新規エノラート化機構によるカルボン酸の触媒的α-官能基化反応

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博士学位論文

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総論

①カルボン酸のエノラート化について

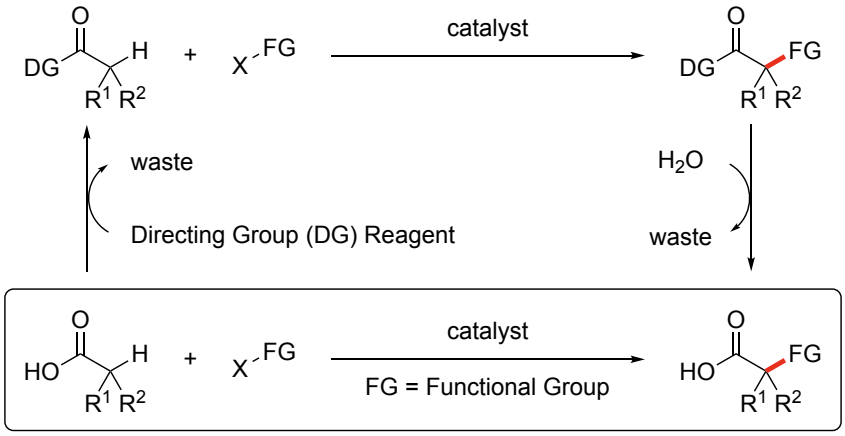
有機化学が対象とする炭素を中心とする分子は生物体の構成要素であるだけでなく化成品から医薬品まで広範に及び、これらの機能性分子はその多くが化学合成によって我々の暮らしに供給される。しかし、人工化学反応は無駄のない生体反応と比較して望まない副産物の生成を伴うことも多いため、化学反応開発の分野において環境調和性に優れた触媒反応の開発は重要な研究課題とされている。

また有機合成化学において、カルボニル基のエノラート化は分子構築の基盤である炭素–炭素結合形成反応を行う上で中心的な役割を果たしている。そのため、有機化学の教科書にも複数の章に渡り多くの反応例が記載されており、その重要性が広く認識されている。一方で、およそ 200 年の有機化学の歴史の中でも解決されていないのが「カルボン酸の触媒的なエノラート化」である。カルボン酸は医薬品中に数多く含まれる構造であるのみならず、様々な官能基の前駆体として汎用される重要な構造であり、その合成化学的な有用性は他のカルボニル化合物と比べて一線を画す。実際に、医薬品中に数多く含まれるエステルやアミドといった構造はカルボン酸から容易に調製が可能である。近年ではレドックス活性な触媒系におけるラジカル源試薬としてカルボン酸が利用されており、その有用性はさらに高まりつつある[1]。そのため、より多様な化合物を容易に合成可能にするためにカルボン酸のケミカルスペース拡張および効率的な化学修飾法の開発は重要な研究課題である。そして、カルボン酸の触媒的なエノラート化法は本研究領域の発展のために基盤技術として中枢を担う。

②カルボン酸の直接的化学修飾反応

カルボン酸の化学修飾を行うための手法として、配向基の着脱を経る手法が一般的である(Scheme A)。当研究室でも先行研究として、配向基を有するカルボン酸等価体である 2-アシルイミダゾールのラジカル機構による触媒的 α-アルキル化反応を報告している[2]。本反応ではカルボニル化合物の効率的な活性化のために配向基を用いることで、カルボニル化合物の活性化と系中でのアルキルラジカル種の発生を両立した反応を達成することができた。しかし、このような配向基を用いる反応では配向基を着脱するステップが必須となり、合成ステップや廃棄物の増加および本ステップにおける基質一般性の制限などが問題となっていた。配向基を有するカルボン酸等価体は一般的に、入手性の高いカルボン酸などから合成される。そこで、配向基を必要としないカルボン酸の直接的化学修飾反応を開発することで、配向基の使用により生じる諸問題の改善が可能であると考えた(Scheme B)。

Scheme A. Directing Group-Assisted Catalytic α-Functionalization



Scheme B. Direct Catalytic α-Functionalization of Carboxylic Acids

③本研究におけるデータの帰属

本研究で扱ったデータの帰属を、章節番号を用いて以下に示す。

著者

第 1 章 1-1–1-6

第 2 章 2-1–2-4, 2-5-1, 2-5-2, 2-6

第 3 章 3-1–3-3, 3-4-1

鶴田朗人氏

第 2 章 2-5-3 (Figure 2-3)

古賀祐之介氏

第 3 章 3-4-2 (Scheme 3-7)

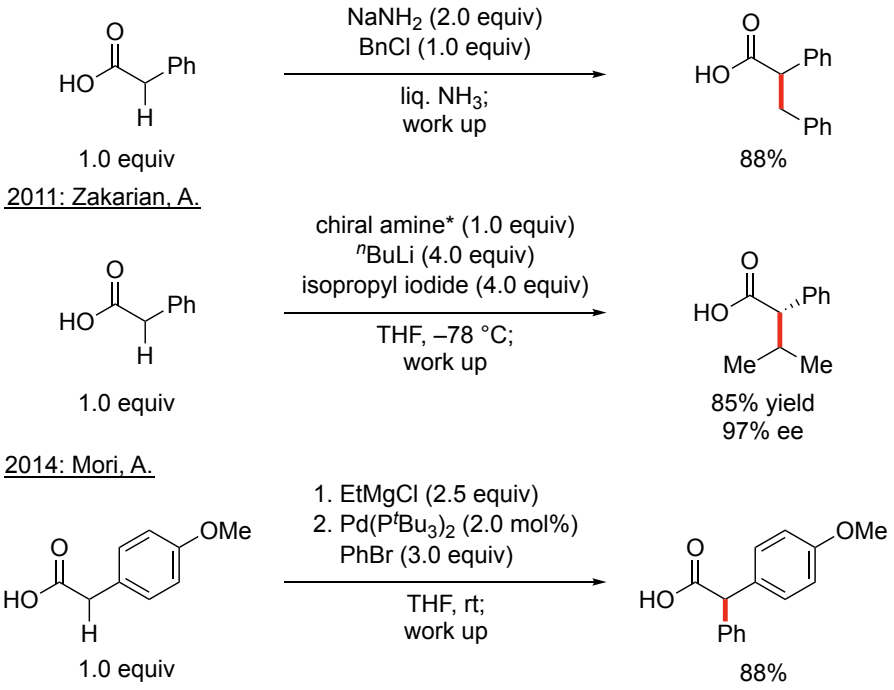
第 1 章　ラジカル機構によるカルボン酸の触媒的 α-酸化反応

1-1. 序論

1-1-1. 二電子型反応によるカルボン酸の α-官能基化反応

カルボン酸のエノラート化を達成するためには、カルボキシラートのエノラート化によってジアニオン性のエンジオラートを生成する必要がある。そのため、塩基のみでカルボン酸のエノラート化を行うためにはリチウムアミドなどの強塩基を 2.0 当量以上使用する必要があり、官能基許容性の低下や廃棄物の増加が問題となっていた(Scheme 1-1)[3]。本手法によるカルボン酸の α-アルキル化反応ではエナンチオ選択的な反応も達成されており、Zakarian らはキラルなリチウムアミドを用いることでカルボン酸の高収率・高エナンチオ選択的な直接的不斉 α-アルキル化反応を達成した [4]。また、本手法をパラジウム触媒系に適用することで Mori らはカルボン酸の α-アリール化反応を達成した [5]。

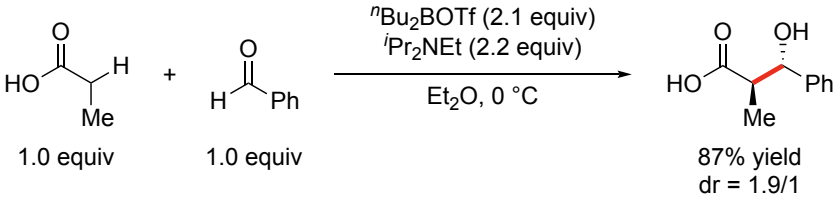
Scheme 1-1. Enolization of Carboxylic Acids Using Brønsted Base



カルボン酸のエノラート化は強塩基を用いる手法だけでなく、Brønsted 塩基と Lewis 酸を併用する手法も報告されている。Evans らは化学量論量のホウ素を用いることで強塩基を必要としないカルボン酸の活性化を達成し、カルボン酸の直接的アルドール反応の開発に成功した(Scheme 1-2)[6]。

Scheme 1-2. Soft-Enolization of Carboxylic Acids

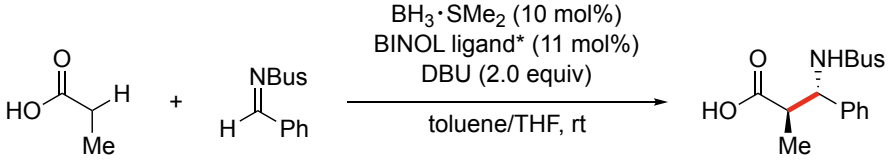
1981: Evans, D. A.



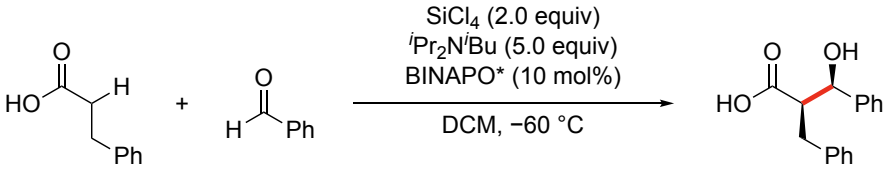
近年では、Kanai、Shimizu らによる触媒量のホウ素を用いる Mannich 反応や[7]、Nakajima、Kotani らによるケイ素を用いるアルドール反応が報告されている(Scheme 1-3)[8]。このように、カルボン酸の活性化法は急速に発展しつつあるものの、いずれの反応も化学量論量の外部塩基を必要とする上に、これらの反応で用いられる Lewis 酸はレドックス不活性であるため、カップリングパートナーが二電子型反応の求電子剤に限定されていた。一方で、二電子型反応と相補的なラジカル機構による α-官能基化反応の報告例は、次節に示す一例のみであった。

Scheme 1-3. Catalytic Enolization of Carboxylic Acids

2015: Kanai, M.; Shimizu, Y.



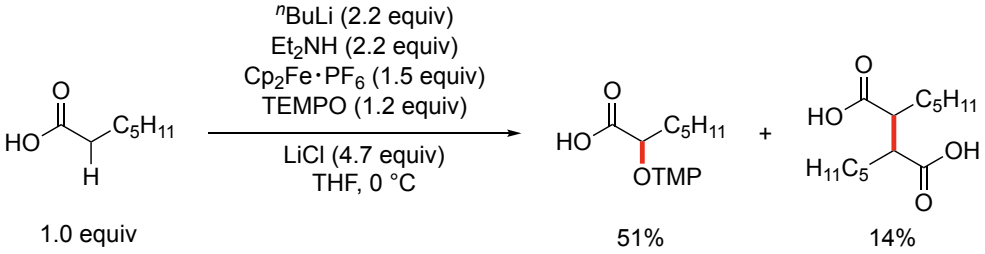
2018: Nakajima, M.; Kotani, S.



1-1-2. ラジカル機構によるカルボン酸の α-官能基化反応

ラジカル機構によるカルボン酸の α-官能基化反応として、カルボン酸と TEMPO（2,2,6,6-テトラメチルピペリジン-1-オキシルラジカル）のクロスカップリング反応が 2012 年に Jahn らによって報告されている。しかし、本反応は化学量論量の強塩基と金属酸化剤を用いる上に、ネイキッドなカルボン酸 α-ラジカル種生成のために二量体化副反応が避けられない点に改善の余地を残していた(Scheme 1-4)[9]。

Scheme 1-4. α-Functionalization of Carboxylic Acids via Radical-Radical Process
2012: Jahn, U.

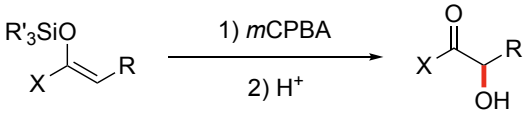


1.0 equiv　　51%　　14%

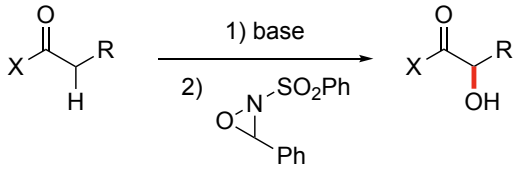
1-1-3. カルボニル化合物の α-酸化反応

カルボン酸等価体の古典的な α-酸化反応として、Rubottom 反応や Davis 反応が開発されている [10]。本反応はカルボン酸と同様に市販品の種類が豊富な低級エステル群を基質として用いることで、無保護ヒドロキシ基を直接導入可能である一方で、Rubottom 反応では基質であるシリルエノールエーテルの合成に、Davis 反応ではエノラートの形成に化学量論量の強塩基が必要であり、官能基許容性の低下や化学量論量の廃棄物が問題となっていた(Scheme 1-5)。

Scheme 1-5. Classical α-Oxidation of Carbonyl Compounds
Rubottom Oxidation

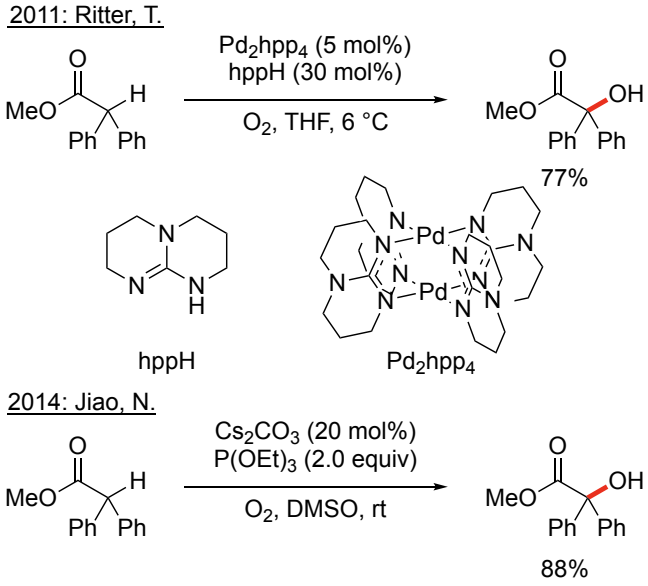


Davis Oxidation



強塩基を必要としない温和な条件での α-酸化反応として、Ritter らが二核パラジウム触媒を用いた手法を [11]、Jiao らが触媒量の炭酸セシウムを用いた手法をそれぞれ報告している [12]。これらの反応は酸素源試薬として酸素分子を用いているため環境調和性に優れた反応であるものの、本反応では過剰酸化が起こらず、エノラート化しやすい活性な α,α-二置換の基質にしか適用できない点で制限があった(Scheme 1-6)。

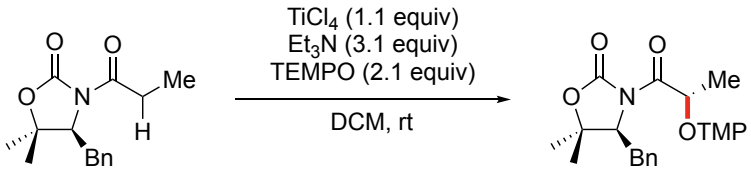
Scheme 1-6. Tertiary Alcohol Synthesis by α-Oxidation



過剰酸化の進行を抑制可能な手法として、立体的にかさ高い TEMPO を酸素源試薬として用いる手法が近年注目を集めている(Scheme 1-7)。2014 年に、Zakarian らは *N*-アシルオキサゾリジノンの α-酸化反応を報告しており、本反応は補助基を利用することで立体選択的な反応を達成している [13]。また、2017 年に Maulide らが三級アミドをトリフルオロメタンスルホン酸無水物によって [14]、Jiao らが二級アミドをトリイソプロピルシリルトリフラートとピリジンによって活性化し [15]、TEMPO によるアミドの α-酸化反応を報告している。上記の反応はいずれも強塩基を用いることなく温和な条件下でアミドを活性化し、過剰酸化が起こりにくい TEMPO を用いて α-酸化反応を達成している。その一方で、アミドの活性化に化学量論量の試薬を必要とする上に、アミド結合が強固であるために反応生成物の多様な変換が困難である点に改善の余地を残していた。

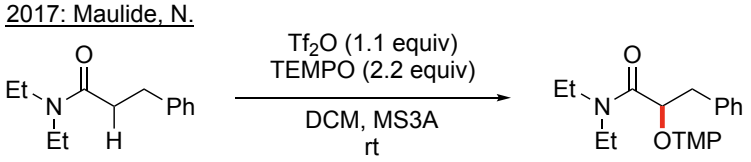
Scheme 1-7. α-Oxidation of Amide Using TEMPO

2014: Zakarian, A.



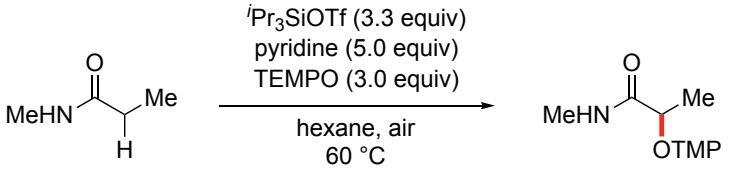
67%, dr = 1/14

2017: Maulide, N.



75%

2017: Jiao, N.

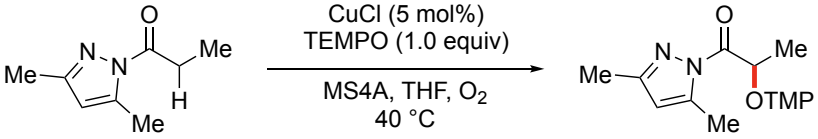


91%

また、当研究室では、2017 年に TEMPO によるカルボン酸等価体の触媒的 α-酸化反応を報告している(Scheme 1-8)[16]。本反応は TEMPO を酸素源試薬とする手法としては世界初となる触媒条件を達成したものである一方で、配向基の着脱が必須である点に改善の余地を残していた。

Scheme 1-8. Catalytic α-Oxidation of Carboxylic Acid Equivalent

2017: Ohshima, T.; Yazaki, R.



1.5 equiv

83%

1-1-4. 本研究の目的

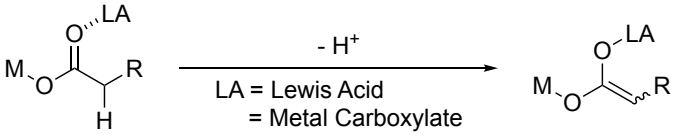
以上の背景のもと、ラジカル機構によるカルボン酸の直接的触媒的 α-酸化反応の開発を目的とした。本反応は配向基の着脱を必要としないため環境調和性に優れており、基質合成・変換反応での基質適用範囲の制限が最小限である。また、本反応ではラジカル種である TEMPO をカップリングパートナーとして用いることで、過剰酸化反応が進行しにくい α-ヒドロキシ酸誘導体の合成が可能であり、エノラートの形成に強塩基を必要としない点や基質合成が最小限である点と併せてカルボン酸誘導体のケミカルスペース拡充が可能であると考えられる。

1-2. 反応設計と初期検討

1-2-1. 反応設計

レドックス活性な Lewis 酸によるカルボン酸のエノラート化を達成するために、金属カルボキシラート種の性質に注目した。金属カルボキシラート種は陽性元素である金属の電子求引性誘起効果によってカルボキシラートの α 位の酸性度を向上させることが可能である [5]。そのため、反応系中で生成した金属カルボキシラート種は、Lewis 酸触媒によるエノラート化が可能であると考えた。すなわち、二分子の金属カルボキシラートが協働する機構によりカルボン酸のエノラート化が進行することを想定した(Scheme 1-9)。そこで初期検討として、本反応設計を実現可能な金属種の探索を行うこととした。

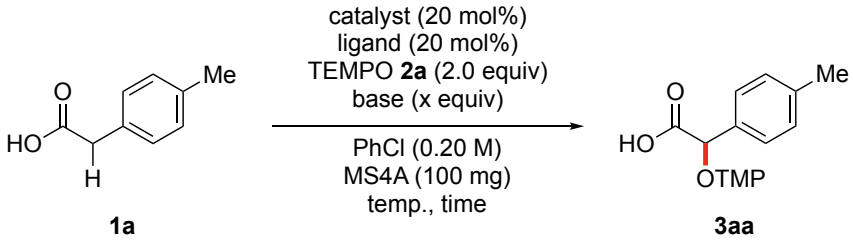
Scheme 1-9. Activation Strategy for Carboxylic Acids



1-2-2. 初期検討

金属種の探索を行うにあたり、初めに反応条件の設定を行った。ラジカル機構による α-官能基化反応では、クロスカップリング反応が進行する際に触媒の一電子還元が起こる。そこで、TEMPO は α-酸化試薬としてだけでなく触媒の再酸化剤としても機能すると考え、2.0 当量用いた。さらに、基質のカルボン酸の酸性プロトンはエンジオラートの生成を阻害すると考えたため、塩基として炭酸塩を加えた。炭酸塩はプロトン化されることで H_2O を生じるため、H_2O によって反応が阻害されることを防ぐ目的で、乾燥剤として MS4A を添加した(Table 1-1)。

Table 1-1. Initial Study for α-Oxidation of Carboxylic Acid



1a
0.20 mmol

3aa

entry	catalyst	ligand	base (equiv)	temp. (°C)	time (h)	**3aa** (%)	**1a** (%)
1	$Fe(OAc)_2$	—	Cs_2CO_3 (0.8)	120	3	2	93
2	CuOAc	—	Cs_2CO_3 (0.8)	120	3	N.D.	— [a]
3	$Fe(OAc)_2$	—	Na_2CO_3 (0.8)	80	5	27	68
4	$Fe(OAc)_2$	—	Na_2CO_3 (3.0)	80	24	33	57
5	$Fe(OAc)_2$	phen	Na_2CO_3 (3.0)	80	24	>99	<1

Yields were determined by ^{1}H NMR analysis using 2-methoxynaphthalene as an internal standard.
[a] Yield could not be calculated. TMP = 2,2,6,6-tetramethylpiperidino

