mmol of base, 0.8 mmol of MeOH, 5 mol% of $[Rh(COD)Cl]_2$ and 20 mol% of PPh_3 at 60 °C in CH_3CN. [b] Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] Conversion ratio was for 24 h. [d] 6 equiv of TEA was used. [e] 20 equiv of TEA was used.

With an effective catalyst identified, we next investigated the base which would undoubtedly affect the generation of a metal alkynyl. In the absence of a base, the reaction gave only side product **1a'** after 19 h (62%), which was generated by oxygenative nucleophilic addition without the intramolecular cyclization via *β*-alkylation (entry 1). When pyridine was used as a base, the conversion of starting material was not complete and only 6% yield of the product **1a** was obtained from the reaction (entry 2). The use of *N*-methylmolpholine, an efficient base in Rh-catalyzed alkylation/[2+2]

cycloaddition, afforded only a 18% yield of **1a** (entry 3). When the strong amine base DBU was used, formation of the desired product **1a** was observed, but only in 25% yield (entry 4). The reaction could also be carried out with DABCO, albeit with only a slight increase in yield (entry 5). Further screening revealed that trialkylamines such as DIPEA and TEA are competent, but TEA is a better base increasing the yield to 66% (entries 6 and 7).

With TEA shown to be the optimal base, we set out to examine the effect of its amount. Interestingly, it was found that the higher the base equivalent was, the higher the yield of desired product **1a** and the lower the yield of side product **1a'** were. Also, faster conversion was observed with increased amounts of a base (entries 8 and 9). However, the use of more than 6 equivalents of base did not result in further improvement. When more than 6 equivalents of bases were employed, more than 90% of alkyne **1** was consumed within 15 min and complete conversion was observed within 40 min. Thus, the reaction of **1** with 6 equivalent of TEA could afford **1a** in 74% yield along with only 3% yield of side product **1a'.**

Table 3. Screening of Oxidants[a]



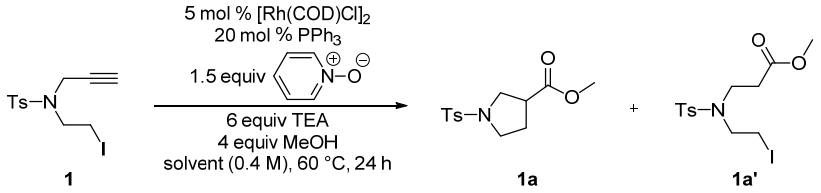
Entry	Oxidant	**1a**[b](%)	**1a'**[b](%)
1[d]	*N*-Methylmorpholine *N*-oxide	-	-
2	Pyridine *N*-oxide	78	2
3[c],[e]	Pyridine *N*-oxide	82	4
4	4-Picoline *N*-oxide	75	3
5	4-Phenylpyridine *N*-oxide	77	2
6	2-Phenylpyridine *N*-oxide	74	-
7[d]	4-Methoxypyridine *N*-oxide	55	11
8[d]	4-(Dimethylamino)pyridine *N*-oxide	46	16
9[d]	4-Acetylpyridine *N*-oxide	42	-
10[d]	3,5-Dibromopyridine *N*-oxide	11	-
11[d]	3,5-Dichloropyridine *N*-oxide	8	-
12[d]	2,6-Lutidine *N*-oxide	-	-

[a] All reactions were performed with 0.2 mmol of alkyne, 0.25 mmol of oxidant, 1.2 mmol of TEA, 0.8 mmol of MeOH, 5 mol% of $[Rh(COD)Cl]_2$ and 20 mol% of PPh_3 at 60 °C in CH_3CN. [b] Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] 1.5 equiv of oxidant was used. [d] 2 equiv of TEA was used. [e] Isolated yield.

Having established the feasibility of oxygenative alkyne addition concomitantly with an intramolecular *β*-alkylation, we next turned our attention to screening of the ability of various *N*-oxides to serve as oxygen donors in the oxygenative coupling of alkyne with methanol. As observed in our previous studies, the most popular oxygen donor NMO was ineffective for this reaction, leading to rapid decomposition of the rhodium catalyst (entry 1). In sharp contrast, when pyridine *N*-oxide was used as an oxidant, desired product **1a** was produced in 78% yield (entry 2).

The conversion efficiency of vinylidenemetal to metalloketene mediated by an oxidant should have a considerable effect on the overall reaction yield. Thus, a variety of pyridine *N*-oxide derivatives having an electron-donating or –withdrawing group were examined. Indeed, the efficiency of the transformation correlates with the electronic character of the oxidant (Table 3). Pyridine *N*-oxide oxidants that have an electron-donating group (entries 2-8) give better results than those having an electron-withdrawing group (entries 9-11). The use of 2,6-lutidine *N*-oxide was none-too-promising, as no reaction took place presumably due to steric hinderance caused by 2,6-methyl substituents (entry 12). However, an increase of electron density in the *N*-oxide by methoxy- or dimethylamino-group led to the raised yield of the side product **1a'** (entries 7 and 8). This result implies that these oxidants had powerful ability to donate an oxygen to monosubstituted metal vinylidene intermediates prior to the *β*-alkylation. On the other hand, oxidants having an electron-withdrawing group were not efficient for this transformation, but the use of them led to producing only desired product with none of the side product (entries 9-11). Although optimal results were obtained from the use of pyridine *N*-oxide and 4-phenylpyridine *N*-oxide, the former presented a handling problem due to its high hygroscopic property and the latter was prohibitively expensive. Therefore, it was decided to employ 1.5 equiv of pyridine *N*-oxide instead of 4-phenylpyridine *N*-oxide (entries 3 vs 5).

Table 4. Screening of Solvents[a]



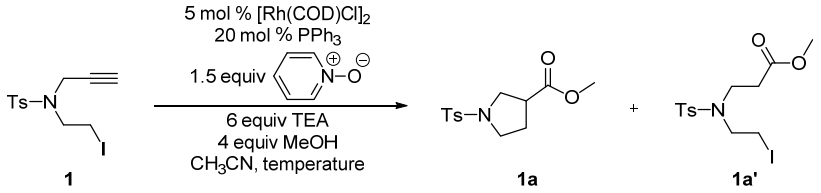
Entry	Solvent	**1a**[b](%)	**1a'**[b](%)
1	Dioxane	5	9
2	THF	-	-
3[c]	$CHCl_3$	-	-
4	DCE	5	trace
5	Acetone	-	-
6[d]	DMF	18	-
7	DMSO	11	-
8	CH_3CN	80	2
9[e]	CH_3CN	78	2
10	MeOH	-	-

[a] All reactions were performed with 0.2 mmol of alkyne, 0.3 mmol of pyridine *N*-oxide, 1.2 mmol of TEA, 0.8 mmol of MeOH, 5 mol % of $[Rh(COD)Cl]_2$ and 20 mol % of PPh_3 at 60 °C in indicated solvent. [b] Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] Conversion was 70% for 24 h. [d] in 0.25 M at 85 °C. [e] in 0.25 M.

Solvent screening experiments revealed that the efficiency of the reaction depends significantly on the solvent. The use of THF, $CHCl_3$, acetone and MeOH as a reaction solvent led to decomposition, producing only an intractable mixture with none of the desired product (entries 2, 3, 5, and 10). Further screening revealed that dioxane, DCE and DMSO are not competent (entries 1, 4, and 7). Whereas only a 18% yield of **1a** was obtained from a reaction in DMF at 85 °C for 24 h (entry 6), the yield of the transformation could be boosted by using CH_3CN. Under these conditions, complete conversion was observed within 40 min to provide **1a** in 80% yield (entry 8). In addition, various

concentrations were screened. Increasing the concentration from 0.25 M to 0.4 M increased the yield and reaction rates (entries 8 and 9). In a reaction carried out at less than 0.1 M in CH_3CN, the starting materials were not completely consumed, and the expected product **1a** or **1a'** was barely observed. The reaction could be carried out in CH_3CN at more than 0.5 M, albeit with a slight reduction in the yield of the desired product **1a**.

Table 5. Screening of Reaction Temperatures[a]



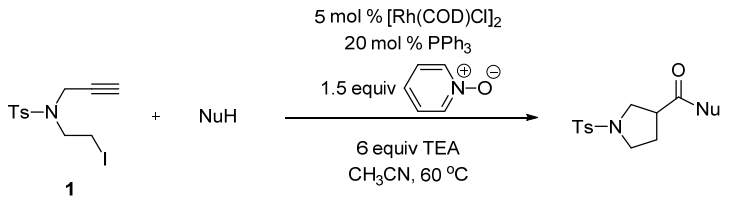
Entry	Temperature (°C)	Time (h)	**1a**[b](%)	**1a'**[b](%)
1	RT	48	63	3
2	40	<24	77	3
3	50	<4	77	3
4	60	0.5	82	4
5	70	<0.15	72	2
6	80	<0.15	78	2

[a] All reactions were performed with 0.2 mmol of alkyne, 0.3 mmol of pyridine *N*-oxide, 1.2 mmol of TEA, 0.8 mmol of MeOH, 5 mol% of $[Rh(COD)Cl]_2$ and 20 mol% of PPh_3 at indicated temperature(°C) in 0.4M of CH_3CN. [b] Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

The CH_3CN solvent provided the formation of **1a** at room temperature although a reaction time of 2 days was need for the complete conversion of **1** (Table 5, entry 1). Further reaction temperature screening revealed that the complete conversion of **1** could be achieved within 10 min when the reaction was run at 70 °C or 80 °C. However, a slightly lower temperature, 60 °C, was found to be optimal increasing the yield to 82% (entries 4-6).

2. Nucleophile Scope

Table 6. Reaction Scope with Various Alcohols and Amines[a]

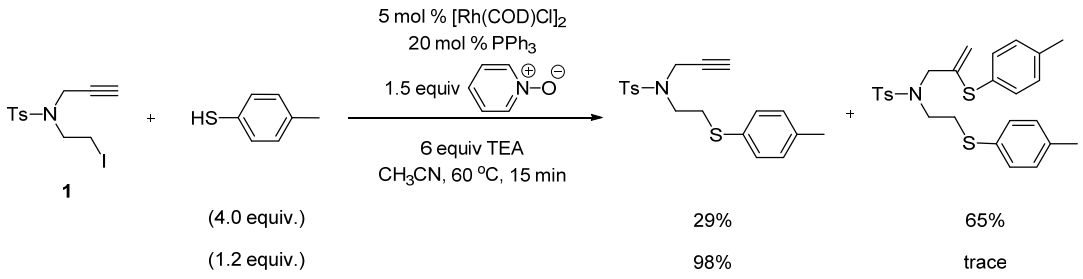


Entry	NuH	Time (h)	Yield[b](%)
1	Ethyl alcohol	1	68 **(1a-1)**
2	Isopropyl alcohol	1.5	56 **(1b)**
3	*tert*-Butyl alcohol	0.5	30 **(1c)**
4	Phenol	1	77 **(1d)**
5[c]	H_2O	2	72 **(1e)**
6	Diethylamine	2	85 **(1g)**
7	Aniline	1	74 **(1h)**
8	*N*-Methylaniline	1	68 **(1i)**

[a] All reactions were performed with 0.5 mmol of alkyne, 2.0 mmol of alcohol and 0.6 mmol of amine in 1.25 ml of solvent at 60 °C. [b] Isolated yield. [c] H_2O (5 mmol).

With these optimized conditions in hand, we tested various nucleophiles to probe the scope and limitations of the alkylation and oxygenative coupling reaction. As summarized in Table 6, the diversity of nucleophiles suitable for this reaction proved quite extensive. In the reactions of alkyne **1**, both aliphatic and aromatic alcohols and amines were found to be competent nucleophiles to give ester and amide products (entries 1-4, 6-8). Especially, these amide-forming reactions benefited from the use of free amines rather than ammonium salts as nucleophiles, as higher yields were obtained from the reactions of free amines compared to those of amine salts, but further studies are need (entry 6). Notably, the reaction proceeded well in wet acetonitrile to furnish a carboxylic acid as the

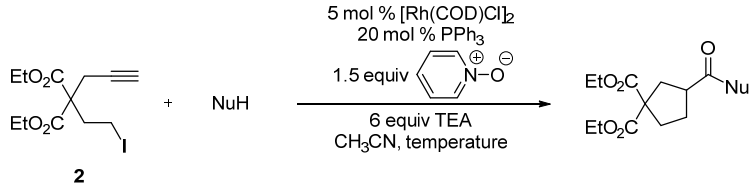
product (entry 5). The findings from this study are significant in several respects. They demonstrate that terminal alkynes can be directly transformed into carboxylic acid derivatives with concomitant alkylation under mild rhodium catalysis by a novel catalytic mechanism. Also, the rich chemistry of ketenes might be harnessed in the context of catalytic alkyne functionalization.



Scheme 8. 4-Methylbenzenethiol as a Nucleophile in the Rh-Catalyzed Cyclization.

In addition, we examined whether thiols could also participate well in the reaction to give rise to thioesters (Scheme 8). However, the use of 4-methylbenzenethiol as a nucleophile afforded undesired products via thiol substitution with the alkyl iodide and hydrothiolation of the alkyne.[10]

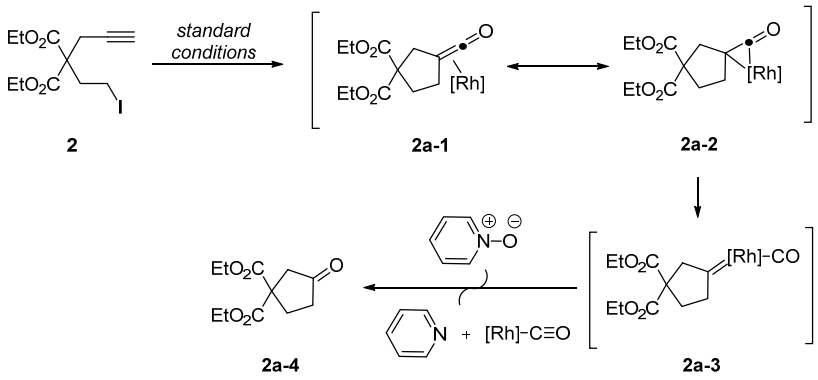
Table 7. Reaction Scope with Various Alcohols and Amines[a]



Entry	NuH	Time (h)	Yield[b](%)
1	Methyl alcohol	2	96 **(2a)**
2	Isopropyl alcohol	2	81 **(2b)**
3	*tert*-Butyl alcohol	2.5	32 **(2c)**
4	Phenol	1.5	97 **(2d)**
5[c]	H_2O	2	77 **(2e)**
6[d]	*N*-hydroxyphthalimide	1	77 **(2f)**
7	Diethylamine	1	92 **(2g)**
8	Aniline	2	89 **(2h)**
9	*N*-Methylaniline	2	83 **(2i)**

[a] All reactions were performed with 0.5 mmol of alkyne, 2.0 mmol of alcohol and 0.6 mmol of amine in 2.0 ml of CH_3CN at 60 ^oC. [b] Isolated yield. [c] H_2O (5 mmol). [d] *N*-hydroxyphthalimide (1 mmol)

We additionally attempted to probe the scope of this reaction with malonate-tethered haloalkyne **2** using alcohol and arylamine nucleophiles (Table 7). Whereas cyclization of *N*-Tosyl alkyne **1** afforded product **1a** in a maximum yield of 82% yield, the yield of cyclization could be significantly enhanced with this malonate-tethered substrate. When alkyne **2** was employed, various alcohol and amine afforded the corresponding esters and amides in improved yields up to 97%.



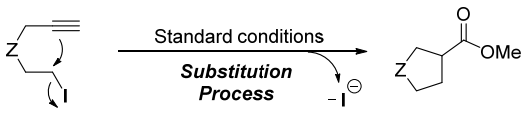
Scheme 9. Formation of Cyclopentanone **2a-4** via Rhodium Ketene Complexes.

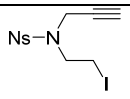
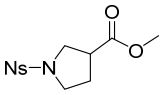
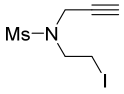
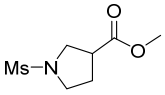
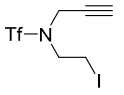
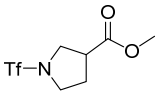
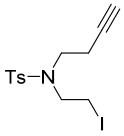
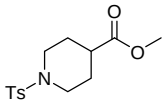
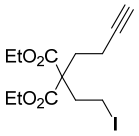
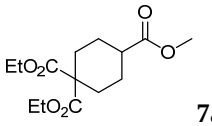
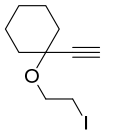
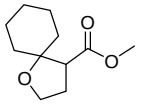
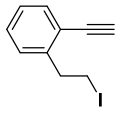
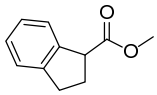
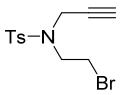
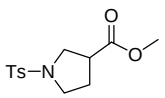
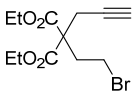
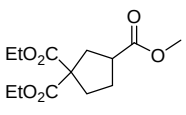
Furthermore, when alkyne **2** was subjected to the standard conditions using *tert*-butyl alcohol as a nucleophile, we observed formation of cyclopentanone **2a-4** in 12% yield (Scheme 9). The isolation of cyclopentanone **2a-4** lends support to the intermediacy of a ketene species, which was generated presumably by the oxidation of alkylidene **2a-3** derived from CO deinsertion of rhodium ketene complex **2a-1**/**2a-2**.

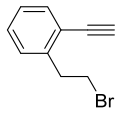
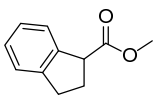
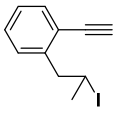
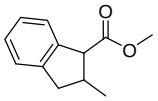
3. Substrate Scope

3.1. via *β*-Alkylation

Table 8. Reaction Scopes with Various Alkynyl Iodides[a]



Entry	Reactant	Product	Time (h)	Yield[b](%)
1	 **3**	 **3a**	1.5	75
2	 **4**	 **4a**	0.5	74
3	 **5**	 **5a**	0.5	66
4[c]	 **6**	 **6a**	2	53
5[c]	 **7**	 **7a**	4	41
6	 **8**	 **8a**	2	79
7	 **9**	 **9a**	0.2	52
8	 **10**	 **1a**	1	42[d]
9	 **11**	 **2a**	2.5	95

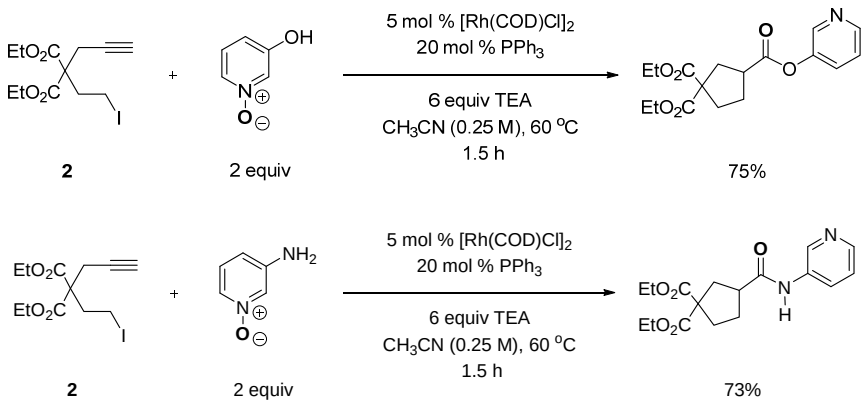
10	 **12**	 **9a**	2	57
11	 **13**	 **13a**	0.2	40[e]

[a] All reactions were performed with 0.5 mmol of alkyne, 0.75 mmol of pyridine *N*-oxide, 3.0 mmol of TEA, 2.0 mmol of MeOH, 5 mol% of $[Rh(COD)Cl]_2$ and 20 mol% of PPh_3 at 60 °C in CH_3CN. [b] Isolated yield.[c] 1.5 equiv of 2-phenylpyridine *N*-oxide was used instead of pyridine *N*-oxide as an oxidant. [d] at 75 °C [e] Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

Having established a broad scope with regard to nucleophiles, we next turned our attention to examining reaction efficiency with a range of alkyne substrates (Table 8).

Terminal alkynes with various sulfonate groups proceeded well to give the corresponding azacycles in good yields (entries 1, 2 and 3). Interestingly, when *N*-tosyl-tethered homopropargyl alkyne was subjected to the standard conditions, the desired product was formed in 53% yield, which was slightly more efficient to malonate-tethered substrate (entries 4 and 5). Gratifyingly, 5-membered oxacycle as well as carbocycle were accessed from the corresponding alkynyl iodides (entries 6 and 7). In addition to alkynyl iodides, a cyclization of alkyne could be performed with bromo substrates (entries 8, 9, and 10). Similarly to the results of the model studies, malonate-tethered substrates were cyclized more efficiently than *N*-tosyl-tethered substrates providing higher yields in longer reaction times. Unfortunately, the corresponding chloride substrates did not give the desired product. In the case of the chloride, the simple oxygenative α-addition took place to give rise to side products without the β-alkylation as a consequence of the low reactivity of the chloride as a leaving group.

When secondary iodide was subjected to the standard conditions, we observed the formation of the desired product in 40% yield in only 10 minutes (entry 11). A rapid decomposition process seemed to be operative independent of the desired product formation, a serious problem encountered in most cases.

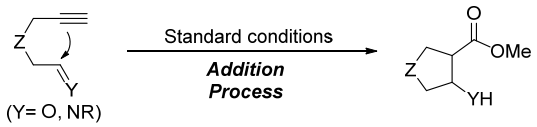


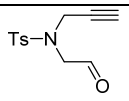
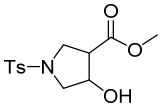
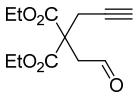
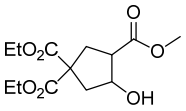
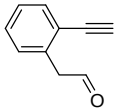
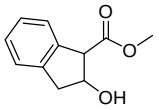
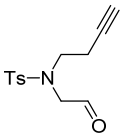
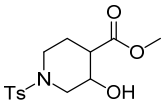
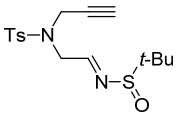
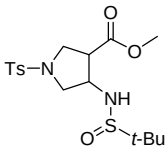
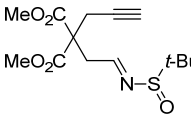
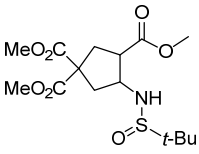
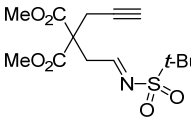
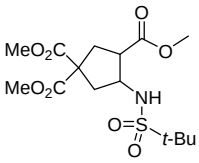
Scheme 10. Rh-Catalyzed Cyclization with Pyridine *N*-oxide Bearing a Hydroxy or Amino Group Both as an Oxidant and a Nucleophile

In addition, we attempted to atom-economically synthesize esters and amides using specific pyridine *N*-oxides. The reaction proved feasible with 3-hydroxypyridine *N*-oxide both as an oxidant and a nucleophile, generating pyridinyl cyclopentanecarboxylate in 75% yields. When 3-aminopyridine *N*-oxide was subjected to the standard conditions, we observed the formation of the pyridinyl cyclopentanecarboxamide in 73% yield.

3.2. via *β*-Addition

Table 9. Reaction Scopes with Various Alkynyl Aldehydes and Imines[a]



Entry	Reactant	Product	Time (h)	Yield[b] (%)	*dr*
1	 **1.4**	 **1.4a**	1.5	40	2.1:1
2	 **14**	 **14a**	1	71	1.6:1
3	 **9.5**	 **9.5a**	0.7	22	3.5:1
4	 **6.3**	 **6.3a**	0.7	33	1.5:1
5	 **15**	 **15a**	1	45	1.2:1.2:1:1
6	 **16**	 **16a**	1	70	1.2:1.2:1:1
7	 **17**	 **17a**	0.5	52	1:1

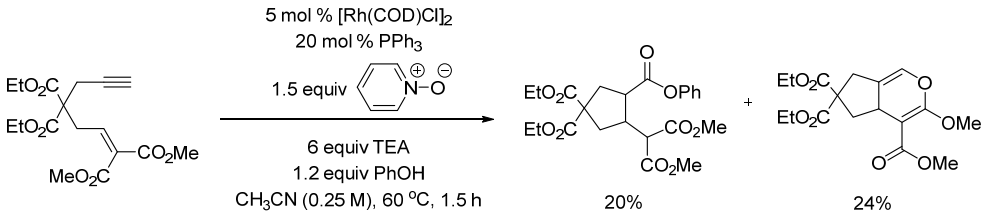
[a] All reactions were performed with 0.5 mmol of alkyne, 0.75 mmol of pyridine *N*-oxide, 3.0 mmol of TEA, 2.0 mmol of MeOH, 5 mol% of $[Rh(COD)Cl]_2$ and 20 mol% of PPh_3 at 60 ^oC in CH_3CN. [b] Isolated yield.

In order to expand the scope of the reaction to include electrophiles other than alkyl halides and halide equivalents, we prepared various alkynyl aldehydes (Table 9). Interestingly, the reaction with the rhodium COD complex at 60 °C for 1.5 h produced alcohol as a 2.1:1 mixture of diastereomers in 40% yield (entry 1). This outcome shows that the formation of the disubstituted rhodium vinylidene predominates over various pathways available by rhodium catalysis, such as decarbonylation or intramolecular hydroacylation. When aldehyde **14** having a malonate tether was subjected to the standard conditions, the desired alcohol **14a** was formed in 71% yield within 1 h (entry 2). Unfortunately, the homobenzaldehyde **9.5** and homopropargyl aldehyde **6.3** proved much less efficient, resulting in only 22% and 33% yield of the desired products (entries 3 and 4).

We additionally attempted to use sulfinylimine groups as electrophiles. The exposure of *N*-tosyl sulfinylimine **15** to the rhodium-catalyzed cyclization conditions led to the formation of the 5-membered ring attached to a *β*-amino carbonyl group in 45% yield (entry 5). Whereas cyclization of *N*-tosyl sulfinylimine afforded only a 45% yield of product, the yield of the cyclization could be boosted by dimethyl malonate substituents. Both sulfinylimine and sulfonylimine proceeded well to give the corresponding carbocycles in good yields (entries 6 and 7).

These results demonstrate that alkynes with aldehydes or imines could be excellent participants of the reaction, affording the alcohol and amine products in moderate yield. Indeed, these results mark the rare catalytic transformations of disubstituted metal vinylidenes. Furthermore, the efficient formation of

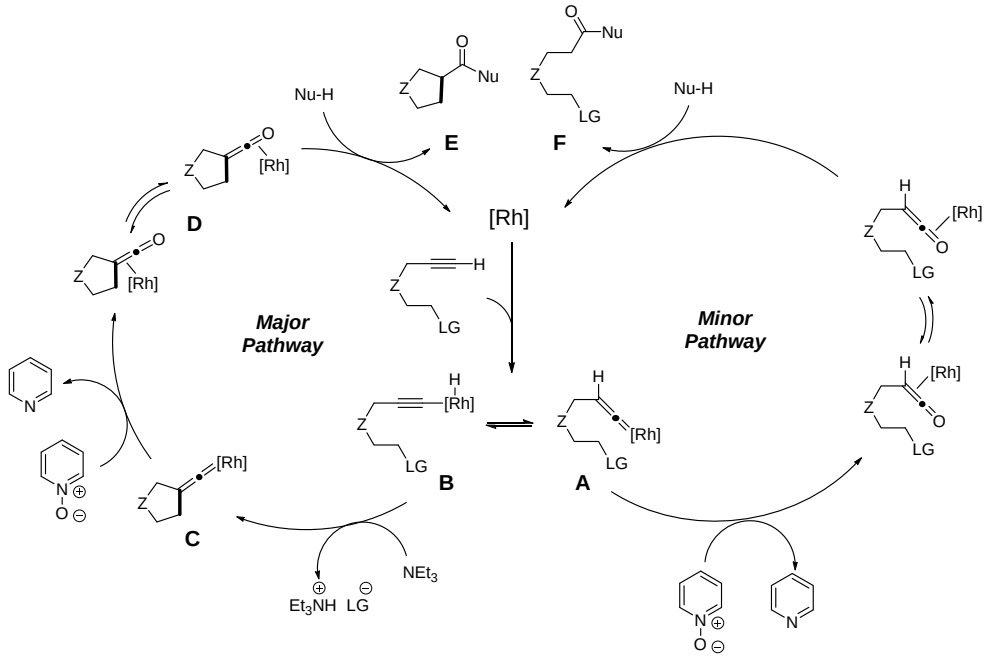
various 5-membered ring attached to carbonyl groups suggests the potential application of this chemistry to natural product synthesis.



Scheme 11. Rhodium-Catalyzed Cyclization and Oxygenative Addition of Terminal Alkyne with Michael Acceptor as an Electrophiles.

Recently, we found out that the exposure of terminal alkyne with a Michael acceptor to the rhodium-catalyzed cyclization conditions led to the formation of 5-membered ring in 20% yield (Scheme 11). However, the formation of 5,6-fused pyran product indicated that the enolate was formed after cyclization and underwent the addition to a disubstituted metal vinylidene in presence to pyridine *N*-oxide. In an effort to increase the formation of the desired product, further experiments are currently underway in our laboratory.