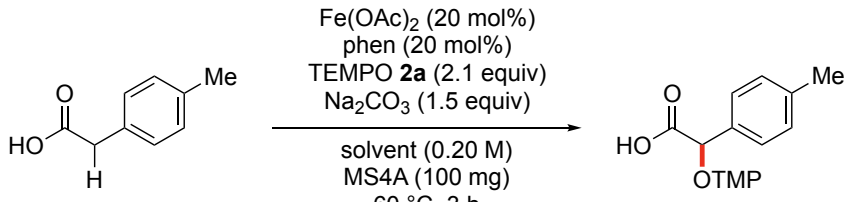
レドックス活性のある Lewis 酸として一般的な鉄と銅を用いて初期検討を行った。その結果、鉄を用いた際にわずかながら反応の進行が確認された(entries 1,2)。塩基を炭酸セシウムから炭酸ナトリウムに変更することで反応性が向上した(entry 3)。フェナントロリンを配位子として添加することで反応性が向上し、原料がほぼ消失することを確認した(entry 5)。本条件をもとに、次に反応条件の最適化を行った。

1-3. 反応条件の検討

1-3-1. 溶媒

比較のために反応が終結しない反応温度と反応時間を設定し、初めに溶媒の検討を行った(Table 1-2)。

Table 1-2. Screening of Solvents



1a
0.20 mmol

3aa

entry	solvent	**3aa** (%)	**1a** (%)	entry	solvent	**3aa** (%)	**1a** (%)
1	toluene	38	58	9	MeOH	N.D.	83
2	PhCl	44	49	10	DMF	57	43
3	DCE	35	58	11	1,4-dioxane	62	38
4	**THF**	**72**	**27**	12	CPME	47	47
5	EtOAc	61	35	13	TBME	8	88
6	acetone	53	42	14	anisole	48	43
7	MeCN	18	84	15	DME	68	30
8	$MeNO_2$	8	85				

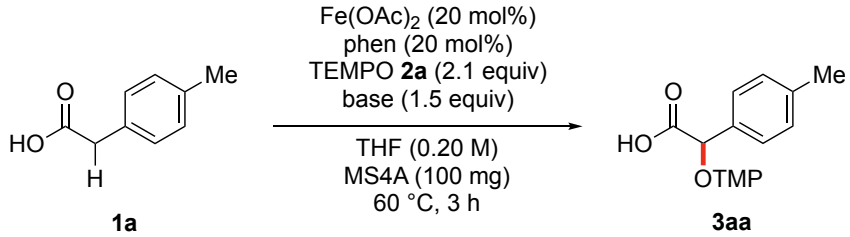
Yields were determined by ^{1}H NMR analysis using 2-methoxynaphthalene as an internal standard. TMP = 2,2,6,6-tetramethylpiperidino, CPME = cyclopentyl methyl ether, TBME = *tert*-butyl methyl ether, DME = 1,2-dimethoxyethane

極性がほとんどないトルエンやクロロベンゼン、1,2-ジクロロエタンを用いた条件よりも、中程度の極性を持つ THF、酢酸エチル、アセトンを用いた際に目的物の収率が高くなる傾向が見られた(entries 1–6)。高極性のアセトニトリルやニトロメタン、メタノールを用いた際に目的物の収率は大きく低下した(entries 7–9)。一方で、高極性溶媒である DMF を用いた際には中程度の収率で目的物が得られた(entry 10)。結果として、THF を用いた際に最も良い収率で目的物が得られた(entry 4)。そのため、続いてエーテル系溶媒について重点的に検討を行ったものの、THF よりも良い結果を示す溶媒を見出すことはできなかった(entries 11–15)。TBME を用いた際に反応がほとんど進行しなかった原因として、ターシャリーブチル基の立体効果により溶解性が悪く、$Fe(OAc)_2$ の溶解性が悪かったことが考えられる(entry 13)。

1-3-2. 塩基

次に塩基の検討を行った(Table 1-3)。

Table 1-3. Screening of Bases



1a
0.20 mmol

3aa

entry	base	**3aa** (%)	**1a** (%)	entry	base	**3aa** (%)	**1a** (%)
1	Li_2CO_3	37	59	8	K_3PO_4	29	67
2	Na_2CO_3	72	27	9	K_2HPO_4	29	64
3	$NaHCO_3$	38	59	10	KO^tBu	1	>99
4	K_2CO_3	17	78	11	Et_3N	55	44
5	Cs_2CO_3	2	94	12	Py	46	53
6	$Na_3PO_4 \cdot 12H_2O$	N.D.	94	13	DBU	78	19
7	Na_3PO_4	56	44	**14**	**—**	**75**	**23**

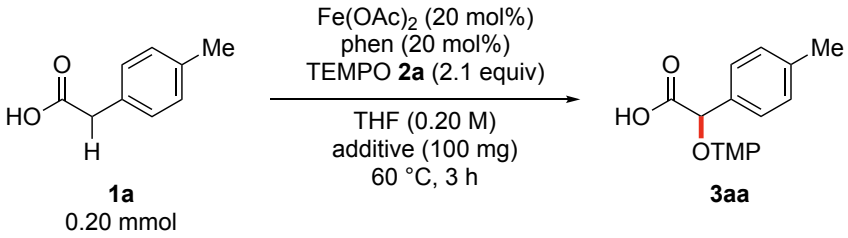
Yields were determined by ^1H NMR analysis using 2-methoxynaphthalene as an internal standard. TMP = 2,2,6,6-tetramethylpiperidino

初めに、塩基として炭酸塩の検討を行った。塩の金属種は本反応に大きく影響することが明らかとなり、炭酸ナトリウムを用いた際に最も良好な結果を示した(entries 1–5)。リン酸ナトリウムを用いた無水物塩と水和物塩の比較により、本反応は H_2O の存在により悪影響を受けることが確認できた(entries 6,7)。また炭酸塩の場合と同様に、リン酸塩の場合でもカリウム塩よりナトリウム塩の方が良好な結果を示した(entries 7–9)。強塩基であるアルコキシドを添加した場合、反応はほとんど進行しなかった(entry 10)。有機塩基についても検討を行ったところ、DBU を用いた際に良好な結果が得られた(entries 11–13)。最後に塩基非添加条件での実験を行ったところ、炭酸ナトリウムや DBU を添加した条件と同程度の収率で目的物が得られた(entry 14)。この結果から本反応は塩基非添加条件でも良好に進行することが明らかとなり、塩基非添加条件を最適条件とした。

1-3-3. モレキュラーシーブス

次にモレキュラーシーブスの検討を行った(Table 1-4)。

Table 1-4. Screening of Molecular Sieves



1a
0.20 mmol

3aa

entry	additive	**3aa** (%)	**1a** (%)
1	MS3A	53	32
2	**MS4A**	**75**	**23**
3	MS5A	37	57
4	MS13X	20	73
5	—	5	91

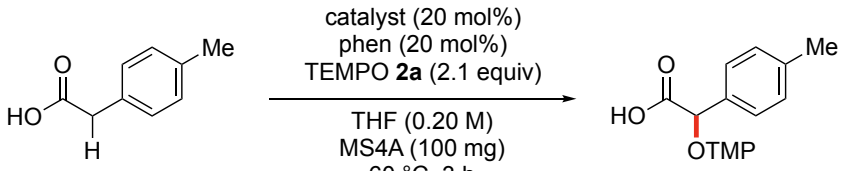
Yields were determined by ^{1}H NMR analysis using 2-methoxynaphthalene as an internal standard.
TMP = 2,2,6,6-tetramethylpiperidino

モレキュラーシーブスは本反応に大きく影響することが明らかとなり、MS4A を用いた際に最も良好な結果を示した(entries 1–4)。一方、モレキュラーシーブスを添加しない条件では反応はほとんど進行しなかった(entry 5)。

1-3-4. 金属触媒

次に金属触媒の検討を行った(Table 1-5)。

Table 1-5. Screening of Catalysts



1a
0.20 mmol

3aa

entry	catalyst	**3aa** (%)	**1a** (%)	entry	catalyst	**3aa** (%)	**1a** (%)
1	$MnCl_2$	4	96	10	$FeBr_2$	7	91
2	$FeCl_2$	10	89	11	$Fe(OTf)_2$	1	97
3	$FeCl_3$	<1	97	12	$Fe(OTf)_3$	N.D.	88
4	$CoCl_2$	N.D.	97	13	$FeSO_4 \cdot 7H_2O$	1	96
5	$NiCl_2$	N.D.	99	**14**	**$Fe(OAc)_2$**	**75**	**23**
6	CuCl	2	93	15	$Fe(acac)_3$	11	70
7	$CuCl_2$	<1	99	16	FeO(OH)	N.D.	99
8	$ZnCl_2$	N.D.	98	17	CuOAc	3	94
9	FeF_2	N.D.	95	18	$Cu(OAc)_2$	2	93

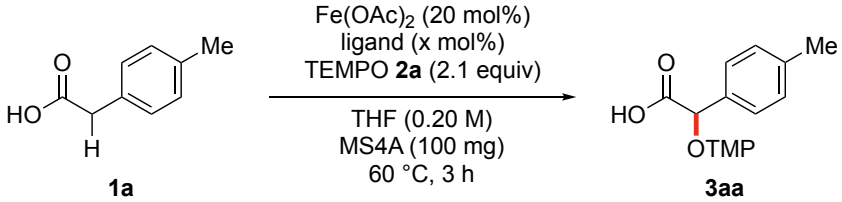
Yields were determined by ^{1}H NMR analysis using 2-methoxynaphthalene as an internal standard. TMP = 2,2,6,6-tetramethylpiperidino

鉄だけでなく、マンガンや銅を触媒とした際にもわずかながら反応の進行が確認できた(entries 1–3,6,7)。コバルト、ニッケル、亜鉛を触媒とした際には目的物を検出することはできなかった(entries 4,5,8)。次に、最も良い結果を与えた鉄について検討を行った(entries 9–16)。その結果、$Fe(OAc)_2$ を用いた際に最も良い収率で目的物が得られた(entry 14)。CuOAc や $Cu(OAc)_2$ を用いた条件では反応はほとんど進行しなかった(entries 17,18)。

1-3-5. 配位子

次に配位子の検討を行った(Table 1-6)。

Table 1-6. Screening of Ligands

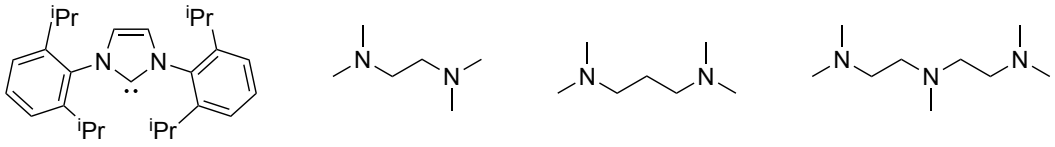


1a
0.20 mmol

3aa

entry	ligand (mol%)	**3aa** (%)	**1a** (%)	entry	ligand (mol%)	**3aa** (%)	**1a** (%)
1	—	47	53	8	Ph_3P=S (40)	44	54
2	IPr (20)	44	61	**9**	**phen (20)**	**75**	**23**
3	DMAP (20)	46	51	**10**	**bpy (20)**	**74**	**28**
4	DMAP (40)	63	37	**11**	**TMEDA (20)**	**75**	**20**
5	Et_3N (40)	50	44	12	TMPDA (20)	50	47
6	Ph_3P (40)	46	48	13	PMDTA (20)	60	42
7	Ph_3P=O (40)	45	58	14	*rac*-BINAP (20)	46	53

Yields were determined by ^{1}H NMR analysis using 2-methoxynaphthalene as an internal standard. TMP = 2,2,6,6-tetramethylpiperidino



IPr

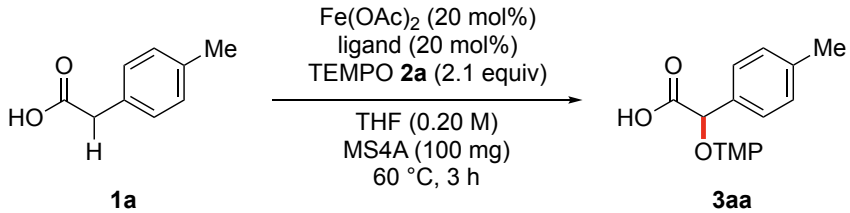
TMEDA

TMPDA

PMDTA

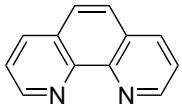
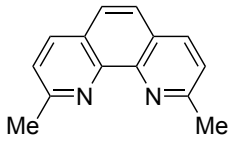
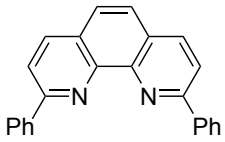
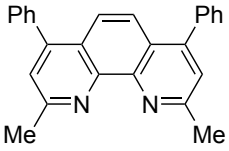
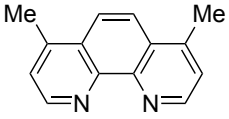
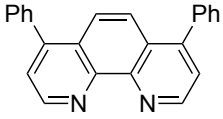
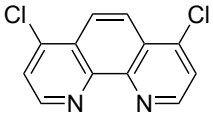
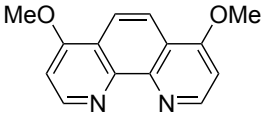
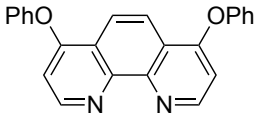
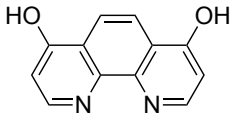
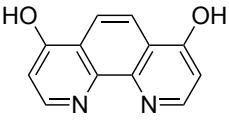
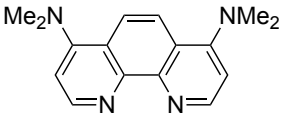
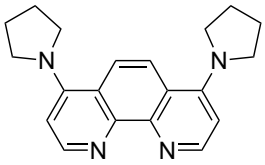
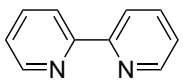
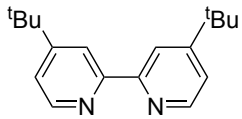
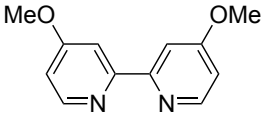
本反応は配位子を添加しない条件でも進行することが確認できた(entry 1)。単座配位子を用いた場合、DMAP を 40 mol%用いた entry 4 の条件以外では配位子添加による反応の促進は確認できなかった(entries 2–8)。次に多座配位子の検討を行った(entries 9–14)。その結果、1,10-フェナントロリン、2,2'-ビピリジン、TMEDA を用いた際に良好に反応が促進された(entries 9–11)。そこで次に、置換基による電子状態の調節が容易な 1,10-フェナントロリン誘導体と 2,2'-ビピリジン誘導体について追加の検討を行った(Table 1-7)。

Table 1-7. Screening of 1,10-Phenanthroline and 2,2'-Bipyridine Derivatives as Ligands



1a
0.20 mmol

3aa

			
phen **3aa**: 75%, **1a**: 23%	**L1**·1/2 H_2O **3aa**: 29%, **1a**: 67%	**L2** **3aa**: 48%, **1a**: 49%	**L3** **3aa**: 24%, **1a**: 76%
			
L4 **3aa**: 74%, **1a**: 21%	**L5** **3aa**: 83%, **1a**: 13%	**L6** **3aa**: 25%, **1a**: 65%	**L7** **3aa**: 91%, **1a**: 8%
			
L8 **3aa**: 86%, **1a**: 9%	**L9** **3aa**: 40%, **1a**: 60%	**L9** with Na_2CO_3 (1.5 equiv) **3aa**: 47%, **1a**: 53%	**L10** **3aa**: 96%, **1a**: 3%
			
L11 **3aa**: 80%, **1a**: 19%	bpy **3aa**: 74%, **1a**: 28%	**L12** **3aa**: 77%, **1a**: 22%	**L13** **3aa**: 62%, **1a**: 35%

Yields were determined by ^{1}H NMR analysis using 2-methoxynaphthalene as an internal standard. TMP = 2,2,6,6-tetramethylpiperidino

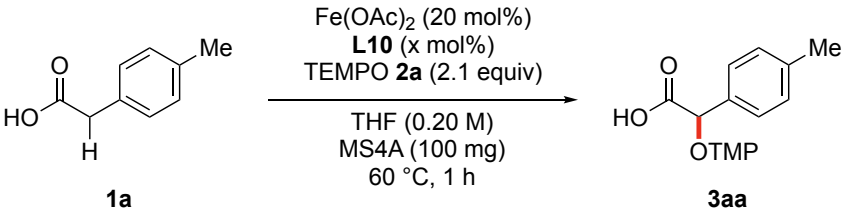
2,9 位に置換基を導入した 1,10-フェナントロリン誘導体を用いたところ、目的物の収率は低下した(**L1**, **L2**, **L3**)。電子的にほとんど中性であるメチル基やフェニル基を有する 1,10-フェナントロリン誘導体を用いた場合、無置換の 1,10-フェナントロリンと同様の結果となった(**L4**, **L5**)。4,7 位に電子求引基であるクロロ基を有する 1,10-フェナントロリン誘導体を用いたところ、目的物の収率は低下した(**L6**)。4,7 位に電子供与基を有する 1,10-フェナントロリン誘導体を用いた際に反応が加速される傾向があった(**L7**, **L8**, **L10**, **L11**)。その中でも、ジメチルアミノ基を有する 1,10-フェナントロリン誘導体を用いた際に最も良い収率で目的物が得られた(**L10**)。4,7 位にヒドロキシ基を有する 1,10-フェナントロリンを塩基と共に用い

ることでより高い電子供与性を実現できると考えたものの、本条件での目的物の収率は中程度であった(**L9**)。2,2'-ビピリジン系配位子の場合では置換基の導入による収率の改善は見られなかった(**L12**, **L13**)。

1-3-6. 配位子の当量

次に配位子の当量について検討を行った(Table 1-8)。

Table 1-8. Optimization of Ligand Amount



1a
0.20 mmol

3aa

entry	**L10** (mol%)	**3aa** (%)	**1a** (%)
1	0	24	77
2	5	41	62
3	10	50	52
4	**20**	**52**	**52**
5	30	46	54

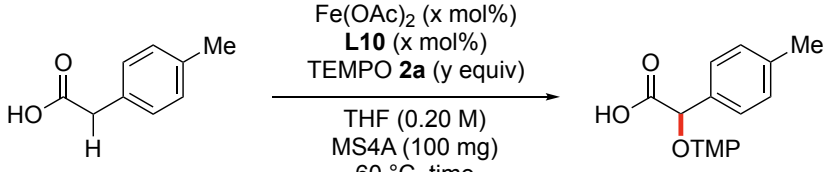
Yields were determined by ^{1}H NMR analysis using 2-methoxynaphthalene as an internal standard.
TMP = 2,2,6,6-tetramethylpiperidino

$Fe(OAc)_2$ 20 mol%に対して 1 当量(20 mol%)の配位子を加えた際に最も良い収率で目的物が得られた(entry 4)。

1-3-7. 種々試薬の添加量と反応温度・反応時間

次に、種々試薬の添加量と反応温度・反応時間の検討を行った(Table 1-9)。

Table 1-9. Optimization of Each Reagent Amount, Temperature and Time



1a
0.20 mmol

3aa

entry	$Fe(OAc)_2$/**L10** (mol%)	**2a** (equiv)	time (h)	**3aa** (%)	**1a** (%)
1	20	2.1	3	96	3
2[a]	20	2.1	3	74	25
3	**5**	**2.1**	**24**	**>99 (95)[d]**	**N.D.**
4[b]	5	2.1	24	63	37
5[c]	5	2.1	7	75	N.D.
6	5	1.4	24	98	1

Yields were determined by ^{1}H NMR analysis using 2-methoxynaphthalene as an internal standard. [a] 50 mg/mL of MS4A was used. [b] Reaction was performed at 40 °C. [c] Reaction was performed without MS4A at 100 °C using 1,4-dioxane insted of THF [d] Isolated yield was shown. TMP = 2,2,6,6-tetramethylpiperidino

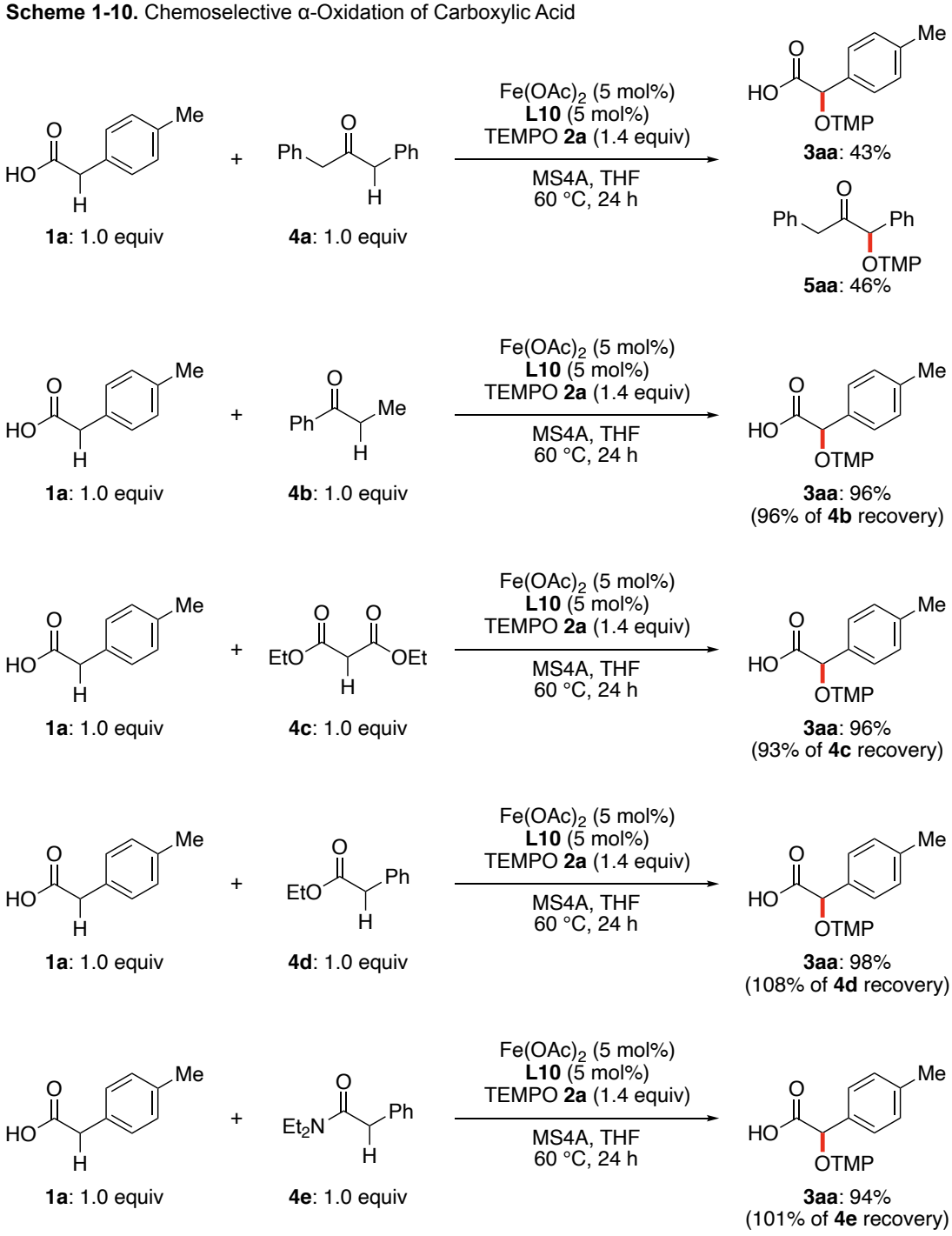
MS4A の添加量を 100 mg から 50 mg に低減すると目的物の収率は低下した(entries 1,2)。触媒量を 5 mol%に低減した条件でも反応は良好に進行し、反応時間を 24 時間とすることで 95%の単離収率で目的物が得られた(entry 3)。反応温度を 40 °C に低減すると反応は 24 時間では終結しなかった(entry 4)。モレキュラーシーブスを添加しない条件でも反応温度を 100 °C に昇温することで反応は進行したものの、目的物の収率はモレキュラーシーブス添加・60 °C の条件と比較して低下した(entry 5)。またその際、N–O 結合の開裂を伴う脱炭酸により目的物から生じたと考えられる 4-メチルベンズアルデヒドが観測された。本反応では TEMPO を 1.4 当量に低減することが可能であったが、わずかながら原料の残存が確認された(entry 6)。精製の際に原料と目的物を分離することが困難であったため、再現良く原料が消失する 2.1 当量の TEMPO を用いる entry 3 の条件を最適条件とした。