4. Proposed Reaction Mechanism



Scheme 12. Proposed Reaction Mechanism for Rhodium-Catalyzed Cyclization and Oxygenative Addition

Our proposed mechanism for the cyclization and oxygenative addition is depicted in Scheme 12. The reaction is initiated by rhodium coordination onto the alkyne. After reversible formation of rhodium alkynyl complex **B**, β –alkylation occurs via deprotonation by TEA, which is irreversible and the key process in this mechanism. This alkylation forms disubstituted metal vinylidene intermediate **C** followed by transfer oxygenation to generate a metalloketene **D**, which then undergoes nucleophilic addition to give rise to the desired product **E** such as **1a**. When the alkylation step is slow or infeasible, intermediate **A**, existing in equilibrium with **B**, may directly enter on the oxygenation process to generate non-cyclized product **F** such as **1a'**.

CONCLUSION

In summary, we have developed a rhodium-catalyzed oxygenative α-addition and β-alkylation of terminal alkynes. The reaction allows for formation of 5-membered ring structures attached to a carbonyl group in a single step under mild conditions through an unusual mechanism that involves catalytic generation of a disubstituted metal vinylidene complex and its conversion to a metalloketene species. Using a rhodium catalyst, the reaction can be carried out with a broad range of nucleophiles such as alcohols and amines in the presence of a suitable base and oxidant, which can provide diverse ester and amide products. The transformation represents a new type of alkyne functionalization in which one carbon-carbon and two carbon-heteroatom bonds are formed in a reaction mediated by a single catalyst.

EXPERIMENTAL SECTION

1. General information.

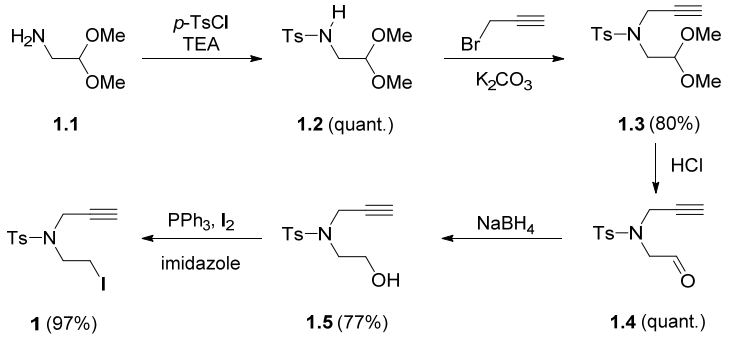
NMR spectra were obtained on a Bruker DPX-300 (300MHz), an Agilent 400-MR DD2 Magnetic Resonance System (400 MHz) and a Varian/Oxford As-500 (500 MHz) spectrophotometer. Chemical shift values were recorded as parts per million relative to tetramethylsilane as an internal standard unless otherwise indicated, and coupling constants in Hertz. The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were measured on a Thermo Scientific Nicolet 6700 spectrometer. High resolution mass spectra were recorded on a JEOL JMS-600W or a JEOL JMS-700 spectrometer using electron impact (EI) or chemical ionization (CI) method. CHI650B potentiostat, and gas chromatography data were obtained on a Hewlett Packard HP 6890 Series GC systems.

The progress of reaction was checked on thin layer chromatography (TLC) plates (Merck 5554 Kiesel gel 60 F254), and the spots were visualized under 254 nm UV light and/or charring after dipping the TLC plate into a vanillin solution (15.0 g of vanillin and 2.5 mL of concentrated sulfuric acid in 250 mL of ethanol), a $KMnO_4$ solution (3.0 g of $KMnO_4$, 20.0 g of K_2CO_3, and 5.0 mL of 5% NaOH solution in 300 mL of water), a phosphomolybdic acid solution (250 mg phosphomolybdic acid in 50 mL ethanol), or Ceric ammonium molybdate solution (4 g of ceric ammonium sulfate, 10 g of ammonium molybdate, 40 mL conc. HCl, 360 mL H_2O). Column chromatography was performed on silica gel (Merck 9385 Kiesel gel 60) using hexanes-EtOAc (v/v). All solvents were obtained by passing through

activated alumina columns of solvent purification systems from Glass Contour. Commercially available reagents were obtained from Sigma-Aldrich, Tokyo Chemical Industry (TCI), Acros organic, Strem, or Alfa Aesar.

2. Preparation of characterization of substrates

Preparation of alkynyl iodide 1[11]



To a stirred solution of aminoacetaldehyde dimethyl acetal **1.1** (18 ml, 166.6 mmol) and dry TEA (46.47 ml, 333.2 mmol) in dry DCM (333 ml) was added dropwise a solution of *p*-toluenesulfonyl chloride (35 g, 183.2 mmol) in dry DCM (333 ml) over 30 min at 0 °C. After 0.5 h, the reaction mixture was diluted with H_2O. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layer was washed with 1 N HCl, H_2O, and saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a pale yellow oil **1.2** (crude yield: almost quant.). The crude acetal **1.2** was used immediately for the next step.

To a mixture of acetal **1.2** (31.12 g, 120 mmol) and solid K_2CO_3 in DMF (200 ml) was added propargyl bromide (16 ml, 80% wt. solution in toluene, 180 mmol) at

[11] M. Ishizaki and O. Hoshino, *Tetrahedron*, 2000, **56**, 8813.

room temperature. The resulting solution was heated at 100 °C for 6 h and then was quenched by addition of H_2O. The aqueous layer was extracted with ether, washed with brine, and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane:EtOAc = 3:1) to afford the alkyne **1.3** (28.6 g, 80%).

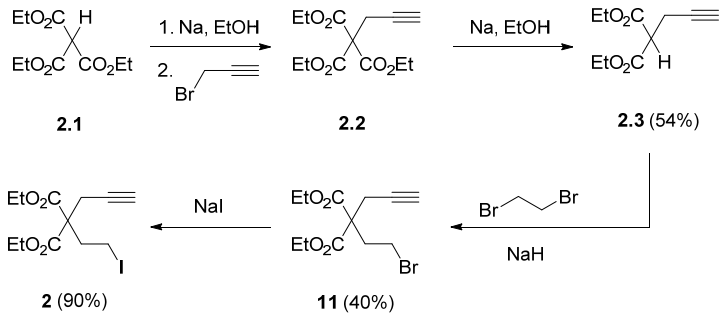
To a solution of acetal **1.3** (27.7 g, 93 mmol) in THF (280 ml) was added 2 M HCl (326 ml, 650 mmol) at room temperature. The reaction mixture was heated to 70 °C for 2 h, and then the solvent was removed *in vacuo*. The mixture was dissolved in water and extracted with diethyl ether. The organic extract were washed with H_2O and brine, successively, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane:EtOAc = 3:1) afforded aldehyde **1.4** (crude yield: almost quant.). R_f = 0.30 (hexane:EtOAc = 2:1).
^{1}H NMR (499 MHz, $CDCl_3$) δ 9.65 (t, *J* = 1.2 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 4.16 (d, *J* = 2.5 Hz, 2H), 3.94 (d, *J* = 0.9 Hz, 2H), 2.42 (s, 3H), 2.15 (t, *J* = 2.5 Hz, 1H). IR (neat): ν_{max} 3277, 1734, 1598, 1348, 1163, 1008, 662 cm^{-1}

To a solution of aldehyde **1.4** (21.45 g, 85.36 mmol) in MeOH (213 ml) at 0 °C was added $NaBH_4$ (1.61 g, 42.7 mmol) in one portion. After stirring at room temperature for 2 h, the reaction was quenched with H_2O. The solvent was evaporated under reduced pressure to give a residue, which was taken up in $CHCl_3$. The organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to furnish alcohol product **1.5** (16.7 g, 77%) as colorless crystals.

To a solution of the alcohol **1.5** (5.07 g, 20 mmol) in THF (133 ml) at 0 °C were added triphenylphosphine (7.9 g, 30 mmol), imidazole (4.1 g, 60 mmol) and iodine (7.6 g, 30 mmol). After stirring for 45 min, the resulting solution was diluted with ether and washed with saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Purification by flash column chromatography (hexane:EtOAc = 8:1) afforded iodide **1** (7.05 g, 97%). R_f 0.60 (hexane:EtOAc = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.11 (d, *J* = 6.8 Hz, 2H), 3.57 – 3.45 (t, 2H), 3.29 (t, *J* = 8.8, 7.1 Hz, 2H), 2.42 (s, 3H), 2.09 (t, *J* = 2.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.95, 135.34, 129.69, 127.49, 76.53, 74.40, 49.34, 37.42, 21.59, 1.60. IR (neat): ν_{max} 3288, 2973, 2922, 2121, 1597, 1349, 1161, 901 cm^{-1}

Preparation of alkynyl iodide 2 and alkynyl bromide 11[12]



A solution of sodium ethoxide in ethanol was prepared by treating sodium metal (1.6 g, 70 mmol) with absolute ethanol (17 ml) and cooled in an ice bath. To the ethanolic solution was added, dropwise, triethyl methanetricarboxylate **2.1** (10.6 ml,

[12] G. Revol, T. McCallum, M. Morin, F. Gagosz and L. Barriault, *Angew. Chem. Int. Ed.*, 2013, **52**, 13342.

50 mmol) in 50 ml diethyl ether. Upon the addition, a white precipitate formed, which was isolated via filtration. The white solid was washed with diethyl ether and dried. Sodium triethyl methanetricarboxylate was isolated as white flowing powder and used immediately for the next step. Propargyl bromide (8.91 ml, 80% wt. solution in toluene, 80 mmol) was added to a solution of triethyl sodiomethanetricarboxylate in toluene-DMF (100 ml, toluene:DMF = 1:1) and the mixture was stirred and heated at 80 °C for 1.5 h. The resultant, cooled yellow suspension was filtered and the residue washed with toluene. The combined filtrates were washed with water, evaporated and dried to give a pale yellow liquid **2.2** which was used immediately for the next step.

A solution of sodium ethoxide in ethanol was prepared by treating sodium metal (1.44 g, 62.5 mmol) with absolute ethanol (40 ml) and cooled in an ice bath. To the ethanolic solution was added, dropwise, triethyl methanetricarboxylate **2.2** (10.6 ml, 50 mmol) in 150 ml THF. After being stirred at room temperature for 1 h, the reaction mixture was acidified with hydrochloric acid and the aqueous layer separated and extracted with DCM. The combined extracts were dried over $MgSO_4$ and evaporated to give a brown liquid **2.3** (5.4 g, 54%) which was used immediately for the next step.

To a suspension of NaH (244 mg, 60% dispersion in oil, 6.1 mmol) in THF (17 ml) at 0 °C was added a solution of alkyne **2.3** (604 mg, 3.05 mmol) in THF (3.05 ml). The mixture was stirred at the same temperature for 1 h, and then a solution of 1,2-dibromoethane (0.39 ml, 4.57 mmol) in THF (4.4 ml) was added. The cold bath was removed, and the solution was stirred for 24 h at 70 °C. The reaction was

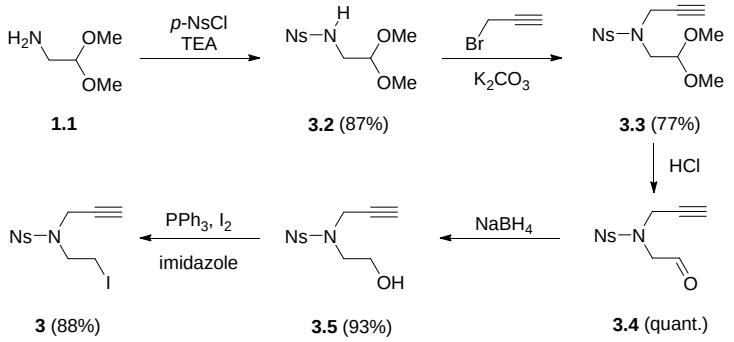
quenched by addition of H_2O and diluted with ether. The organic layer was separated, and the aqueous layer was further extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane:EtOAc = 30:1) provided the alkynyl bromide **11** (370 mg, 40%). R_f 0.40 (hexane:EtOAc = 10:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 – 4.12 (m, 4H), 3.43 – 3.31 (t, 2H), 2.86 – 2.78 (d, 2H), 2.67 – 2.55 (t, 2H), 2.07 – 1.99 (m, 1H), 1.29 – 1.18 (t, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.54, 78.46, 72.34, 62.32, 57.00, 36.03, 27.17, 23.62, 14.27. IR (neat): ν_{max} 3290, 2983, 1734, 1447, 1197, 1032, 859 cm^{-1}

To a solution of alkynyl bromide **11** (1.18 g, 3.86 mmol) in dry acetone (38.6 ml) was added NaI (1.45 g, 9.65 mmol) at room temperature. The reaction mixture was heated to 70 °C for 16 h, then acetone was evaporated under reduced pressure. The resulting solid was dissolved in water and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane:EtOAc = 20:1) afforded iodide **2** (1.23g, 90%). R_f 0.40 (hexane:EtOAc = 10:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 – 4.14 (m, 4H), 3.17 – 3.04 (m, 2H), 2.79 (d, *J* = 2.7 Hz, 2H), 2.71 – 2.56 (m, 2H), 2.03 (dd, *J* = 3.0, 2.4 Hz, 1H), 1.30 – 1.16 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.38, 78.47, 72.31, 62.29, 58.49, 37.63, 23.33, 14.30, -2.58. IR (neat): ν_{max} 3293, 2982, 1734, 1444, 1197, 859 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{17}INaO_4$ (M^++Na): 375.0069, found 375.0063.

Preparation of alkynyl iodide 3



To a stirred solution of aminoacetadehyde dimethyl acetal **1.1** (1.33 ml, 12.32 mmol) and dry TEA (5.16 ml, 36.96 mmol) in dry DCM (40 ml) was added dropwise a solution of *p*-nitrobenzenesulfonyl chloride (3.00 g, 13.55 mmol) in dry DCM (10 ml) over 30 min at 0 °C. After 18 h, the reaction mixture was diluted with H_2O. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layer was washed with 1 N HCl, H_2O, and saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a pale yellow oil **3.2**. Purification by flash chromatography (hexane:EtOAc = 3:1) afforded the acetal **3.2** (3.107g, 87%).

To a mixture of acetal **3.2** (3.107 g, 10.7 mmol) and solid K_2CO_3 (2.218g, 16.05 mmol) in DMF (17 ml) was added propargyl bromide (1.79 ml, 80% wt. solution in toluene, 16.05 mmol) at room temperature. The resulting solution was heated at 100 °C for 18 h and then was quenched by addition of H_2O. The aqueous layer was extracted with ether, washed with brine, and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane:EtOAc = 5:1) to afford the alkyne **3.3** (2.718 g, 77%).

To a solution of acetal **3.3** (2.718 g, 8.278 mmol) in THF (27 ml) was added 2 M HCl (16.6 ml, 4 mmol) at room temperature. The reaction mixture was heated to 70 °C for 24 h, and then the solvent was removed *in vacuo*. The mixture was dissolved in water and extracted with diethyl ether. The organic extract were washed with H_2O and brine, successively, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane:EtOAc = 3:1) afforded aldehyde **3.4** (almost quant.). R_f = 0.40 (hexane:EtOAc = 1:1).

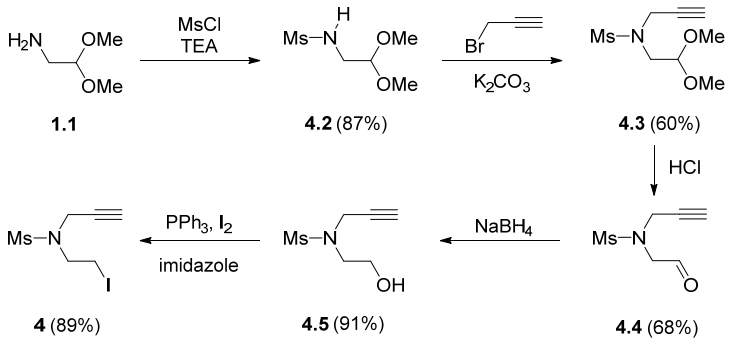
To a solution of aldehyde **3.4** (1 g, 3.54 mmol) in MeOH (18 ml) at 0 °C was added $NaBH_4$ (67 mg, 1.77 mmol) in one portion. After stirring at room temperature for 1 h, the reaction was quenched with H_2O. The solvent was evaporated under reduced pressure to give a residue, which was taken up in $CHCl_3$. The organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to furnish alcohol product **3.5** (930.1 mg, 93%).

To a solution of the alcohol **3.5** (930.1 mg, 3.27 mmol) in THF (22 ml) at 0 °C were added triphenylphosphine (1.287 g, 4.9 mmol), imidazole (669.6 mg, 9.81 mmol) and iodine (1.244 g, 4.9 mmol). After stirring for 21 h, the resulting solution was diluted with ether and washed with saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Purification by flash column chromatography (hexane:EtOAc = 7:1) afforded iodide **3** (1.134 g, 88%). R_f 0.35 (hexane:EtOAc = 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.35 (m, 2H), 8.10 – 8.04 (m, 2H), 4.25 (t, *J* = 2.0 Hz, 2H), 3.60 (t, *J* = 7.6 Hz, 2H), 3.37 – 3.29 (m, 2H), 2.15 – 2.11 (m, 1H).

^{13}C NMR (101 MHz, cdcl$_3$) δ 150.39, 144.60, 129.13, 124.52, 75.89, 75.14, 75.05, 49.52, 37.57.

Preparation of alkynyl iodide 4



1.1 **4.2** (87%) **4.3** (60%) **4.4** (68%) **4.5** (91%) **4** (89%)

To a stirred solution of aminoacetadehyde dimethyl acetal **1.1** (2.16 ml, 20 mmol) and dry TEA (8.37 ml, 60 mmol) in dry DCM (80 ml) was added dropwise a solution of methanesulfonyl chloride (1.7 ml, 22 mmol) over 30 min at 0 °C. After 18 h, the reaction mixture was diluted with H_2O. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layer was washed with 1 N HCl, H_2O, and saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a pale yellow oil **4.2**. Purification by flash chromatography (hexane:EtOAc = 1:1) afforded the acetal **4.2** (3.177g, 87%).

To a mixture of acetal **4.2** (2.912 g, 15.89 mmol) and solid K_2CO_3 (3.29 g, 23.84 mmol) in DMF (26 ml) was added propargyl bromide (2.655 ml, 80% wt. solution in toluene, 23.84 mmol) at room temperature. The resulting solution was heated at 100 °C for 12 h and then was quenched by addition of H_2O. The aqueous layer was extracted with ether, washed with brine, and the combined organic layers were

dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane:EtOAc = 3:1) to afford the alkyne **4.3** (2.125 g, 60%).

To a solution of acetal **4.3** (2.125 g, 9.6 mmol) in THF (32 ml) was added 2 M HCl (19.2 ml, 38.4 mmol) at room temperature. The reaction mixture was heated to 70 °C for 24 h, and then the solvent was removed *in vacuo*. The mixture was dissolved in water and extracted with diethyl ether. The organic extract were washed with H_2O and brine, successively, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane:EtOAc = 2:1) afforded aldehyde **4.4** (1.142 g, 68%). R_f = 0.30 (hexane:EtOAc = 1:1).

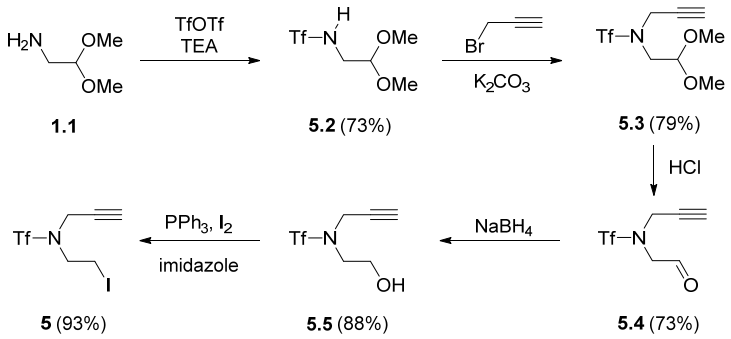
To a solution of aldehyde **4.4** (525.6 mg, 3 mmol) in MeOH (15 ml) at 0 °C was added $NaBH_4$ (56.73 mg, 1.5 mmol) in one portion. After stirring at room temperature for 1 h, the reaction was quenched with H_2O. The solvent was evaporated under reduced pressure to give a residue, which was taken up in $CHCl_3$. The organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to furnish alcohol product **4.5** (484.2 mg, 91%).

To a solution of the alcohol **4.5** (484.2 mg, 2.73 mmol) in THF (18.2 ml) at 0 °C were added triphenylphosphine (1.077 g, 4.1 mmol), imidazole (559 mg, 8.2 mmol) and iodine (1.041 g, 4.1 mmol). After stirring for 23 min, the resulting solution was diluted with ether and washed with saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary

evaporation. Purification by flash column chromatography (hexane:EtOAc = 4:1) afforded iodide **4** (699.3 mg, 89%). R_f 0.20 (hexane:EtOAc = 5:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 – 4.12 (m, 2H), 3.62 (t, *J* = 7.6 Hz, 2H), 3.34 – 3.28 (m, 2H), 2.99 – 2.96 (m, 3H), 2.42 – 2.40 (m, *J* = 2.5, 1.8, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 74.90, 74.75, 49.57, 38.70, 38.66, 37.36.

Preparation of alkynyl iodide 5



1.1 **5.2** (73%) **5.3** (79%) **5.4** (73%) **5.5** (88%) **5** (93%)

To a stirred solution of aminoacetadehyde dimethyl acetal **1.1** (1.226 ml, 11.347 mmol) and dry TEA (4.75 ml, 34.04 mmol) in dry DCM (40 ml) was added dropwise a solution of trifluoromethanesulfonic anhydride (2.1 ml, 12.482 mmol) in dry DCM (5 ml) over 30 min at 0 °C. After 18 h, the reaction mixture was diluted with H_2O. The organic layer was separated, and the aqueous layer was extracted with DCM. The combined organic layer was washed with 1 N HCl, H_2O, and saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a pale yellow oil **5.2**. Purification by flash chromatography (hexane:EtOAc = 4:1) afforded the acetal **5.2** (1.963 g, 73%).

To a mixture of acetal **5.2** (1.963 g, 8.276 mmol) and solid K_2CO_3 (1.716 g, 12.41 mmol) in DMF (13 ml) was added propargyl bromide (1.38 ml, 80% wt. solution in

toluene, 12.4 mmol) at room temperature. The resulting solution was heated at 100 °C for 12 h and then was quenched by addition of H_2O. The aqueous layer was extracted with ether, washed with brine, and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (hexane:EtOAc = 10:1) to afford the alkyne **5.3** (1.806 g, 79%).

To a solution of acetal **5.3** (1.806 g, 6.56 mmol) in THF (22 ml) was added 2 M HCl (13.1 ml, 26.25 mmol) at room temperature. The reaction mixture was heated to 70 °C for 24 h, and then the solvent was removed *in vacuo*. The mixture was dissolved in water and extracted with diethyl ether. The organic extract were washed with H_2O and brine, successively, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane:EtOAc = 5:1) afforded aldehyde **5.4** (1.103 g, 73%). R_f = 0.25 (hexane:EtOAc = 3:1).

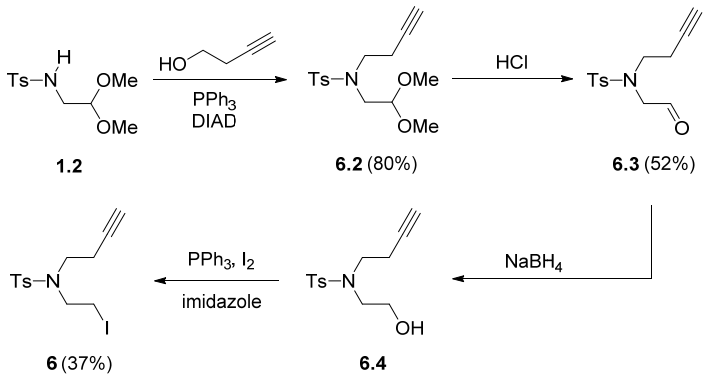
To a solution of aldehyde **5.4** (573 mg, 2.5 mmol) in MeOH (12.5 ml) at 0 °C was added $NaBH_4$ (47.3 mg, 1.25 mmol) in one portion. After stirring at room temperature for 3 h, the reaction was quenched with H_2O. The solvent was evaporated under reduced pressure to give a residue, which was taken up in $CHCl_3$. The organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to furnish alcohol product **5.5** (507.8 mg, 88%).

To a solution of the alcohol **5.5** (507.8 mg, 2.2 mmol) in THF (15 ml) at 0 °C were added triphenylphosphine (865.2 mg, 3.3 mmol), imidazole (450.5 mg, 6.6 mmol) and iodine (837.9 mg, 3.3 mmol). After stirring for 16 h, the resulting solution was

diluted with ether and washed with saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Purification by flash column chromatography (hexane:EtOAc = 20:1) afforded iodide **5** (656 mg, 93%). R_f 0.50 (hexane:EtOAc = 7:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (d, 2H), 3.84 (t, 2H), 3.34 (t, *J* = 6.9 Hz, 2H), 2.46 (dt, *J* = 3.7, 2.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 121.44, 118.23, 75.68, 75.52, 50.23, 38.37.

Preparation of alkynyl iodide 6



Under N_2 atmosphere, DIAD (15 ml, 76 mmol) was added to a stirred mixture of 3-butyn-1-ol (4.6 ml, 60.8 mmol), triphenylphosphine (19.93 g, 76 mmol), and acetal **1.2** (13.14 g, 50.66 mmol) in THF (253 ml) at 0 °C. After the addition was complete, the ice bath was removed and stirring was continued for 24 h. All the volatiles were removed under reduced pressure, and the resultant residue was purified by flash chromatography (hexane:EtOAc = 7:1) to yield product **6.2** (12.56 g, 80%).

To a solution of acetal **6.2** (6.23 g, 20 mmol) in THF (60 ml) was added 2 M HCl

(70 ml, 140 mmol) at room temperature. The reaction mixture was heated to 70 °C for 3 h, and then the solvent was removed *in vacuo*. The mixture was dissolved in water and extracted with diethyl ether. The organic extract were washed with H_2O and brine, successively, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane:EtOAc = 3:1) afforded aldehyde **6.3** (2.74 g, 52%).

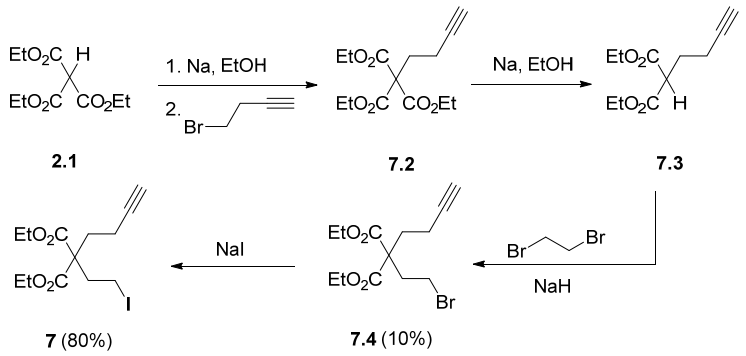
To a solution of aldehyde **6.3** (1.86 g, 7 mmol) in MeOH (35 ml) at 0 °C was added $NaBH_4$ (132.4 mg, 3.5 mmol) in one portion. After stirring at room temperature for 0.5 h, the reaction was quenched with H_2O. The solvent was evaporated under reduced pressure to give a residue, which was taken up in $CHCl_3$. The organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to furnish alcohol product **6.4** (crude yield: almost quant.), which was used immediately for the next step.

To a solution of the crude alcohol **6.4** in THF (64 ml) at 0 °C were added triphenylphosphine (3.77 g, 14.3 mmol), imidazole (1.96 g, 28.7 mmol) and iodine (3.64 g, 14.3 mmol). After stirring for 40 min, the resulting solution was diluted with ether and washed with saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Purification by flash column chromatography (hexane:EtOAc = 7:1) afforded iodide **6** (1.32 g, 37%). R_f 0.40 (hexane:EtOAc = 4:1)

^{1}H NMR (499 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 3.53 – 3.46 (m, 2H), 3.34 – 3.26 (m, 4H), 2.47 (td, *J* = 7.1, 2.6 Hz, 2H), 2.41 (s,

3H), 2.03 (m, J = 5.0, 2.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.11, 136.30, 130.17, 127.35, 80.94, 77.72, 77.30, 76.88, 70.95, 52.23, 48.34, 21.79, 20.27, 2.45. IR (neat): v_{max} 3290, 1598, 1451, 1343, 1159, 974, 730 cm^{-1}. HRMS (ESI) calcd. for $C_{13}H_{16}INNaO_2S$ (M^++Na): 399.9844, found 399.9837.

Preparation of alkynyl iodide 7



A solution of sodium ethoxide in ethanol was prepared by treating sodium metal (576.1 mg, 25 mmol) with absolute ethanol (10 ml) and cooled in an ice bath. To the ethanolic solution was added, dropwise, triethyl methanetricarboxylate **2.1** (3.8 ml, 17.9 mmol) in 20 ml diethyl ether. Upon the addition, a white precipitate formed, which was isolated via filtration. The white solid was washed with diethyl ether and dried. Sodium triethyl methanetricarboxylate was isolated as white flowing powder and used immediately for the next step.

4-bromo-1-butyne (2.5 ml, 28.8 mmol) was added to a solution of triethyl sodiomethanetricarboxylate in toluene-DMF (36 ml, toluene:DMF = 1:1) and the mixture was stirred and heated at 80 °C for 13 h. The resultant, cooled suspension was filtered and the residue washed with toluene. The filtrate was concentrated, extracted with DCM, and dried over Na_2SO_4. The filtrate was concentrated *in*

vacuo and the residue **7.2** was used immediately for the next step.

A solution of sodium ethoxide in ethanol was prepared by treating sodium metal (517.3 mg, 22.5 mmol) with absolute ethanol (7.5 ml) and cooled in an ice bath. To the ethanolic solution was added, dropwise, above alkyne **7.2** in 42 ml THF. After being stirred at room temperature for 1 h, the reaction mixture was acidified with hydrochloric acid and the aqueous layer separated and extracted with DCM. The combined extracts were dried over $MgSO_4$ and evaporated to give alkyne **7.3** which was used immediately for the next step.

To a suspension of NaH (1.44 g, 60% dispersion in oil, 36 mmol) in THF (100 ml) at 0 °C was added dropwise a solution of the above alkyne **7.3** in THF (18 ml). The mixture was stirred at room temperature for 1 h, and then 1.2-dibromoethane (2.33 ml, 27 mmol) was added dropwise. The solution was stirred at 70 °C for 19 h and quenched by addition of H_2O. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane:EtOAc = 40:1) provided the alkynyl bromide **7.4** (575 mg, 10% for 3 steps). R_f = 0.40 (hexane:EtOAc = 10:1).

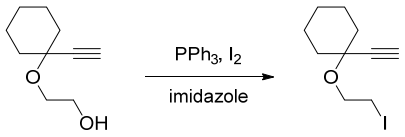
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 – 4.05 (q, 4H), 3.31 – 3.19 (t, 2H), 2.44 – 2.32 (t, 2H), 2.15 – 2.04 (m, 4H), 1.95 – 1.88 (s, 1H), 1.23 – 1.05 (t, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.09, 82.85, 69.28, 61.81, 57.28, 36.38, 32.06, 27.03, 14.12.

To a solution of alkynyl bromide **7.4** (160 mg, 0.5 mmol) in dry acetone (5 ml) was added NaI (187 mg, 1.25 mmol) at room temperature. The reaction mixture was

heated to 70 °C for 16 h, then acetone was evaporated under reduced pressure. The resulting solid was dissolved in water and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (hexane:EtOAc = 25:1) afforded alkynyl iodide **7** (145.5 mg, 80%). R_f = 0.50 (hexane:EtOAc = 10:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 – 4.08 (q, 4H), 3.08 – 2.94 (t, 2H), 2.51 – 2.38 (t, 2H), 2.17 – 2.03 (m, 4H), 1.97 – 1.90 (m, 1H), 1.27 – 1.12 (t, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.03, 82.94, 69.30, 61.86, 58.78, 37.99, 31.79, 14.22, 14.18, -2.38. IR (neat): ν_{max} 3299, 2981, 1730, 1448, 1258, 1191, 861 cm^{-1}. HRMS (ESI) calcd. for $C_{13}H_{19}INaO_4$ (M^++Na): 389.0226, found 389.0221.

Preparation of alkynyl iodide 8



8.1 **8** (68%)

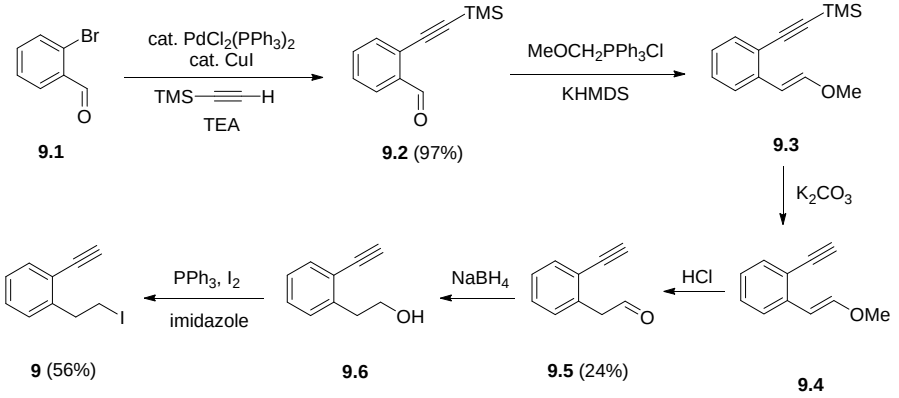
To a solution of the alcohol **8.1**[13] (200 mg, 1.19 mmol) in DCM (6 ml) at 0 °C were added triphenylphosphine (375 mg, 1.43 mmol), imidazole (97.4 mg, 1.43 mmol) and iodine (363 mg, 1.43 mmol). After stirring for 160 min, the resulting solution was diluted with ether and washed with saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Purification by flash column chromatography (hexane:EtOAc = 10:1)

[13] T. Harada, K. Muramatsu, K. Mizunashi, C. Kitano, D. Imaoka, T. Fujiwara and H. Kataoka, *J. Org. Chem.*, 2008, **73**,249.

afforded iodide **8**[14] **(**225 mg, 68%). R_f 0.85 (hexane:EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 – 3.76 (m, 2H), 3.30 – 3.21 (m, 2H), 2.48 (s, 1H), 1.86 (dd, *J* = 11.3, 6.9 Hz, 2H), 1.75 – 1.58 (m, 4H), 1.58 – 1.42 (m, 3H), 1.30 (dt, *J* = 12.7, 7.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 85.29, 77.62, 77.30, 76.98, 74.20, 74.01, 64.66, 37.39, 25.56, 22.80, 4.27. IR (neat): ν_{max} 3289, 3056, 2936, 2857, 1438, 1261, 1194, 1119, 722 cm^{-1}.

Preparation of alkynyl iodide 9



To a mixture of $PdCl_2(PPh_3)_2$ (877.4 mg, 1.25 mmol) and 2-bromobenzaldehyde **9.1** (2.92 ml, 25 mmol) in THF (170 ml) was added TEA (10.5 ml, 75 mmol). After being stirred for 10 min at room temperature, trimethylsilylacetylene (5.3 ml, 37.5 mmol) and CuI (238 mg, 1.25 mmol) were added to the mixture. The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with saturated aqueous ammonium chloride, extracted with EtOAc three times, and washed with brine. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure after filtration. Purification by flash chromatography (hexane:EtOAc = 30:1) provided the silyl-protected

[14] A. G. Schultz and P. Sundararaman, *J. Org. Chem.*, 1984, **49**, 2455.

ethynylbenzaldehyde **9.2** (4.9g, 97%).

To a suspension of (methoxymethyl)triphenylphosphonium chloride (6.86g, 20 mmol) in anhydrous THF was added 0.5 M solution of KHMDS in toluene (36.4 ml, 18.2 mmol) at −78 °C. The mixture was stirred at the same temperature for 1 h, and then a solution of aldehyde **9.2** (2.02 g, 10 mmol) in anhydrous THF (20 ml) was added to the mixture. The resulting mixture was allowed to warm up to 0 °C over 3 h and then diluted with hexane and passed through Celite. The residual solid was washed with hexane thoroughly. The filtrate was concentrated under reduced pressure. The crude mixture was taken up in THF and treated with 2 M HCl. The mixture was stirred at a refluxing temperature (65 °C) overnight. Then, the reaction mixture was quenched with saturated aq. Na_2CO_3, extracted with EtOAc three times, and washed with brine. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure after filtration. The resulting residue **9.3** was used immediately for the next step.

To a solution of the above vinyl ether **9.3** in MeOH (20 ml) was added solid K_2CO_3 (138.2 mg, 1 mmol) at room temperature. After the solution was stirred at the same temperature for 2 h. the reaction was quenched with saturated aqueous NH_4Cl. After extraction with EtOAc, the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting residue **9.4** was used immediately for the next step.

To a solution of the above desilylated product **9.4** in THF (20 ml) was added 2 M HCl (24 ml) at 0 °C. After the solution was heated at 80 °C for 2 h, the reaction

was quenched with saturated aqueous Na_2CO_3. After extraction with EtOAc, the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (hexane:EtOAc = 30:1) provide the homobenzaldehyde **9.5** (345 mg, 24% for 3 steps). R_f = 0.18 (hexane:EtOAc = 20:1).

To a solution of $NaBH_4$ (108.7 mg, 2.87 mmol) in EtOH (4 ml) was added a solution of aldehyde **9.5**[15] (345 mg, 2.39 mmol) in EtOH (3 ml) at 0 °C under an argon atmosphere. The mixture was stirred at 0 °C for 1 h. After addition of an aqueous ammonium chloride solution, the mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude acetal **9.6** was used immediately for the next step without further purification (crude yield: almost quant.).

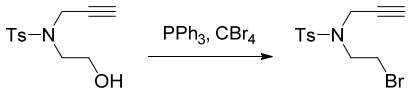
To a solution of the crude alcohol **9.6** (146.2 mg, 1 mmol) in THF (6.7 ml) at 0 °C were added triphenylphosphine (394 mg, 1.5 mmol), imidazole (205 mg, 3 mmol) and iodine (381 mg, 1.5 mmol). After stirring for 1 h at 0 °C, the resulting solution was diluted with ether and washed with saturated aqueous $Na_2S_2O_3$. The aqueous layer was extracted with ether. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Purification by flash column chromatography (hexane:EtOAc = 100:1) afforded iodide **9** (143 mg, 56%). R_f = 0.60 (hexane:EtOAc = 20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.33 – 7.25 (m, 1H), 7.22 (ddd, *J* = 9.9, 4.9, 2.5 Hz, 2H), 3.45 – 3.31 (m, 4H), 3.30 – 3.26 (m, 1H). IR

[15] H. Tsukamoto, T. Ueno and Y. Kondo, *J. Am. Chem. Soc.*, 2006, **128**, 1406.

(neat): ν_{max} 3295, 1483, 1174, 758 cm^{-1}.

Preparation of alkynyl bromide 10

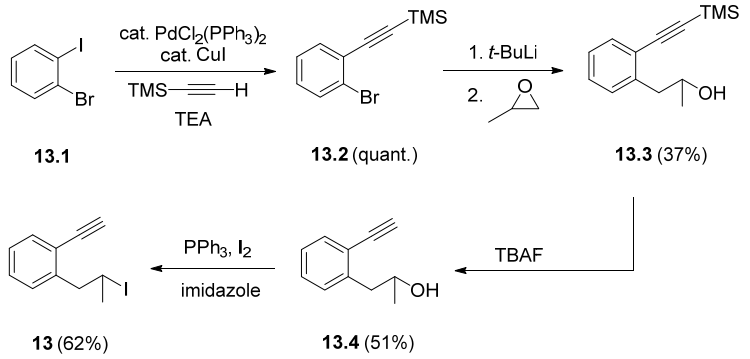


1.5 **10** (95%)

To a solution of alcohol **1.5** (1.26 g, 5 mmol) in DCM (50 ml) at 0 °C were added triphenylphosphine (1.7 g, 6.5 mmol) and carbon tetrabromide (2.16 g, 6.5 mmol). After stirring at room temperature for 11 h, solvent was removed under reduced pressure and the resulting residue was extracted with DCM, dried over Na_2SO_4, filtered, and concentrated under vacuum. The resulting residue was purified by flash chromatography (hexane:EtOAc = 15:1) to give the alkynyl bromide **10** (1.5 g, 95%). R_f 0.17 (hexane:EtOAc = 8:1).

^{1}H NMR (499 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.0 Hz, 2H), 7.31 (d, *J* = 7.4 Hz, 2H), 4.16 (d, *J* = 2.4 Hz, 2H), 3.53 (d, *J* = 4.5 Hz, 4H), 2.42 (s, 3H), 2.10 (dd, *J* = 3.1, 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.89, 172.18, 171.82, 77.62, 77.30, 76.98, 61.88, 60.47, 43.38, 37.04, 34.01, 29.23, 14.27. IR (neat): ν_{max} 3283, 1597, 1451, 1350, 1161, 1091, 909 cm^{-1}.

Preparation of alkynyl iodide 13[16]



To an oven dried flask containing a magnetic stir bar was added the 2-bromoiodobenzene **13.1** (2.5 ml, 20 mmol), $PdCl_2(PPh_3)_2$ (281 mg, 0.4 mmol), and CuI (114 mg, 0.6 mmol). The vessel was then sealed with a rubber septum, evacuated and backfilled with argon three times. A co-solvent of THF (80 ml) was added followed by TEA (8.4 ml, 60mmol), then trimethylsilylacetylene (4.24 ml, 30 mmol) was added. After the reaction was completed at room temperature, monitored by TLC, solvent was removed under reduced pressure and the resulting residue was extracted with DCM, dried over Na_2SO_4, filtered, and concentrated under vacuum. The resulting residue was purified by flash chromatography (only hexane) to give the silyl-protected ethynylarene intermediate **13.2** (5.06g, >99%).

To a stirred solution of aryl bromide **13.2** (1.27g, 5 mmol) in dry THF (25 ml) at -30 °C was added *tert*-butyllithium (8.82ml, 1.7 M in pentane, 15 mmol). The solution was stirred for 30 min at -30 °C whereupon propylene oxide (1.75 ml, 25 mmol) was added and the solution allowed to warm to room temperature and stirred for a further 2 h. The reaction was quenched by the addition of saturated

[16] A. Varela-Fernández, C. García-Yebra, J. A. Varela, M. A. Esteruelas and C. Saá, *Angew. Chem. Int. Ed.*, 2010, **49**, 4278.

ammonium chloride (50 ml) and diethyl ether (100 ml) added. The organic extract was washed with water and dried over $MgSO_4$ and the solvent removed under reduced pressure to yield the crude products which were purified by flash column chromatography on silica (hexane:EtOAc = 10:1) to yield the pure 1-aryl propan-2-ol **13.3** (425 mg, 37%).

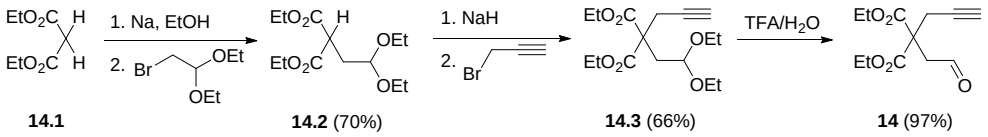
A solution of TBAF (2.29 ml, 1.0 M in THF, 2.29 mmol) was added dropwise to a solution of 1-aryl propan-2-ol **13.3** in THF (18 ml) at 0 °C and the mixture was stirred at 0 °C for 5 min. After addition of an aqueous ammonium chloride solution, the mixture was extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The resulting residue was purified by flash chromatography (hexane:EtOAc = 5:1) to give the desilylated alcohol **13.4** (150 mg, 51%).

A 25 ml round-bottom flask equipped with a Teflon-coated magnetic stirrer was charged with triphenylphosphine (147 mg, 0.56 mmol), imidazole (38 mg, 0.56 mmol), and DCM (4 ml). The reaction mixture was stirred at room temperature until the white solids dissolved to form a clear solution. Iodine (142 mg, 0.56 mmol) were then added slowly in a few portions into the reaction mixture, and the resulting mixture was stirred until all iodine granules dissolved. Alcohol **13.4** (64 mg, 0.4 mmol) was then slowly added into the reaction mixture, and the resulting mixture was stirred for 1.5 h. The mixture was diluted with hexanes and then filtered to remove the solid residues. The filtrate was then concentrated *in vacuo* with the aid of a rotary evaporator. The residue was purified by flash column chromatography with silica gel using hexanes as an eluent to afford the alkynyl

iodide product **13** (67 mg, 62%). R_f = 0.70 (only hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.4 Hz, 1H), 7.34 – 7.26 (m, 1H), 7.22 (t, *J* = 8.2 Hz, 2H), 4.59 – 4.45 (m, 1H), 3.46 (dd, *J* = 13.8, 7.3 Hz, 1H), 3.30 (s, 1H), 3.29 – 3.22 (m, 1H), 1.90 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.62, 133.35, 130.04, 129.10, 127.09, 122.01, 82.22, 81.70, 48.22, 28.45, 27.54.

Preparation of alkynyl aldehyde 14[17]



14.1 **14.2** (70%) **14.3** (66%) **14** (97%)

Sodium (2.76 g, 120 mmol) was dissolved in dry ethanol (84 ml) and the solution was heated to 80 °C. Diethylmalonate **14.1** (15.2 ml, 100 mmol) was added and the mixture was stirred for further 1 h. After the addition of bromoacetaldehyde diethyl acetal (20 ml, 133 mmol), the mixture was refluxed for 48 h. The mixture was allowed to cool down to room temperature and the solvent was removed *in vacuo*. The resulting residue was extracted with DCM, washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The resulting residue was purified by flash chromatography (hexane:EtOAc = 20:1) to give acetal **14.2** (22.72 g,70%).

To a suspension of NaH (1.1 g, 60% dispersion in oil, 27 mmol) in THF (80 ml) at 0 °C was added a solution of acetal **14.2** (6.3 g, 22.8 mmol) in THF (20 ml). The mixture was stirred at room temperature for 0.5 h, and then propargyl bromide (3.82 ml, 80% wt. solution in toluene, 34 mmol) was added. The solution was

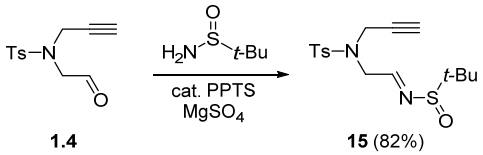
[17] J. C. Carretero and J. Adrio, *Synthesis*, 2001, **2001**, 1888.

stirred for 16 h and quenched by addition of H_2O. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexane:EtOAc = 20:1) provided the alkyne **14.3** (4.72g, 66%).

To a solution of alkynyl acetal 11.3 (3.05 g, 9.7 mmol) in DCM (24 ml) and H_2O (12 ml) was added TFA (12.14 ml) at 0 °C. After being stirred at room temperature for 16 h, the reaction mixture was quenched by saturated aqueous $NaHCO_3$. The resulting residue was extracted with ether, washed with saturated aqueous $NaHCO_3$, and brine, and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (hexane:EtOAc = 10:1) to give alkynyl aldehyde **14** (2.27 g,97%). R_f= 0.25 (hexane:EtOAc = 8:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 4H), 3.22 (s, 2H), 2.96 (d, *J* = 2.7 Hz, 2H), 2.04 (s, 1H), 1.23 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.85, 169.04, 78.91, 72.38, 62.51, 54.18, 46.13, 24.01, 14.17. IR (neat): ν_{max} 2959, 1785, 1737, 1351, 1164, 1034, 779 cm^{-1}.

Preparation of sulfinylimine 15



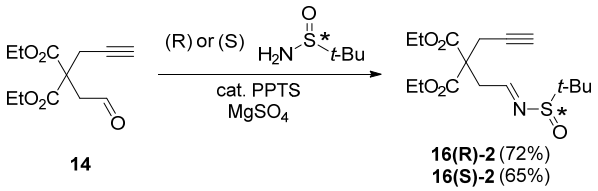
1.4 **15** (82%)

To a solution of *tert*-butanesulfinamide (266.6 mg, 2.2 mmol) in DCM (3.3 ml) was added successively pyridinium p-toluenesulfonate (25.13 mg, 0.1 mmol), anhydrous $MgSO_4$ (1.2 g, 10 mmol) and aldehyde **1.4** (502.6 mg, 2 mmol). The

mixture was stirred at room temperature for 24 h. $MgSO_4$ was filtered off through a pad of Celite and washed with DCM. The combined filtrates were concentrated and purified by flash chromatography (hexane:EtOAc = 2:1) to provide sulfinylimine **15** (581 mg, 82%). R_f = 0.30 (hexane:EtOAc = 2:1).

^{1}H NMR (499 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 7.7 Hz, 2H), 4.31 (s, 2H), 4.24 (d, *J* = 6.2 Hz, 2H), 2.43 (s, 3H), 2.13 (s, 1H), 1.19 (s, 9H). IR (neat): ν_{max} 3276, 2962, 1633, 1351, 1163, 1092, 816 cm^{-1} HRMS (ESI) calcd. for $C_{16}H_{22}N_2NaO_3S_2$ (M^++Na): 377.0970, found 377.0963.

Preparation of sulfinylimine 16(R)-2 and 16(S)-2



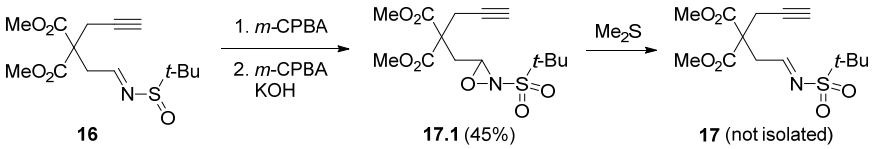
To a solution of (R) or (S) *tert*-butanesulfinamide (266.6 mg, 2.2 mmol) in DCM (3.3 ml) was added successively pyridinium p-toluenesulfonate (25.13 mg, 0.1 mmol), anhydrous $MgSO_4$ (1.2 g, 10 mmol) and aldehyde **14** (480.5 mg, 2 mmol). The mixture was stirred at room temperature for 24 h. $MgSO_4$ was filtered off through a pad of Celite and washed with DCM. The combined filtrates were concentrated and purified by flash chromatography (hexane:EtOAc = 3:1) to provide sulfinylimine **16(R)-2** (492 mg, 72%) and **16(S)-2** (442 mg, 65%).

16(R)-2. R_f 0.35 (hexane:EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (t, *J* = 3.5 Hz, 1H), 4.36 – 4.10 (m, 4H), 3.35 (qt, *J* = 14.4, 7.2 Hz, 2H), 3.10 – 2.99 (m, 2H), 2.06 (s, 1H), 1.27 (td, *J* = 7.1, 3.5 Hz, 6H), 1.19 (s, 9H). ^{13}C NMR (101 MHz,

cdcl$_3$) δ 168.99, 168.95, 165.31, 78.68, 72.37, 62.26, 62.24, 56.95, 55.13, 38.19, 23.38, 22.40, 14.13, 14.09. IR (neat): ν_{max} 3292, 2982, 1738, 1630, 1194, 1088 cm^{-1}. HRMS (ESI) calcd. for $C_{16}H_{25}NNaO_5S$ (M^++Na): 366.1351, found 366.1342.

16(S)-2. R_f 0.35 (hexane:EtOAc = 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 4.1, 3.3 Hz, 1H), 4.32 – 4.09 (m, 4H), 3.34 (qd, *J* = 17.7, 3.7 Hz, 2H), 3.10 – 2.97 (m, 2H), 2.05 (dd, *J* = 2.8, 1.9 Hz, 1H), 1.25 (tdd, *J* = 7.1, 3.5, 0.8 Hz, 6H), 1.18 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.05, 169.01, 165.36, 78.73, 72.39, 62.32, 62.29, 57.01, 55.18, 38.24, 23.43, 22.45, 14.18, 14.13. IR (neat): ν_{max} 3292, 2982, 1738, 1630, 1194, 1088 cm^{-1}. HRMS (ESI) calcd. for $C_{16}H_{25}NNaO_5S$ (M^++Na): 366.1351, found 366.1347.

Preparation of sulfonylimine 17



Dry *m*-CPBA (86.3 mg, 0.4 mmol) was added in one portion to a solution of the *N*-sulfinylimine **16** (126.1 mg, 0.4 mmol) in DCM (4.1 ml) at room temperature. The mixture was stirred at room temperature for 5 min. The reaction crude was added over a white suspension of *m*-CPBA (86.3 mg, 0.4 mmol) and powdered KOH (74.1 mg, 1.32mmol) in DCM (3 ml), which was previously prepared and maintained for 10 min at room temperature. After TLC indicated the complete consumption of the starting material, the reaction crude was filtered and the solvent was evaporated to yield pure *N*-sulfonyloxaziridine **17.1** (62 mg, 45%). R_f 0.55 (hexane:EtOAc = 2:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (t, *J* = 4.6 Hz, 1H), 3.77 (d, *J* = 1.5 Hz, 6H), 2.91 (d, *J* = 2.7 Hz, 2H), 2.55 (ddd, *J* = 40.6, 15.2, 4.6 Hz, 2H), 2.07 (t, *J* = 2.7 Hz, 1H), 1.50 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.30, 78.05, 72.62, 71.86, 61.22, 54.52, 53.49, 53.45, 34.45, 24.55, 24.06.

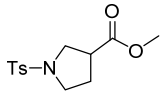
To a solution of oxaziridine **17.1** (62 mg, 0.18 mmol) in DCM (1.8 ml) was added dimethylsulfide (0.02 ml, 0.27 mmol) at room temperature. After stirring at room temperature for 5 min, the reaction mixture was concentrated by rotary evaporation to give the sulfonylimine **17**, which was used immediately for the main reaction without further purification. R_f = 0.30 (hexane:EtOAc = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (t, *J* = 3.5 Hz, 1H), 3.77 (d, *J* = 0.7 Hz, 6H), 3.37 (d, *J* = 3.6 Hz, 2H), 3.03 (d, *J* = 2.7 Hz, 2H), 1.42 (s, 9H). IR (neat): ν_{max} 3340, 3245, 2985, 1730, 1303, 1116, 902 cm^{-1}.

3.1. General procedure for transition metal-catalyzed oxygenative *α*-addition and *β*-alkylation of terminal alkynes

To a round bottom flasks fitted with rubber septa were added a alkyne substrate (0.5 mmol), PPh_3 (26.2 mg, 0.1 mmol, 20 mmol%), pyridine *N*-oxide (71.3 mg, 0.75 mmol), $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol, 5 mmol%), an alcohol (2 mmol) of amine (0.6 mmol) and CH_3CN (1.25 mL). After sealing the flask with rubber septa, the resulting yellow solution was heated at 60 °C under a positive pressure of argon. And the reaction was closely monitored by TLC analysis. Upon complete consumption of the starting alkyne, the reaction mixture was cooled to ambient temperature, and concentrated *in vacuo*. Purification by flash column chromatography afforded the ester or amide product in an analytically pure form.

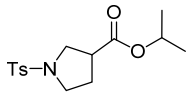
3.2. Characterization of products



Methyl 1-tosylpyrrolidine-3-carboxylate (1a, Table 6)

Following the general procedure, $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), TEA (41.8 μL, 3 mmol), pyridine *N*-oxide (71.3 mg, 0.75 mmol), methanol (81 μL, 2 mmol), and alkynyl iodide **1** (181.5 mg, 0.5 mmol) were reacted in CH_3CN for 0.5 h to give **1a** (116.9 mg, 82%) after purification by flash column chromatography. R_f 0.20 (hexane:EtOAc = 4:1).

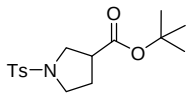
^1H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.68 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.61 (s, 3H), 3.57 (dd, *J* = 10.3, 8.1 Hz, 1H), 3.32 (dddd, *J* = 13.9, 9.8, 9.0, 6.6 Hz, 4H), 3.01 – 2.90 (m, 1H), 2.44 (s, 3H), 2.11 – 1.99 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.97, 143.85, 133.63, 129.93, 127.87, 52.39, 50.13, 47.55, 42.87, 28.58, 21.76. IR (neat): ν_{max} 2955, 1737, 1598, 1346, 1162, 1040, 818 cm^{-1} HRMS (ESI) calcd. for $C_{13}H_{17}NNaO_4S$ (M^++Na): 306.0776, found 306.0770.



Isopropyl 1-tosylpyrrolidine-3-carboxylate (1b, Table 6)

Following the general procedure, $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), TEA (41.8 μL, 3 mmol), pyridine *N*-oxide (71.3 mg, 0.75 mmol), isopropyl alcohol (153 μL, 2 mmol), and alkynyl iodide **1** (181.5 mg, 0.5 mmol) were reacted in CH_3CN for 1.5 h to give **1b** (86.8 mg, 56%) after purification by flash column chromatography. R_f 0.30 (hexane:EtOAc = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 771 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.91 (dp, *J* = 12.5, 6.2 Hz, 1H), 3.55 (t, *J* = 9.2 Hz, 1H), 3.40 – 3.21 (m, 3H), 2.96 – 2.83 (m, 1H), 2.42 (s, 3H), 2.09 – 1.92 (m, 2H), 1.15 (d, *J* = 6.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.00, 143.79, 133.64, 129.89, 127.80, 68.74, 50.06, 47.60, 43.18, 28.55, 21.83, 21.81, 21.72. IR (neat): ν_{max} 2981, 1730, 1598, 1347, 1163, 1108, 818 cm^{-1} HRMS (ESI) calcd. for $C_{15}H_{21}NNaO_4S$ (M^++Na): 334.1089, found 334.1082.