1-4. 基質の検討・変換反応

1-4-1. 化学選択的 α-酸化反応

カルボニル化合物の存在下における本触媒系の化学選択性についての実験を行った。種々カルボニル化合物 **4** を 1.0 当量添加して反応を行うことで、本触媒系の化学選択性について知見が得られると考えた(Scheme 1-10)。

Scheme 1-10. Chemoselective α-Oxidation of Carboxylic Acid

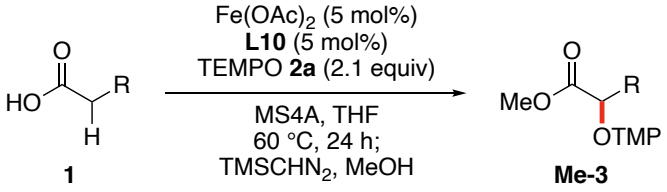


α-アリールケトン **4a** を添加した場合、カルボン酸 **1a** と **4a** の活性化が競合することが明らかとなった。しかし、α-アルキルケトン **4b** やジエチルマロネート **4c**、α-アリールエステル **4d**、α-アリールアミド **4e** を添加した条件においてはカルボン酸のみの化学選択的な活性化を達成した。

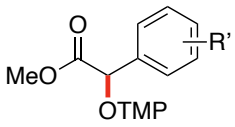
1-4-2. 基質一般性

次に、最適条件における基質一般性の検討を行った(Table 1-10)。その際、反応終了後の溶液に MeOH と $TMSCHN_2$ を加えて処理し、生成物をメチルエステルに変換して単離した。

Table 1-10. Substrate Scope of Carboxylic Acids



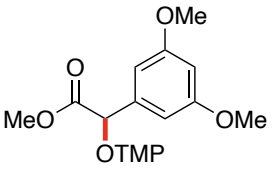
1 **Me-3**



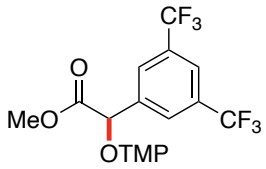
R' = *p*-Me (**Me-3aa**) 85%
m-Me (**Me-3ba**) 88%
o-Me (**Me-3ca**) 86%[a]

R' = *p*-Br (**Me-3da**) 80%
m-Br (**Me-3ea**) 88%
o-Br (**Me-3fa**) 93%[a]
p-F (**Me-3ga**) 83%
p-Cl (**Me-3ha**) 84%
p-I (**Me-3ia**) 81%
p-Ph (**Me-3ja**) 75%
p-OH (**Me-3ka**) 50%[b]

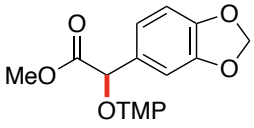
R' = *p*-OMe (**Me-3la**) 86%
m-OMe (**Me-3ma**) 88%
p-CF_3 (**Me-3na**) 81%
m-CF_3 (**Me-3oa**) 84%
p-SO_2Me (**Me-3pa**) 79%
p-SMe (**Me-3qa**) 81%
p-NHBoc (**Me-3ra**) 90%
p-CN (**Me-3sa**) 55%



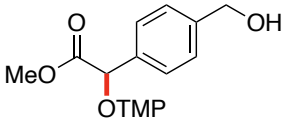
Me-3ta: 82%



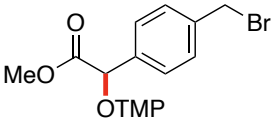
Me-3ua: 67%



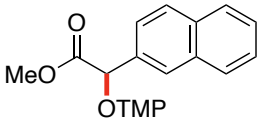
Me-3va: 86%



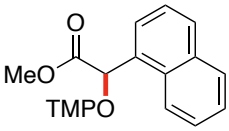
Me-3wa: 79%



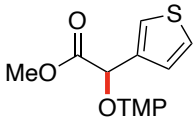
Me-3xa: 36%



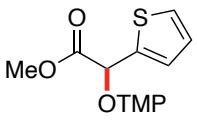
Me-3ya: 91%



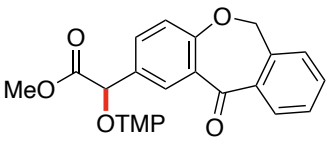
Me-3za: 92%[a]



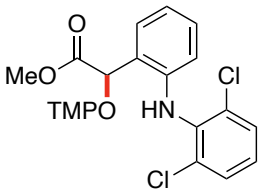
Me-3αa: 82%



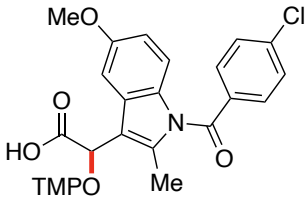
Me-3βa: 40%



Me-3γa: 85%



Me-3δa: 74%[c]



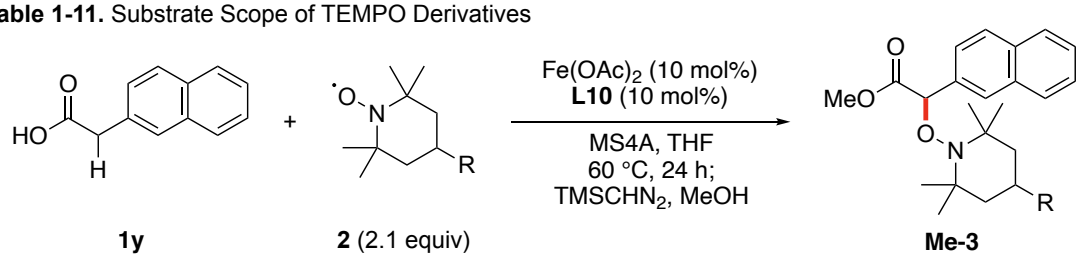
3εa: 61%[a,d]

[a] 4.0 equiv of TEMPO **2a**, and 10 mol% of $Fe(OAc)_2$ and **L10** were used. [b] 2-(4-acetoxyphenyl)acetic acid (**1k-Ac**) was used as a substrate. [c] 4.0 equiv of TEMPO **2a**, and 20 mol% of $Fe(OAc)_2$ and **L10** were used. [d] Yield was determined by ^1H NMR analysis using dibenzyl as an internal standard. TMP = 2,2,6,6-tetramethylpiperidino

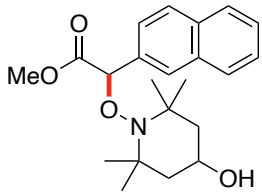
芳香環に置換されたメチルやハロゲン、フェニル、アセトキシ、メトキシ、トリフルオロメチル、スルホニルなどの官能基は、本反応の進行に悪影響を及ぼさなかった (**Me-3aa**–**Me-3pa**)。LDA 等の強塩基条件でリチウム-ハロゲン交換が進行しうるヨード基は本反応条件に許容され、ヨード基を有する目的物が高収率で得られた(**Me-3ia**)。反応点近傍が混雑した基質では反応の進行は遅くなったものの、触媒および TEMPO の当量を増やすことにより高収率で目的物を得ることができた(**Me-3ca**, **Me-3fa**, **Me-3za**, **Me-3δa**, **3εa**)。2-(4-アセトキシフェニル)酢酸(**1k-Ac**)を基質としたところ、MeOH と $TMSCHN_2$ を用いたエステル化の際に脱アセチル化が進行した(**Me-3ka**)。比較的酸化を受けやすいチオエーテルを有する基質を用いたところ、チオエーテルは酸化されず α-酸化反応のみが進行した(**Me-3qa**)。Boc 保護されたアニリン構造は本反応条件において許容された(**Me-3ra**)。シアノ基を有する基質を用いたところ、目的物の収率は中程度であった(**Me-3sa**)。電子豊富・電子不足の二置換性基質の両方が本反応に適用可能であり、目的物は高収率で得られた(**Me-3ta**–**Me-3va**)。容易に酸化される無保護のベンジル位ヒドロキシ基は触媒反応後も変換されておらず、本反応では古典的な TEMPO 酸化で一般的に生成すると考えられているオキソニウムカチオン中間体は生成していないことが示唆された(**Me-3wa**)。低収率ではあるものの、反応性の高い臭化ベンジル構造を有する基質も本反応に適用可能であった(**Me-3xa**)。ナフチル基を有する基質を用いた際にも高収率で目的物を得ることができた(**Me-3ya**, **Me-3za**)。3-チエニル酢酸を用いたところ高収率で目的物を得ることができた一方で、2-チエニル酢酸では触媒への不適切な配位効果により収率が低下した(**Me-3αa**, **Me-3βa**)。また、本反応は医薬品であるイソキセパック、ジクロフェナク、インドメタシンの後期化学修飾に適用可能であった(**Me-3γa**, **Me-3δa**, **3εa**)。

次に、官能基を有する TEMPO 誘導体を用いた基質一般性の検討を行った(Table 1-11)。

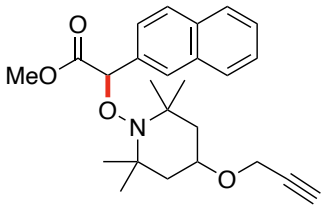
Table 1-11. Substrate Scope of TEMPO Derivatives



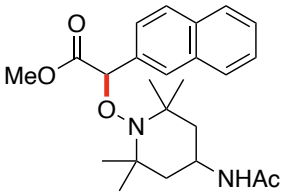
1y **2** (2.1 equiv) **Me-3**



Me-3yb: 89%



Me-3yc: 90%



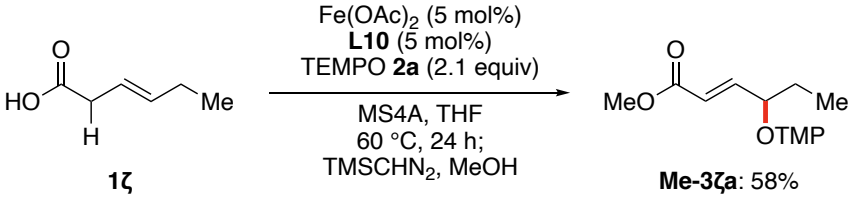
Me-3yd: 62% (78%[a])

[a] Yield based on recovered esterified starting material (**Me-1y**) was shown.

ヒドロキシ基やアルキニル基を有する TEMPO 誘導体を用いた場合においても反応は良好に進行した(**Me-3yb**, **Me-3yc**)。アミドを有する TEMPO 誘導体も本反応に適用可能であり、目的物を 62%の収率で得ることができた(**Me-3yd**)。

β,γ-不飽和カルボン酸を基質として用いたところ、α,β-不飽和-γ-置換体である **Me-3ζa** が 58%の収率で選択的に得られた。一方、α,β-不飽和カルボン酸は本反応に適用することはできなかった(Scheme 1-11)。

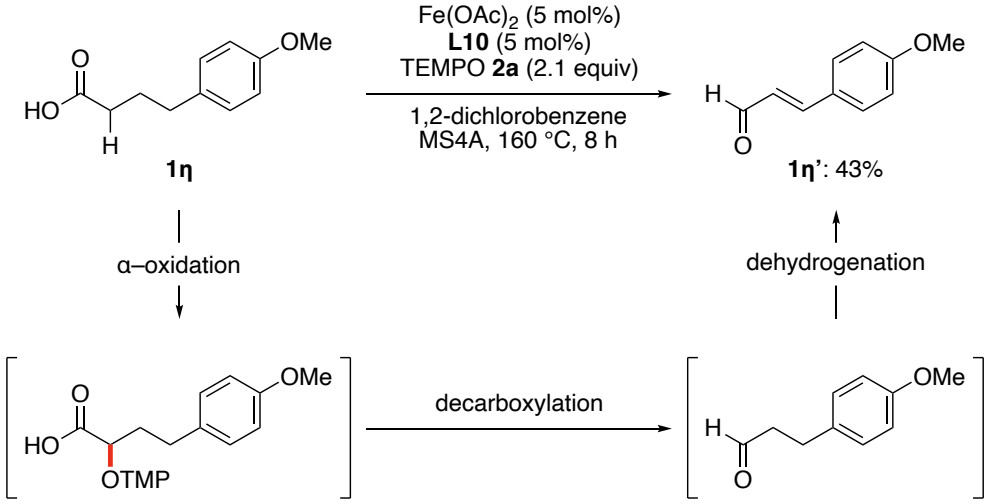
Scheme 1-11. Application to β,γ-Unsaturated Carboxylic Acid



1ζ **Me-3ζa**: 58%

脂肪族カルボン酸 **1η** は 60 °C の低温条件では反応しなかったものの、160 °C の高温条件では **1η** の活性化が可能であった(Scheme 1-12)。しかし、本条件では α-酸化に続いて脱炭酸・不飽和化の過剰反応を経て、シンナムアルデヒド誘導体 **1η'**が主生成物として観測された。

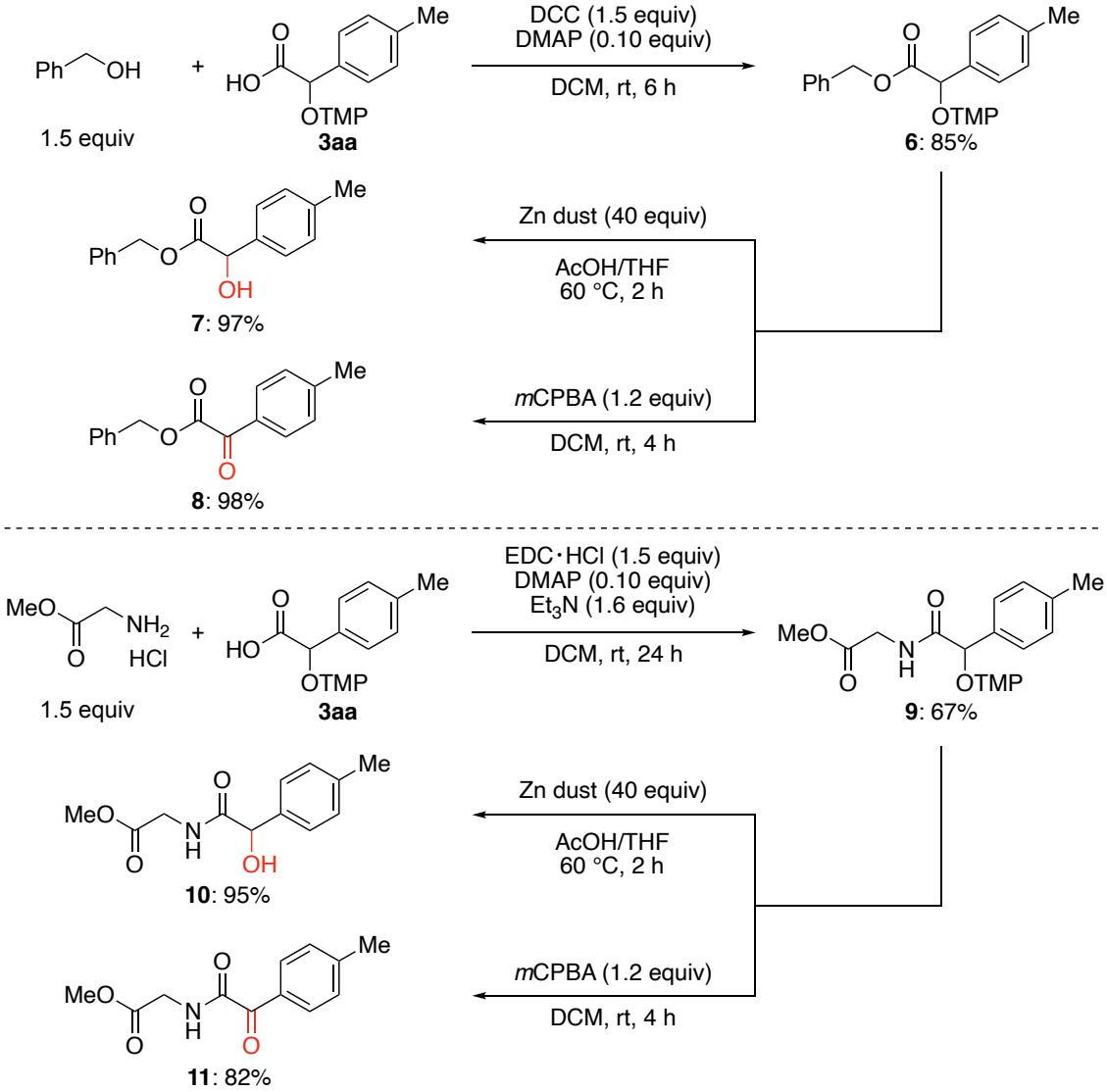
Scheme 1-12. Aliphatic Carboxylic Acid under Heated Conditions



1-4-3. 反応生成物の変換反応

本反応で得られた生成物の変換反応を行った(Scheme 1-13)。

Scheme 1-13. Transformation of the Product

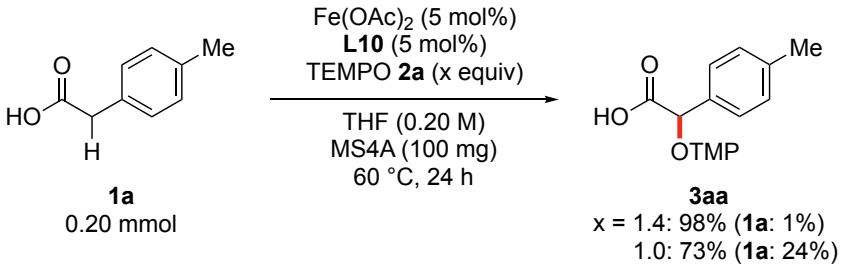


カルボン酸である生成物 **3aa** は縮合反応によってエステル **6** やアミド **9** に変換することが可能であった。また、縮合後の化合物に対して Zn dust を作用させることで N–O 結合の切断が可能であり、α-ヒドロキシエステル **7** や α-ヒドロキシアミド **10** への変換を達成した[9,16]。また、エステル **6** やアミド **9** に対して *m*CPBA を作用させることで 1,2-ケトエステル **8** や 1,2-ケトアミド **11** の合成が可能であった[17]。

1-5. 反応機構の解析

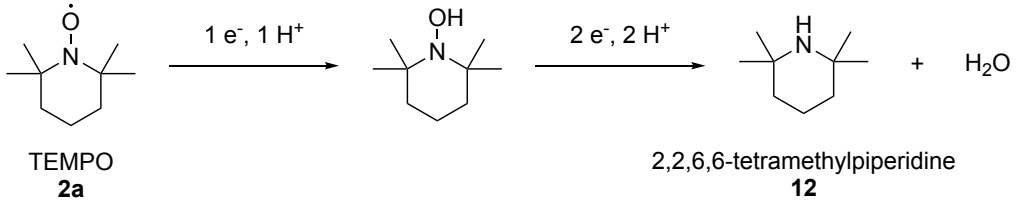
1-5-1. 酸化剤としての TEMPO の機能

Scheme 1-14. Control Experiments in Terms of TEMPO



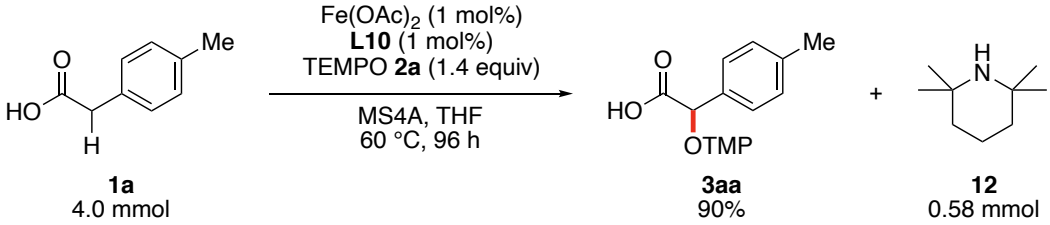
TEMPO を 1.4 当量に低減した条件ではわずかに原料の残存が確認されたものの、反応はほとんど終結した(Scheme 1-14)。しかし、TEMPO を 1.0 当量にまで低減すると目的物の収率はおよそ 75%となった。これらの結果は、二価の鉄を三価に再酸化するために消費される TEMPO が、1 分子で 3 電子及び 3 プロトンを受け取ることを示唆している(Scheme 1-15)。また、その際に N–O 結合が還元され、H_2O と 2,2,6,6-テトラメチルピペリジンが生じると考えられる。