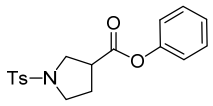


***tert*-Butyl 1-tosylpyrrolidine-3-carboxylate (1c, Table 6)**

Following the general procedure, $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), TEA (41.8 μL, 3 mmol), pyridine *N*-oxide (71.3 mg, 0.75 mmol), tert-butanol (191 μL, 2 mmol), and alkynyl iodide **1** (181.5 mg, 0.5 mmol) were reacted in CH_3CN for 1.5 h to give **1c** (49.1 mg, 30%) after purification by flash column chromatography. R_f 0.25 (hexane:EtOAc = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 3.56 – 3.45 (m, 1H), 3.29 (dt, *J* = 21.4, 7.1 Hz, 3H), 2.91 – 2.77 (m, 1H), 2.40 (s, 3H), 2.04 – 1.90 (m, 2H), 1.35 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.65, 143.72, 133.62, 129.85, 127.75, 81.48, 50.08, 47.59, 43.92, 28.52, 28.03, 21.66.

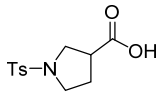
IR (neat): ν_{max} 2977, 1729, 1598, 1347, 1161, 1036, 817 cm^{-1} HRMS (ESI) calcd. for $C_{16}H_{23}NNaO_4S$ (M^++Na): 348.1245, found 348.1240.



Phenyl 1-tosylpyrrolidine-3-carboxylate (1d, Table 6)

Following the general procedure, $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), TEA (41.8 μL, 3 mmol), pyridine *N*-oxide (71.3 mg, 0.75 mmol), phenol (176 μL, 2 mmol), and alkynyl iodide **1** (181.5 mg, 0.5 mmol) were reacted in CH_3CN for 1 h to give **1d** (132.4 mg, 77%) after purification by flash column chromatography. R_f 0.23 (hexane:EtOAc = 4:1).

^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.40 – 7.28 (m, 4H), 7.23 (t, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 2H), 3.75 – 3.66 (m, 1H), 3.55 (dd, *J* = 9.8, 7.2 Hz, 1H), 3.46 – 3.31 (m, 2H), 3.27 – 3.16 (m, 1H), 2.42 (s, 3H), 2.20 (q, *J* = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.22, 150.48, 143.91, 133.53, 129.99, 129.66, 127.86, 126.31, 121.39, 50.07, 47.60, 43.13, 28.67, 21.76. IR (neat): ν_{max} 2956, 1757, 1596, 1346, 1162, 1033, 818 cm^{-1} HRMS (ESI) calcd. for $C_{18}H_{19}NNaO_4S$ (M^++Na): 368.0932, found 368.0928.

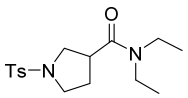


1-Tosylpyrrolidine-3-carboxylic acid[18] (1e, Table 6)

Following the general procedure, $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), TEA (0.42 mL, 3 mmol), pyridine *N*-oxide (71.3 mg, 0.0.75 mmol), H_2O (90 μL, 5 mmol), and alkynyl iodide **1** (181.5 mg, 0.5 mmol) were reacted in CH_3CN for 2 h to give **1e** (96.7 mg, 72%) after purification by flash column chromatography.

[18] M. Winkler, D. Meischler and N. Klempier, *Adv. Synth. Catal.*, 2007, **349**, 1475.

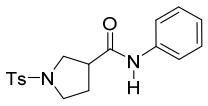
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 3.53 (dd, *J* = 10.3, 8.0 Hz, 1H), 3.47 – 3.38 (m, 1H), 3.31 (dd, *J* = 12.0, 5.0 Hz, 2H), 3.03 – 2.90 (m, 1H), 2.43 (s, 3H), 2.14 – 1.99 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.10, 143.97, 133.44, 129.93, 127.87, 49.84, 47.46, 42.69, 28.48, 21.77. IR (neat): ν_{max} 2967, 1714, 1343, 1161, 818 cm^{-1}



***N, N*-Diethyl-1-tosylpyrrolidine-3-carboxamide (1g, Table 6)**

Following the general procedure, $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), TEA (41.8 μL, 3 mmol), pyridine *N*-oxide (71.3 mg, 0.75 mmol), diethylamine (81 μL, 1 mmol), and alkynyl iodide **1** (181.5 mg, 0.5 mmol) were reacted in CH_3CN for 2 h to give **1g** (116.9 mg, 82%) after purification by flash column chromatography. R_f 0.28 (hexane:EtOAc = 1:1)

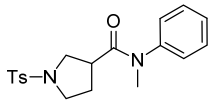
^{1}H NMR (400 MHz, $cdcl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.64 (dd, *J* = 9.1, 7.3 Hz, 1H), 3.42 (dt, *J* = 9.8, 7.5 Hz, 1H), 3.34 – 3.18 (m, 5H), 3.18 – 3.04 (m, 2H), 2.42 (s, 3H), 2.06 – 1.91 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.09 – 1.00 (m, 3H). ^{13}C NMR (101 MHz, $cdcl_3$) δ 170.78, 143.87, 133.53, 129.99, 127.92, 77.62, 77.30, 76.98, 51.47, 47.73, 42.13, 40.70, 40.37, 29.50, 21.79, 15.07, 13.21. IR (neat): ν_{max} 2974, 2934, 2884, 1640, 1460, 1344, 1163, 819 cm^{-1} HRMS (ESI) calcd. for $C_{16}H_{24}N_2NaO_3S$ (M^++Na): 347.1405, found 347.1402



***N*-Phenyl-1-tosylpyrrolidine-3-carboxamide (1h, Table 6)**

Following the general procedure, $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), TEA (41.8 μL, 3 mmol), pyridine *N*-oxide (71.3 mg, 0.75 mmol), aniline (55 μL, 0.6 mmol), and alkynyl iodide **1** (181.5 mg, 0.5 mmol) were reacted in CH_3CN for 1 h to give **1h** (126.2 mg, 73%) after purification by flash column chromatography. R_f 0.18 (hexane:EtOAc = 2:1).

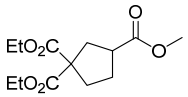
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.70 (d, *J* = 7.4 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.23 (d, *J* = 7.4 Hz, 2H), 7.06 (t, *J* = 7.3 Hz, 1H), 3.67 (t, *J* = 8.6 Hz, 1H), 3.43 – 3.18 (m, 3H), 3.12 – 2.98 (m, 1H), 2.40 (s, 3H), 2.10 – 2.00 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.22, 144.14, 137.93, 132.80, 129.99, 128.95, 127.68, 124.47, 120.08, 51.14, 47.70, 44.94, 28.95, 21.63. IR (neat): ν_{max} 3342, 1692, 1542, 1343, 1161, 758 cm^{-1} HRMS (ESI) calcd. for $C_{18}H_{20}N_2NaO_3S$ (M^++Na): 367.1092, found 367.1086.



***N*-Methyl-*N*-phenyl-1-tosylpyrrolidine-3-carboxamide (1i, Table 6)**

Following the general procedure, $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), TEA (41.8 μL, 3 mmol), pyridine *N*-oxide (71.3 mg, 0.75 mmol), *N*-methyl aniline (65 μL, 0.6 mmol), and alkynyl iodide **1** (181.5 mg, 0.5 mmol) were reacted in CH_3CN for 1 h to give **1i** (121.5 mg, 68%) after purification by flash column chromatography. R_f 0.18 (hexane:EtOAc = 2:1).

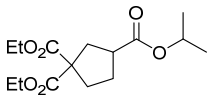
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.48 – 7.31 (m, 3H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.13 – 7.07 (m, 2H), 3.38 (dt, *J* = 15.5, 7.8 Hz, 1H), 3.18 (s, 3H), 3.21 – 3.11 (m, 3H), 2.86 – 2.69 (m, 1H), 2.39 (s, 3H), 2.03 – 1.86 (m, 1H), 1.85 – 1.60 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.70, 143.60, 143.33, 133.37, 130.20, 129.80, 128.42, 127.64, 127.29, 51.49, 47.58, 41.02, 37.78, 29.54, 21.65. IR (neat): ν_{max} 2957, 1657, 1596, 1495, 1344, 1162 cm^{-1} HRMS (ESI) calcd. for $C_{19}H_{22}N_2NaO_3S$ (M^++Na): 381.1249, found 381.1241.



1,1-Diethyl 3-methyl cyclopentane-1,1,3-tricarboxylate (2a, Table 7)

Following the general procedure, $[Rh(COD)Cl]_2$ (7.4 mg, 0.015 mmol), PPh_3 (15.7 mg, 0.06 mmol), TEA (25 μL, 1.8 mmol), pyridine *N*-oxide (42.8 mg, 0.45 mmol), methanol (49 μL, 1.2 mmol), and alkynyl iodide **2** (105.7 mg, 0.3 mmol) were reacted in CH_3CN for 2 h to give **2a** (79.4 mg, 97%) after purification by flash column chromatography. R_f 0.55 (hexane:EtOAc = 3:1).

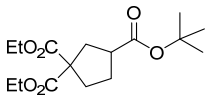
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (q, *J* = 7.1 Hz, 4H), 3.65 (s, 3H), 3.02 – 2.79 (m, 1H), 2.57 (dd, *J* = 13.7, 8.3 Hz, 1H), 2.42 – 2.29 (m, 2H), 2.19 – 2.08 (m, 1H), 2.06 – 1.84 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.31, 172.13, 171.69, 61.68, 61.65, 60.27, 52.01, 43.39, 37.20, 33.79, 29.19, 14.17. IR (neat): ν_{max} 2985, 1734, 1441, 1260, 1177 cm^{-1} HRMS (ESI) calcd. for $C_{13}H_{20}NaO_6$ (M^++Na): 295.0932, found 295.1154.



1,1-Diethyl 3-isopropyl cyclopentane-1,1,3-tricarboxylate (2b, Table 7)

Following the general procedure, $[Rh(COD)Cl]_2$ (7.4 mg, 0.015 mmol), PPh_3 (15.7 mg, 0.06 mmol), TEA (25 μL, 1.8 mmol), pyridine *N*-oxide (42.8 mg, 0.45 mmol), isopropyl alcohol (49 μL, 1.2 mmol), and alkynyl iodide **2** (105.7 mg, 0.3 mmol) were reacted in CH_3CN for 2 h to give **2b** (72.9 mg, 81%) after purification by flash column chromatography. R_f 0.40 (hexane:EtOAc = 7:1).

^1H NMR (400 MHz, $CDCl_3$) δ 5.05 – 4.90 (m, 1H), 4.24 – 4.06 (m, 4H), 2.90 – 2.80 (m, 1H), 2.56 (dd, *J* = 13.7, 8.3 Hz, 1H), 2.42 – 2.26 (m, 2H), 2.20 – 2.07 (m, 1H), 2.04 – 1.84 (m, 2H), 1.30 – 1.14 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.41, 172.28, 171.79, 68.00, 61.70, 61.65, 60.36, 43.84, 37.22, 33.85, 29.21, 21.96, 14.21. IR (neat): ν_{max} 2983, 1733, 1259, 1180, 1109 cm^{-1} HRMS (ESI) calcd. for $C_{15}H_{24}NaO_6$ (M^++Na): 323.1471, found 323.1466.

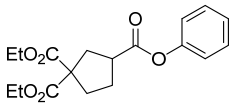


3-(*tert*-Butyl) 1,1-diethyl cyclopentane-1,1,3-tricarboxylate (2c, Table 7)

Following the general procedure, $[Rh(COD)Cl]_2$ (7.4 mg, 0.015 mmol), PPh_3 (15.7 mg, 0.06 mmol), TEA (25 μL, 1.8 mmol), pyridine *N*-oxide (42.8 mg, 0.45 mmol), tert-butanol (115 μL, 1.2 mmol), and alkynyl iodide **2** (105.7 mg, 0.3 mmol) were reacted in CH_3CN for 2.5 h to give **2c** (29.5 mg, 31%) after purification by flash column chromatography. R_f 0.40 (hexane:EtOAc = 7:1).

^1H NMR (400 MHz, $CDCl_3$) δ 4.25 – 4.09 (m, 4H), 2.86 – 2.74 (m, 1H), 2.55 (dd, *J* = 13.7, 8.3 Hz, 1H), 2.40 – 2.27 (m, 2H), 2.19 – 2.07 (m, 1H), 2.04 – 1.83 (m,

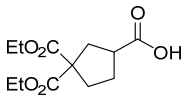
2H), 1.42 (s, 9H), 1.23 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.17, 172.31, 171.82, 80.53, 61.64, 61.59, 60.34, 44.62, 37.24, 33.83, 29.20, 28.20, 14.19. IR (neat): ν_{max} 2980, 1732, 1368, 1259, 1156 cm^{-1} HRMS (ESI) calcd. for $C_{16}H_{26}NaO_6$ (M^++Na): 337.1627, found 337.1622.



1,1-Diethyl 3-phenyl cyclopentane-1,1,3-tricarboxylate (2d, Table 7)

Following the general procedure, $[Rh(COD)Cl]_2$ (7.4 mg, 0.015 mmol), PPh_3 (15.7 mg, 0.06 mmol), TEA (25 μL, 1.8 mmol), pyridine *N*-oxide (42.8 mg, 0.45 mmol), phenol (105 μL, 1.2 mmol), and alkynyl iodide **2** (105.7 mg, 0.3 mmol) were reacted in CH_3CN for 1.5 h to give **2d** (97.5 mg, 97%) after purification by flash column chromatography. R_f 0.35 (hexane:EtOAc = 7:1).

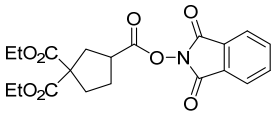
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, J = 7.7 Hz, 2H), 7.21 (td, J = 7.3, 3.5 Hz, 1H), 7.10 – 7.02 (m, 2H), 4.26 – 4.11 (m, 4H), 3.24 – 3.10 (m, 1H), 2.70 (dd, J = 13.8, 8.4 Hz, 1H), 2.55 (dd, J = 13.8, 8.4 Hz, 1H), 2.49 – 2.37 (m, 1H), 2.29 – 2.18 (m, 1H), 2.18 – 2.04 (m, 2H), 1.31 – 1.16 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.54, 172.32, 171.85, 151.13, 129.68, 126.08, 121.73, 61.93, 61.90, 60.47, 43.74, 37.37, 33.98, 29.26, 14.32. IR (neat): ν_{max} 2980, 1731, 1493, 1262, 1196, 1031 cm^{-1} HRMS (ESI) calcd. for $C_{18}H_{22}NaO_6$ (M^++Na): 357.1314, found 357.1310.



3, 3-bis(Ethoxycarbonyl)cyclopentane-1-carboxylic acid (2e, Table 7)

Following the general procedure, $[Rh(COD)Cl]_2$ (7.4 mg, 0.015 mmol), PPh_3 (15.7 mg, 0.06 mmol), TEA (0.25 mL, 1.8 mmol), pyridine *N*-oxide (42.8 mg, 0.45 mmol), H_2O (54 μL, 3 mmol), and alkynyl iodide **2** (105.7 mg, 0.3 mmol) were reacted in CH_3CN for 2 h to give **2e** (67.1 mg, 78%) after purification by flash column chromatography.

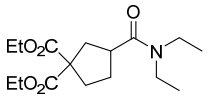
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (q, *J* = 7.1 Hz, 4H), 3.02 – 2.89 (m, 1H), 2.60 (dd, *J* = 13.8, 8.5 Hz, 1H), 2.46 – 2.32 (m, 2H), 2.23 – 2.10 (m, 1H), 2.08 – 1.93 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.89, 172.18, 171.82, 77.62, 77.30, 76.98, 61.88, 60.47, 43.38, 37.04, 34.01, 29.23, 14.27. IR (neat): ν_{max} 2981, 1731, 1439, 1261, 1160, 725 cm^{-1}



3-(1,3-Dioxoisoindolin-2-yl) 1,1-diethyl cyclopentane-1,1,3-tricarboxylate (2f, Table 7)

Following the general procedure, $[Rh(COD)Cl]_2$ (1.23 mg, 0.0025 mmol), PPh_3 (2.62 mg, 0.01 mmol), TEA (0.04 mL, 0.3 mmol), pyridine *N*-oxide (7.13 mg, 0.075 mmol), *N*-hydroxyphthalimide (16.3 mg, 0.1 mmol), and alkynyl iodide **2** (17.6 mg, 0.05 mmol) were reacted in CH_3CN (0.2 ml) for 1 h to give **2f** (15.4 mg, 77%) after purification by flash column chromatography. R_f 0.18 (hexane:EtOAc = 5:1).

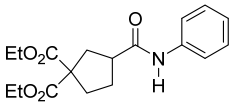
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dt, *J* = 7.6, 3.7 Hz, 2H), 7.77 (dd, *J* = 5.3, 3.1 Hz, 2H), 4.26 – 4.11 (m, 4H), 3.36 – 3.23 (m, 1H), 2.78 (dd, *J* = 13.9, 8.5 Hz, 1H), 2.54 (dd, *J* = 13.9, 8.8 Hz, 1H), 2.49 – 2.38 (m, 1H), 2.29 – 2.13 (m, 3H), 1.24 (q, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.92, 171.45, 171.23, 162.14, 135.03, 129.22, 124.25, 62.05, 62.00, 60.58, 40.66, 37.11, 33.94, 29.52, 14.32, 14.29. IR (neat): ν_{max} 2984, 1788, 1747, 1368, 1261, 878 cm^{-1} HRMS (ESI) calcd. for $C_{20}H_{21}NNaO_8$ (M^++Na): 426.1165, found 426.1154.



Diethyl 3-(diethylcarbamoyl)cyclopentane-1,1-dicarboxylate (2g, Table 7)

Following the general procedure, $[Rh(COD)Cl]_2$ (7.4 mg, 0.015 mmol), PPh_3 (15.7 mg, 0.06 mmol), TEA (25 μL, 1.8 mmol), pyridine *N*-oxide (42.8 mg, 0.45 mmol), diethylamine (49 μL, 1.2 mmol), and alkynyl iodide **2** (105.7 mg, 0.3 mmol) were reacted in CH_3CN for 1 h to give **2g** (85.7 mg, 91%) after purification by flash column chromatography. R_f 0.20 (hexane:EtOAc = 3:1).

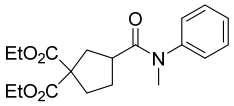
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 – 4.04 (m, 4H), 3.41 – 3.25 (m, 4H), 3.00 (dt, *J* = 16.3, 8.1 Hz, 1H), 2.55 – 2.41 (m, *J* = 15.2, 11.2, 7.2 Hz, 2H), 2.28 (dd, *J* = 13.2, 9.9 Hz, 1H), 2.12 – 1.98 (m, *J* = 20.5, 13.9, 6.7 Hz, 1H), 1.98 – 1.79 (m, 2H), 1.20 (td, *J* = 7.1, 4.3 Hz, 6H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.24, 172.76, 171.54, 61.55, 61.50, 60.43, 41.86, 41.01, 40.34, 38.25, 33.65, 29.82, 14.93, 14.16, 13.16. IR (neat): ν_{max} 2980, 1731, 1641, 1449, 1260, 1098, 862 cm^{-1} HRMS (ESI) calcd. for $C_{16}H_{27}NNaO_5$ (M^++Na): 336.1787, found 336.1780.



Diethyl 3-(phenylcarbamoyl)cyclopentane-1,1-dicarboxylate (2h, Table 7)

Following the general procedure, $[Rh(COD)Cl]_2$ (7.4 mg, 0.015 mmol), PPh_3 (15.7 mg, 0.06 mmol), TEA (25 μL, 1.8 mmol), pyridine *N*-oxide (42.8 mg, 0.45 mmol), aniline (33 μL, 0.36 mmol), and alkynyl iodide **2** (105.7 mg, 0.3 mmol) were reacted in CH_3CN for 2 h to give **2h** (88.6 mg, 89%) after purification by flash column chromatography. R_f 0.25 (hexane:EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.08 (t, *J* = 7.2 Hz, 1H), 4.31 – 4.10 (m, 4H), 2.98 – 2.82 (m, 1H), 2.52 (d, *J* = 8.6 Hz, 2H), 2.46 – 2.36 (m, *J* = 12.9, 7.9, 4.6 Hz, 1H), 2.28 – 2.17 (m, 1H), 2.17 – 2.05 (m, *J* = 12.3, 7.6 Hz, 1H), 2.05 – 1.91 (m, *J* = 17.6, 12.8, 8.7 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.98, 172.45, 172.22, 138.41, 129.08, 124.26, 119.97, 61.98, 61.79, 60.67, 46.62, 37.61, 34.26, 30.43, 14.21. IR (neat): ν_{max} 3311, 2982, 1731, 1543, 1259, 757 cm^{-1} HRMS (ESI) calcd. for $C_{18}H_{23}NNaO_5$ (M^++Na): 356.1474, found 356.1471.

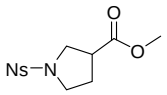


Diethyl 3-(methyl(phenyl)carbamoyl)cyclopentane-1,1-dicarboxylate (2i, Table 7)

Following the general procedure, $[Rh(COD)Cl]_2$ (7.4 mg, 0.015 mmol), PPh_3 (15.7 mg, 0.06 mmol), TEA (25 μL, 1.8 mmol), pyridine *N*-oxide (42.8 mg, 0.45 mmol), *N*-methylaniline (39 μL, 0.36 mmol), and alkynyl iodide **2** (105.7 mg, 0.3 mmol) were reacted in CH_3CN for 2 h to give **2i** (86.6 mg, 83%) after purification by flash

column chromatography. R_f 0.23 (hexane:EtOAc = 3:1).

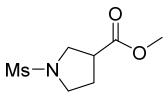
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.02 (dt, *J* = 13.8, 6.9 Hz, 2H), 3.23 (s, 3H), 2.81 – 2.67 (m, 1H), 2.45 – 2.26 (m, 3H), 2.00 – 1.85 (m, 2H), 1.67 (t, *J* = 11.8 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.39, 172.11, 171.43, 143.82, 129.74, 127.85, 127.34, 61.35, 61.24, 60.41, 41.50, 38.23, 37.65, 33.65, 30.06, 14.00, 13.89. IR (neat): ν_{max} 2984, 1731, 1657, 1497, 1259, 703 cm^{-1} HRMS (ESI) calcd. for $C_{19}H_{25}NNaO_5$ (M^++Na): 370.1630, found 370.1627.



4-(3-(Methoxycarbonyl)pyrrolidin-1-yl)-3-nitrobenzenesulfonic acid (3a, Table 8)

Following the general procedure, $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), TEA (41.8 μL, 3 mmol), pyridine *N*-oxide (71.3 mg, 0.75 mmol), methanol (81 μL, 2 mmol), and alkynyl iodide **3** (197.09 mg, 0.5 mmol) were reacted in CH_3CN for 1.5 h to give **3a** (116.1 mg, 75%) after purification by flash column chromatography. R_f 0.15 (hexane:EtOAc = 3:1).

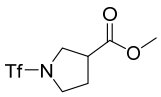
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dt, *J* = 9.2, 2.0 Hz, 2H), 8.02 (dt, *J* = 9.2, 2.0 Hz, 2H), 3.65 – 3.56 (m, 4H), 3.52 – 3.44 (m, 1H), 3.42 (ddd, *J* = 7.5, 4.9, 1.5 Hz, 1H), 3.32 (dt, *J* = 9.5, 7.1 Hz, 1H), 3.09 – 2.96 (m, 1H), 2.22 – 2.01 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.58, 150.24, 142.66, 128.73, 124.45, 52.43, 52.32, 49.96, 47.46, 42.70, 28.68.



Methyl 1-(methylsulfonyl)pyrrolidine-3-carboxylate (4a, Table 8)

Following the general procedure, $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), TEA (41.8 μL, 3 mmol), pyridine *N*-oxide (71.3 mg, 0.75 mmol), methanol (81 μL, 2 mmol), and alkynyl iodide **4** (143.56 mg, 0.5 mmol) were reacted in CH_3CN for 0.5 h to give **4a** (77.1 mg, 74%) after purification by flash column chromatography. R_f 0.27 (hexane:EtOAc = 1:1).

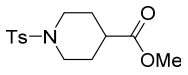
^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.65 – 3.53 (m, 2H), 3.46 (dt, *J* = 9.7, 6.6 Hz, 1H), 3.40 – 3.29 (m, 1H), 3.21 – 3.07 (m, 1H), 2.86 (s, 3H), 2.31 – 2.15 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.41, 52.34, 49.77, 47.17, 42.93, 34.69, 29.24.



Methyl 1-((trifluoromethyl)sulfonyl)pyrrolidine-3-carboxylate (5a, Table 8)

Following the general procedure, $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), TEA (41.8 μL, 3 mmol), pyridine *N*-oxide (71.3 mg, 0.75 mmol), methanol (81 μL, 2 mmol), and alkynyl iodide **5** (170.55 mg, 0.5 mmol) were reacted in CH_3CN for 0.5 h to give **5a** (86.3 mg, 66%) after purification by flash column chromatography. R_f 0.37 (hexane:EtOAc = 3:1).

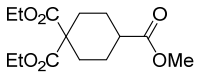
^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (d, *J* = 7.2 Hz, 2H), 3.75 (s, 3H), 3.71 – 3.54 (m, 2H), 3.20 (p, *J* = 7.1 Hz, 1H), 2.36 – 2.21 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.19, 122.09, 118.87, 52.67, 50.73, 48.36, 43.29, 29.18.



Methyl 1-tosylpiperidine-4-carboxylate[19] (6a, Table 8)

Following the general procedure, $[Rh(COD)Cl]_2$ (7.4 mg, 0.015 mmol), PPh_3 (15.7 mg, 0.06 mmol), TEA (25 μL, 1.8 mmol), 2-phenylpyridine *N*-oxide (77.04 mg, 0.45 mmol), methanol (49 μL, 1.2 mmol), and alkynyl iodide **6** (113.2 mg, 0.3 mmol) were reacted in CH_3CN (1.2 ml) for 2 h to give **6a** (47.5 mg, 53%) after purification by flash column chromatography. R_f 0.15 (hexane:EtOAc = 3:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 7.0 Hz, 2H), 3.72 – 3.56 (m, 5H), 2.45 (dd, *J* = 12.9, 6.3 Hz, 5H), 2.32 – 2.20 (m, 1H), 1.97 (d, *J* = 13.4 Hz, 2H), 1.82 (dd, *J* = 24.3, 10.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.50, 143.79, 133.33, 129.88, 127.89, 77.55, 77.23, 76.91, 52.10, 45.62, 40.15, 27.65, 21.76. IR (neat): ν_{max} 2848, 1735, 1598, 1450, 1338, 1164, 934, 727 cm^{-1}



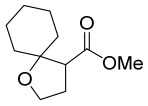
1,1-Diethyl 4-methyl cyclohexane-1,1,4-tricarboxylate (7a, Table 8)

Following the general procedure, $[Rh(COD)Cl]_2$ (1.86 mg, 0.004 mmol), PPh_3 (3.95 mg, 0.015 mmol), TEA (0.063 mL, 0.45 mmol), 2-phenylpyridine *N*-oxide (19.36 mg, 0.11 mmol), methanol (0.012 mL, 0.3 mmol), and alkynyl iodide **7** (27.6 mg, 0.075 mmol) were reacted in CH_3CN for 4 h to give **7a** (8.8 mg, 41%) after purification by flash column chromatography. R_f 0.25 (hexane:EtOAc = 7:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 – 4.08 (m, 4H), 3.66 (s, *J* = 4.6 Hz, 3H), 2.44 – 2.27 (m, 3H), 1.91 (m, *J* = 22.0, 8.7 Hz, 2H), 1.75 (m, *J* = 13.1, 3.3 Hz, 2H), 1.69 –

[19] M. Liniger, D. G. VanderVelde, M. K. Takase, M. Shahgholi and B. M. Stoltz, *J. Am. Chem. Soc.*, 2016, **138**, 969.

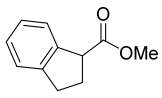
1.54 (m, J = 13.4, 10.8, 4.0 Hz, 2H), 1.24 (m, J = 11.1, 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.68, 172.22, 170.93, 61.61, 61.48, 54.36, 51.86, 41.72, 30.24, 25.27, 14.28, 14.23. IR (neat): ν_{max} 2981, 1734, 1453, 1070 cm^{-1} HRMS (ESI) calcd. for $C_{14}H_{22}NaO_6$ (M^++Na): 309.1314, found 309.1310.