Scheme 1-15. Reduction of TEMPO as an Oxidant



N–O 結合の還元が起こっていることを確かめるために、2,2,6,6-テトラメチルピペリジン **12** の検出を行った(Scheme 1-16)。

Scheme 1-16. Detection of 2,2,6,6-Tetramethylpiperidine **12**

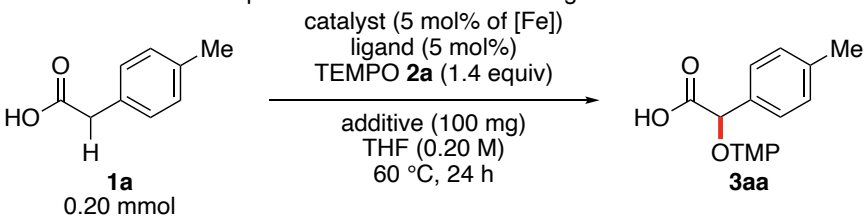


TEMPO を 1.4 当量用いて反応を行ったところ、2,2,6,6-テトラメチルピペリジン **12** の検出に成功した。このことから、二価の鉄を再酸化するために消費される TEMPO が、一分子で三電子及び三プロトンを受け取り、N–O 結合の還元と切断が起こると考えられる。また、モレキュラーシーブスはその際に副生する H_2O を吸着する脱水剤として機能していると考えられる。

1-5-2. コントロール実験

反応機構解析のため、触媒、配位子、添加剤が反応系に与える影響についてコントロール実験を行った(Table 1-12)。

Table 1-12. Control Experiments for Mechanistic Insight



entry	catalyst	ligand	additive	**3aa** (%)	**1a** (%)
1	$Fe(OAc)_2$	**L10**	MS4A	98	1
2	—	**L10**	MS4A	N.D.	96
3	$Fe(OAc)_2$	—	MS4A	34	62
4	$Fe(OAc)_2$	**L10**	—	10	91
5 [a]	$Fe(OAc)_2$	**L10**	MS4A	25	68
6 [b]	$Fe_3O(OAc)_6 \cdot ClO_4$	**L10**	MS4A	95	1

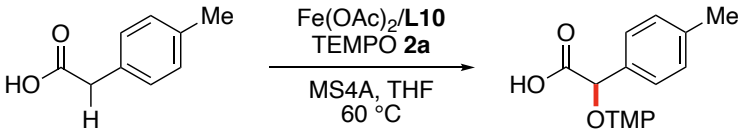
Yields were determined by ^1H NMR analysis using 2-methoxynaphthalene as an internal standard. [a] MS4A was not pre-dried. [b] 2.1 equiv of TEMPO was used. TMP = 2,2,6,6-tetramethylpiperidino

基本となる条件において、目的物は 98%の収率で得られた(entry 1)。触媒非添加条件では反応は全く進行しなかった(entry 2)。配位子とモレキュラーシーブスは本反応に必須ではないものの、反応を促進するために重要であることが確認できた(entry 3,4)。また、モレキュラーシーブスは TEMPO の還元による H_2O の生成量が少ない反応の初期段階から反応の進行に大きな影響を与えたことから、脱水剤としてだけでなく、その他の機能も有していることが示唆された。事前乾燥を行わずにモレキュラーシーブスを使用したところ、目的物の収率は大きく低下した(entry 5)。この結果から、モレキュラーシーブスの脱水剤としての機能も本反応において重要であると考えられる。三価の酢酸鉄として μ-oxo-三核錯体を用いたところ、二価の酢酸鉄を用いた場合と同様に高い収率で目的物が得られた(entry 6)。この結果から、本反応において鉄触媒は二価と三価のどちらを用いた場合でも系中で同一の活性種に誘導されると考えられる。

1-5-3. 反応次数の解析

より詳細な反応機構に関する知見を得るために、基質のカルボン酸、TEMPO、触媒の反応次数を測定した(Table 1-13)。実験手順については Experimental Section 1-7-2 に記載している。

Table 1-13. Initial-Rate Kinetic Study



1a **3aa**

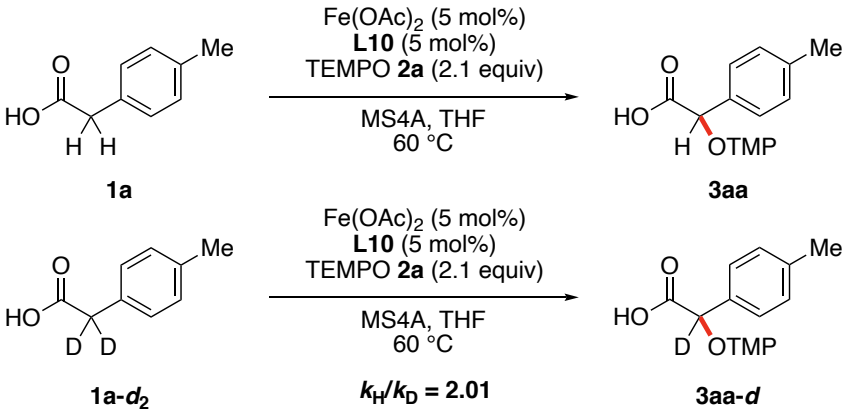
	Reaction Order
1a	-0.7th
TEMPO **2a**	0th
catalyst ($Fe(OAc)_2$/**L10**)	0.7th

反応次数を測定した結果、基質のカルボン酸の反応次数が-0.7 次、TEMPO の反応次数が 0 次、触媒の反応次数が 0.7 次であることが明らかとなった。TEMPO が 0 次であったことから、C–O 結合形成の過程および鉄触媒の再酸化の過程は律速段階ではないことが示唆された。

1-5-4. 速度論同位体効果

本反応の律速段階を明らかにするため、基質であるカルボン酸の速度論同位体効果に関する実験を行った(Scheme 1-17)。本実験では α-軽水素カルボン酸 **1a** と α-重水素カルボン酸 **1a-*d*$_2$** を用いた際の反応初速度をそれぞれ測定して k_H/k_D 値を算出した。

Scheme 1-17. Parallel Kinetic Isotope Effect under Optimized Conditions



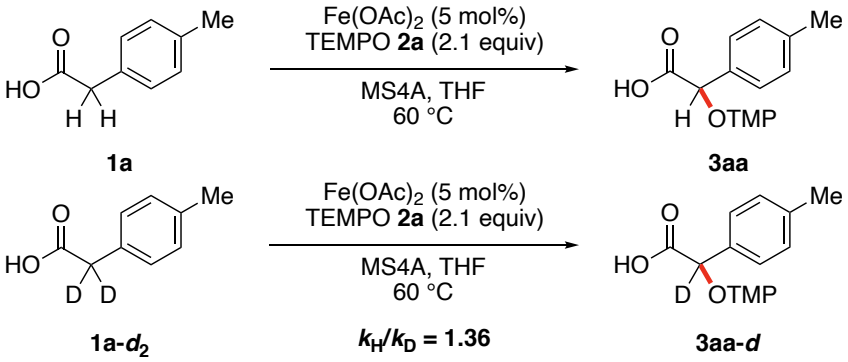
1a **3aa**

1a-*d*$_2$ **3aa-*d***

最適条件を用いて反応初速度の測定を行ったところ、k_H/k_D 値は 2.01 となった。この結果から、エノラート化の過程は律速段階への寄与が大きいと考えられる。

次に、配位子の効果についての知見を得るために、配位子非添加条件で α-軽水素カルボン酸 **1a** と α-重水素カルボン酸 **1a-*d*$_2$** を用いた際の反応初速度をそれぞれ測定して k_H/k_D 値を算出した(Scheme 1-18)。

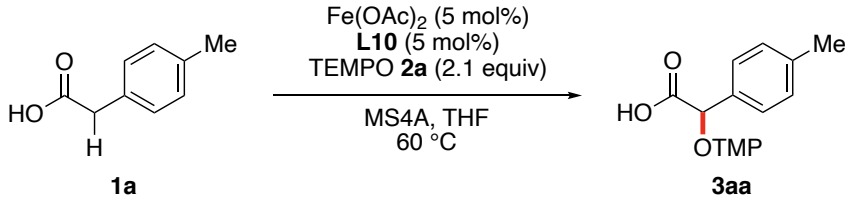
Scheme 1-18. Parallel Kinetic Isotope Effect without **L10**



配位子非添加条件で反応初速度の測定を行ったところ、k_H/k_D 値は 1.36 となった。仮に配位子の添加によりエノラート化の過程が促進されるのであれば、配位子非添加条件での k_H/k_D 値は最適条件よりも大きくなるはずである。しかし、実際は最適条件と比較して k_H/k_D 値が小さくなったことから、配位子の添加により促進される過程はエノラート化以外の過程であると考えられる。

1-5-5. モレキュラーシーブスの役割

1-5-1 の結果から、二価の鉄を再酸化するために消費される TEMPO が、1 分子で 3 電子及び 3 プロトンを受け取り、N–O 結合の還元が起こると同時に H_2O が生成することが示唆されていた。このことからモレキュラーシーブスは本反応において脱水剤として機能していることが示唆されていた。しかし、1-5-2 の結果から、モレキュラーシーブスは H_2O の生成量が少ない反応の初期段階から反応の進行に大きな影響を与えており、脱水剤としてだけでなく、その他の機能も有していることが示唆されていた。そこで、モレキュラーシーブスの役割を解明するために、モレキュラーシーブスの添加量が反応初速度に与える影響について調査を行った(Figure 1-1)。



1a **3aa**

MS4A (mg/mL)	*d* [**3aa**]/*d* t (M/min)
25	0.0004163
50	0.0005475
75	0.0007921
100	0.0009982

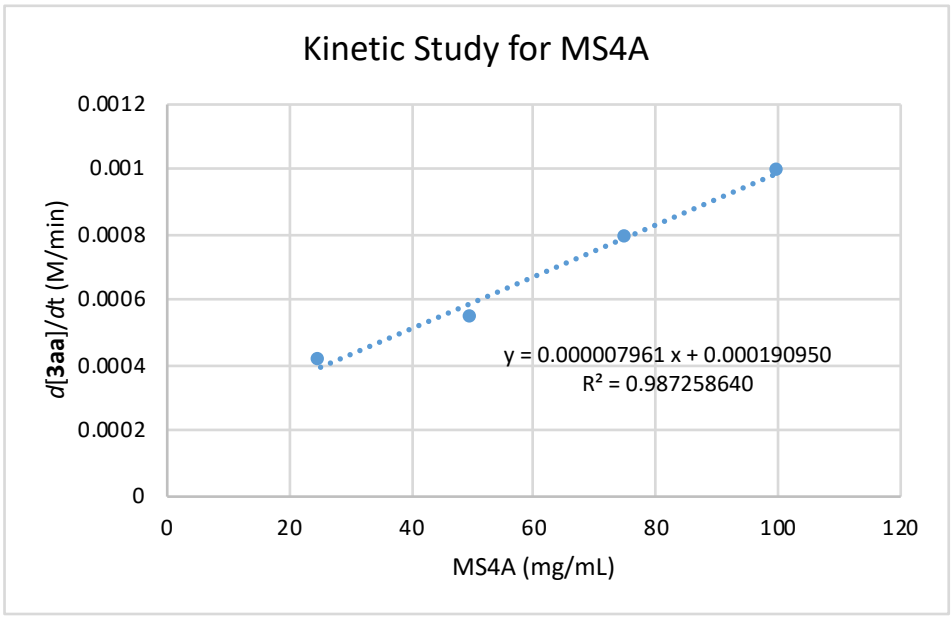


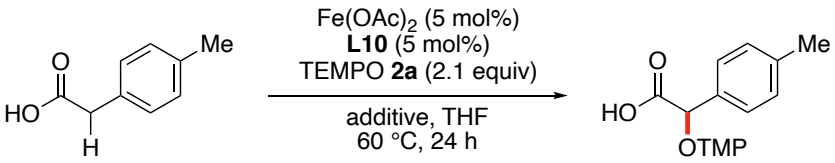
Figure 1-1. Kinetic Study for MS4A

モレキュラーシーブスの添加量が増加するにつれて反応初速度が大きくなることが明らかとなった。この結果から、モレキュラーシーブスは律速段階であるエノラート化の過程を促進していることが示唆されており、モレキュラーシーブスが脱水剤以外の機能を有して

いることがより強く示唆された。そこで次に、モレキュラーシーブスによる反応の促進に関する機能を解明するための実験を行った(Table 1-14)。

モレキュラーシーブスは二酸化ケイ素等からなる骨格部分とアルカリ金属塩等の無機塩から構成されているため [18]、無機塩由来の成分がエノラート化の促進に寄与しているとの仮説を立てた。

Table 1-14. Effect of Alkali Metal Salts



1a
0.20 mmol

3aa

entry	additive	yield (%)
1	MS4A (100 mg)	>99
2	—	5
3	Na_2SO_4 (100 mg)	10
4	NaOAc (20 mol%)	64
5	KOAc (20 mol%)	47
6	$Ca(OAc)_2 \cdot H_2O$ (20 mol%)	8
7	NaOTf (20 mol%)	11

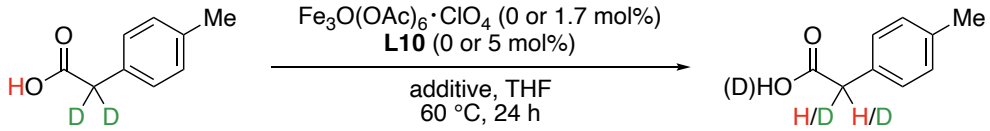
MS3A: K_2O (0.4), Na_2O (0.6) + framework
MS4A: Na_2O (1) + framework
MS5A: CaO (0.8), Na_2O (0.2) + framework

モレキュラーシーブスを添加する最適条件では目的物が定量的に得られた(entry 1)。一方、モレキュラーシーブスを添加しない条件では反応はほとんど進行しなかった(entry 2)。脱水剤として Na_2SO_4 を添加したところ、モレキュラーシーブスを添加しない条件と同様の結果となった(entry 3)。この結果から、モレキュラーシーブスは脱水剤以外の働きによって本反応を促進していることが再度示唆された。酢酸ナトリウムや酢酸カリウムを添加した条件で収率の向上が見られた(entries 4,5)。一方で、酢酸カルシウムやトリフルオロメタンスルホン酸ナトリウムを添加した条件では収率の向上は見られなかった(entries 6,7)。これらの結果から、基質のカルボン酸とモレキュラーシーブスから生じたアルカリ金属カルボキシラートが Brønsted 塩基として機能することによって、律速段階であるエノラート化の過程が促進されていると考えた。

そこで次に、α 位を重水素置換した基質 **1a-*d*₂** を用いて、エノラート化に対するアルカリ金属カルボキシラートの影響を確認した(Table 1-15)。α 位を重水素置換した基質はエノラー

ト化が進行すると逆反応によってプロトン化され、重水素化率が低下すると考えた。また、本反応では二価の酢酸鉄と TEMPO によって三価の鉄が生じることを想定しているため、三価の酢酸鉄として μ-oxo-三核錯体を用いて実験を行った。

Table 1-15. Effect of Alkali Metal Carboxylate for Enolization



1a-*d*$_2$ (97% D)
0.20 mmol

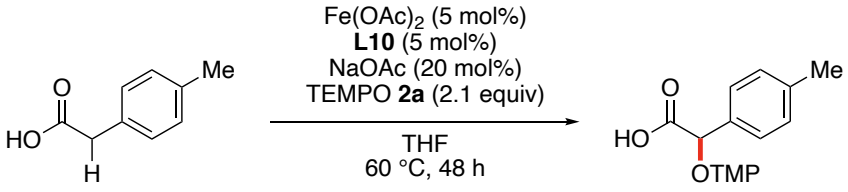
1a/1a-*d*/1a-*d*$_2$

entry	catalyst	additive	(H/H+D %)
1	$Fe_3O(OAc)_6$·ClO_4/**L10**	MS4A (100 mg)	51
2	$Fe_3O(OAc)_6$·ClO_4/**L10**	—	6
3	—	MS4A (100 mg)	6
4	—	—	3
5	$Fe_3O(OAc)_6$·ClO_4/**L10**	NaOAc (20 mol%)	37
6	—	NaOAc (20 mol%)	4

鉄触媒とモレキュラーシーブスを同時に用いる条件で α 位の重水素化率の低下が見られた(entry 1)。ネガティブコントロールとして鉄触媒のみを用いる条件、モレキュラーシーブスのみを用いる条件、両方を除いた条件で実験を行ったところ、α 位の重水素化率が低下は見られなかった(entries 2–4)。これらの結果から、鉄触媒とモレキュラーシーブスの組み合わせがカルボン酸の効率的なエノラート化に重要であることが明らかとなった。次に、鉄触媒と酢酸ナトリウムを同時に用いる条件で実験を行ったところ、α 位の重水素化率の低下が見られた(entry 5)。ネガティブコントロールとして酢酸ナトリウムのみを用いる条件でも実験を行ったが、α 位の重水素化率の低下は見られなかった(entry 6)。この結果から、本反応は基質とモレキュラーシーブスから生じたアルカリ金属カルボキシラートが Brønsted 塩基として機能することによって律速段階であるエノラート化の過程が促進されていることと、鉄とアルカリ金属による異種金属協働型エノラート化機構によってカルボン酸の効率的なエノラート化が進行することが示唆された。

モレキュラーシーブスの代わりに触媒量の酢酸ナトリウムを用い、反応時間を 48 時間とすることで 85%の収率で目的物を得ることができた(Scheme 1-19)。このように、本反応ではアルカリ金属カルボキシラートが Brønsted 塩基触媒として機能しており、化学量論量の外部塩基を必要としないカルボン酸のエノラート化を世界で初めて達成した。

Scheme 1-19. Catalytic Fe/Na Bimetallic Conditions



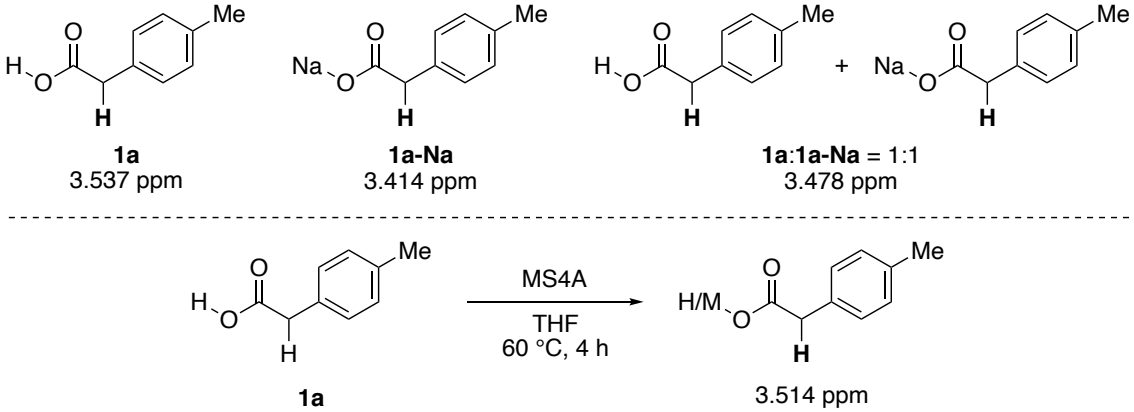
1a
0.20 mmol

3aa
85%

1-5-6. ^{1}HNMR 実験

カルボン酸とモレキュラーシーブスからアルカリ金属カルボキシラートが生成することを確認するために ^{1}H NMR 実験を行った(Scheme 1-20)。

Scheme 1-20. ^{1}H NMR Analysis of Carboxylic Acid and Sodium Salt



1a
3.537 ppm

1a-Na
3.414 ppm

1a:**1a-Na** = 1:1
3.478 ppm

1a

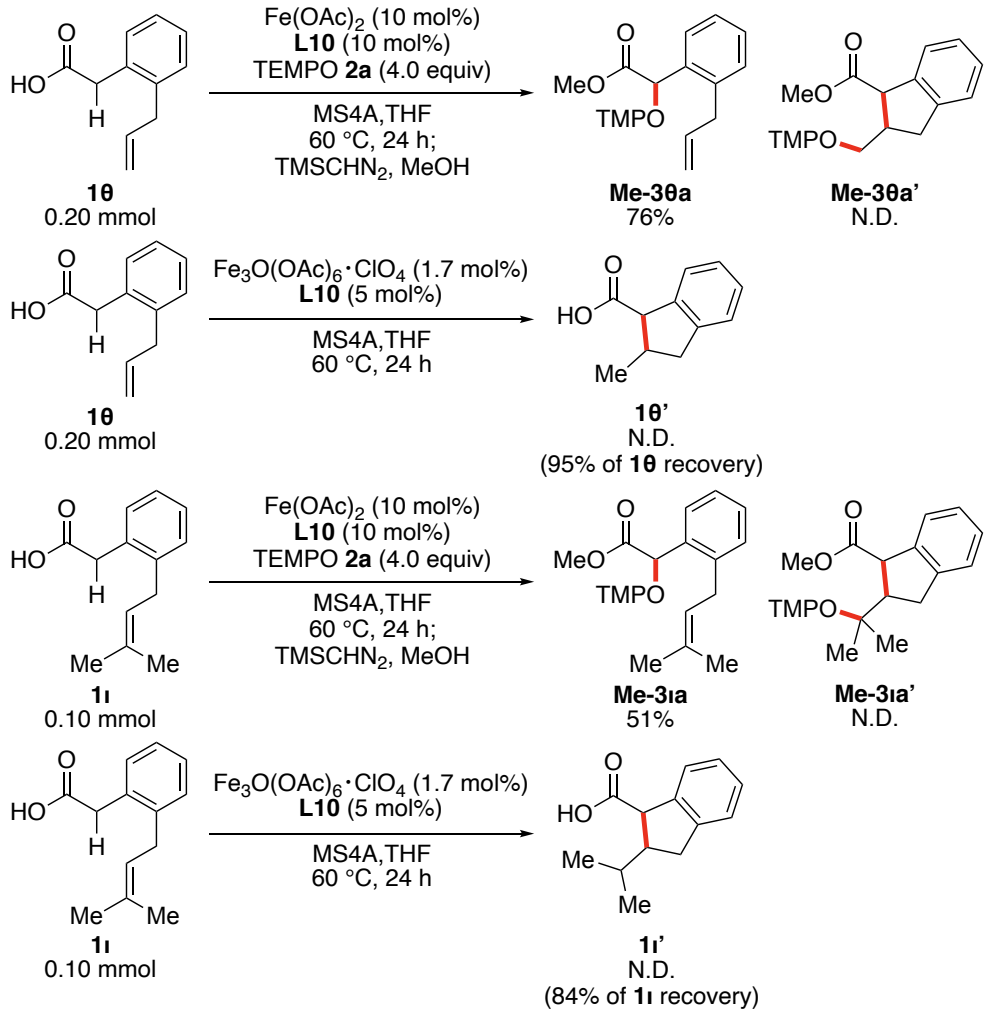
3.514 ppm

カルボン酸 **1a** の α 位のピークは 3.537 ppm、ナトリウム塩 **1a-Na** の α 位のピークは 3.414 ppm に見られた。また、カルボン酸 **1a** とナトリウム塩 **1a-Na** を 1:1 で混合したサンプルではこれらのほぼ中央となる 3.478 ppm に単一のピークが見られた。カルボン酸をモレキュラーシーブス条件に伏したサンプルでは 3.514 ppm に単一のピークを示し、カルボン酸からの高磁場シフトが見られたことから、カルボン酸とモレキュラーシーブスからアルカリ金属カルボキシラートが生成していると考えられる。

1-5-7. ラジカルクロック実験

活性中間体についての知見を得るためにラジカルクロック実験を行った(Scheme 1-21)。

Scheme 1-21. Radical Clock Experiments

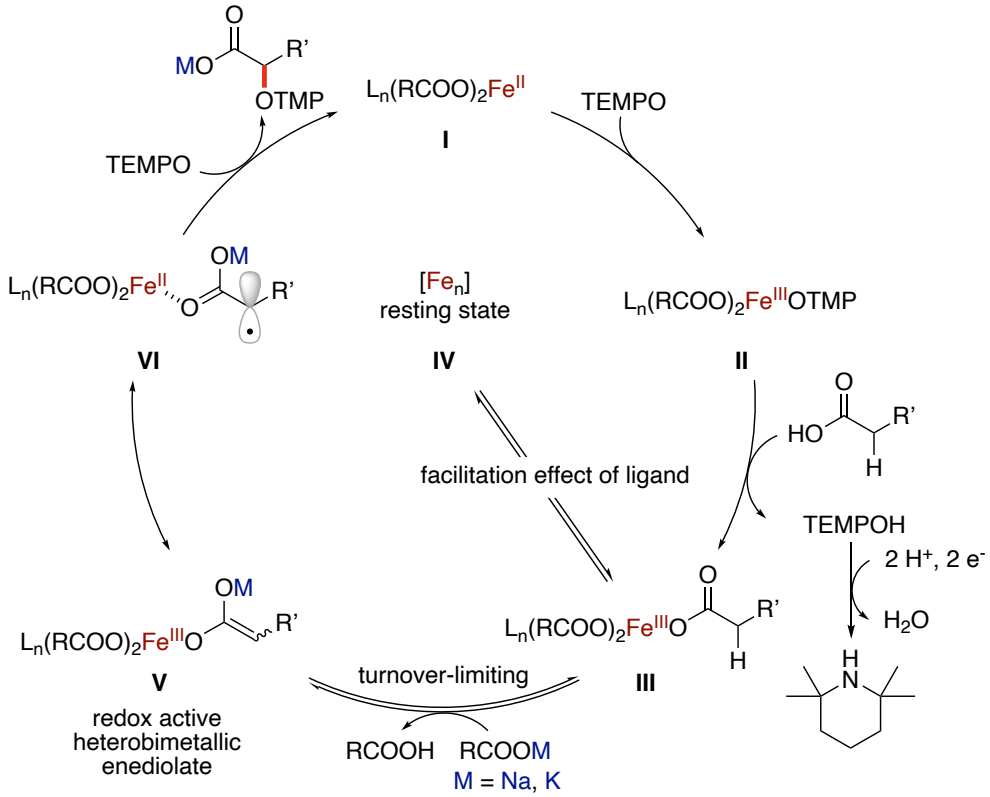


1θ や **1ι** を基質とした際に、ラジカル種の生成を示唆する環化生成物の **Me-3θa'**や **Me-3ιa'** は観測されず、α-酸化生成物である **Me-3θa** や **Me-3ιa** のみが生成した。また、三価の酢酸鉄条件下、TEMPO を加えない条件においても環化生成物や基質の二量化は観測されなかった。このことから、本反応の活性種は Fe^{III}-エノラート種との共鳴により安定化された Fe^{II}-α-ラジカル種であると考えられる。

1-5-8. 推定反応機構

以上の反応解析実験の結果を踏まえた推定の反応機構を示す(Scheme 1-22)。

Scheme 1-22. Proposed Catalytic Cycle



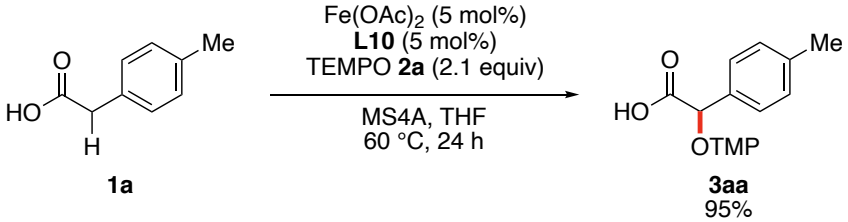
初めに、Fe^{II} 種 **I** が TEMPO によって酸化されて Fe^{III} 種 **II** が生成する。次に、カルボン酸との交換によってカルボン酸 Fe^{III} 種 **III** が生成する。このカルボン酸 Fe^{III} 種 **III** は休止状態の多核の鉄種 **IV** と平衡状態にあると考えている。配位子 **L10** は、単核のカルボン酸 Fe^{III} 種 **III** の形成を促進していると考えている。続いてカルボン酸とモレキュラーシーブスから生じたアルカリ金属カルボキシラートによりエノラート化が進行し、レドックス活性な鉄/アルカリ金属の異種金属型エノラート **V** が生成する。この Fe^{III}-エノラート種は Fe^{II}-α-ラジカル種 **VI** と共鳴関係にあり、TEMPO とのカップリングにより Fe^{II} 種 **I** を再生しながら生成物が得られる。また、カルボン酸 Fe^{III} 種 **III** が生成する際に生じる TEMPOH は更なる還元を受けることで N–O 結合が開裂し、2,2,6,6-テトラメチルピペリジンが生成する。

1-6. 結論

1-6-1. 結論

ラジカル機構によるカルボン酸の直接的触媒的 α-酸化反応の開発を行い、酸素源試薬として TEMPO を用いることで過剰酸化反応を抑制した α-ヒドロキシ酸誘導体の合成を達成した(Scheme 1-23)[19]。本反応はカルボン酸の活性化に外部塩基を必要としない上に、触媒量 1 mol%での目的物の合成を達成しており、温和かつ環境調和性に優れた反応であると言える。また、本反応はエステルやアミド、α-アルキルケトンの存在下においてもカルボン酸のみの α-酸化反応が可能であり、本触媒系が有するカルボン酸に対する高い化学選択性が明らかとなった。さらに、本反応生成物は合成化学的に有用な α-ヒドロキシエステルや α-ヒドロキシアミド、1,2-ケトエステル、1,2-ケトアミドに変換可能であった。

Scheme 1-23. Direct Catalytic α-Oxidation of Carboxylic Acid



1a **3aa** 95%

1-6-2. 今後の展望および課題

本研究では、鉄とアルカリ金属が協働するカルボン酸の新規エノラート化法の開発に成功した。本反応はラジカル機構によるカルボン酸の触媒的 α-官能基化を達成した世界初の例であり、本触媒系を基盤として従来の二電子型反応では困難な β 位四級炭素構築反応等への展開が期待できる。また、本手法は Brønsted 塩基触媒によるカルボン酸のエノラート化を達成した触媒系としても世界初であった。一方で、本触媒系は基質適用範囲が比較的エノラート化しやすい α-アリールカルボン酸または β,γ-不飽和カルボン酸に限定されており、脂肪族カルボン酸への適用が困難な点に改善の余地を残していた。その原因として、中間体であるジアニオン性の異種金属型エンジオラートが不安定であることが考えられた。そのため、モノアニオン性エノラートを活性中間体とする触媒系へと発展させることで脂肪族カルボン酸への基質適用範囲の拡大が可能であると考えた。このような着想のもと、第 2 章では酸無水物触媒を用いた新規触媒系の開発に取り組んだ。

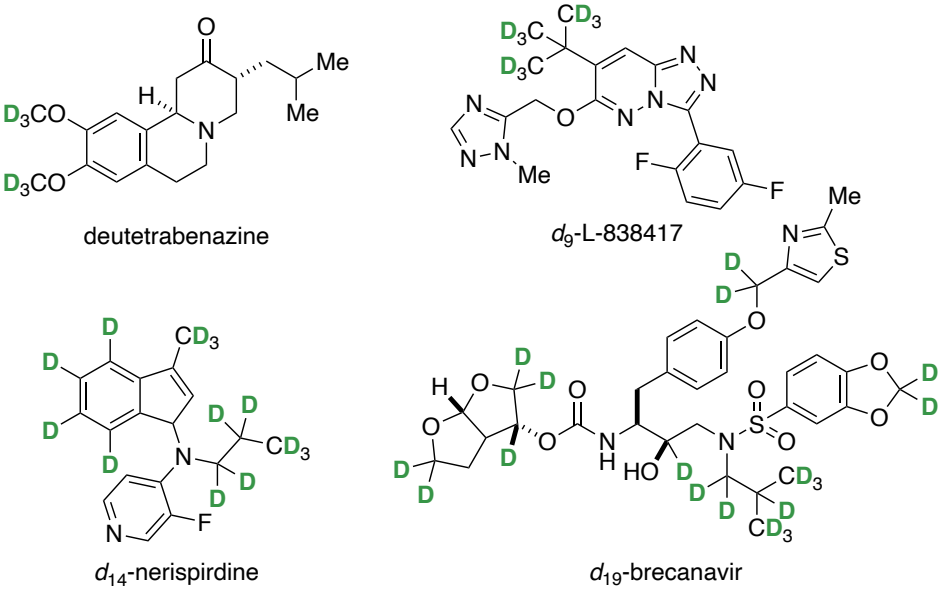
第 2 章　カルボン酸の触媒的 α-重水素化反応

2-1. 序論

2-1-1. 重水素置換化合物の有用性

医薬品への重水素の導入により代謝安定性の向上などによる体内動態の改善が可能である[20]。2017 年にはデューテトラベナジンが世界初の含重水素医薬品として FDA に承認された。そのような背景から重水素置換は創薬研究において近年注目を集めている(Figure 2-1)。

Figure 2-1. Examples of Deuterated Pharmaceuticals



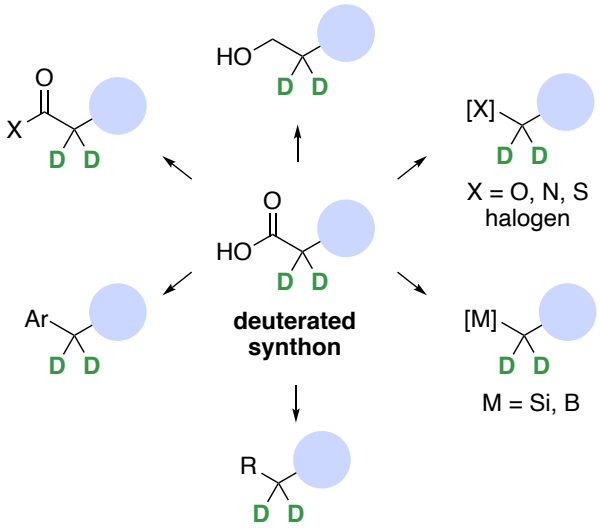
また、重水素標識された化合物は NMR や MS、D-MRI、ラマン分散イメージングによる解析が可能であり、薬物動態のモニタリングや代謝物の解明などのツールとして利用されている[21]。また、有機合成化学においても重水素は保護基の安定性向上や反応機構解析等に利用されている[22,23]。そのため、重水素置換化合物のケミカルスペース拡張は創薬研究や有機合成化学をはじめとした諸分野でのイノベーションの礎となりうる。

2-1-2. 合成素子としてのカルボン酸

カルボン酸は天然物や非ステロイド性抗炎症薬(NSAIDs)をはじめとする医薬品に含まれるユビキタスな構造であるのみならず、縮合によってエステルやアミド、ヒドリド還元によってアルコール、Curtius 転位によってアミンなど、様々な官能基へ変換可能な合成素子としても重要である。近年では、遷移金属やフォトレドックス触媒を用いたレドックス反応でのアルキルラジカル前駆体としての利用も広まりつつある[1]。そのため、重水素化カルボン酸は含重水素合成素子として有用であると考えられ、カルボン酸の化学選択的かつ温和な重水素化法を開発することで様々な重水素置換分子を迅速に合成可能になることが期待で

きる(Figure 2-2)。

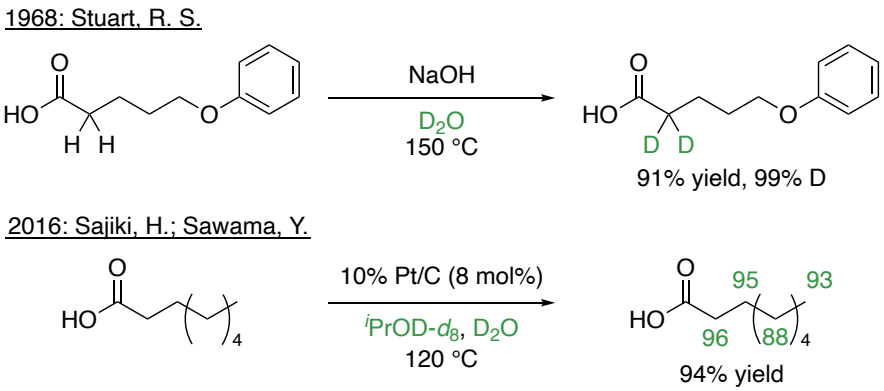
Figure 2-2. Versatility of Carboxylic Acids



2-1-3. カルボン酸の重水素化における従来法

カルボン酸に重水素を導入するための手法として、温和で触媒的な反応の開発は長年の課題であった(Scheme 2-1)[24]。モノ重水素化はリチウムジイソプロピルアミンなどの強塩基でエノラートを形成し、重水素試薬で処理することで達成可能である。一方で、ジ重水素化には高い反応温度で強塩基を用いる過酷な条件が必要であった[24a]。Sajiki、Sawama らによって報告された触媒法ではカルボン酸の全重水素置換が可能であるものの、100 °C を越える高温条件と貴金属が必要である上にカルボン酸の α 位選択的な重水素化は達成されていなかった[24b–24d]。

Scheme 2-1. Previous Reports about Deuteration of Carboxylic Acids

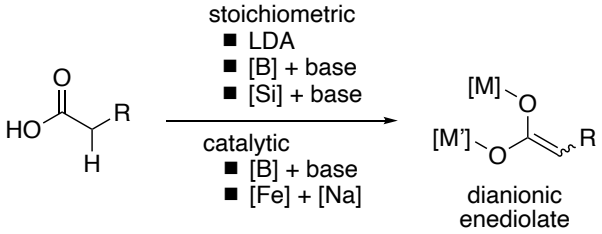


2-1-4. カルボン酸の触媒的エノラート化

カルボン酸のエノラート化を達成するためには、カルボキシラートのエノラート化によってジアニオン性のエンジオラートを生成する必要がある(Scheme 2-2)。そのため、塩基の

みでカルボン酸のエノラート化を行うためにはリチウムアミドなどの強塩基を 2.0 当量以上使用する必要があった[3–5]。その後、Lewis 酸と弱塩基を併用する温和なエノラート化法が開発された[6–8]。本手法では化学量論量または触媒量のホウ素やケイ素と、化学量論量の Brønsted 塩基を用いて効率的に 1,1-エンジオラートを生成し、続いてアルデヒドやイミンなどの求電子剤を添加することでアルドール反応や Mannich 反応が開発された。さらに発展的な触媒系として、我々はアルカリ金属カルボキシラートを Brønsted 塩基触媒として利用することで化学量論量の外部塩基を必要としないカルボン酸のエノラート化を開発し、第 1 章に記した[19]。本触媒系では鉄とアルカリ金属の異種金属協働型機構によってカルボン酸の効率的なエノラート化が可能である一方で、活性中間体が不安定なジアニオン性エノラートであるために基質適用範囲が α-アリールカルボン酸または β,γ-不飽和カルボン酸に限定される点に改善の余地を残していた。

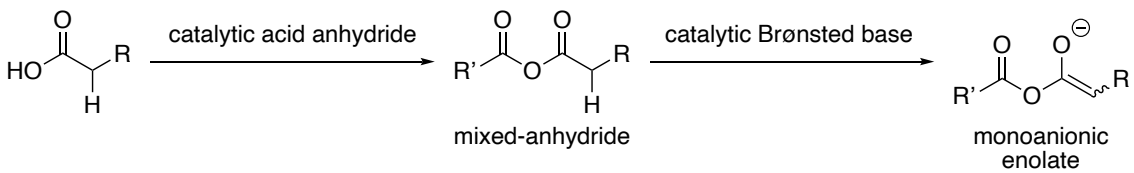
Scheme 2-2. Activation Modes of Carboxylic Acid



2-1-5. 本研究の目的

本研究では、Brønsted 塩基触媒によるエノラート化法の脂肪族カルボン酸への基質適用範囲の拡大を目的とした。そのために系中で酸無水物を形成し、モノアニオン性エノラートを活性中間体とする戦略を考案した(Scheme 2-3)。そして、本手法により生成したエノラートを重水素化することで、これまで困難であった温和な条件でのカルボン酸のジ重水素化が実現できると考えた。カルボン酸は天然物や医薬品の構造に数多く見られることから、late-stage での重水素導入に適用可能な手法となることを期待した。また、カルボン酸は合成素子としても有用であることから、生成物の α-重水素カルボン酸を多様な変換反応に適用することで複雑な重水素置換分子の容易な合成が可能となることを期待した。

Scheme 2-3. Anhydride-Mediated Activation Strategy for Carboxylic Acids



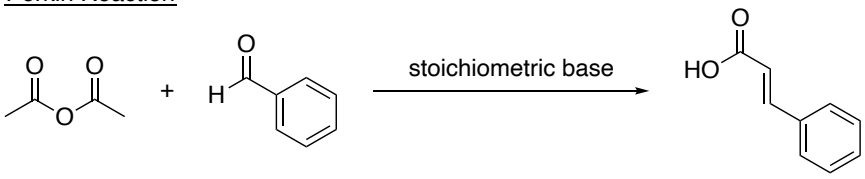
2-2. 反応設計と初期検討

2-2-1. 反応設計

系中でモノアニオン性の酸無水物エノラートを形成するために、基質のカルボン酸を系中で酸無水物構造に誘導する必要があると考えた。そのためにカルボン酸無水物を用いることで基質のカルボン酸との酸無水物の組み換え反応が起こり、混合酸無水物が生成すると考えた。また、生成した混合酸無水物をエノラート化するための Brønsted 塩基としてアルカリ金属カルボキシラートが利用できると考えた。このような反応設計のもと、基質のカルボン酸、酢酸無水物、酢酸カリウムをそれぞれ 1.0 当量ずつ用いる条件を初期条件として、以降に記す初期検討を行った。なお、酸無水物のエノラート化を利用した反応として Perkin 反応が知られており、本反応では酸無水物と芳香族アルデヒドからケイ皮酸誘導体を合成することが可能である(Scheme 2-4)[25]。

Scheme 2-4. Stoichiometric Enolization of Anhydride

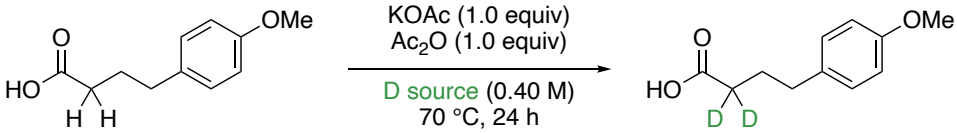
Perkin Reaction



2-2-2. 重水素源の検討

初めに重水素源の検討を行った(Table 2-1)。

Table 2-1. Screening of Deuterium Sources



13a **13a-d_2**

entry	D source (equiv)	yield (%)	deuterated ratio (% D)
1	D_2O (138)	not determined	<5
2	methanol-d_4 (55)	>95	6
3	$CDCl_3$ (31)	90	<5
4	DMSO-d_6 (35)	not determined	<5
5	acetonitrile-d_3 (48)	>95	<5
6	**acetone-d_6 (34)**	**>95**	**95**

Yields were shown as incorporated yields for carboxylic acid and acid anhydride.

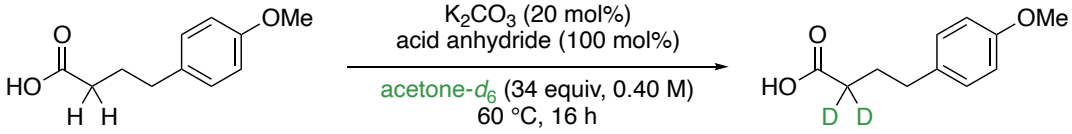
重水素源として D_2O、メタノール-d_4、クロロホルム-d、DMSO-d_6、アセトニトリル-d_3 を用いた場合、重水素はカルボン酸に導入されなかった(entries 1–5)。重水素源としてアセト

ン-d_6 を用いた場合にカルボン酸への重水素の導入が可能であった(entry 6)。アセトン-d_6 は酢酸カリウムによってエノラート化することで CH_3COOD を生成し、重水素源として機能していると考えられる。なお、アセトン(pK_a: 26.5)は DMSO (pK_a: 35.1)やアセトニトリル(pK_a: 31.3)と比較して酸性度が低く、エノラート化しやすい。

2-2-3. 酸無水物の検討

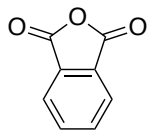
次に、触媒量の炭酸カリウムを塩基として用いて酸無水物の検討を行った(Table 2-2)。

Table 2-2. Screening of Acid Anhydrides

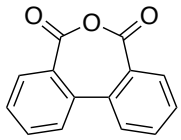


13a **13a-d_2**

entry	acid anhydride	deuterated ratio (% D)
1	Ac_2O	57
2	**Piv_2O**	**>95**
3	$(CF_3CO)_2O$	37
4	Bz_2O	18
5	phthalic anhydride	5
6	diphenic anhydride	6



phthalic anhydride



diphenic anhydride

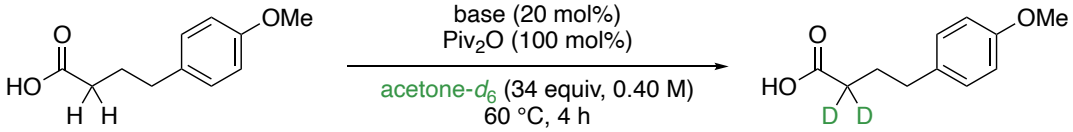
Deuterated ratios were determined after isolation by PTLC.