Methyl 1-oxaspiro[4.5]decane-4-carboxylate[4] (8a, Table 8)

Following the general procedure, $[Rh(COD)Cl]_2$ (4.9 mg, 0.01 mmol), PPh_3 (10.5 mg, 0.04 mmol), TEA (170 μL, 1.2 mmol), pyridine *N*-oxide (28.5 mg, 0.3 mmol), methanol (32 μL, 0.8 mmol), and alkynyl iodide **8** (55.6 mg, 0.2 mmol) were reacted in CH_3CN for 2 h to give **8a** (31.3 mg, 79%) after purification by flash column chromatography. R_f 0.57 (hexane:EtOAc = 4:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (td, J = 8.4, 5.2 Hz, 1H), 3.81 (dd, J = 15.4, 7.9 Hz, 1H), 3.69 (s, 3H), 2.71 (t, J = 8.0 Hz, 1H), 2.39 – 2.26 (m, 1H), 2.17 – 2.03 (m, 1H), 1.68 – 1.46 (m, 8H), 1.26 – 1.09 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.51, 83.62, 77.62, 77.30, 76.98, 65.61, 53.81, 51.93, 37.12, 32.18, 28.95, 25.73, 23.29, 22.53. IR (neat): ν_{max} 2934, 2860, 1738, 1448, 1169, 1056, 711 cm^{-1}



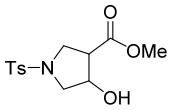
Methyl 2,3-dihydro-*1H*-indene-1-carboxylate[20] (9a, Table 8)

Following the general procedure, $[Rh(COD)Cl]_2$ (10.8 mg, 0.022 mmol), PPh_3 (23.07 mg, 0.088 mmol), TEA (0.368 mL, 2.64 mmol), pyridine *N*-oxide (62.76 mg,

[20] A. R. Katritzky, L. Xie and L. Serdyuk, *J. Org. Chem.*, 1996, **61**, 7564.

0.66 mmol), methanol (71 μL, 1.76 mmol), and alkynyl iodide **9** (112.68 mg, 0.44 mmol) were reacted in CH_3CN for 0.2 h to give **9a** (40.4 mg, 52%) after purification by flash column chromatography. R_f 0.51 (hexane:EtOAc = 5:1).

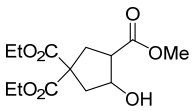
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, *J* = 9.7 Hz, 4H), 7.26 – 7.14 (m, 11H), 4.11 – 4.01 (m, 4H), 3.74 (s, 13H), 3.19 – 3.07 (m, 5H), 2.97 – 2.84 (m, 5H), 2.45 (ddt, *J* = 13.0, 8.6, 6.4 Hz, 5H), 2.39 – 2.25 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.68, 144.39, 140.96, 127.83, 126.71, 125.08, 124.96, 77.62, 77.30, 76.98, 52.29, 50.39, 32.05, 29.05. IR (neat): ν_{max} 2952, 1738, 1435, 1169, 753 cm^{-1}



Methyl 4-hydroxy-1-tosylpyrrolidine-3-carboxylate (1.4a, Table 9)

Following the general procedure, $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), TEA (0.42 mL, 3 mmol), pyridine *N*-oxide (71.3 mg, 0.0.75 mmol), methanol (81 μL, 2 mmol), and alkynyl aldehyde **1.4** (125.65 mg, 0.5 mmol) were reacted in CH_3CN (1.25 ml) for 1.5 h to give **1.4a** (58.7 mg, 40%, *dr*=2.1:1) after purification by flash column chromatography. R_f 0.10 (hexane:EtOAc = 2:1).

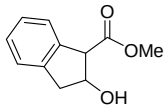
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (t, *J* = 7.7 Hz, 2H), 7.31 (dd, *J* = 8.3, 4.1 Hz, 2H), 4.54 – 4.38 (m, 1H), 3.71 – 3.57 (m, 4H), 3.53 – 3.29 (m, 3H), 3.19 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.04 – 2.75 (m, 2H), 2.45 – 2.35 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.72, 170.75, 144.06, 143.96, 133.63, 133.14, 129.94, 127.81, 127.71, 72.56, 70.90, 55.62, 54.37, 52.54, 52.50, 51.12, 48.71, 48.30, 47.14, 21.71. IR (neat): ν_{max} 3486, 2956, 1738, 1438, 1162, 817, 667 cm^{-1} HRMS (ESI) calcd. for $C_{13}H_{17}NNaO_5S$ (M^++Na): 322.0725, found 322.0722.



Trimethyl 4-hydroxycyclopentane-1,1,3-tricarboxylate (14a, Table 9)

Following the general procedure, $[Rh(COD)Cl]_2$ (12.3 mg, 0.025 mmol), PPh_3 (26.2 mg, 0.1 mmol), TEA (0.42 mL, 3 mmol), pyridine *N*-oxide (71.3 mg, 0.0.75 mmol), methanol (81 μL, 2 mmol), and alkynyl aldehyde **14** (120.13 mg, 0.5 mmol) were reacted in CH_3CN (2 ml) for 1 h to give **14a** (101.9 mg, 71%, *dr*=1.6:1) after purification by flash column chromatography. R_f 0.15 (hexane:EtOAc = 3:1).

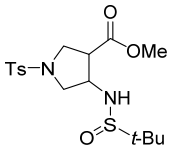
^1H NMR (400 MHz, $CDCl_3$) δ 4.56 – 4.38 (m, 1H), 4.26 – 4.12 (m, 4H), 3.72 (d, *J* = 6.3 Hz, 3H), 3.14 – 2.16 (m, 7H), 1.25 (ddd, *J* = 11.7, 7.0, 4.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.87, 172.95, 172.34, 172.26, 172.19, 171.29, 74.84, 73.49, 62.02, 61.99, 61.90, 61.82, 58.37, 57.58, 52.14, 52.05, 51.91, 49.83, 42.16, 41.36, 34.50, 33.85, 14.05. IR (neat): ν_{max} 3524, 2958, 1736, 1438, 1270, 1205 cm^{-1} HRMS (ESI) calcd. for $C_{13}H_{20}NaO_7$ (M^++Na): 311.1107, found 309.1310.



Methyl 2-hydroxy-2,3-dihydro-*1H*-indene-1-carboxylate (9.5a, Table 9)

Following the general procedure, $[Rh(COD)Cl]_2$ (11.8 mg, 0.024 mmol), PPh_3 (25.1 mg, 0.096 mmol), TEA (0.40 mL, 2.87 mmol), pyridine *N*-oxide (68.3 mg, 0.72 mmol), methanol (77 μL, 1.91 mmol), and alkynyl aldehyde **9.5** (69.0 mg, 0.48 mmol) were reacted in CH_3CN for 1 h to give **9.5a** (20.0 mg, 22%, *dr*=3.5:1) after purification by flash column chromatography. R_f 0.30 (hexane:EtOAc = 2:1).

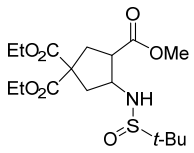
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.25 (m, 4H), 5.01 – 4.81 (m, 1H), 4.08 (dd, *J* = 50.3, 4.4 Hz, 1H), 3.87 – 3.77 (m, 3H), 3.46 – 3.31 (m, 1H), 3.17 (dd, *J* = 38.3, 16.3 Hz, 1H), 2.94 (dd, *J* = 15.8, 4.2 Hz, 1H), 2.54 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.93, 140.59, 137.83, 128.23, 127.21, 125.89, 125.33, 125.17, 75.98, 74.25, 58.60, 54.71, 52.41, 41.03, 40.55, 30.52. IR (neat): ν_{max} 3456, 2952, 1734, 1436, 1170, 1020, 746 cm^{-1} HRMS (ESI) calcd. for $C_{11}H_{12}NaO_3$ (M^++Na): 215.0684, found 215.0678.



Methyl 4-((*tert*-butylsulfinyl)amino)-1-tosylpyrrolidine-3-carboxylate (15a, Table 9)

Following the general procedure, $[Rh(COD)Cl]_2$ (7.4 mg, 0.015 mmol), PPh_3 (15.7 mg, 0.06 mmol), TEA (25 μL, 1.8 mmol), pyridine *N*-oxide (42.8 mg, 0.45 mmol), methanol (49 μL, 1.2 mmol), and sulfinylimine **15** (106.3 mg, 0.3 mmol) were reacted in CH_3CN for 1 h to give **15a** (54.3 mg, 45%, *dr*=1.2:1) after purification by flash column chromatography. R_f 0.25 (hexane:EtOAc = 1:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 10.5, 8.3 Hz, 2H), 7.33 (dd, *J* = 8.1, 2.5 Hz, 2H), 4.17 – 3.98 (m, 1H), 3.63 – 3.58 (m, 3H), 3.58 – 3.48 (m, *J* = 19.3, 7.7 Hz, 2H), 3.42 (dd, *J* = 11.1, 3.3 Hz, 1H), 3.39 – 3.20 (m, 1H), 3.16 – 2.93 (m, *J* = 21.2, 14.4, 7.4 Hz, 1H), 2.41 (d, *J* = 3.7 Hz, 3H), 1.08 (d, *J* = 24.5 Hz, 9H). IR (neat): ν_{max} 3200, 2958, 1739, 1347, 1164, 1054, 817 cm^{-1} HRMS (ESI) calcd. for $C_{17}H_{26}N_2NaO5S_2$ (M^++Na): 425.1181, found 425.1174.



1,1-Diethyl 3-methyl 4-((tert-butylsulfinyl)amino)cyclopentane-1,1,3-tricarboxylate (16(R)-2a)

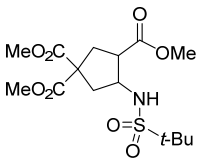
Following the general procedure, $[Rh(COD)Cl]_2$ (7.4 mg, 0.015 mmol), PPh_3 (15.7 mg, 0.06 mmol), TEA (25 μL, 1.8 mmol), pyridine *N*-oxide (42.8 mg, 0.45 mmol), methanol (49 μL, 1.2 mmol), and sulfinylimine **16(R)-2** (103.0 mg, 0.3 mmol) were reacted in CH_3CN for 2 h to give **16(R)-2a** (54 mg, 46%, *dr*=1.3:1) after purification by flash column chromatography. R_f 0.35-0.45 (hexane:EtOAc = 1:2). ^1H NMR (400 MHz, $CDCl_3$) δ 4.16 (dd, *J* = 6.6, 2.5 Hz, 4H), 4.04 (dt, *J* = 14.7, 7.4 Hz, 1H), 3.66 (s, 3H), 3.58 (d, *J* = 7.5 Hz, 1H), 2.81 (dd, *J* = 16.8, 8.5 Hz, 1H), 2.72 (dd, *J* = 14.2, 7.7 Hz, 1H), 2.58 (dd, *J* = 13.9, 8.3 Hz, 1H), 2.40 (dd, *J* = 13.8, 9.8 Hz, 1H), 2.26 (dd, *J* = 14.2, 6.8 Hz, 1H), 1.21 (td, *J* = 7.0, 2.3 Hz, 6H), 1.15 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.39, 172.18, 171.02, 62.21, 62.02, 60.20, 58.37, 56.02, 52.31, 52.27, 51.25, 41.18, 35.39, 22.65, 14.18. IR (neat): ν_{max} 3270, 2977, 1735, 1254, 1055, 780 cm^{-1} HRMS (ESI) calcd. for $C_{17}H_{29}NNaO_7S$ (M^++Na): 414.1562, found 414.1559.

1,1-Diethyl 3-methyl 4-((tert-butylsulfinyl)amino)cyclopentane-1,1,3-tricarboxylate (16(S)-2a)

Following the general procedure, $[Rh(COD)Cl]_2$ (7.4 mg, 0.015 mmol), PPh_3 (15.7 mg, 0.06 mmol), TEA (25 μL, 1.8 mmol), pyridine *N*-oxide (42.8 mg, 0.45 mmol), methanol (49 μL, 1.2 mmol), and sulfinylimine **16(S)-2** (103.0 mg, 0.3 mmol) were reacted in CH_3CN for 2 h to give **16(S)-2a** (76 mg, 65%, *dr*=1:1) after purification

by flash column chromatography. R_f 0.35-0.45 (hexane:EtOAc = 1:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (ddd, *J* = 14.2, 7.1, 3.2 Hz, 4H), 4.06 (dt, *J* = 22.1, 7.2 Hz, 1H), 3.67 (s, 3H), 3.60 (d, *J* = 7.6 Hz, 1H), 2.82 (dd, *J* = 17.1, 8.3 Hz, 1H), 2.73 (dd, *J* = 14.2, 7.8 Hz, 1H), 2.59 (dd, *J* = 14.0, 8.3 Hz, 1H), 2.41 (dd, *J* = 14.0, 9.6 Hz, 1H), 2.27 (dd, *J* = 14.2, 6.8 Hz, 1H), 1.22 (td, *J* = 7.1, 3.0 Hz, 6H), 1.16 (s, *J* = 6.6 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.36, 172.14, 170.99, 62.17, 61.98, 60.18, 58.34, 55.99, 52.23, 51.21, 41.15, 35.36, 22.63, 22.43, 14.15. IR (neat): v_{max} 3276, 2982, 1734, 1442, 1266, 1180, 1074, 864 cm^{-1} HRMS (ESI) calcd. for $C_{17}H_{29}NNaO_7S$ (M^++Na): 414.1562, found 414.1556.



Trimethyl 4-((1,1-dimethylethyl)sulfonamido)cyclopentane-1,1,3-tricarboxylate (17a, Table 9)

Following the general procedure, $[Rh(COD)Cl]_2$ (4.4 mg, 0.009 mmol), PPh_3 (9.38 mg, 0.035 mmol), TEA (15 μL, 1.07 mmol), pyridine *N*-oxide (25.5 mg, 0.27 mmol), methanol (29 μL, 0.72 mmol), and sulfonylimine **17** (59.2 mg, 0.179 mmol) were reacted in CH_3CN for 0.5 h to give **17a** (35.4 mg, 52%, *dr*=1:1) after purification by flash column chromatography. R_f 0.35 (hexane:EtOAc = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (dd, *J* = 28.2, 9.9 Hz, 1H), 4.61 (s, 1H), 4.22 – 4.06 (m, 1H), 3.79 – 3.65 (m, 9H), 3.15 (dd, *J* = 15.1, 7.1 Hz, 1H), 2.90 – 2.38 (m, 5H), 2.23 (dd, *J* = 14.3, 6.4 Hz, 1H), 1.42 (s, 3H), 1.35 (s, 8H), 1.27 – 1.21 (m, *J* = 7.5, 6.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.18, 173.06, 172.22, 172.01, 171.23, 60.16, 60.09, 59.17, 58.62, 58.02, 57.40, 56.93, 53.59, 53.47, 53.42, 53.28,

52.50, 52.45, 51.27, 47.60, 41.43, 40.86, 35.91, 35.41, 24.40, 24.37. IR (neat): ν_{max} 3292, 2958, 1736, 1439, 1318, 1132, 912 cm^{-1} HRMS (ESI) calcd. for $C_{15}H_{25}NNaO_8S$ (M^++Na): 402.1199, found 402.1192.

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국문 초록

이 학위 논문은 전이금속 촉매를 이용한 말단 알카인의 고리화 반응과 산화적 친핵체 첨가 반응 개발에 관한 연구를 기술한다. 이 반응을 통해 사이클로펜테인 또는 사이클로헥세인 구조를 가진 카르복실산 유도체들을 생성물로 얻을 수 있다. 알킬 할라이드, 알데하이드, 이민, 마이클수용체 등을 분자 내에 친전자체로 지닌 말단 알카인을 기질로 사용하는 이 반응은 적절한 로듐 촉매, 염기 및 산화제의 존재 하에서 진행되며 비교적 넓은 범위의 알코올과 아민을 친핵체로 도입할 수 있었다. 반응 메커니즘으로는 먼저 말단 알카인이 β-알킬레이션을 통하여 두 자리가 치환된 금속 바이닐리딘 중간체를 형성한 후, 산소 첨가 반응에 의해 키틴 중간체가 형성되고, 뒤이어 친핵체의 첨가반응을 통해 카르보닐 생성물이 얻어지는 경로가 제안되었다. 연구를 통하여 개발된 촉매반응은 5각 또는 6각 고리를 지닌 다양한 에스터와 아마이드를 생성할 수 있음을 확인하였다.

주요어 : 두 자리가 치환된 로듐 바이닐리딘, 키틴, β-알킬레이션, 산화적 α-첨가 반응, 5각 고리 합성, 카보닐 합성

학번 : 2013-20275

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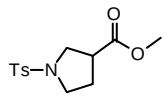
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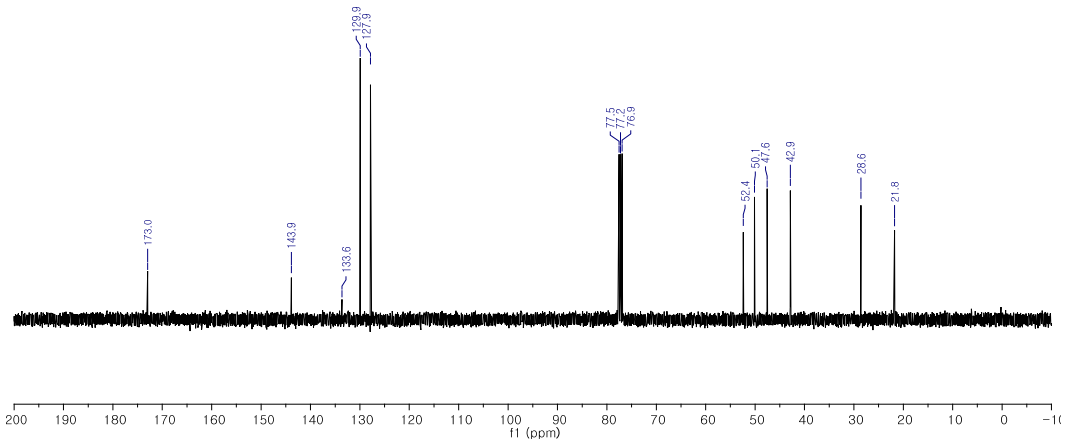
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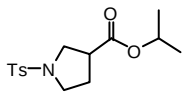
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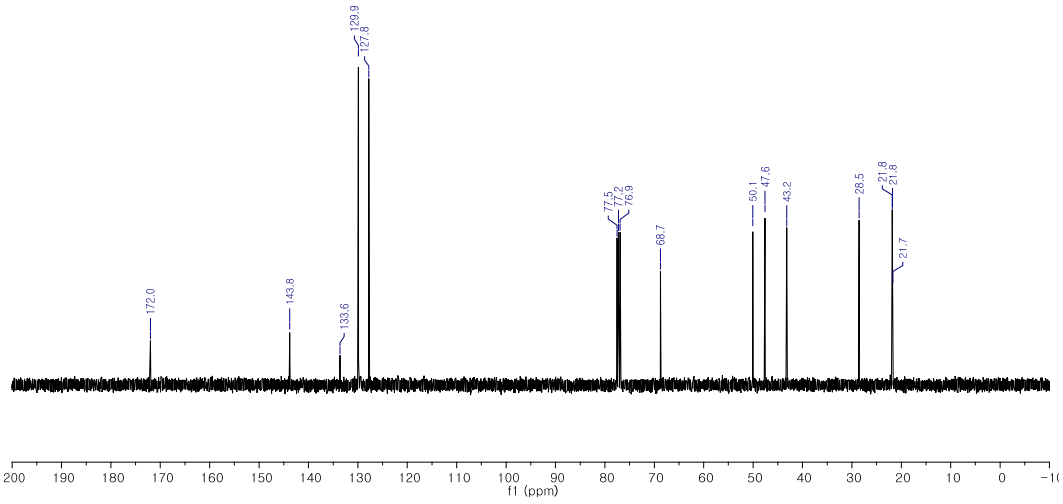
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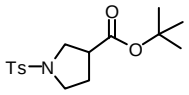
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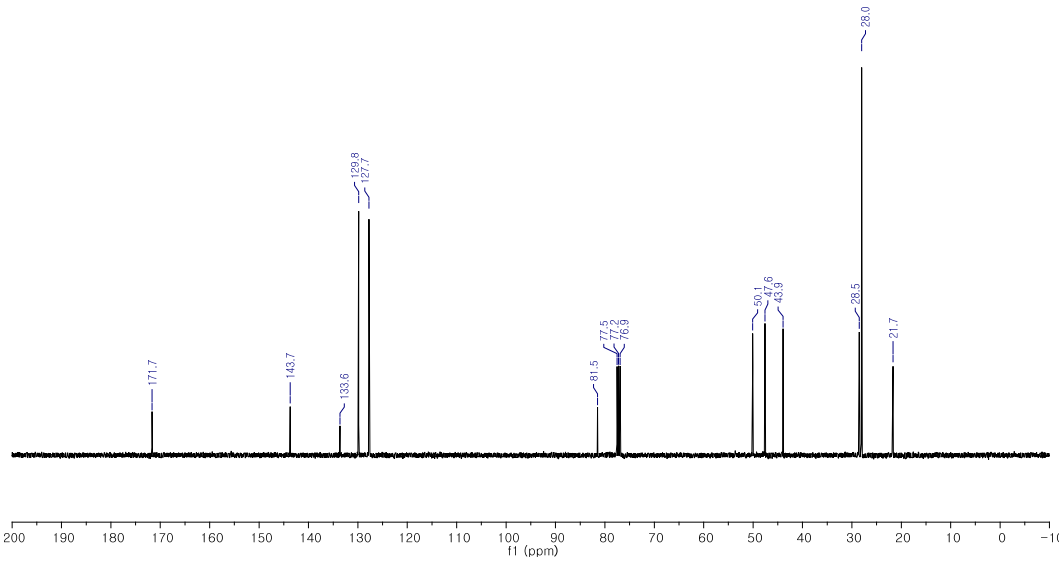
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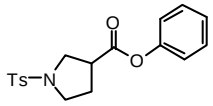
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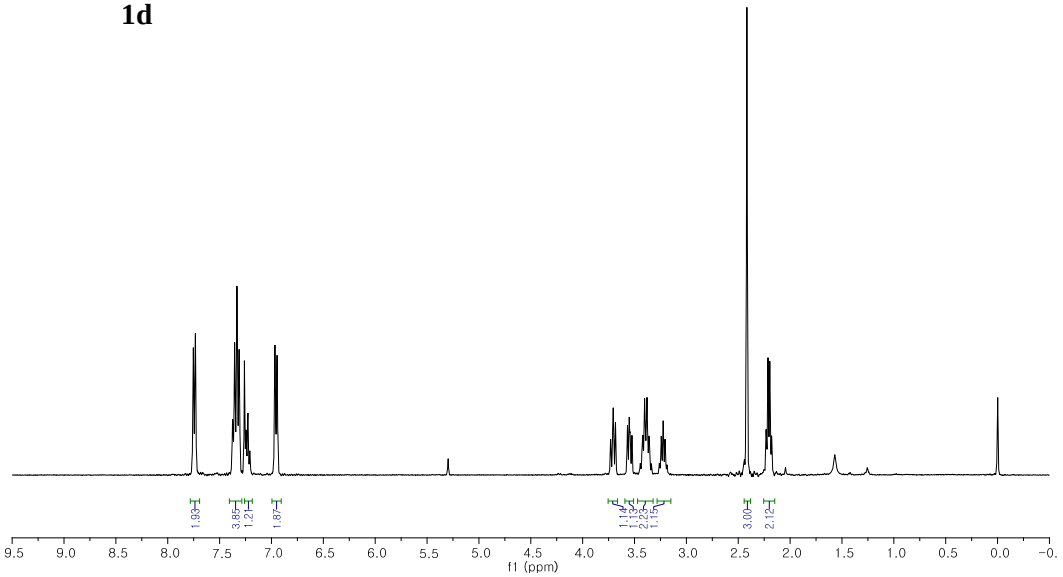
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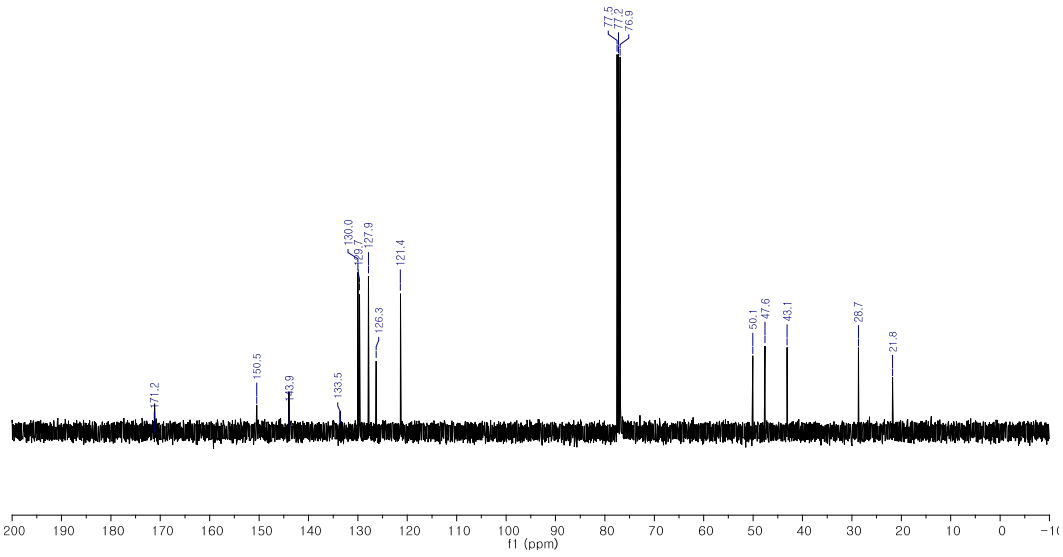
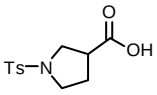
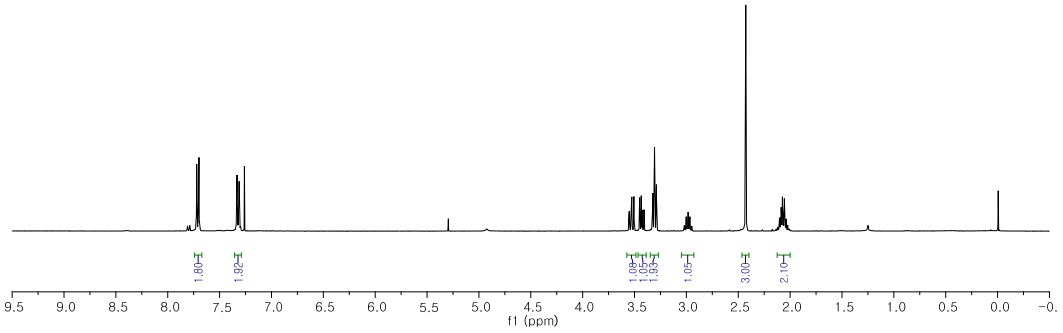
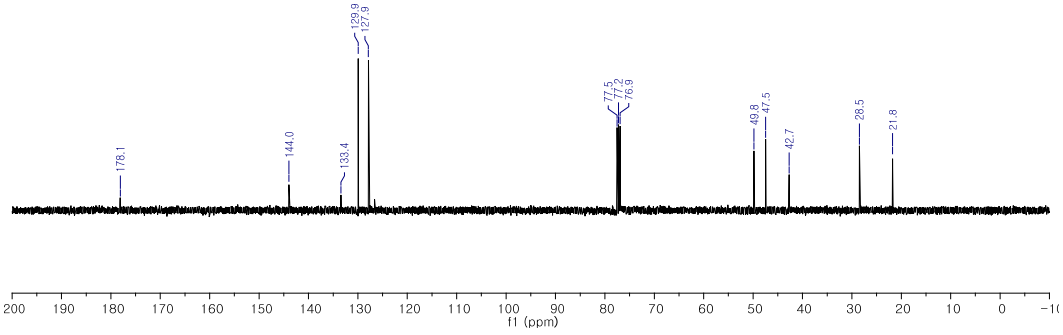
2.12
f1 (ppm)

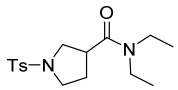

77.5
77.2
76.9
171.2
150.5
143.9
133.5
130.0
129.7
127.9
126.3
121.4
50.1
47.6
43.1
28.7
21.8
f1 (ppm)