酢酸無水物を用いた条件において重水素化率は中程度であった(entry 1)。混合酸無水物を形成した際に基質だけでなく酢酸もエノラート化しうることや、その際に酢酸 α 位由来の軽水素が系中に放出されることが原因であると考えた。そこで次に、α-水素を持たないピバル酸無水物を用いたところ良好な重水素化率を達成した(entry 2)。一方で、ピバル酸無水物と同様に α-水素を持たないトリフルオロ酢酸無水物や安息香酸無水物を用いた条件では重水素化率は低かった(entry 3,4)。トリフルオロ酢酸無水物を用いた際に重水素化率が低かった原因として、系中で発生するトリフルオロ酢酸カリウム塩の Brønsted 塩基性が低いために混合酸無水物やアセトン-d_6 のエノラート化が効率的に進行しなかったことが考えられる。また、安息香酸無水物を用いた際に重水素化率が低かった原因として、系中で発生する安息香酸カリウム塩の溶解性が悪かったことが考えられる。また、環構造を持つ酸無水物を用いた際には重水素化反応はほとんど進行しなかった(entries 5,6)。

2-2-4. 塩基の検討

次に塩基の検討を行った(Table 2-3)。

Table 2-3. Screening of Bases



13a **13a-d_2**

entry	base	deuterated ratio (% D)
1	Li_2CO_3	<5
2	Na_2CO_3	29
3	**K_2CO_3**	**70**
4	Cs_2CO_3	69
5	K_3PO_4	50
6	KOPiv	29
7	CsOPiv	35
8	Et_3N	<5

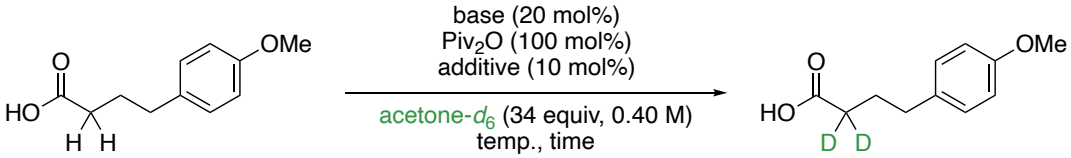
Deuterated ratios were determined after isolation by PTLC.

炭酸リチウムを用いた条件では反応はほとんど進行しなかった(entry 1)。炭酸ナトリウムを用いた条件では反応の進行は遅かった(entry 2)。炭酸カリウムまたは炭酸セシウムを用いた際に良好に反応が進行した(entries 3,4)。リン酸カリウムやピバル酸カリウム、ピバル酸セシウムを用いた条件では炭酸カリウムを用いた条件と比較して反応の進行は遅かった(entries 5–7)。有機塩基であるトリエチルアミンを用いた条件では反応はほとんど進行しなかった(entry 8)。

2-2-5. 添加剤の検討

DMAP は酸無水物によるアルコール等のアシル化反応において触媒として広く利用されている [26]。そこで次に、酸無水物交換の促進を目的とした活性化剤として DMAP を添加して実験を行った(Table 2-4)。その際、DMAP の効果を評価するために低温条件で対照実験を行った。

Table 2-4. Experiment with an Additive



13a **13a-d_2**

entry	base	additive	temp. (°C)	time (h)	deuterated ratio (% D)
1	K_2CO_3	—	60	4	70
2	K_2CO_3	—	40	20	58
3	K_2CO_3	—	rt	20	26
4	**K_2CO_3**	**DMAP**	**rt**	**20**	**>95**

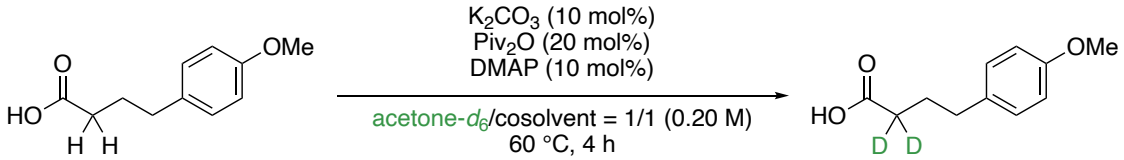
Deuterated ratios were determined after isolation by PTLC.

DMAP 非添加条件において、反応温度の低減に伴って反応速度が低下した(entries1–3)。室温条件で酸無水物の活性化剤として DMAP を添加したところ、反応速度の劇的な向上が観測された(entries 3,4)。

2-2-6. 溶媒の検討

次に、共溶媒の検討を行った(Table 2-5)。

Table 2-5. Screening of Cosolvents



13a **13a-d_2**

entry	cosolvent	deuterated ratio (% D)
1	toluene	63
2	DCE	57
3	THF	79
4	MeCN	72
5	**DMF**	**>95**
6	**DMSO**	**>95**
7	**acetone-d_6 (0.20 M)**	**>95**

Deuterated ratios were determined after isolation by PTLC.

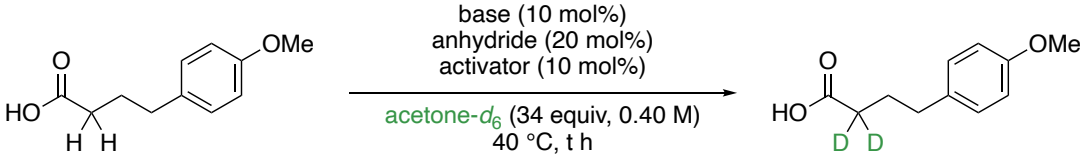
極性の低いトルエンやジクロロメタンを用いた場合、反応の進行は遅かった(entries 1,2)。中程度の極性を持つ THF やアセトニトリルを用いた場合、反応速度に改善が見られた(entries 3,4)。高極性溶媒である DMF や DMSO を用いた場合、反応は良好に進行した(entries 5,6)。共溶媒を加えずに実験を行ったところ、反応は良好に進行した(entry 7)。そのため、溶解性の良好な基質を用いる際には共溶媒を加えず、溶解性の悪い基質を用いる際には DMF や DMSO を共溶媒として用いることとした。

2-3. 反応条件の検討

2-3-1. 反応条件の最適化

初期検討の結果から、塩基、酸無水物、酸無水物活性化剤の組み合わせが重要であることが明らかとなった。そこで、上記の三成分をそれぞれ触媒量用いた条件で反応条件の最適化を行った(Table 2-6)。その際、初期検討の結果から、炭酸カリウム、ピバル酸無水物、DMAPを用いる条件を基本の条件とした。

Table 2-6. Optimization Study



13a **13a-d_2**

entry	base	anhydride	activator	time (h)	deuterated ratio (% D)
1	Na_2CO_3	Piv_2O	DMAP	12	57
2	**K_2CO_3**	**Piv_2O**	**DMAP**	**12**	**79**
3	Cs_2CO_3	Piv_2O	DMAP	12	69
4	K_3PO_4	Piv_2O	DMAP	12	74
5	KOPiv	Piv_2O	DMAP	12	58
6	Et_3N	Piv_2O	DMAP	12	20
7	K_2CO_3	Ac_2O	DMAP	12	53
8	K_2CO_3	Bz_2O	DMAP	12	37
9	K_2CO_3	$(CF_3CO)_2O$	DMAP	12	<5
10	K_2CO_3	succinic anhydride	DMAP	12	<5
11	K_2CO_3	Piv_2O	pyridine	12	7
12	K_2CO_3	Piv_2O	1-methylimidazole	12	14
13	K_2CO_3	Piv_2O	quinuclidine	12	29
14	K_2CO_3	Piv_2O	DABCO	12	20
15	K_2CO_3	Piv_2O	$^nBu_3P$	12	12
16	K_2CO_3	Piv_2O	DMAP	24	94
17	—	Piv_2O	DMAP	24	21
18	K_2CO_3	—	DMAP	24	<5
19	K_2CO_3	Piv_2O	—	24	13

Deuterated ratios were determined after isolation by PTLC.

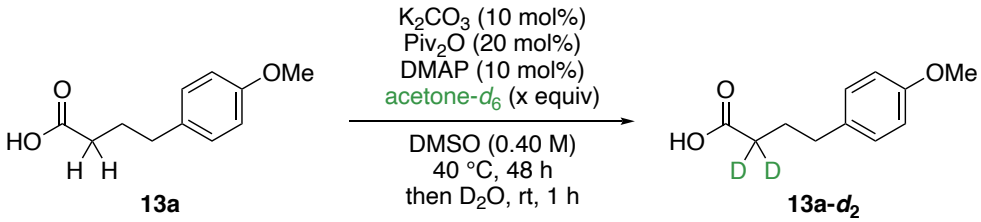
はじめに塩基の検討を行った(entries 1–6)。炭酸塩を用いて金属カチオン（ナトリウム、カリウム、セシウム）の比較を行ったところ、炭酸カリウムを用いた条件が最も良好な結果を示した(entries 1–3)。そこで次に、リン酸カリウム、ピバル酸カリウムを用いてカリウム塩の

検討を行ったところ、炭酸カリウムを上回る結果は得られなかった(entries 4,5)。有機塩基であるトリエチルアミンを用いた条件では反応はほとんど進行しなかった(entry 6)。次に酸無水物の検討を行った(entries 2,7–10)。酢酸無水物や安息香酸無水物を用いた条件でも反応は進行したが、ピバル酸無水物を上回る結果は得られなかった(entries 2,7,8)。トリフルオロ酢酸無水物やコハク酸無水物を用いた条件では反応はほとんど進行しなかった(entries 9,10)。次に活性化剤の検討を行ったところ、DMAP を用いた条件でのみ良好な加速効果が見られ、ピリジン、1-メチルイミダゾール、キヌクリジン、DABCO、トリブチルホスフィンを用いた際には反応はほとんど進行しなかった(entries 2,11–15)。反応時間を 12 時間から 24 時間に延長することで 94%の重水素化率を達成した(entry 16)。また、各成分に関してネガティブコントロール実験を行ったところ、本反応では塩基、酸無水物、求核触媒の三成分の組み合わせが重要であることが明らかとなった(entries 17–19)。

2-3-2. 重水素源の低減化

DMSO を溶媒として用いた条件で、アセトン-d_6 の低減化を検討した(Table 2-7)。

Table 2-7. Reducing Amount of the Deuterium Source



13a **13a-d_2**

entry	acetone-d_6 (equiv)	deuterated ratio (% D)
1	15	95
2	10	94
3	5	84

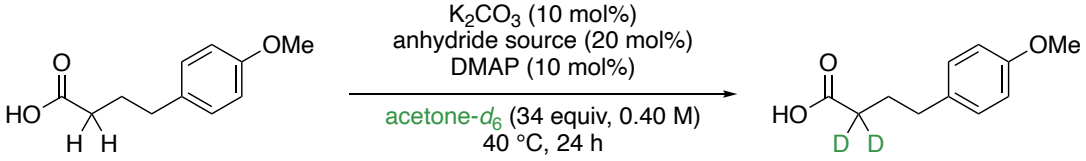
Deuterated ratios were determined after isolation by PTLC.

アセトン-d_6 を 10 当量以上用いた際に良好な重水素化率を達成することができた(entries 1,2)。一方で、アセトン-d_6 を 5 当量に低減すると重水素化率は 84%に低下した(entry 3)。

2-3-3. その他の酸無水物源

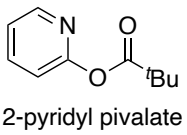
本反応ではカルボン酸無水物だけでなく、Boc_2O や縮合剤、ピリジルエステルが無水物源として利用可能であり、重水素化反応の進行が確認できた(Table 2-8, entries 1–4)。一方で、*p*-トリルエステルを用いた際には重水素化反応は進行しなかった(entry 5)。

Table 2-8. Other Acid Anhydride Sources

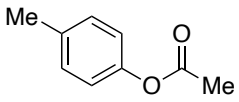


13a **13a-d_2**

entry	anhydride source	deuterated ratio (% D)
1	Piv_2O	94
2	Boc_2O	69
3	DCC	70
4	2-pyridyl pivalate	30
5	*p*-tolyl acetate	0



2-pyridyl pivalate



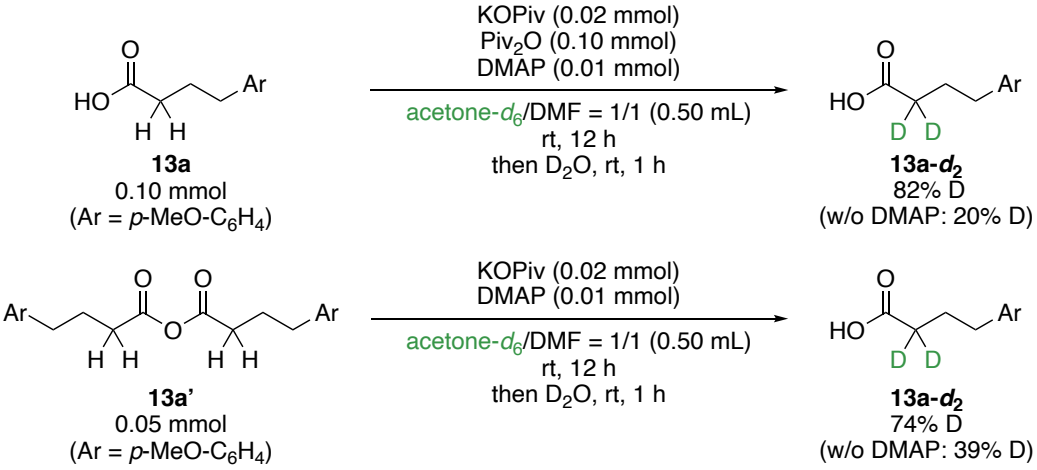
p-tolyl acetate

Deuterated ratios were determined after isolation by PTLC.

2-3-4. 反応機構の解析

本反応では、酸無水物交換過程の促進を目的として DMAP を添加していた。一方で、ベンゾテトラミゾールなどの求核触媒は酸無水物を活性化することでエノラート化を促進することが報告されている[27]。そこで、DMAP の役割について知見を得るために、以下のコントロール実験を行った(Scheme 2-5)。

Scheme 2-5. Control Experiments for Mechanistic Analysis



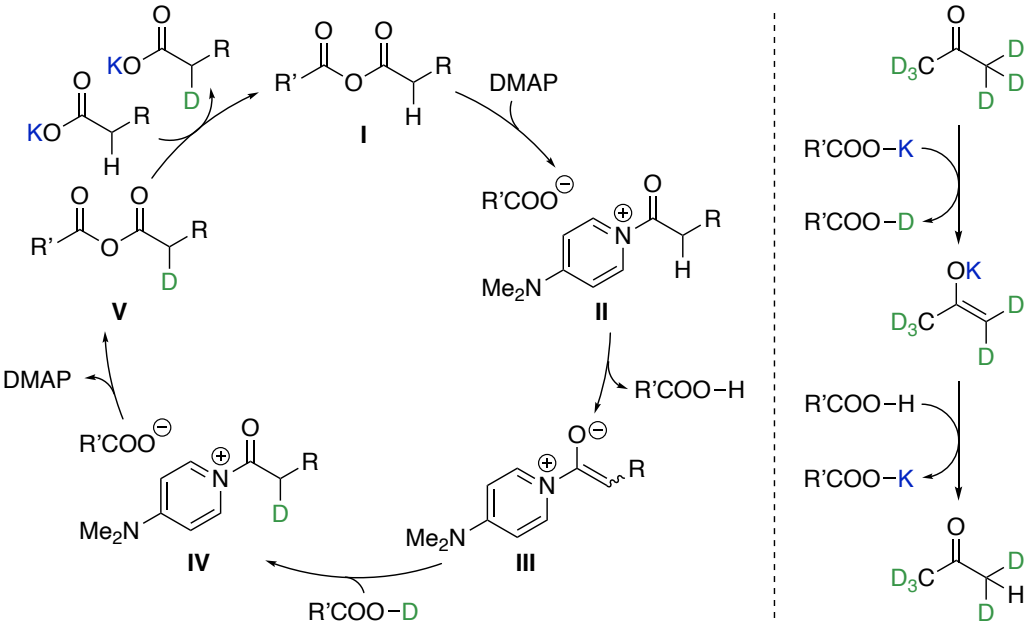
カルボン酸 **13a** とピバル酸無水物を用いた条件に DMAP を添加した条件では重水素化率は 82%で、DMAP を添加しない条件では重水素化率は 20%であった。また、酸無水物 **13a'**

を原料とした条件に DMAP を添加した条件では重水素化率は 74%で、DMAP を添加しない条件では重水素化率は 39%であった。このように、酸無水物 **13a'**を原料とした条件においても DMAP の添加によって反応の促進が観測されたことから、DMAP はエノラート化のステップを促進することが示唆されている。一方で、DMAP が酸無水物交換過程を促進するかについては本実験からは議論できないため、今後さらなる検討が必要である。

2-3-5. 推定反応機構

推定の反応機構を以下に示す(Scheme 2-6)。

Scheme 2-6. Proposed Catalytic Cycle



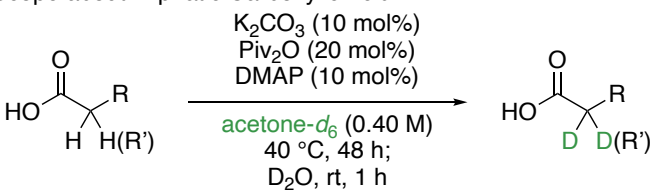
カルボン酸と酸無水物触媒から形成された混合酸無水物 **I** に対して DMAP が作用することで、アシルピリジニウム **II** が生成する。次に、**II** がエノラート化することによってピリジニウムエノラート **III** が生成する。ピリジニウムエノラート **III** はアルカリ金属カルボキシラートとアセトン-d_6 から生成した重水素カルボン酸(R'COO**D**)によって重水素化され、α-重水素アシルピリジニウム **IV** が生成する。その後、DMAP が脱離することで α-重水素混合酸無水物 **V** が生成し、酸無水物交換によって α-重水素カルボン酸が生成する。酸無水物交換の過程(**V**→**I**)は DMAP によって加速されている可能性があるものの、現時点で詳細は明らかとなっていない。

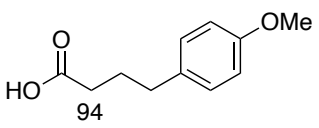
2-4. 基質の検討・変換反応

2-4-1. 基質一般性

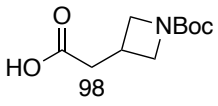
最適条件を用いて基質一般性の検討を行った(Table 2-9,2-10)。溶解性の悪い基質を用いる際には共溶媒として DMSO や DMF を加えた。

Table 2-9. Substrate Scope about Aliphatic Carboxylic Acid

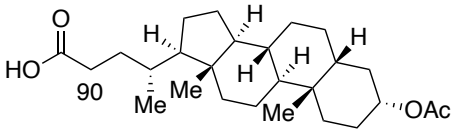




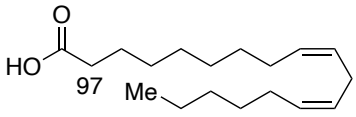
13a-d_2
98% yield
86% yield, 97% D[a]



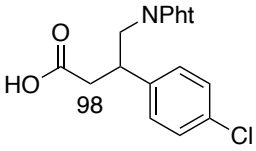
13b-d_2
90% yield



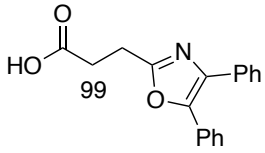
13c-d_2 (Lithocholic acid)
91% yield (w/ DMSO)



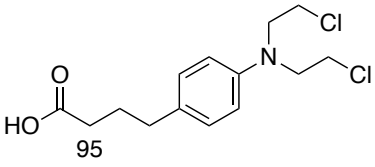
13d-d_2 (Linoleic acid)
>99% yield (60 °C)



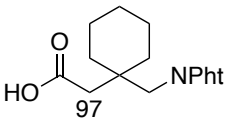
13e-d_2 (Baclofen)
93% yield (w/ DMSO)



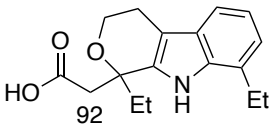
13f-d_2 (Oxaprozin)
96% yield (w/ DMSO)



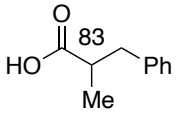
13g-d_2 (Chlorambucil)
97% yield



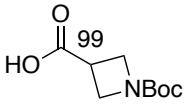
13h-d_2 (Gabapentin)
93% yield (60 °C, w/ DMSO)



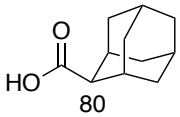
13i-d_2 (Etodolac)
88% yield (60 °C, w/ DMSO)



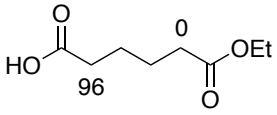
13j-*d*
92% yield (80 °C)



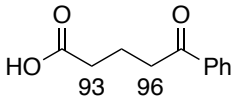
13k-*d*
83% yield (60 °C)



13l-*d*
90% yield (80 °C, w/ DMSO)



13m-d_2
88% yield



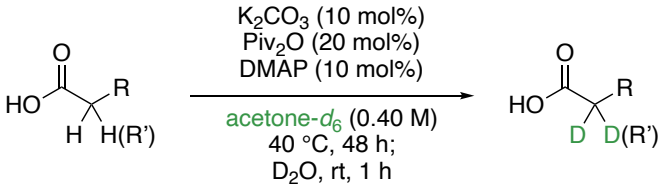
13n-d_4
76% yield (w/ DMSO)

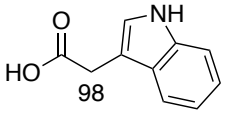
[a] Boc_2O was used instead of Piv_2O.

モデル基質の 4-(4-メトキシフェニル)酪酸を用いた場合、α 位の 94%が重水素置換されたカルボン酸を 98%の収率で得ることができた(**13a-d_2**)。また、Piv_2O の代わりに Boc_2O を用

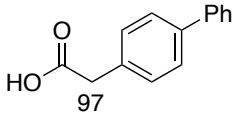
いた条件でもα位の97%が重水素置換されたカルボン酸を86%の収率で得ることができた。創薬ビルディングブロックとして近年注目を集めているアゼチジン構造が本反応では適用可能であった(**13b-*d*$_2$**)。天然物であるリトコール酸やリノール酸も適用可能であった(**13c-*d*$_2$**, **13d-*d*$_2$**)。バクロフェン、オキサプロジン、クロラムブシルといった様々な官能基を持つ医薬品に対してもα-重水素化反応は良好に進行した(**13e-*d*$_2$**–**13g-*d*$_2$**)。注目すべきことに、立体的に混雑したβ-四置換炭素のガバペンチンやエトドラクに対してもα-重水素化反応は良好に進行した(**13h-*d*$_2$**, **13i-*d*$_2$**)。α,α-二置換カルボン酸に対しても重水素の導入は可能であったものの、α-一置換カルボン酸と比較して反応の進行は遅かった(**13j-*d*$_2$**–**13l-*d*$_2$**)。分子内にエステル構造を持つカルボン酸を用いたところカルボン酸α位のみの化学選択的な重水素導入が可能であったものの、ケトン構造を有する基質を用いた場合ではカルボン酸α位とケトンα位の両方に重水素が導入された(**13m-*d*$_2$**, **13n-*d*$_4$**)。

Table 2-10. Substrate Scope about α-Aryl and α-Hetero-Substituted Carboxylic Acid

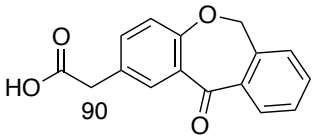




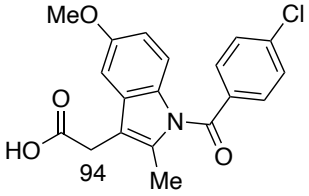
13o-d_2
71% yield (w/ DMSO)



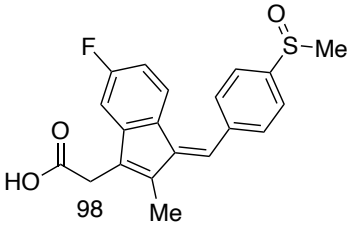
13p-d_2 (Felbinac)
84% yield (60 °C, w/ DMSO)



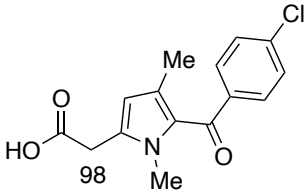
13q-d_2 (Isoxepac)
88% yield (60 °C, w/ DMSO)



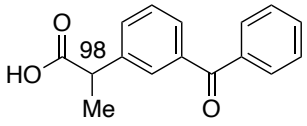
13r-d_2 (Indomethacin)
84% yield (w/ DMSO)



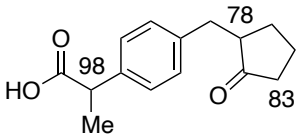
13s-d_2 (Sulindac)
72% yield (60 °C, w/ DMSO)



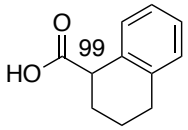
13t-d_2 (Zomepirac)
83% yield (60 °C, w/ DMSO)[a]



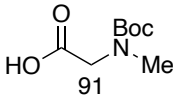
13u-*d* (Ketoprofen)
99% yield (w/ DMSO)



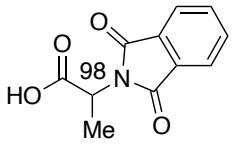
13v-d_4 (Loxoprofen)
96% yield (w/ DMSO)



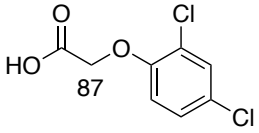
13w-*d*
100% yield



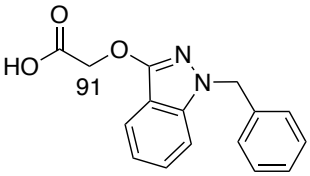
13x-d_2 (Sarcosine)
68% yield (60 °C)



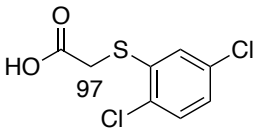
13y-*d* (Alanine)
93% yield



13z-d_2 (2,4-D)
93% yield (60 °C, w/ DMF)



13α-d_2 (Bendazac)
82% yield (60 °C, w/ DMF)



13β-d_2
98% yield (60 °C)

[a] Sodium salt was used as a substrate without the additon of K_2CO_3.

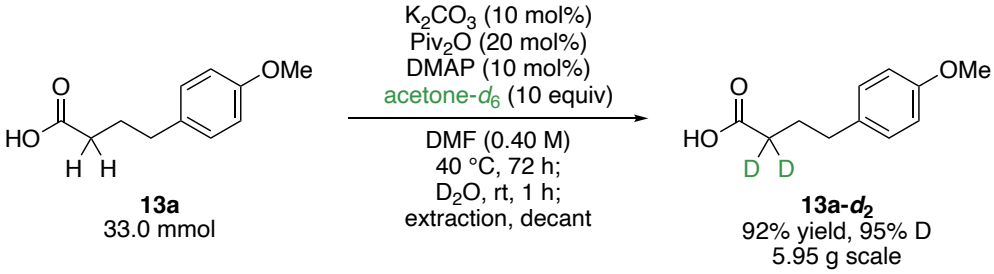
脂肪族カルボン酸だけでなく α-アリールカルボン酸も本反応に適用可能であり、医薬品のフェルビナク、イソキセパック、インドメタシン、スリンダクへの重水素導入が可能であった(**13o-d_2**–**13s-d_2**)。ゾメピラクナトリウム塩は炭酸カリウムを用いずに重水素を導入する

ことが可能であった(**13t-*d*$_2$**)。α,α-二置換-α-アリールカルボン酸であるケトプロフェンやロキソプロフェンも本反応に適用可能であった(**13u-*d*–13w-*d***)。本反応では α-炭素置換カルボン酸のみならず、ヘテロ原子(N, O, S)が α 位に置換した代謝的・酸化的に不安定なカルボン酸への重水素導入も可能であった。α-窒素置換カルボン酸であるサルコシンやアラニンへの重水素導入は良好に進行した(**13x-*d*$_2$**, **13y-*d***)。また、α-酸素置換カルボン酸である 2,4-D やベンダザックへの重水素導入も良好に進行した(**13z-*d*$_2$**, **13α-*d*$_2$**)。さらに、α-硫黄置換カルボン酸を用いた場合も、酸化等の副反応は進行せずに良好な結果が得られた(**13β-*d*$_2$**)。以上の幅広い官能基許容性から、代謝的・酸化的に不安定な部位へ重水素を化学選択的に導入する本手法の高い可能性が示された。

2-4-2. グラムスケール合成

本反応はグラムスケールでの重水素導入に適用可能であった(Scheme 2-7)。その際、カラムクロマトグラフィーによる精製を必要とせず、塩酸水溶液を用いた分液操作とヘキサンでのデカントにより精製することが可能であった。

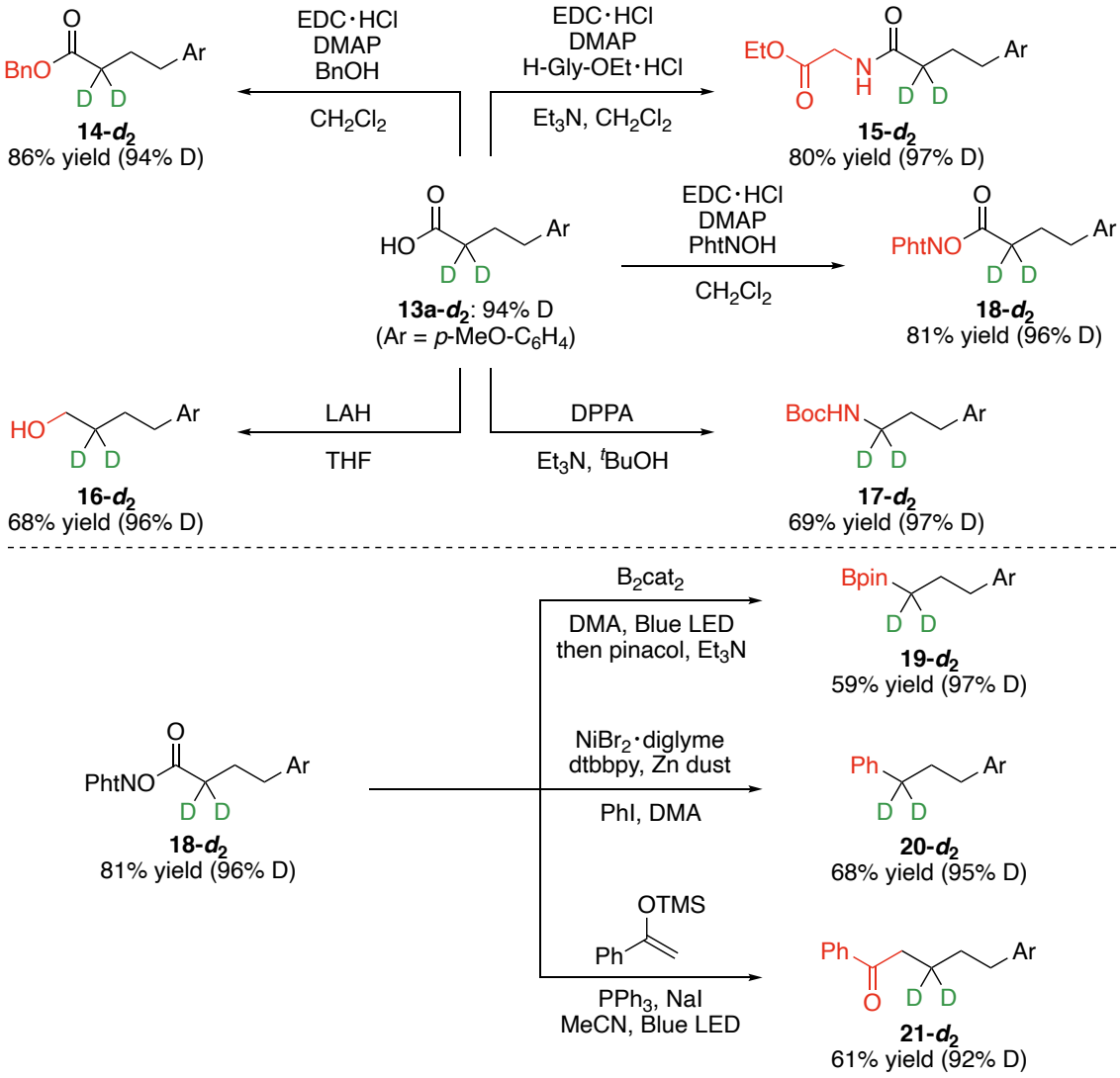
Scheme 2-7. Practical Gram Scale Synthesis



2-4-3. 変換反応

次に、反応生成物である α-重水素カルボン酸の変換を行った(Scheme 2-8)。

Scheme 2-8. Transformation of the Product

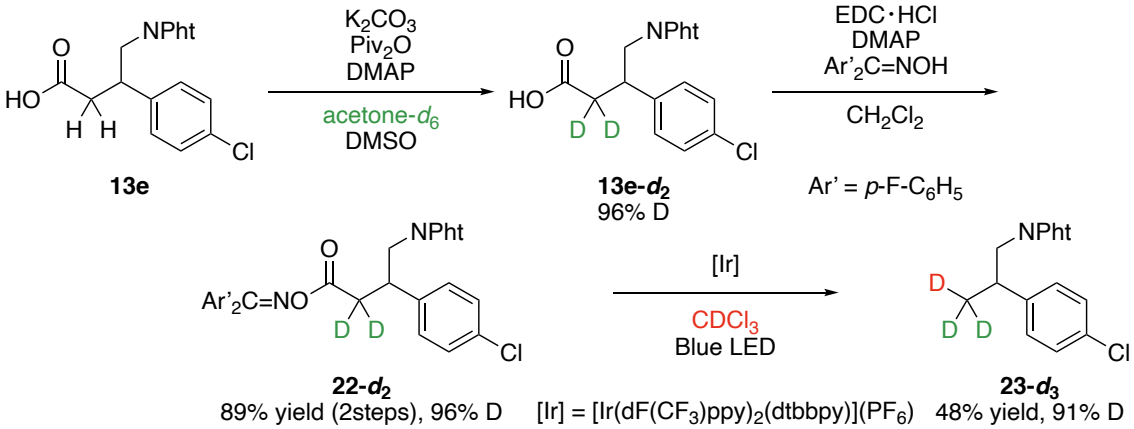


α-重水素カルボン酸は、一般的な縮合条件により重水素化率を維持したままエステルやアミドに変換可能であった(**14-*d*$_2$**, **15-*d*$_2$**)。水素化アルミニウムリチウムを用いて還元することで、β-重水素アルコールが得られた(**16-*d*$_2$**)。Curtius 転位によって、酸化を受けやすい位置に重水素が導入された α-重水素アミンが得られた(**17-*d*$_2$**)。また、レドックス活性エステルである *N*-ヒドロキシフタルイミドエステル **18-*d*$_2$** を用いることで、α-重水素カルボン酸は多様な脱炭酸反応に適用が可能であった。可視光照射条件で脱炭酸的ボリル化反応を行うことで、化合物合成における重要な足場構造であるボロン酸エステルの α-重水素置換体が合成可能であった(**19-*d*$_2$**)[28]。脱炭酸的アリール化反応によって、酸化的に不安定なベンジル位に重水素が導入された化合物が得られた(**20-*d*$_2$**)[29]。可視光照射条件での脱炭酸的アルキル化反応に

より、β-重水素ケトンが得られた(**21-d_2**)[30]。

さらに、オキシムエステルを経由した脱炭酸的重水素化反応によって、末端重水素メチル基の構築が可能であった(Scheme 2-9)[31]。

Scheme 2-9. Construction of Deuterated Methyl Group

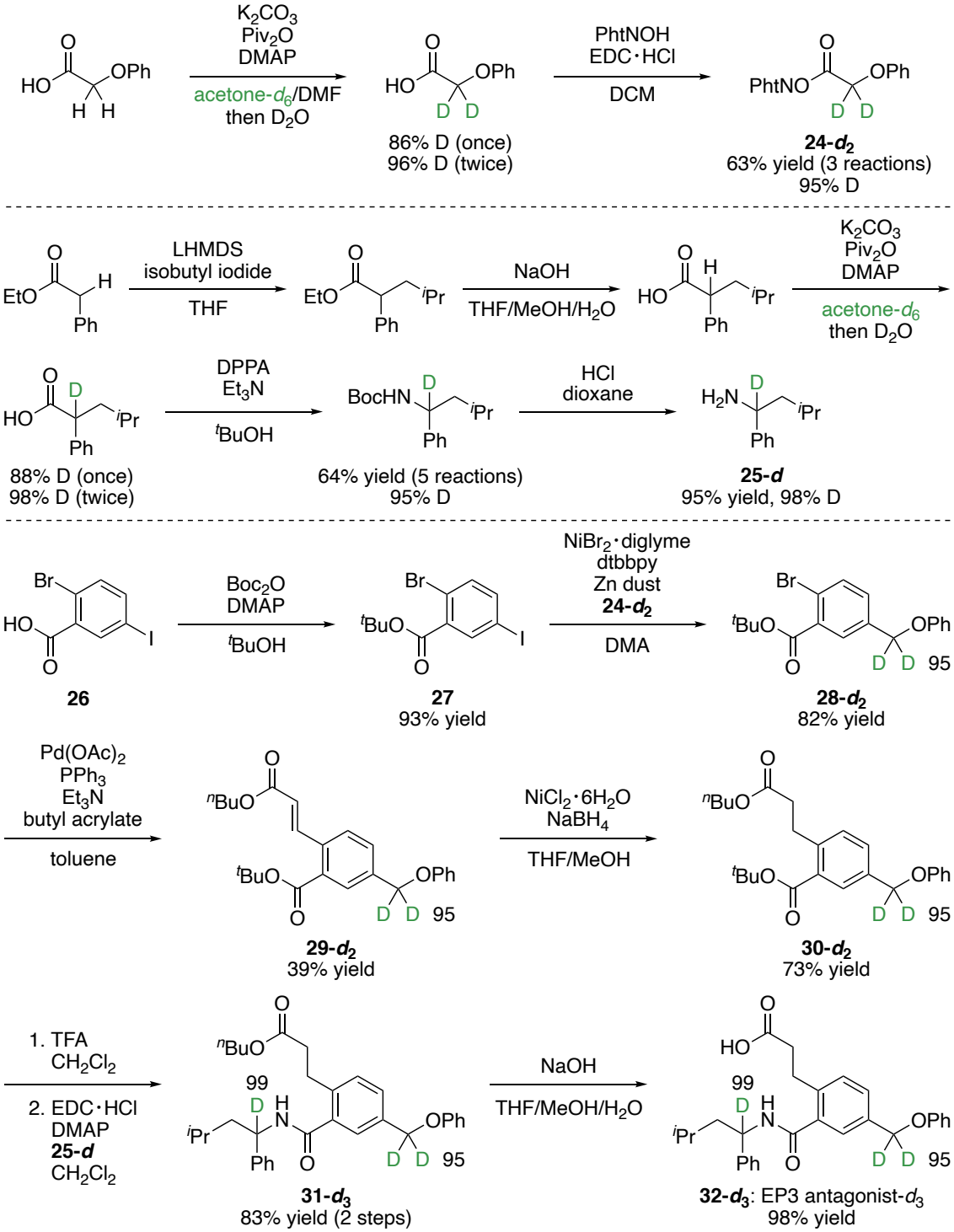


2-5. 重水素置換医薬品候補化合物の合成と評価 [32]

2-5-1. EP3 受容体アンタゴニスト-d_3 の合成

カルボン酸の α-重水素化反応を用いて EP3 受容体アンタゴニストの重水素化体の合成を行った(Scheme 2-10)。

Scheme 2-10. Total Synthesis of Deuterated Bioactive Compound **32-*d*$_3$**

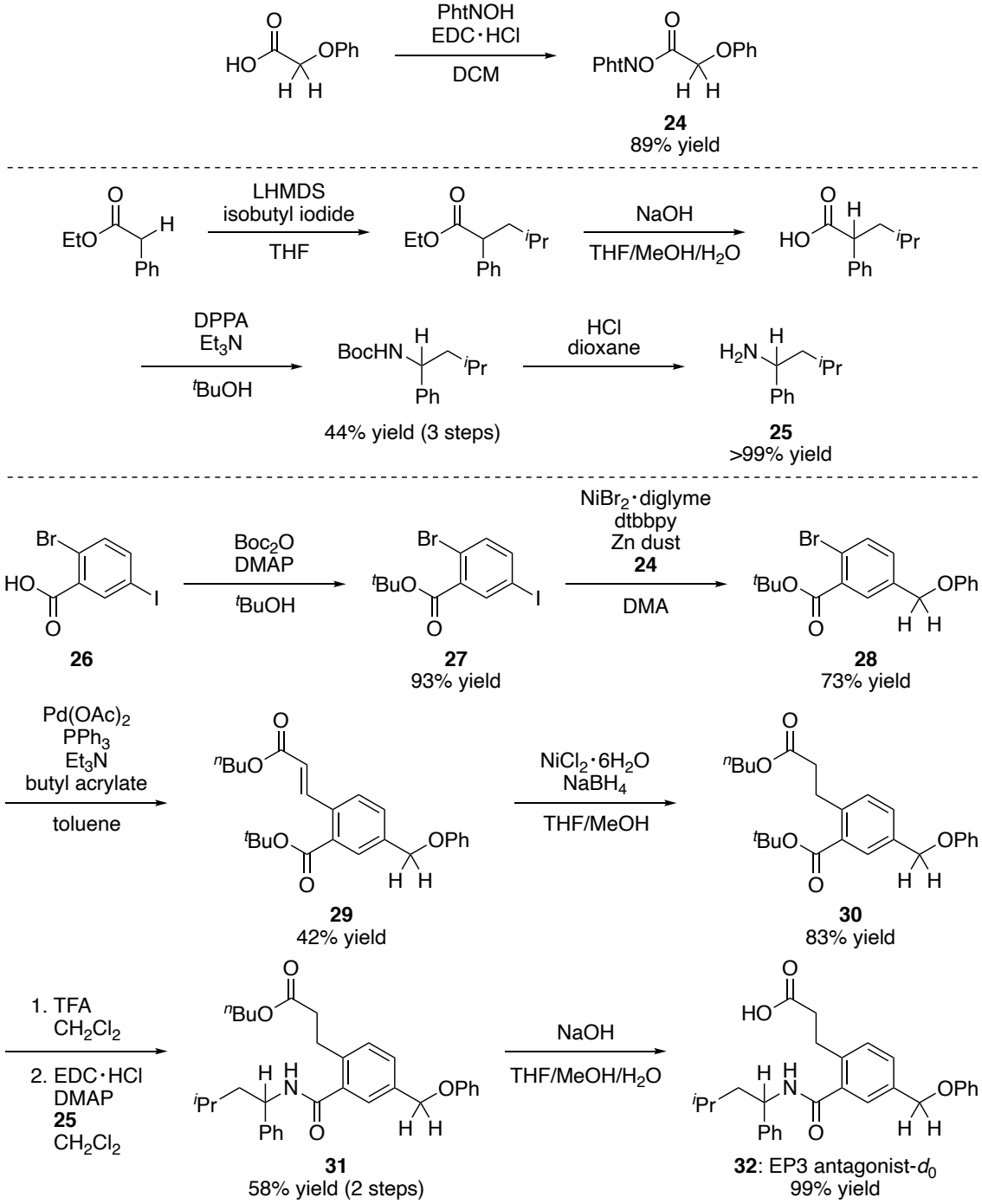


フェノキシ酢酸の α-重水素化反応の後に *N*-ヒドロキシフタルイミドとの縮合によって重水素化フェノキシメチレン化合物 **24-*d*$_2$** を調製した。α-重水素化アミン化合物 **25-*d*** は出発原料であるエステルのアルキル化、加水分解、重水素化、Curtius 転位により調製した。3-ヨード-5-ブロモ安息香酸 **26** を *tert*-ブチルエステル化した後 [33]、重水素化フェノキシメチレン化合物 **27** を用いた脱炭酸的アリール化反応によって **28-*d*$_2$** を合成した。続いて、Heck 反応と還元によって **30-*d*$_2$** を合成した。次に、トリフルオロ酢酸を用いて *tert*-ブチルエステルを選択的に脱保護した後に α-重水素化アミン化合物 **25-*d*** と縮合することで重水素が 3 個導入された **31-*d*$_3$** を合成した。最後に、*n*-ブチルエステルを加水分解することで EP3 受容体アンタゴニストの重水素化体 **32-*d*$_3$** が得られた。