O
OH
Ts–N

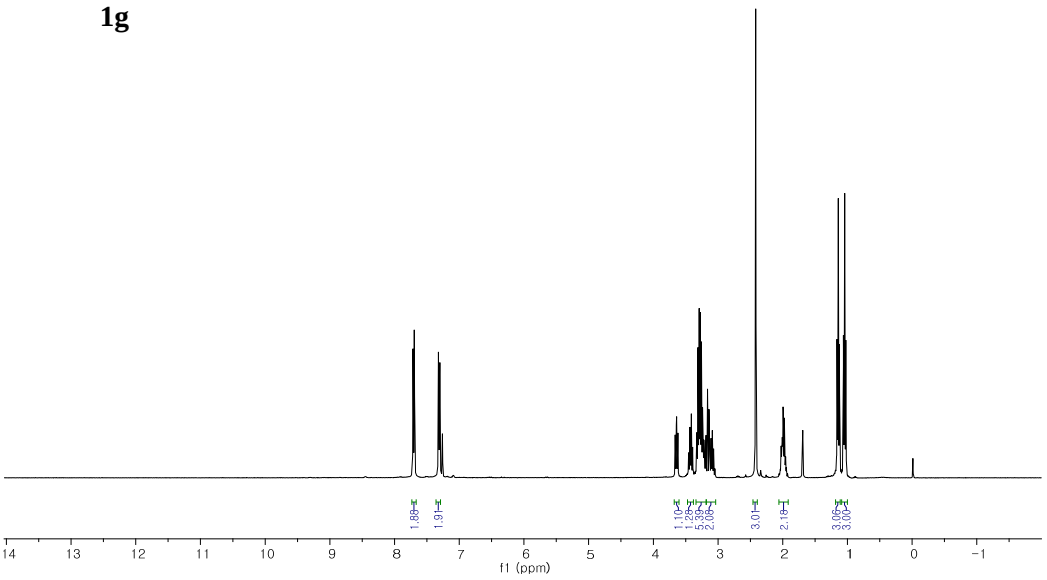
1e

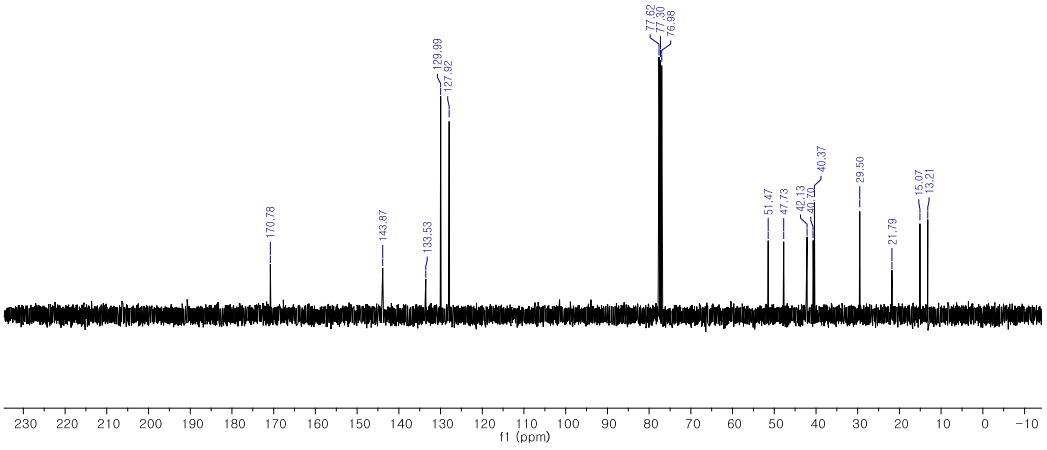

1.80
1.92
1.08
1.05
1.35
1.05
3.00
2.10
f1 (ppm)

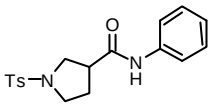

178.1
144.0
133.4
129.9
127.9
77.5
77.2
76.9
49.8
47.5
42.7
28.5
21.8
f1 (ppm)


O
Ts–N
N

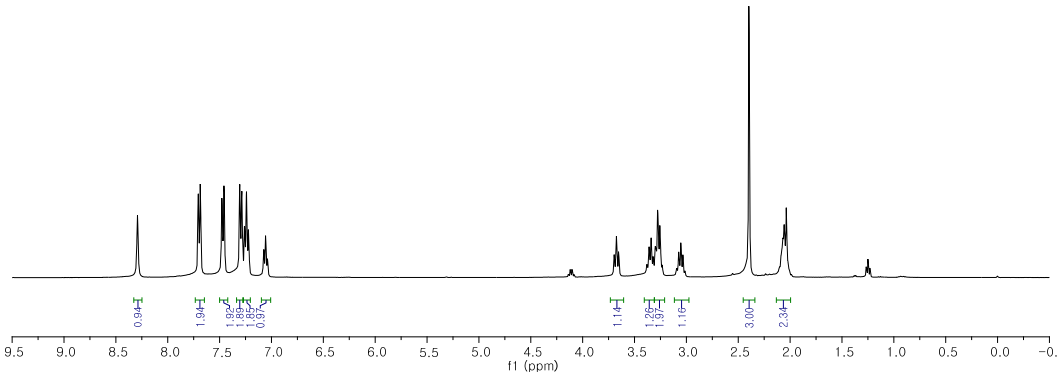
1g

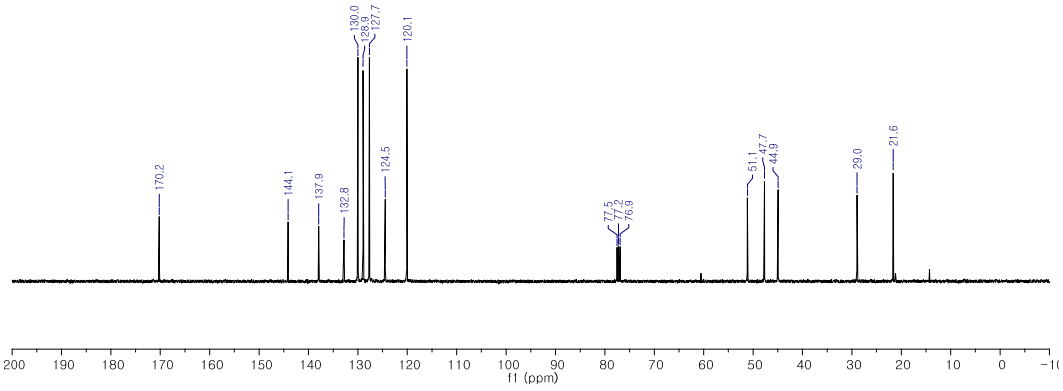

1.88
1.91
1.10
1.26
1.53
2.09
3.01
2.16
3.09
3.00
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 −1
f1 (ppm)

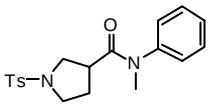

170.78
143.87
133.53
129.99
127.92
77.62
77.30
76.98
51.47
47.73
42.13
40.70
40.37
29.50
21.79
15.07
13.21
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


O
N
H
Ts—N

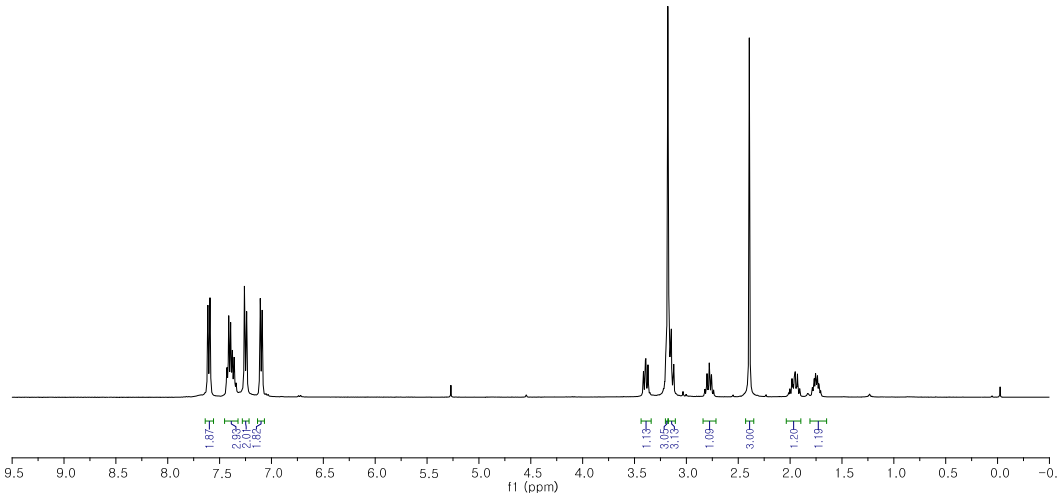
1h

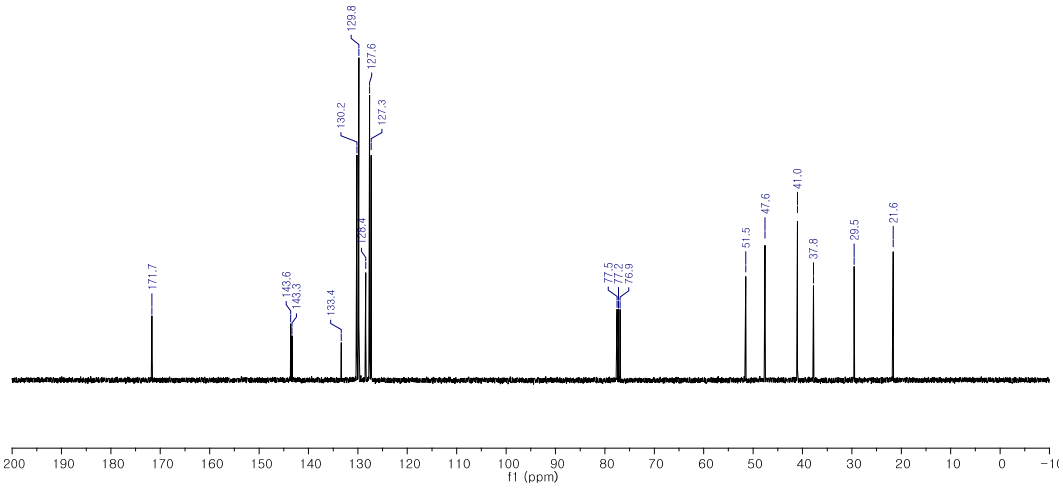

0.94
1.94
1.92
1.89
1.85
0.97
1.14
1.28
1.97
1.16
3.00
2.34
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

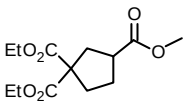

170.2
144.1
137.9
132.8
130.0
128.9
127.7
124.5
120.1
77.5
77.2
76.9
51.1
47.7
44.9
29.0
21.6
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
N
Ts–N

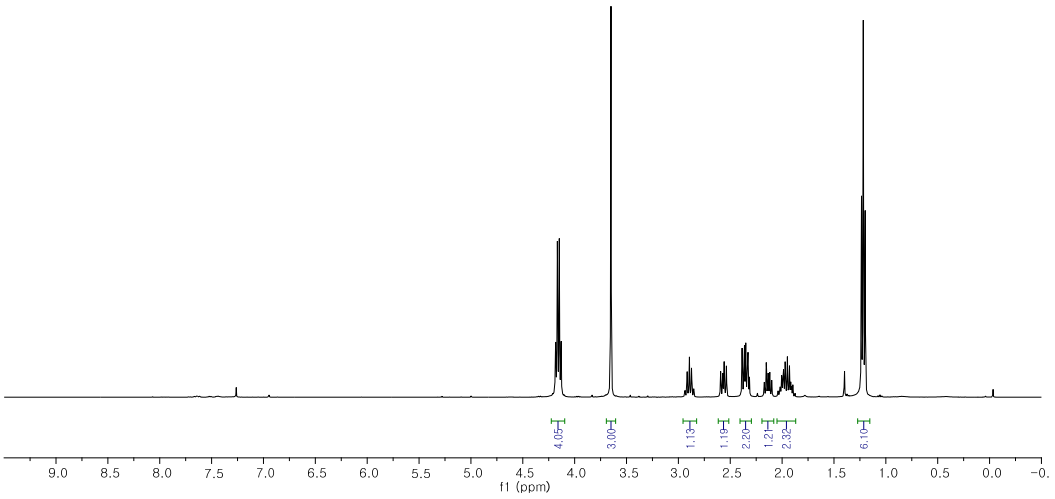
1i

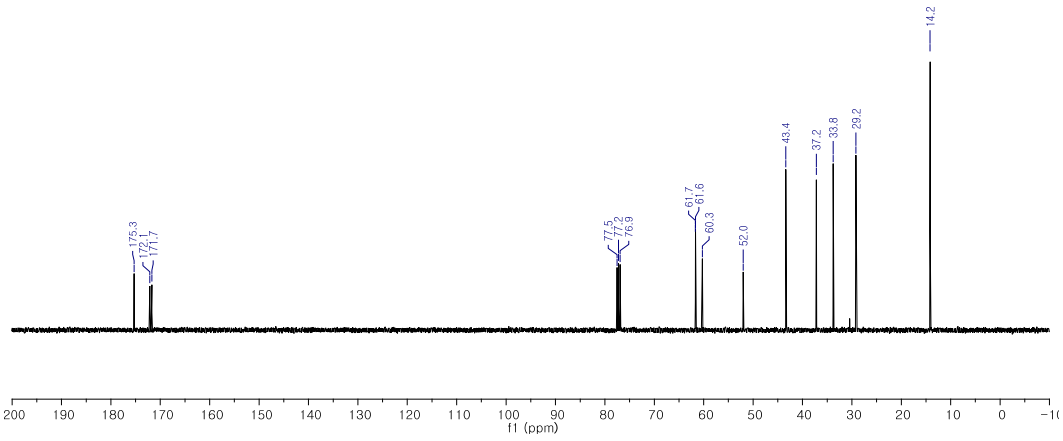

1.87
2.83
2.01
1.82
1.13
3.05
3.13
1.09
3.00
1.20
1.19
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

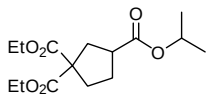

171.7
143.6
143.3
133.4
130.2
129.8
128.4
127.6
127.3
77.5
77.2
76.9
51.5
47.6
41.0
37.8
29.5
21.6
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


EtO2C
EtO2C
O
O

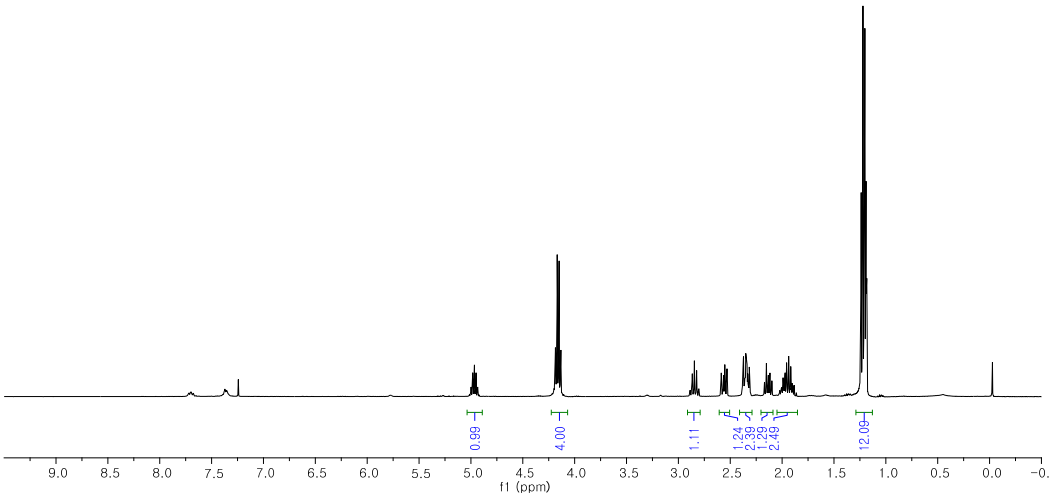
2a

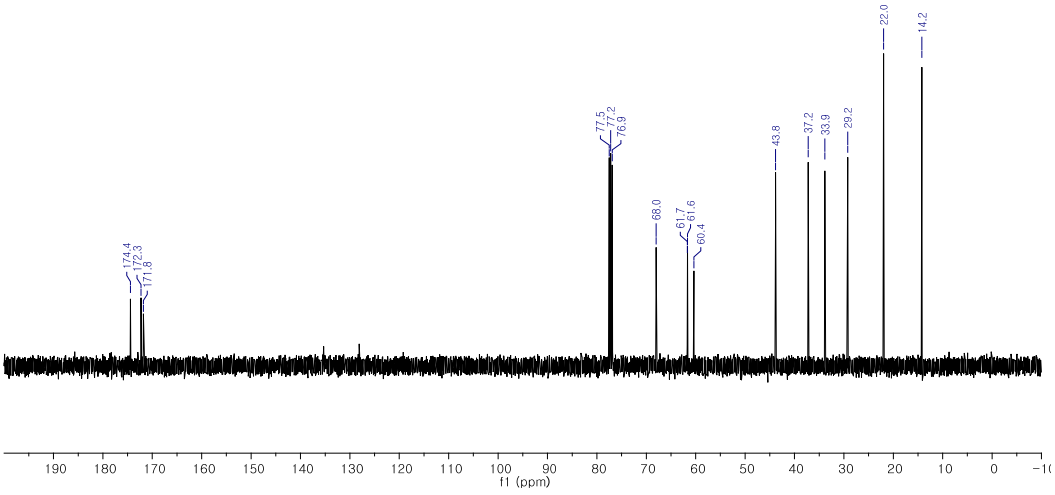

4.05
3.00
1.13
1.19
2.20
1.21
2.32
6.10
f1 (ppm)

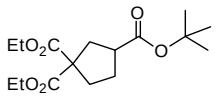

175.3
172.1
171.7
77.5
77.2
76.9
61.7
61.6
60.3
52.0
43.4
37.2
33.8
29.2
14.2
f1 (ppm)


EtO2C
EtO2C
O
O

2b

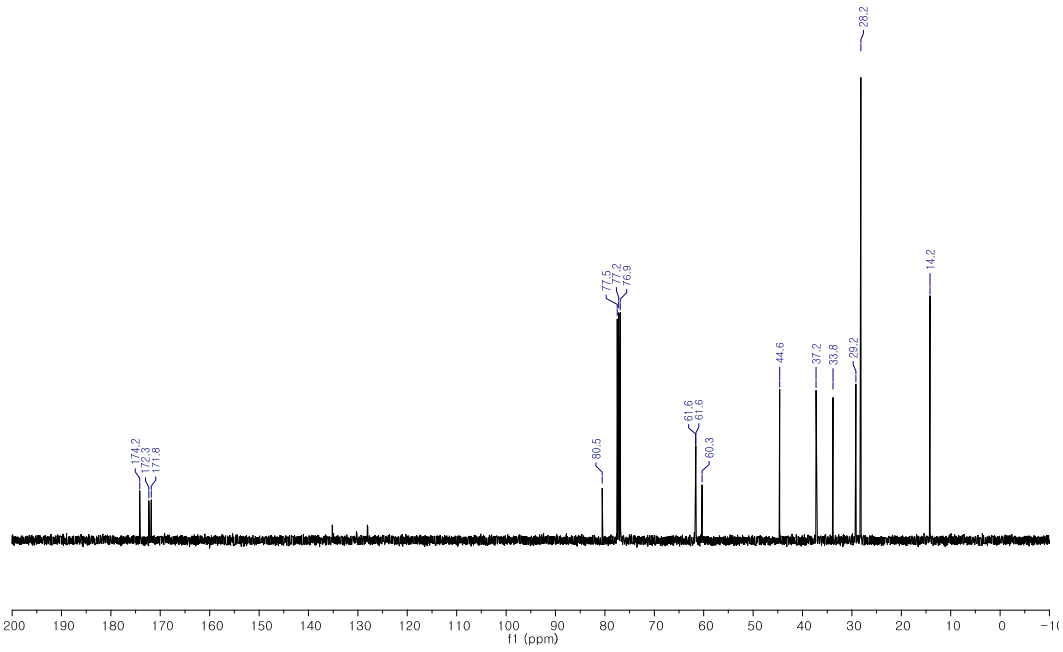

0.99
4.00
1.11
1.24
2.39
1.29
2.49
12.09
f1 (ppm)

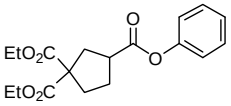

174.4
172.3
171.8
77.5
77.2
76.9
68.0
61.7
61.6
60.4
43.8
37.2
33.9
29.2
22.0
14.2
f1 (ppm)


EtO2C
EtO2C
O
O

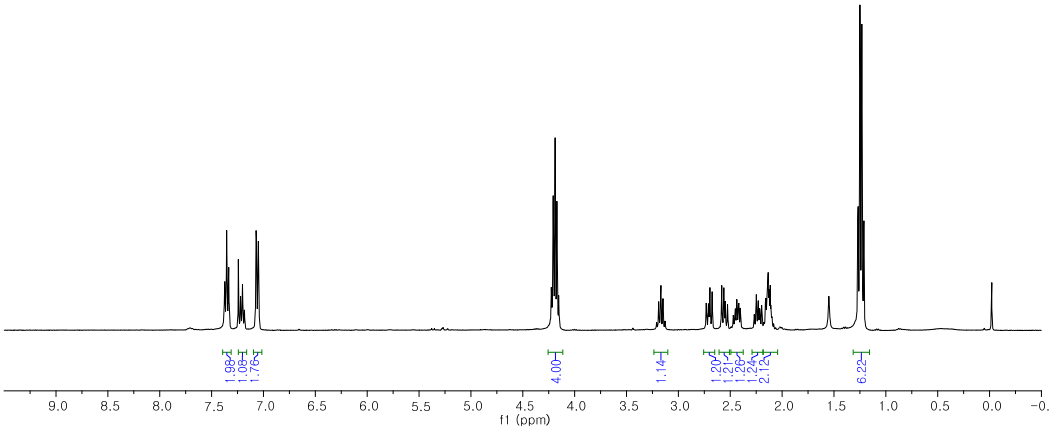
2c

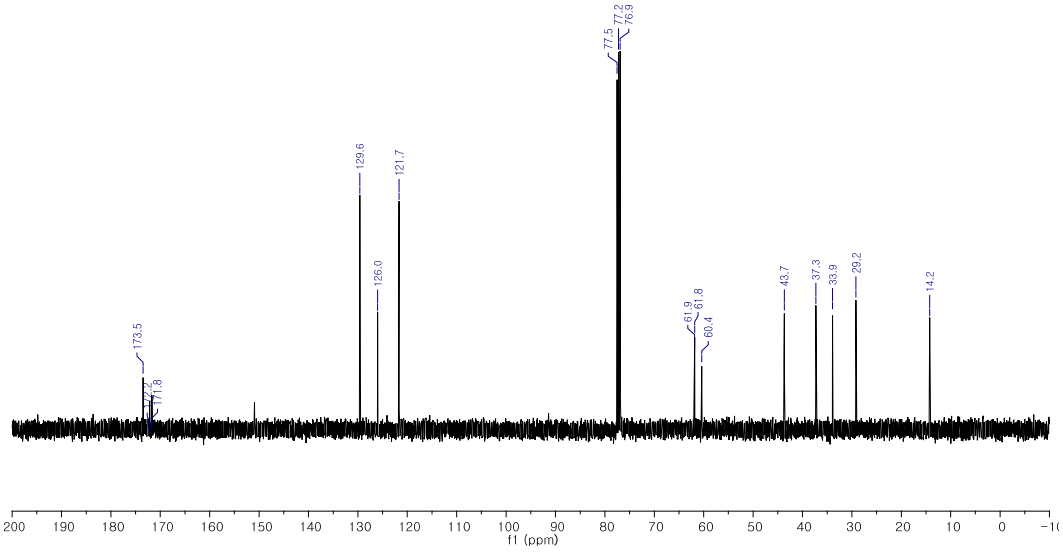
4.00
1.07
1.14
2.23
1.26
2.34
8.77
6.09
f1 (ppm)

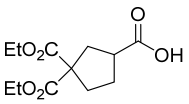

174.2
172.3
171.8
80.5
77.5
77.2
76.9
61.6
61.6
60.3
44.6
37.2
33.8
29.2
28.2
14.2
f1 (ppm)


EtO2C
EtO2C
O
O

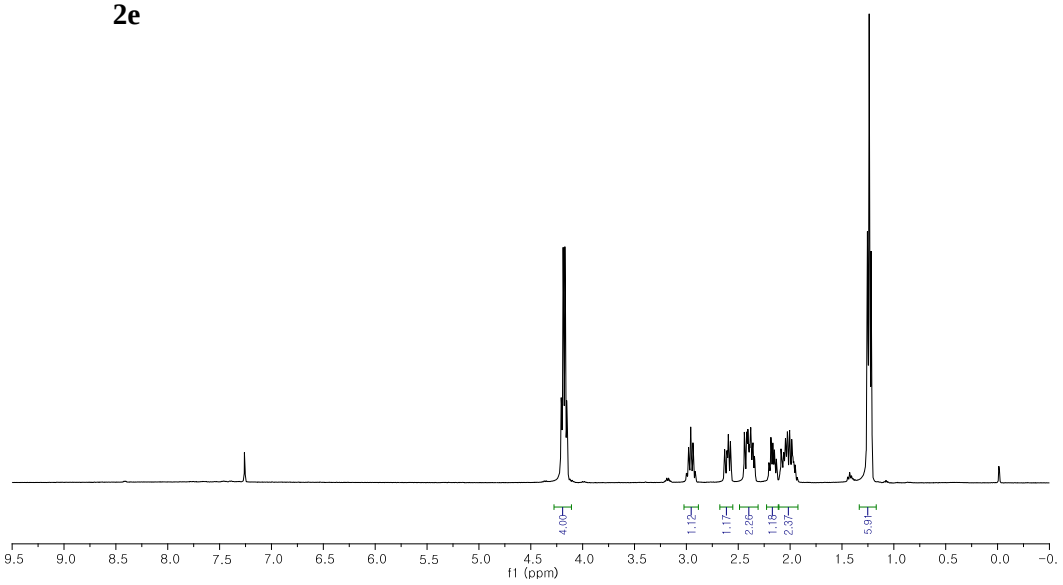
2d

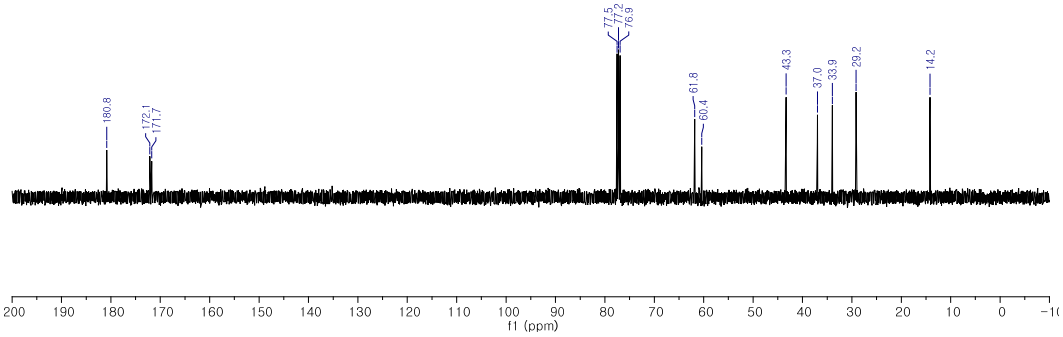

1.98
1.05
1.76
4.00
1.14
1.09
1.22
1.26
1.24
2.12
6.22
f1 (ppm)

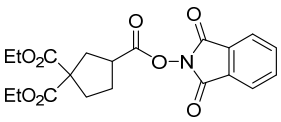

173.5
171.8
129.6
126.0
121.7
77.5
77.2
76.9
61.9
61.8
60.4
43.7
37.3
33.9
29.2
14.2
f1 (ppm)


O
EtO2C
OH
EtO2C

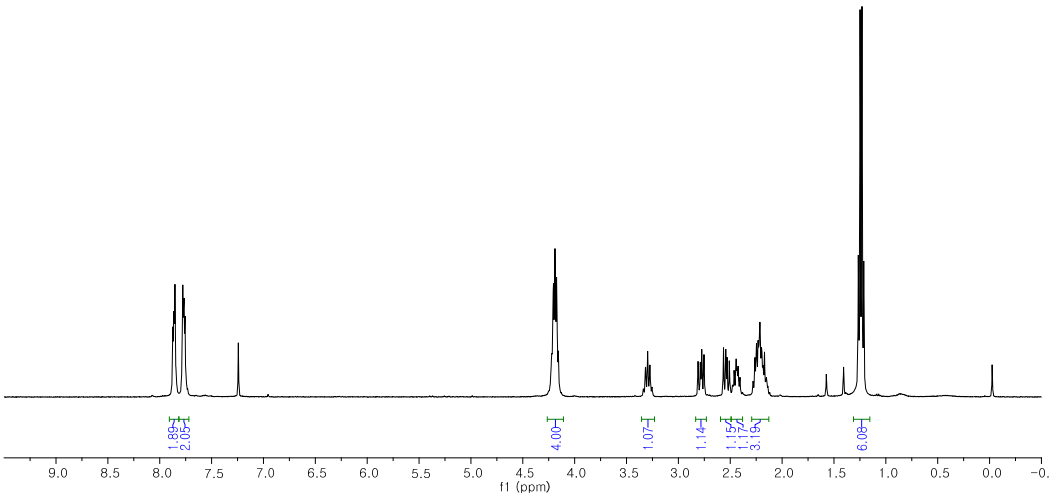
2e

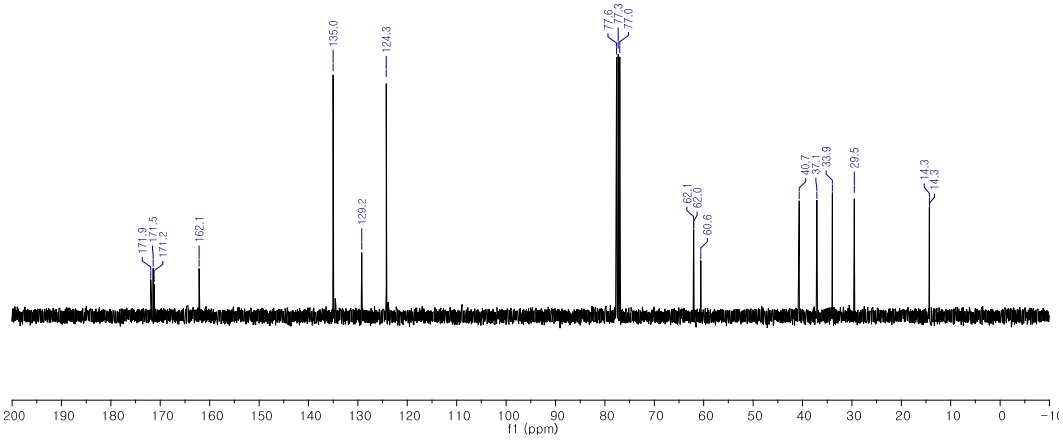

4.00
1.12
1.17
2.26
1.18
2.37
5.91
f1 (ppm)

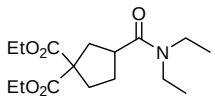

180.8
172.1
171.7
77.5
77.2
76.9
61.8
60.4
43.3
37.0
33.9
29.2
14.2
f1 (ppm)


EtO2C
EtO2C
O
O
O
N
O

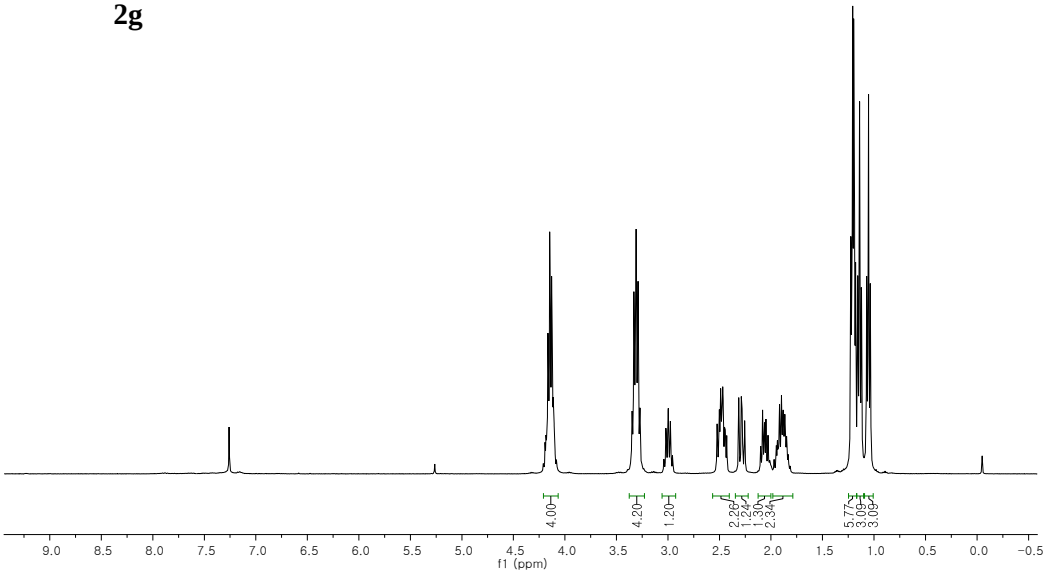
2f

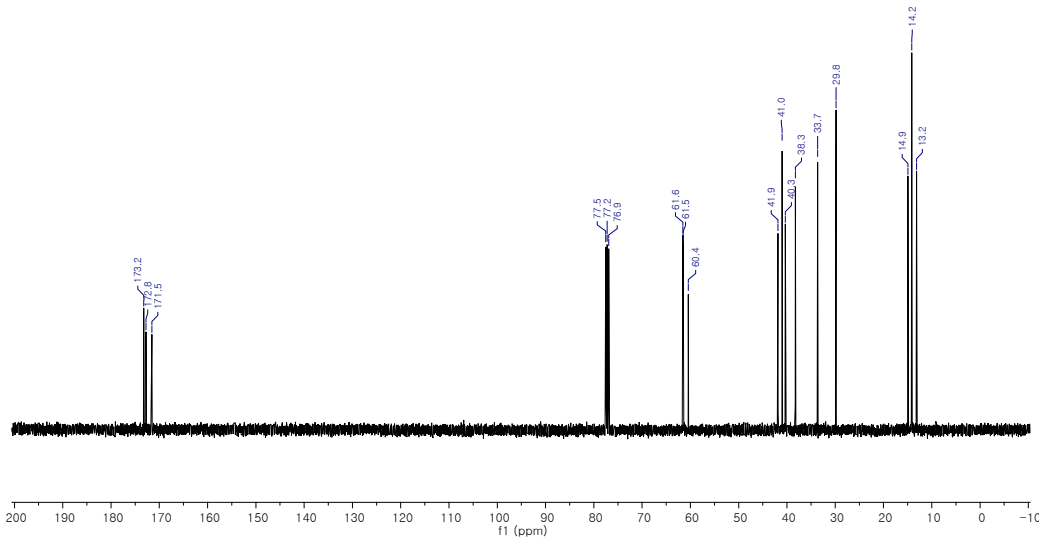

1.89
2.05
4.00
1.07
1.14
1.15
1.17
3.19
6.08
f1 (ppm)

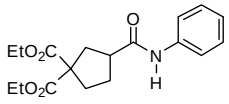

171.9
171.5
171.2
162.1
135.0
129.2
124.3
77.6
77.3
77.0
62.1
62.0
60.6
40.7
37.1
33.9
29.5
14.3
14.3
f1 (ppm)


O
N
EtO2C
EtO2C

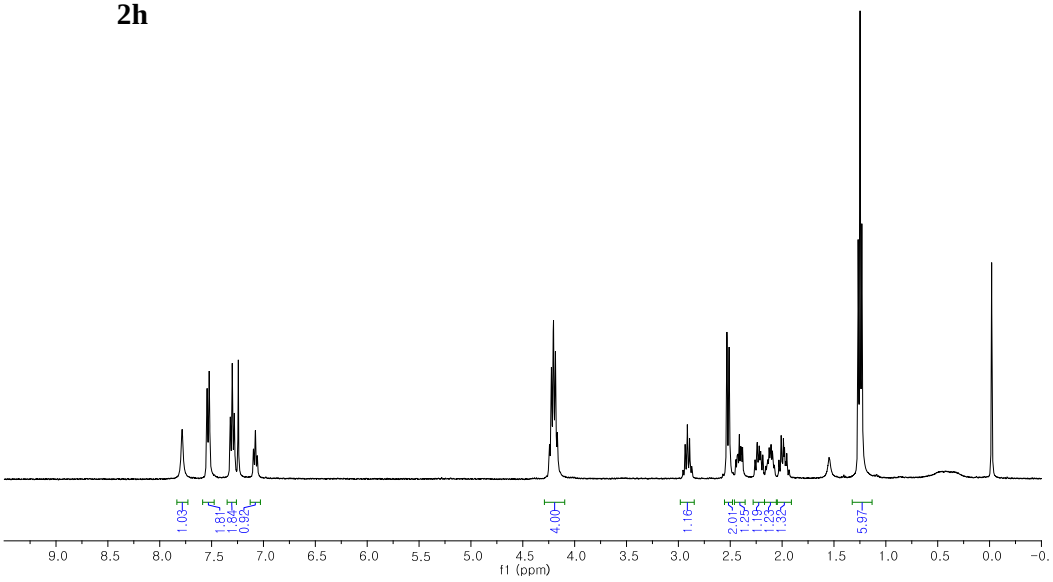
2g

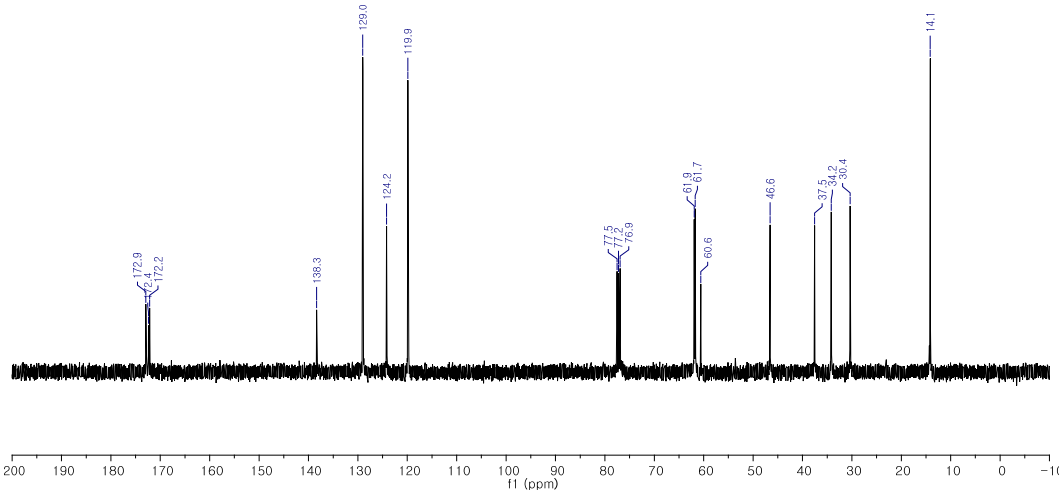

4.00
4.20
1.20
2.26
1.24
1.30
2.34
5.77
3.09
3.09
f1 (ppm)

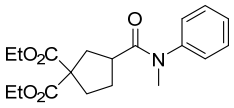

173.2
171.8
171.5
77.5
77.2
76.9
61.6
61.5
60.4
41.9
41.0
40.3
38.3
33.7
29.8
14.9
14.2
13.2
f1 (ppm)


EtO2C
EtO2C
O
N
H

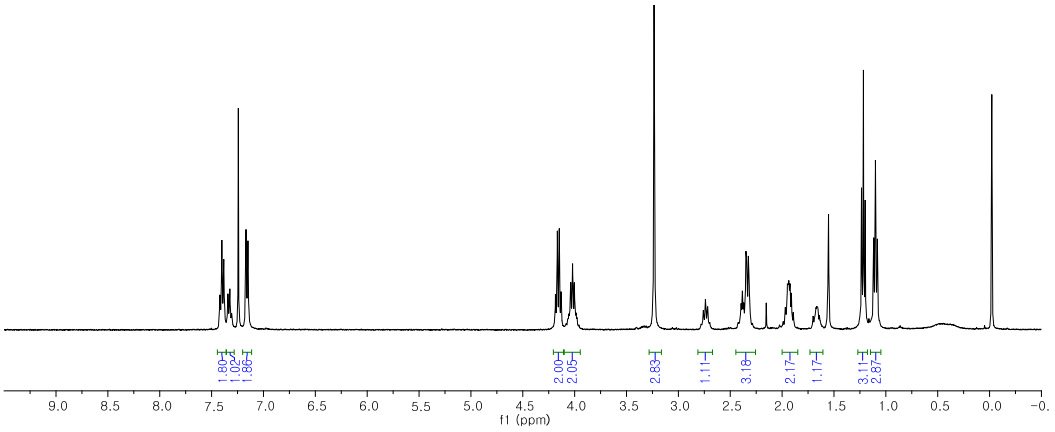
2h

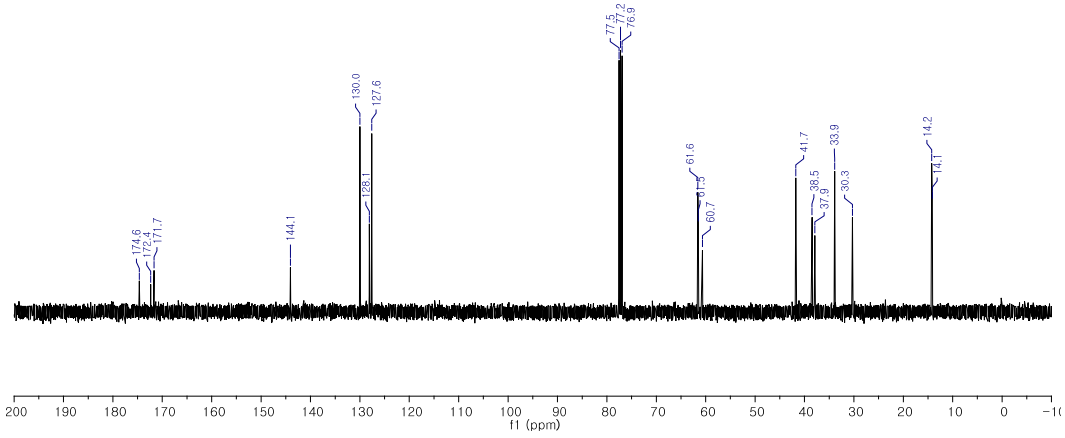

1.03
1.81
1.84
0.92
4.00
1.16
2.01
1.25
1.03
1.32
5.97
f1 (ppm)

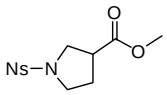

172.9
172.4
172.2
138.3
129.0
124.2
119.9
77.5
77.2
76.9
61.9
61.7
60.6
46.6
37.5
34.2
30.4
14.1
f1 (ppm)


O
N
EtO2C
EtO2C

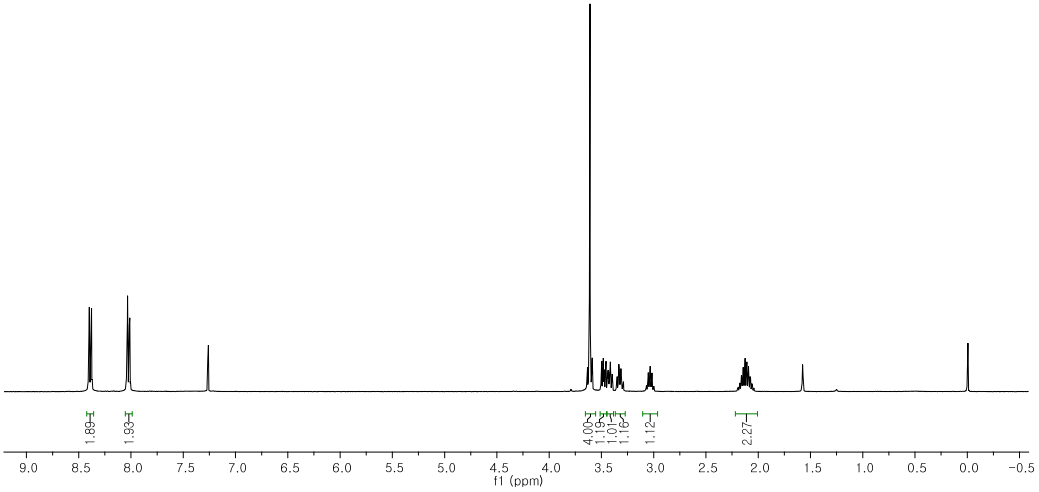
2i

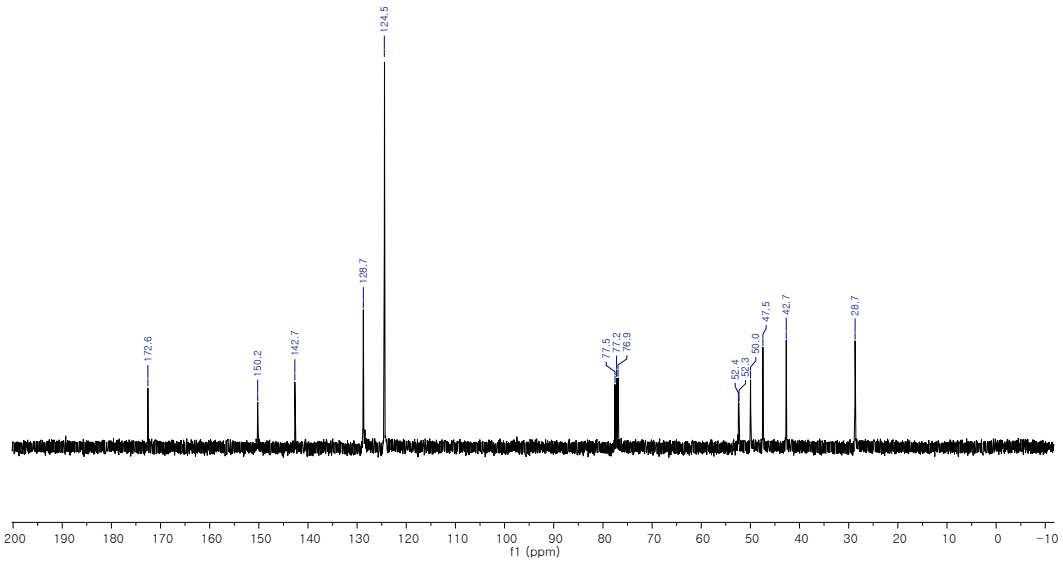

1.80
1.02
1.86
2.00
2.05
2.83
1.11
3.18
2.17
1.17
3.11
2.87
f1 (ppm)

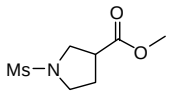

174.6
172.4
171.7
144.1
130.0
128.1
127.6
77.5
77.2
76.9
61.6
61.5
60.7
41.7
38.5
37.9
33.9
30.3
14.2
14.1
f1 (ppm)


O
Ns–N
O

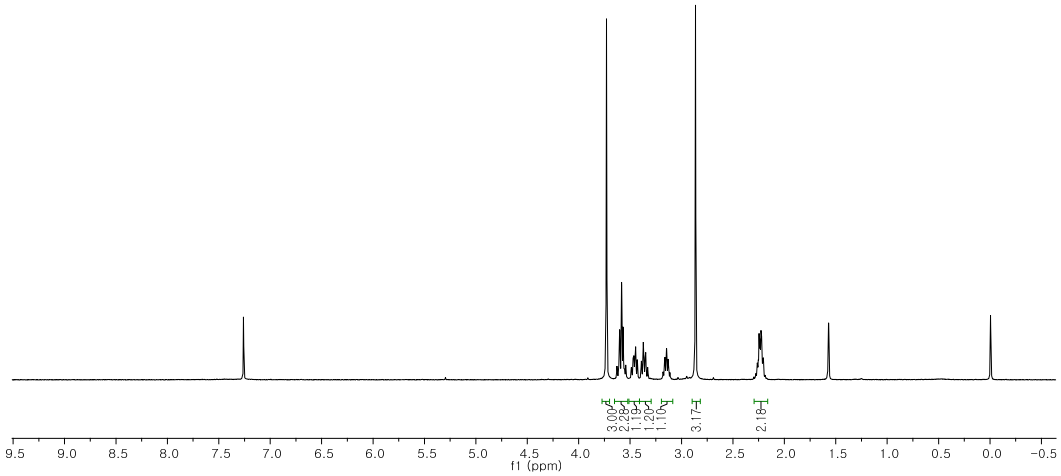
3a

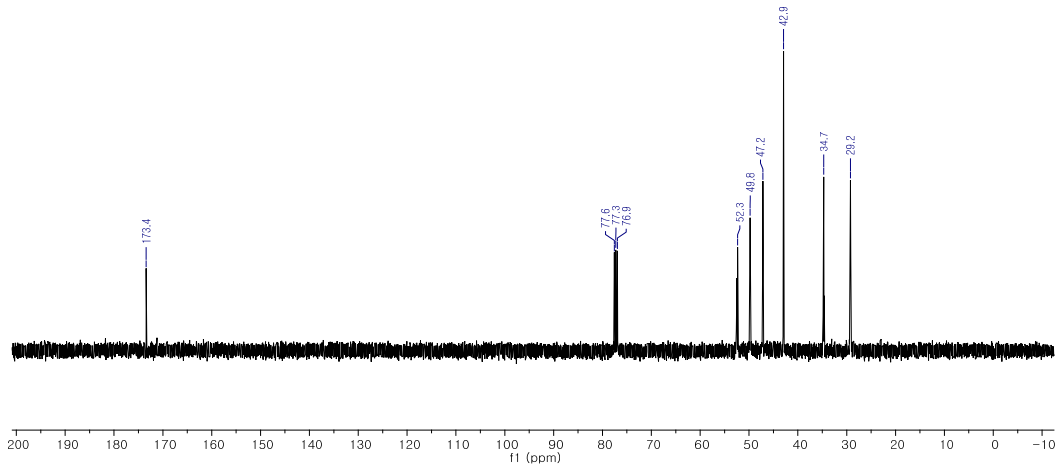

1.89
1.93
4.00
1.16
1.01
1.16
1.12
2.27
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

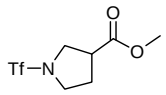

172.6
150.2
142.7
128.7
124.5
77.5
77.2
76.9
52.4
52.3
50.0
47.5
42.7
28.7
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


O
Ms—N
O

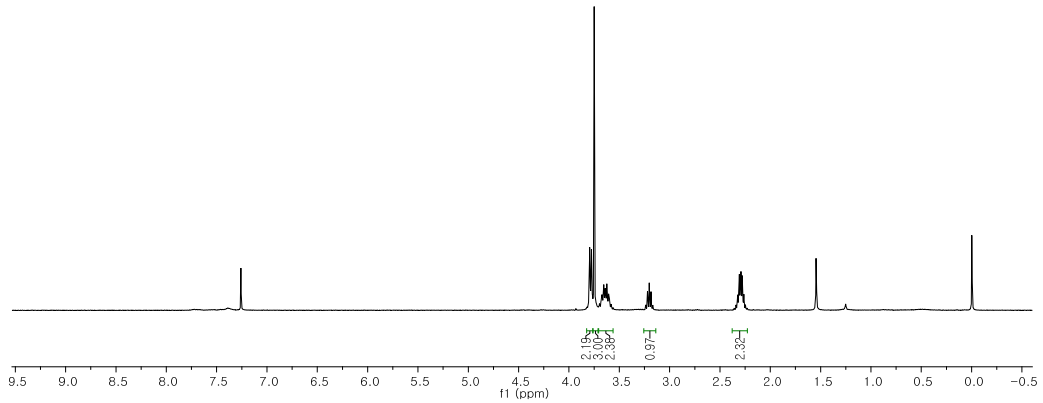
4a

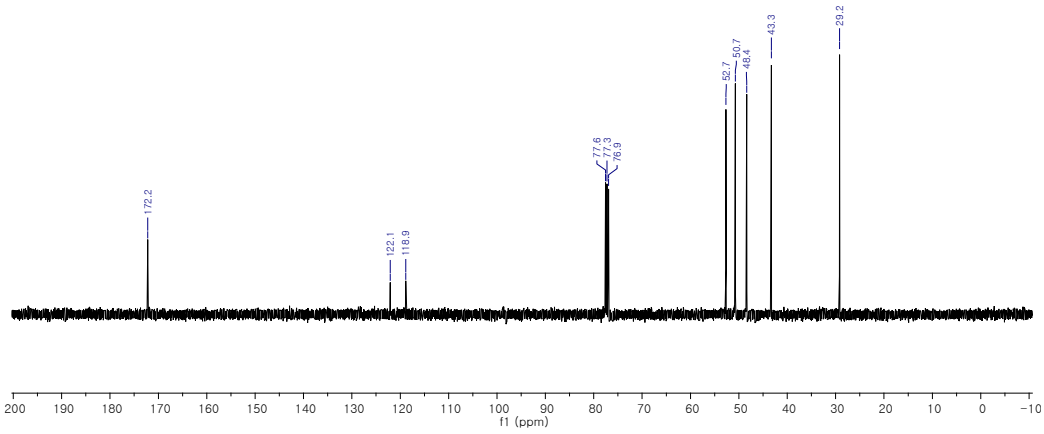

3.00
2.28
1.19
1.20
1.10
3.17
2.18
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

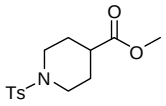

173.4
77.6
77.3
76.9
52.3
49.8
47.2
42.9
34.7
29.2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


O
Tf—N
O

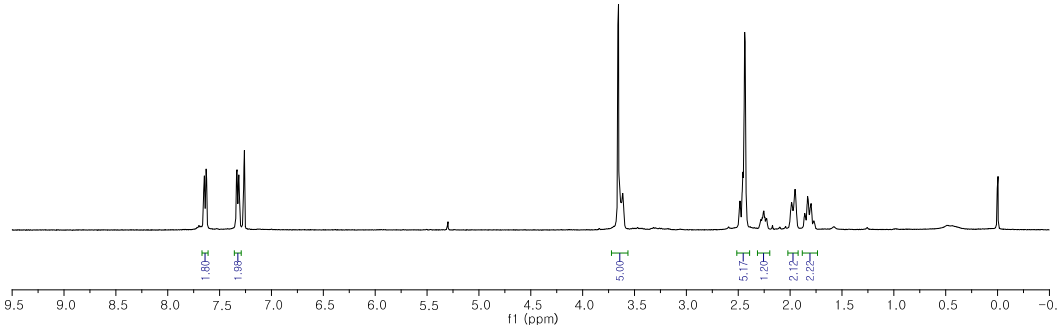
5a

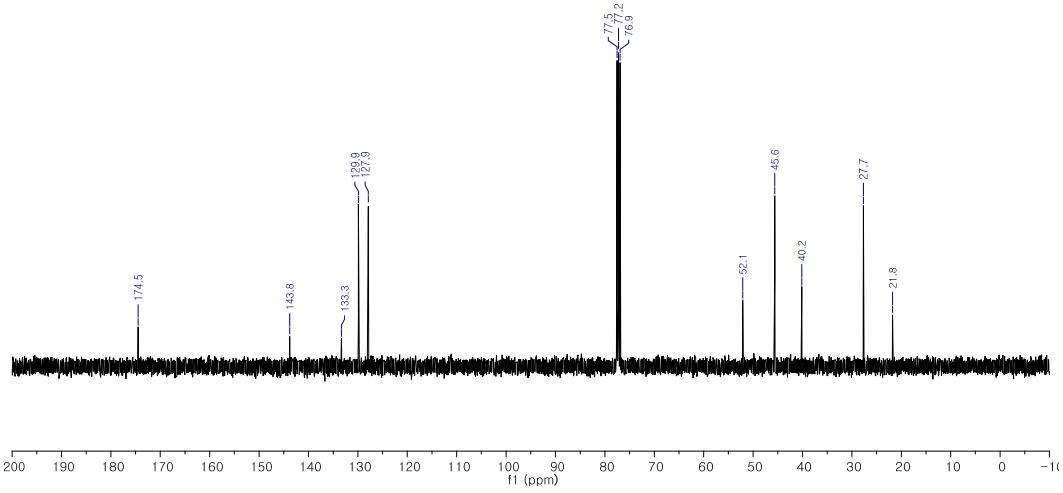

2.15
3.00
2.38
0.97
2.32
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

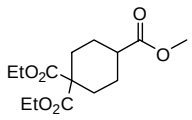

172.2
122.1
118.9
77.6
77.3
76.9
52.7
50.7
48.4
43.3
29.2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


O
O
N
Ts

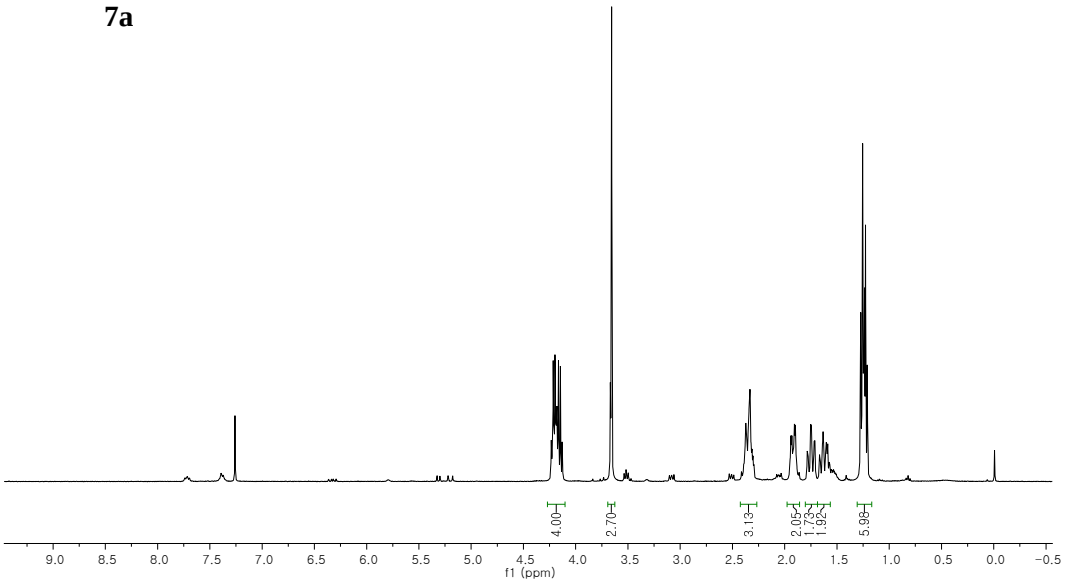
6a

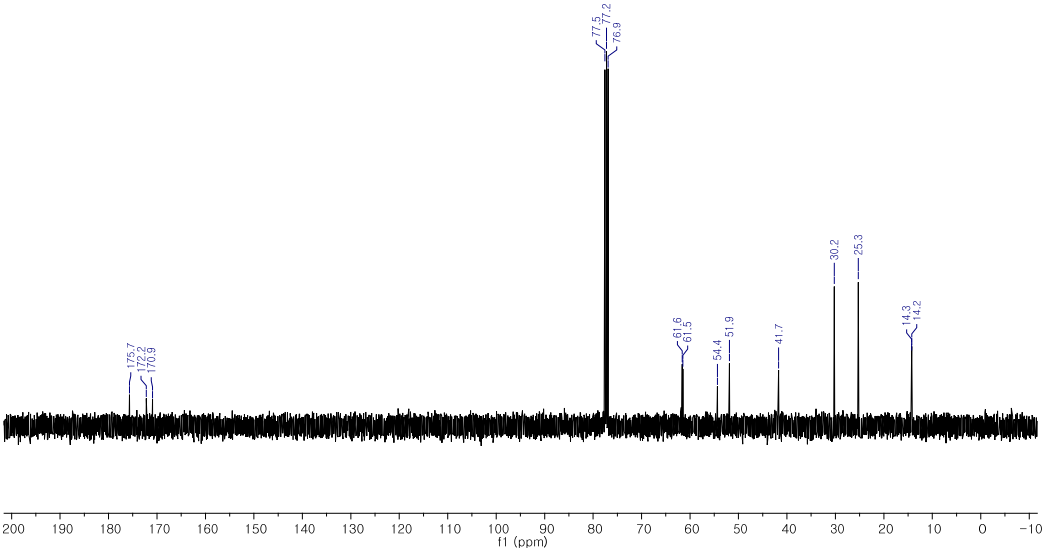

1.80
1.89
5.00
5.17
1.26
2.12
2.22
f1 (ppm)

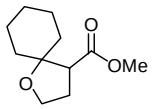

77.5
77.2
76.9
129.9
127.9
174.5
143.8
133.3
52.1
45.6
40.2
27.7
21.8
f1 (ppm)


O
O
EtO2C
EtO2C

7a

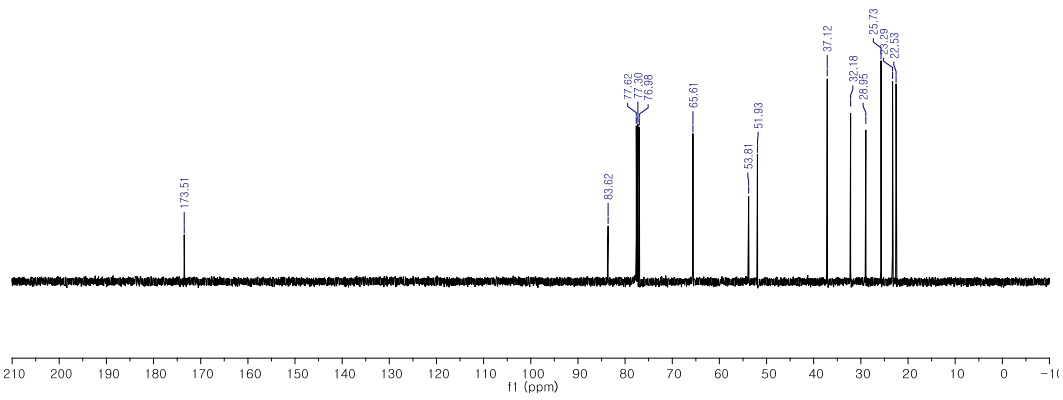

4.00
2.70
3.13
2.05
1.73
1.92
5.98
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

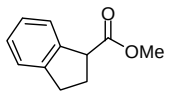

175.7
172.2
170.8
77.5
77.2
76.9
61.6
61.5
54.4
51.9
41.7
30.2
25.3
14.3
14.2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
OMe
O

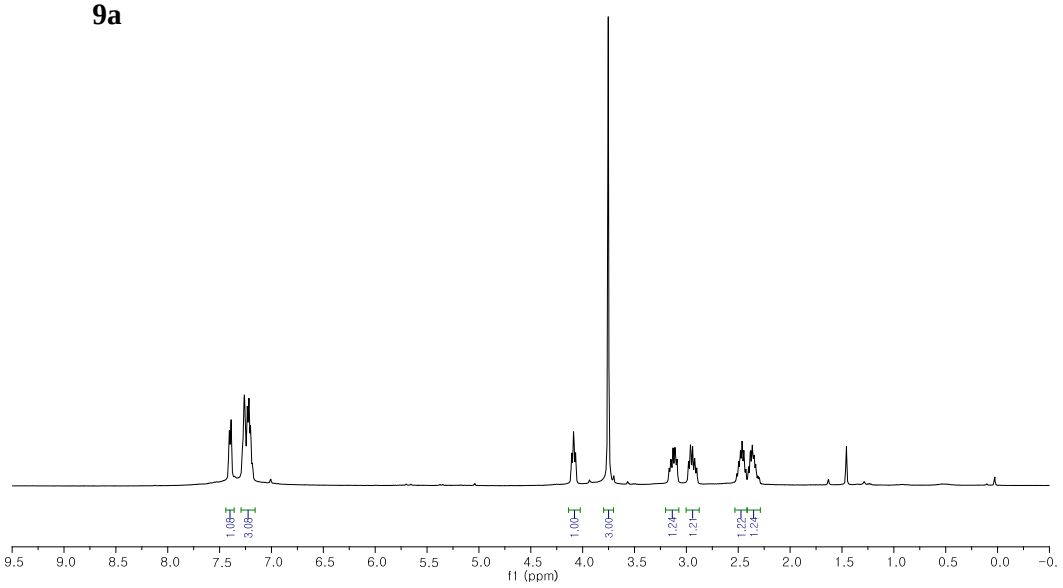
8a

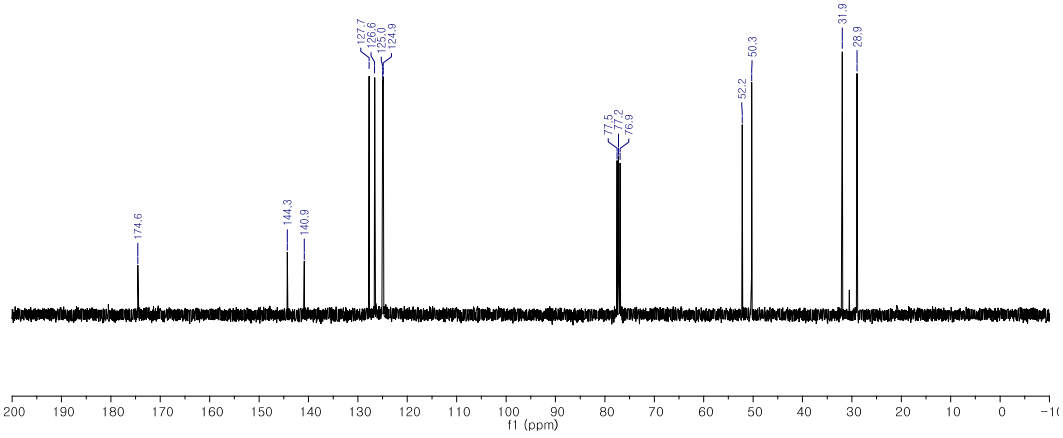
1.00
1.03
2.77
0.94
1.08
1.15
8.39
2.25
f1 (ppm)

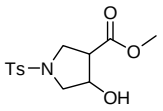

173.51
83.62
77.62
77.00
76.68
65.61
53.61
51.93
37.12
32.18
28.95
25.73
25.29
22.53
f1 (ppm)


O
OMe

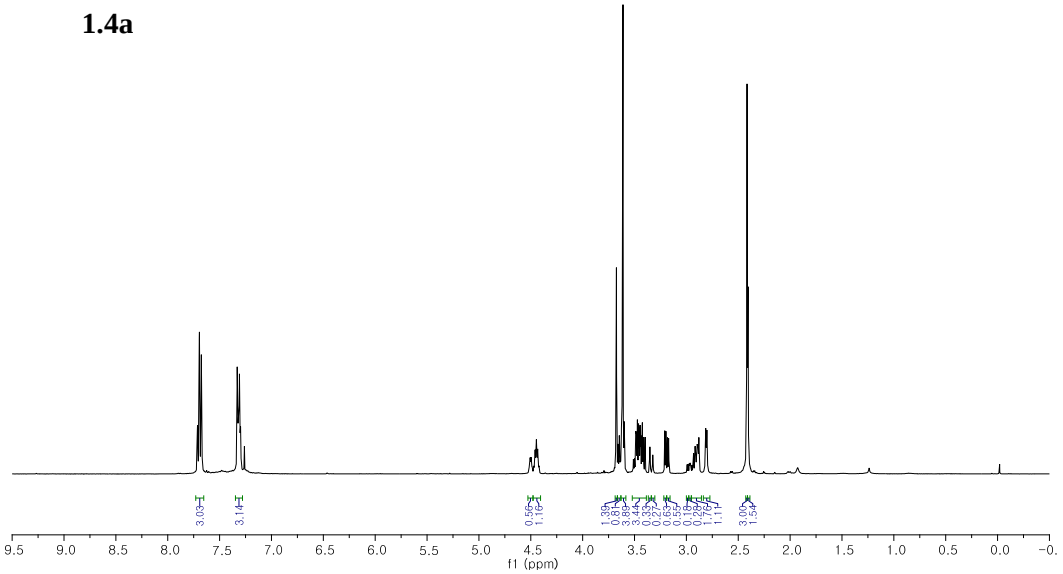
9a

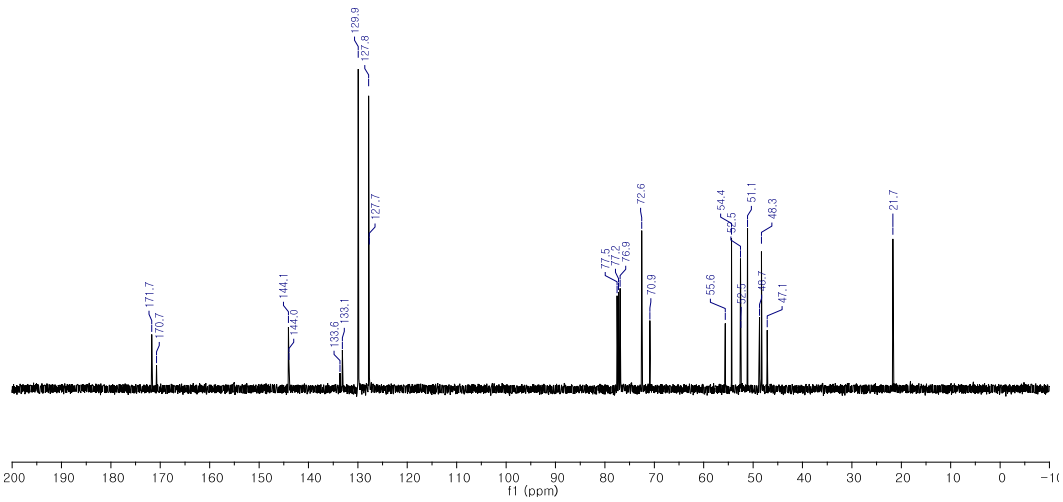

1.09
3.08
1.00
3.00
1.24
1.21
1.22
1.24
f1 (ppm)

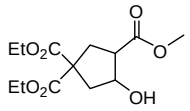

174.6
144.3
140.9
127.7
126.6
125.0
124.9
77.5
77.2
76.9
52.2
50.3
31.9
28.9
f1 (ppm)


O
O
Ts–N
OH

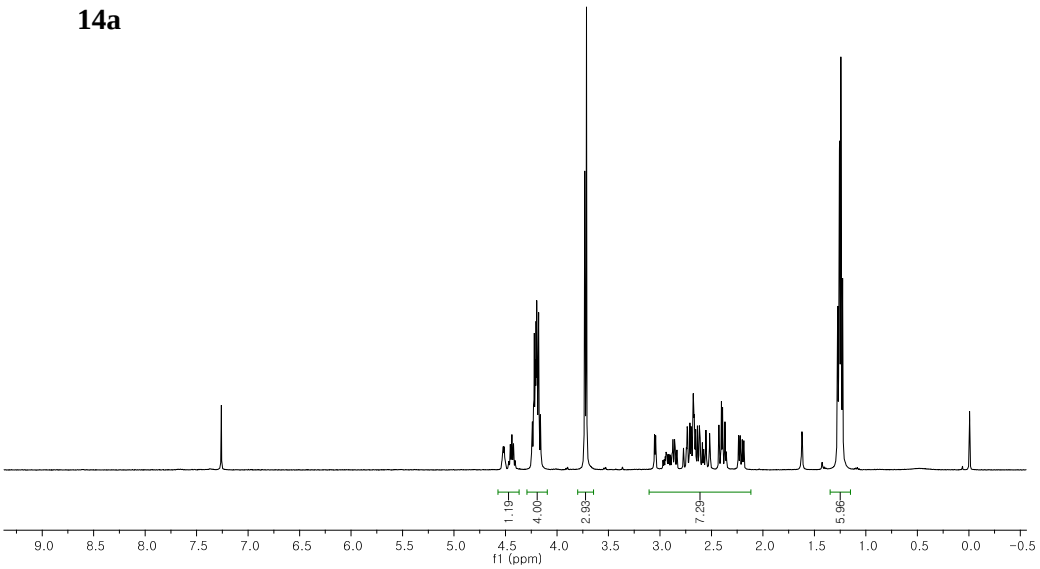
1.4a

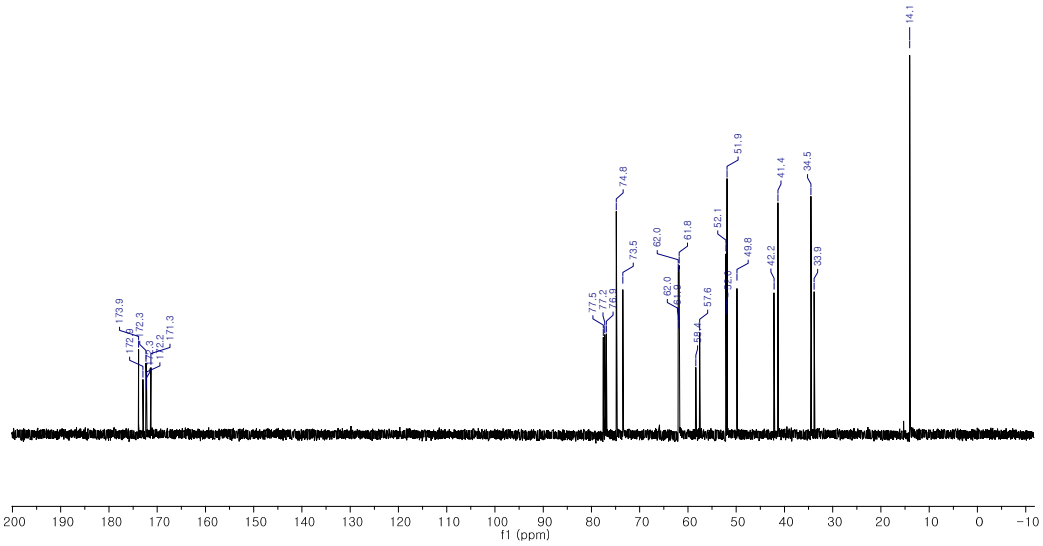

3.03
3.14
0.56
1.18
1.39
0.81
3.49
3.44
0.33
0.27
0.57
0.57
0.18
0.29
1.17
1.11
3.00
1.54
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

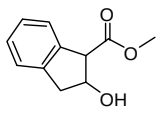

171.7
170.7
144.1
144.0
133.6
133.1
129.9
127.8
127.7
77.5
77.2
76.9
72.6
70.9
55.6
54.4
52.5
51.1
48.3
46.7
47.1
21.7
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
EtO2C
O
EtO2C
OH

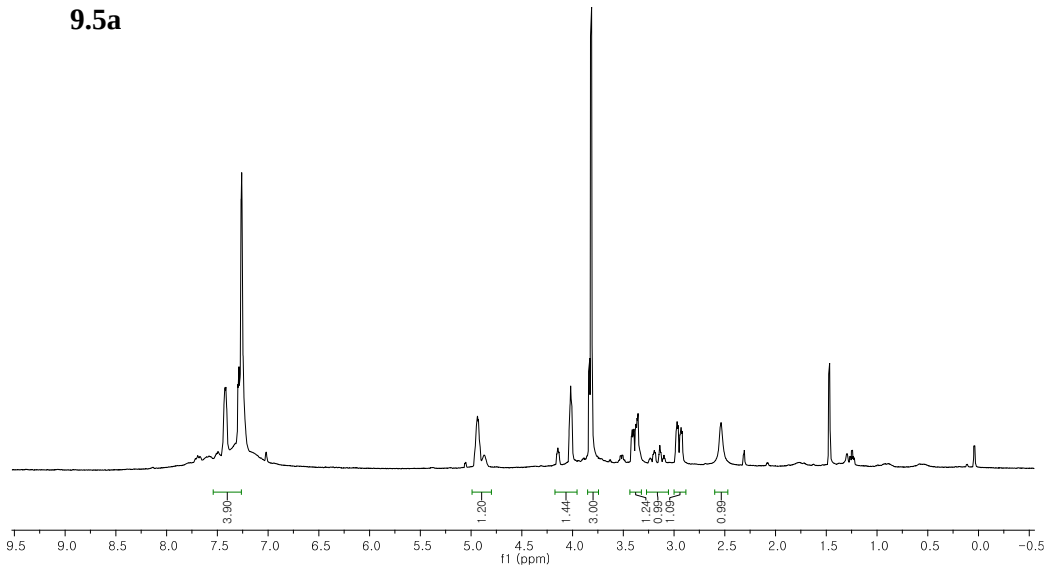
14a

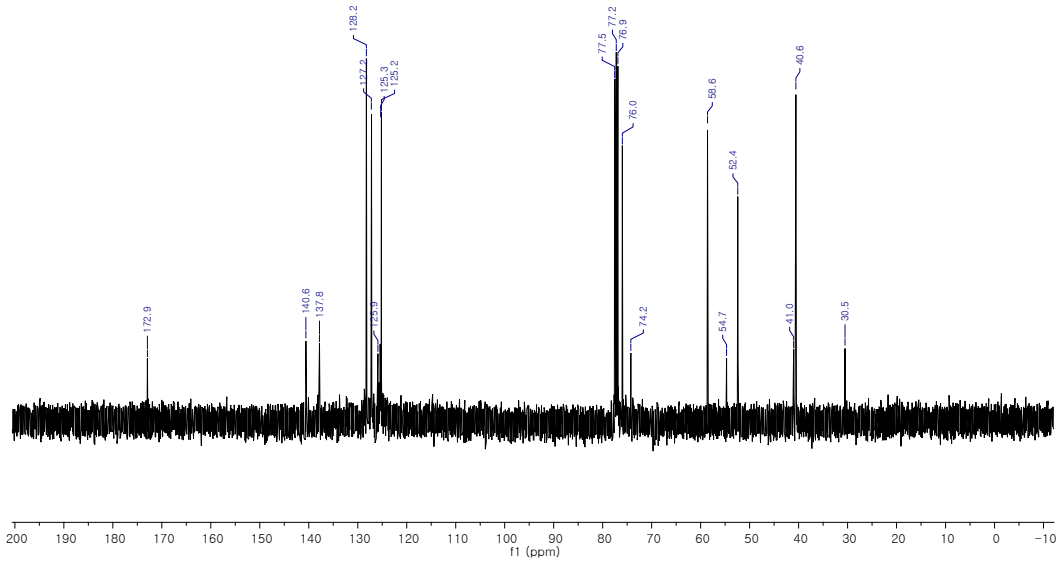

1.19
4.00
2.93
7.29
5.96
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

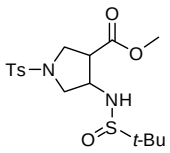

173.9
172.3
171.3
74.8
73.5
62.0
61.8
57.6
52.1
51.9
49.8
42.2
41.4
34.5
33.9
14.1
77.5
77.2
76.9
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


O
O
OH

9.5a

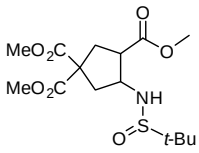

3.90
1.20
1.44
3.00
1.24
0.99
1.05
0.99
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)


172.9
140.6
137.8
128.2
127.2
125.3
125.2
77.5
77.2
76.9
76.0
74.2
58.6
54.7
52.4
41.0
40.6
30.5
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)


O
O
Ts–N
NH
O
S
t-Bu

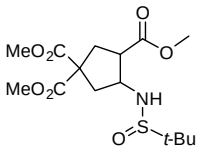
15a

1.81
1.79
1.27
3.00
1.94
0.98
1.23
1.24
2.82
8.18
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5
f1 (ppm)

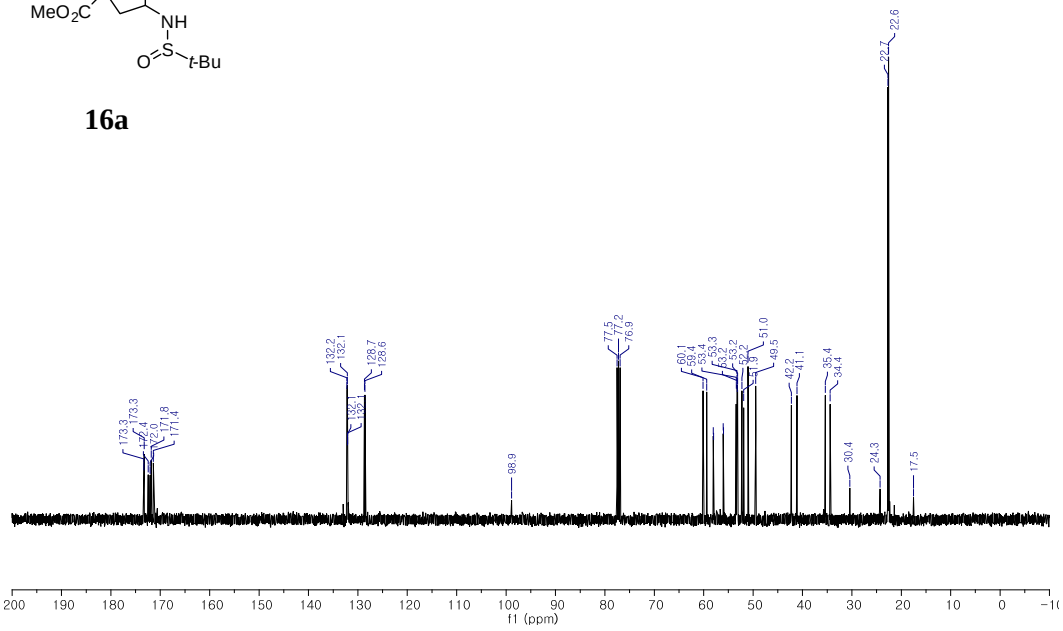

O
O
MeO2C
MeO2C
NH
O
S
t-Bu

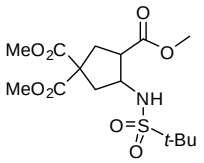
16a

1.96
2.07
1.79
2.66
8.37
1.12
3.37
2.73
1.39
3.26
5.96
1.87
0.65
0.72
0.80
0.36
1.10
8.17
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

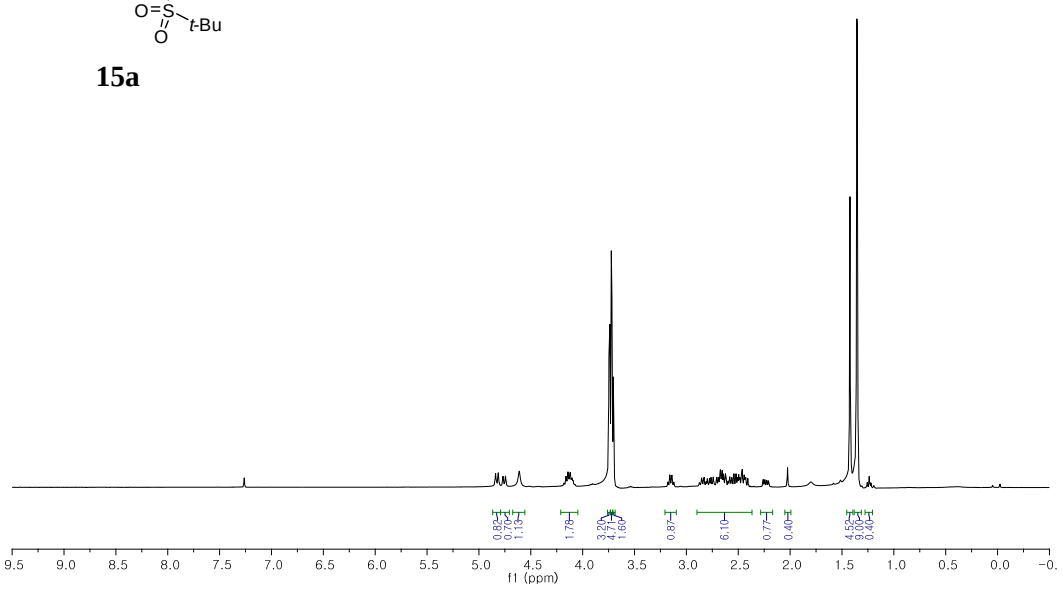


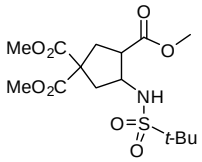
16a


22.6
22.7
132.2
132.1
128.7
128.6
77.5
77.2
76.9
60.1
59.4
53.4
53.3
52.2
51.9
51.0
49.5
42.2
41.1
35.4
34.4
30.4
24.3
17.5
98.9
f1 (ppm)

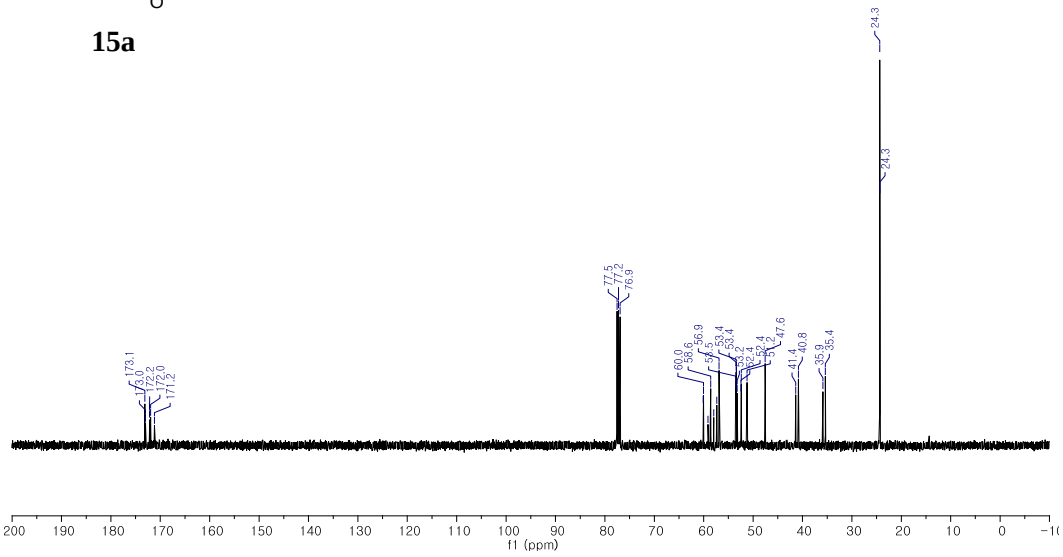


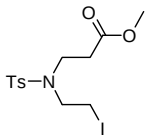
15a


f1 (ppm)

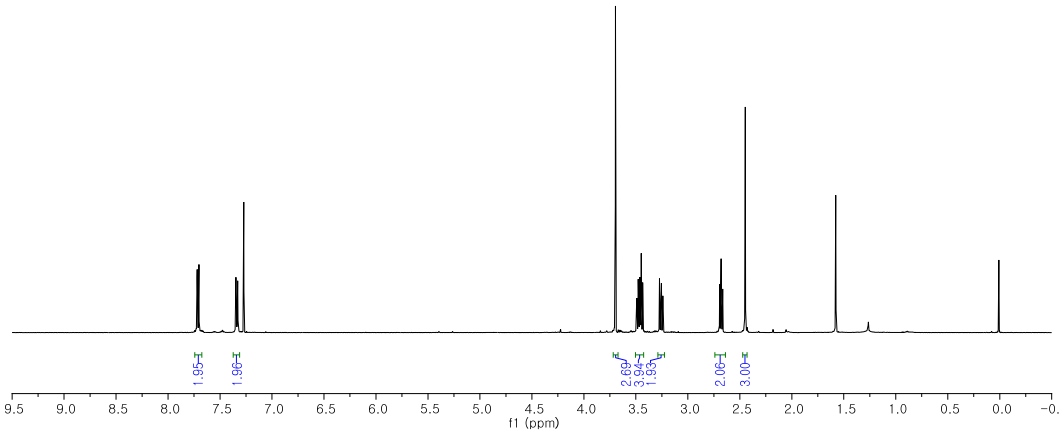

MeO2C
MeO2C
O
O
NH
O=S
O
t-Bu

15a


24.3
24.3
77.5
77.2
76.9
60.0
58.6
56.9
53.4
53.4
53.2
52.4
51.2
47.6
41.4
40.8
35.9
35.4
173.1
173.0
172.2
172.0
171.2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
Ts—N
I

1a’


1.95
1.96
2.69
3.94
1.95
2.06
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)