2-5-2. EP3 受容体アンタゴニスト-d_0 の合成

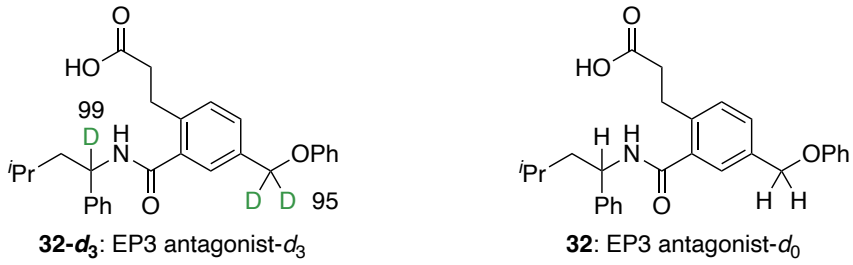
重水素化体の合成手順を基に、重水素を持たない EP3 受容体アンタゴニストの合成を行った(Scheme 2-11)。

Scheme 2-11. Total Synthesis of not Deuterated Bioactive Compound **32**



2-5-3. ヒトミクロソームを用いた代謝安定性試験

最後に、重水素導入による代謝安定性への影響を調べるために、ヒトミクロソームを用いたアッセイを行って EP3 受容体アンタゴニストの重水素化体と軽水素体を比較した(Figure 2-3)。ヒトミクロソーム条件で 8 時間インキュベートしたところ、残存する EP3 受容体アンタゴニストは重水素化体の方が軽水素体よりも多かった。また重水素化体の半減期は、軽水素体の半減期と比較して延長されていた(重水素化体: $t_{1/2}$ = 5.49 h、軽水素体: $t_{1/2}$ = 3.58 h)。このことから、重水素導入によって EP3 受容体アンタゴニストの代謝安定性が向上することが明らかとなった。



32-d_3: EP3 antagonist-d_3 **32**: EP3 antagonist-d_0

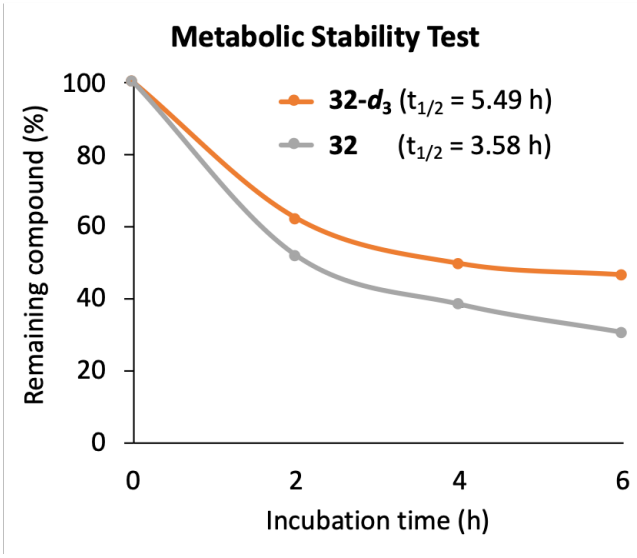


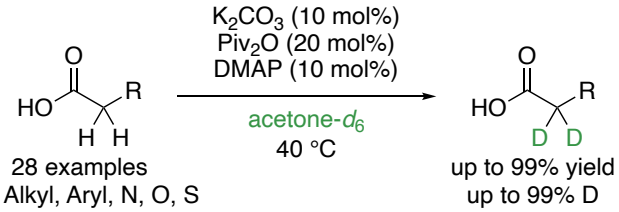
Figure 2-3. Metabolic Assay of **32-d_3** and **32**

2-6. 結論

2-6-1. 結論

本研究では、酸無水物、塩基、求核触媒の三成分を組み合わせた触媒系を開発することによって、アルカリ金属カルボキシラートを Brønsted 塩基触媒としたカルボン酸のエノラート化法の基質適用範囲の拡大を達成した(Scheme 2-12)。本触媒系を利用することによって、これまで困難であった温和な条件でのカルボン酸の α-重水素化反応の開発に成功した。本反応によって、天然物や医薬品に対して高い化学選択性で late-stage での重水素導入が可能であった。また、生成物である α-重水素カルボン酸は重水素化率を維持したまま多様な構造に変換可能であった。そのため、本反応の開発によって複雑な重水素置換分子の容易な合成が可能になると考えられ、実際に生物活性化合物の重水素置換体の合成を行った。合成した重水素置換体に対してヒトミクロソームを用いたアッセイを行ったところ、重水素の導入によって代謝安定性が向上することが明らかとなった。

Scheme 2-12. Catalytic α-Deuteration of Carboxylic Acids



2-6-2. 今後の展望および課題

本研究では Brønsted 塩基触媒によるカルボン酸のエノラート化法の基質適用範囲を拡大し、脂肪族カルボン酸のエノラート化を達成した。今後は、本手法を用いて多様な C–C、C–N、C–O 結合形成反応を開発したいと考えている。現在のところ、パラジウム触媒を用いた α-アリール化反応に適用できると考えており、初期検討を行っている最中である。また、本触媒系を様々な反応に展開していくにあたり反応機構解析実験を行って知見を集め、より効率的なカルボン酸の活性化を実現したいと考えている。

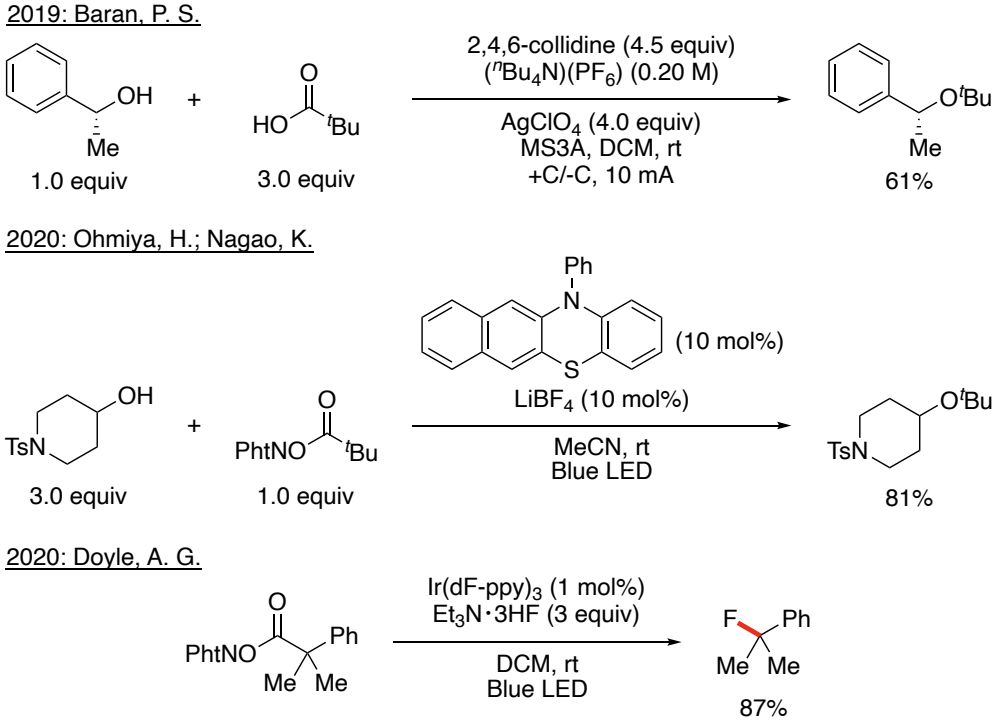
第 3 章　鉄触媒による脱炭酸型 S_N1 反応

3-1. 序論

3-1-1.カルボカチオン生成法の先行例

四置換炭素は有機合成で汎用される S_N2 反応では構築が困難であり、そのケミカルスペースは未だ開拓の途上にある。四置換炭素の構築法としてカルボカチオンと求核剤による S_N1 反応が近年注目されている(Scheme 3-1)。古典的なカルボカチオン生成法として、強力な Lewis 酸や Brønsted 酸条件下でハロゲン化物やアルケンから誘導する手法が知られている。しかし、本手法では過酷な反応条件により求核剤や官能基許容性に改善の余地を残していた。2019 年に Baran らは、電気化学的手法による温和なカルボカチオン生成法を報告した [34]。また、2020 年には Ohmiya らや Doyle らによって光化学的手法による温和なカルボカチオン生成法を報告した [35,36]。このように、温和なカルボカチオン生成法はここ数年の間に飛躍的な進歩を遂げているものの、電気・光・熱を必要としないより理想的な反応は報告されていなかった。

Scheme 3-1. Pioneering Examples for Generation of Carbocation

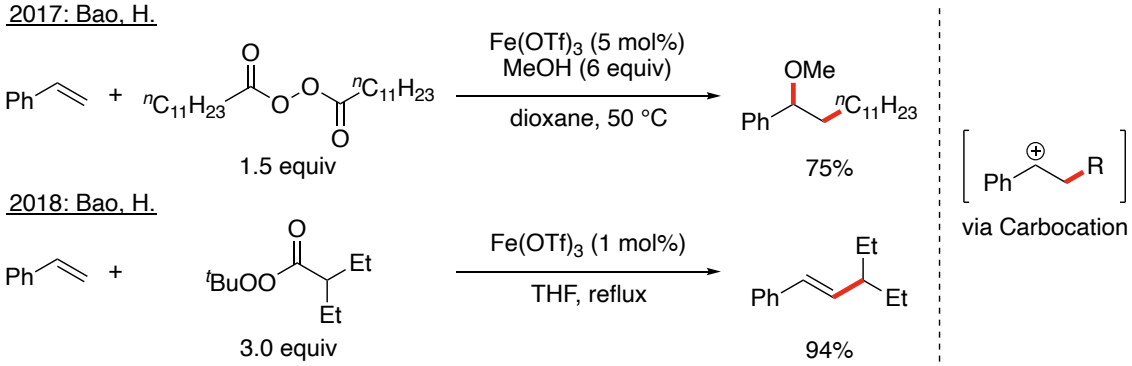


3-1-2. 遷移金属を用いたカルボカチオン生成法

3-1-1 に示した電気化学的手法および光化学的手法は、いずれも系中で生じたラジカル種の一電子酸化によりカルボカチオンを生成するものであった。一方で、第四周期遷移金属群もラジカル種を一電子酸化可能であることが知られている。Bao らによって、鉄触媒と過酸

化物を用いる系でオレフィンへのラジカル付加を経由するカルボカチオン生成法が報告されている(Scheme 3-2)[37]。

Scheme 3-2. Transition Metal-Catalyzed Oxidation of Radical Intermediate



3-1-3. 本研究の目的

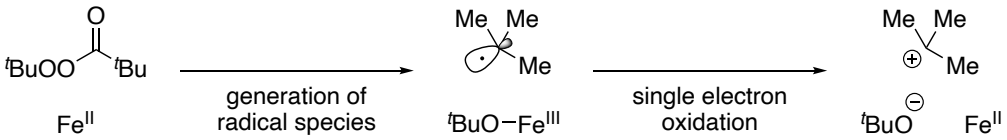
本研究では、電気・光・熱といった外部エネルギーを必要としない触媒系でのカルボカチオン生成法の開発を目的とした。生成したカルボカチオンを求核剤でトラップすることで、S_N2 反応で困難な四置換炭素の構築が可能であると考えた。

3-2. 反応設計と初期検討

3-2-1. 反応設計

鉄触媒と過酸エステルを用いた系を利用し、オレフィンへのラジカル付加を経由することなく過酸エステルから生じたラジカル種を直接一電子酸化する。これにより電気や光といった外部エネルギーを必要としないカルボカチオンの生成が可能であると考えた。本反応は鉄触媒条件下でのラジカル種生成およびラジカル種の一電子酸化によってカルボカチオンが生成する機構を想定している(Scheme 3-3)。また、カルボカチオンが生成する際にアルコキシド系の Brønsted 塩基が生じるため、本反応は外部塩基の添加を必要としない。

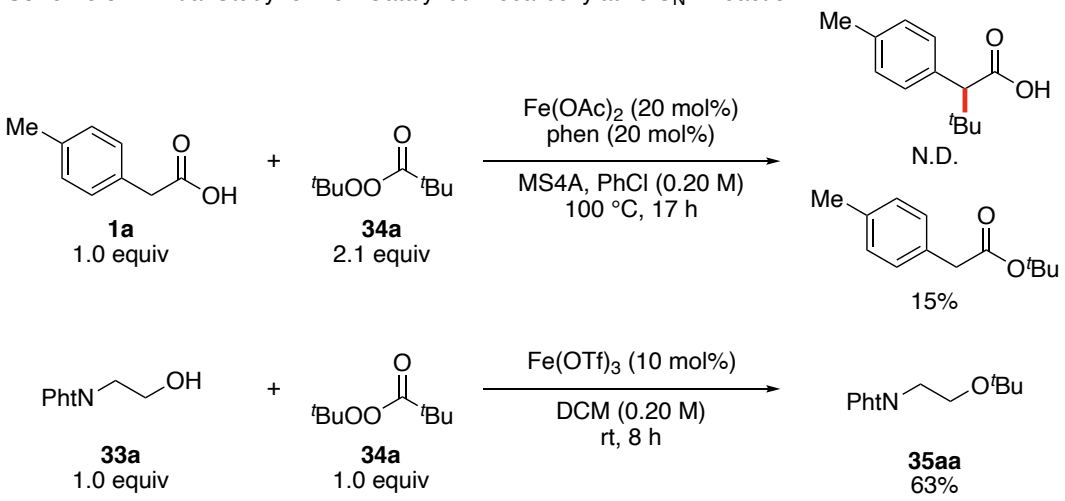
Scheme 3-3. Strategy for Iron-Catalyzed Carbocation Generation



3-2-2. 初期検討

第 1 章に記した鉄とアルカリ金属による触媒系を用いてラジカル機構によるカルボン酸の α-アルキル化反応を試みた際、想定外の副生成物としてターシャリーブチルエステルが生成した(Scheme 3-4)。この結果から、系中で生じたアルキルラジカルが鉄によって一電子酸化されることでカルボカチオンが生成しているのではないかと仮説を立てた。本仮説を実証するためにカルボン酸の代わりにアルコールを求核剤として用いたところ、アルコールのターシャリーブチル化反応が進行した。反応条件について簡単な最適化を行い、Scheme 3-4 に記した条件を初期条件とした。本反応条件をもとに、続いて反応条件の検討を行った。

Scheme 3-4. Initial Study for Iron-Catalyzed Decarboxylative S_N1 Reaction

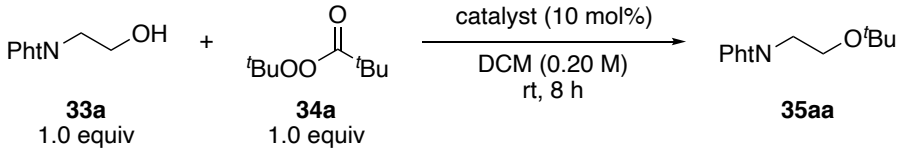


3-3. 反応条件の検討

3-3-1. 触媒の検討

初めに触媒の検討を行った(Table 3-1)。

Table 3-1. Screening of Catalysts



33a 1.0 equiv　　**34a** 1.0 equiv　　**35aa**

entry	catalyst	**35aa** (%)	**33a** (%)	**34a** (%)
1	$Mn(OTf)_2$	N.D.	96	44
2	**$Fe(OTf)_3$**	**63**	**33**	**0**
3	$Fe(OTf)_2$	38	49	0
4	$Co(OTf)_2$	N.D.	99	54
5	$Ni(OTf)_2$	N.D.	92	72
6	$Cu(OTf)_2$	N.D.	89	68
7	CuOTf·benzene	N.D.	95	56
8	$FeCl_3$	5	81	38
9	$FeCl_2$	N.D.	96	34
10	$Fe(OAc)_2$	N.D.	110	67
11	$Fe(acac)_3$	N.D.	109	70
12	ferrocene	N.D.	127	63

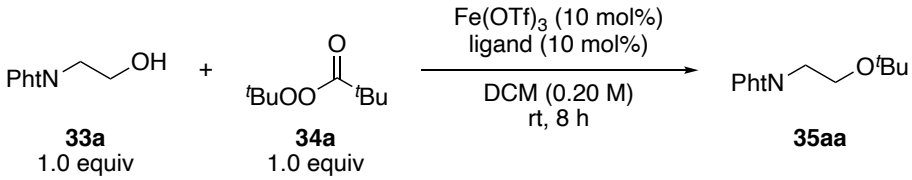
Yields were determined by ^{1}H NMR analysis using dibenzyl as an internal standard.

トリフルオロメタンスルホン酸塩を用いて金属種の検討を行った(entries 1–7)。その結果、二価または三価の鉄を用いた条件で反応が進行した(entries 2,3)。一方でマンガン、コバルト、ニッケル、銅を用いた際には反応は進行しなかった(entries 1,4–7)。次に、種々の鉄触媒の検討を行った(entries 8–12)。その結果、トリフルオロメタンスルホン酸鉄以外の鉄触媒では反応はほとんど進行しないことが明らかとなった。

3-3-2. 配位子の検討

次に配位子の検討を行った(Table 3-2)。

Table 3-2. Screening of Ligands



33a 1.0 equiv　　**34a** 1.0 equiv　　**35aa**

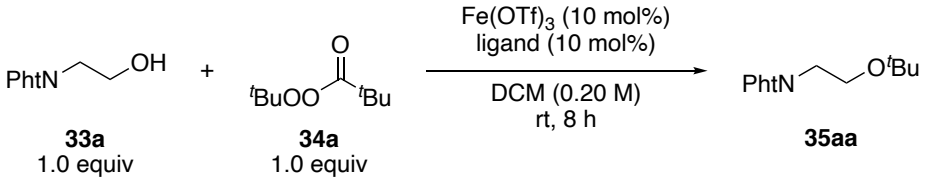
entry	ligand	**35aa** (%)	**33a** (%)	**34a** (%)
1	**—**	**63**	**33**	**0**
2	DMAP	30	63	0
3	Ph_3P	40	68	0
4	Ph_3P=O	44	50	0
5	Ph_3P=S	55	39	0
6	TMEDA	5	89	41
7	phen	39	57	0
8	bpy	32	65	0

Yields were determined by ^{1}H NMR analysis using dibenzyl as an internal standard.

配位子を添加しない条件では目的物の収率は 63%であった(entry 1)。単座配位子、二座配位子を用いて検討を行ったところ、配位子を添加しない条件を上回る結果を得ることはできなかった(entries 2–8)。

次に配位子の電子供与能が本反応に与える影響について知見を得るために、置換基による電子状態の調節が容易な 1,10-フェナントロリン誘導体と 2,2'-ビピリジン誘導体を用いて追加の配位子検討を行った(Table 3-3)。

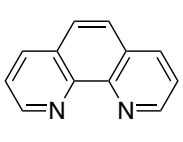
Table 3-3. Screening of 1,10-Phenanthroline and 2,2'-Bipyridine Derivatives as Ligands



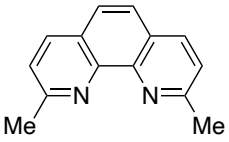
33a 1.0 equiv

34a 1.0 equiv

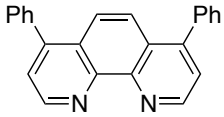
35aa



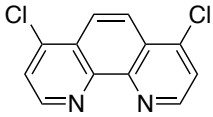
phen, **35aa**: 39%



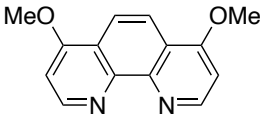
L1・1/2 H_2O, **35aa**: 47%



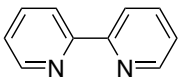
L5, **35aa**: 35%



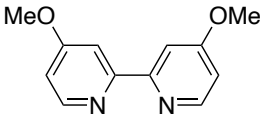
L6, **35aa**: 38%



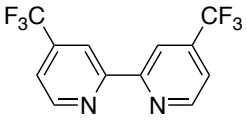
L7, **35aa**: 25%



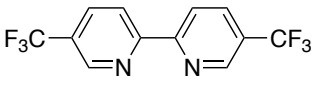
bpy, **35aa**: 32%



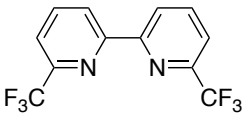
L13, **35aa**: 22%



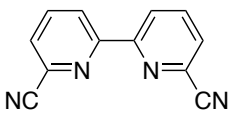
L14, **35aa**: 52%



L15, **35aa**: 51%



L16, **35aa**: 61%



L17, **35aa**: 57%

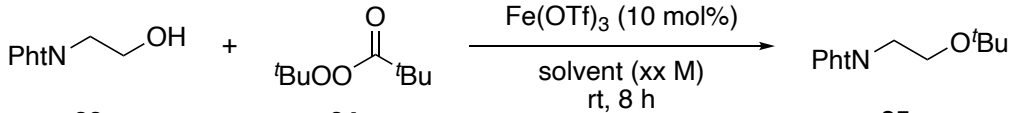
Yields were determined by ^{1}H NMR analysis using dibenzyl as an internal standard.

2,9 位にメチル基を導入した 1,10-フェナントロリン誘導体を用いたところ、目的物の収率は向上した(**L1**)。電子的にほとんど中性であるフェニル基を有する 1,10-フェナントロリン誘導体を用いた場合、無置換の 1,10-フェナントロリンと同様の結果となった(**L5**)。また、4,7 位に電子求引基であるクロロ基を有する 1,10-フェナントロリン誘導体を用いた際にも無置換の 1,10-フェナントロリンを用いた条件と同程度の収率で目的物が得られた(**L6**)。4,7 位に電子供与基であるメトキシ基を有する 1,10-フェナントロリン誘導体を用いたところ、目的物の収率は低下した(**L7**)。2,2'-ビピリジン系配位子の場合でも同様に、電子供与基の導入により目的物の収率は低下した(**L13**)。一方で、電子求引基の導入により目的物の収率は向上したものの、配位子非添加条件を上回る結果は得られなかった(**L14**–**L17**)。これらの結果から、本反応では鉄触媒が電子不足であることが重要であると考えられ、高い Lewis 酸性または高い酸化ポテンシャルが重要であると考えられる。

3-3-3. 溶媒の検討

次に溶媒の検討を行った(Table 3-4)。

Table 3-4. Screening of Solvents



33a 1.0 equiv　　**34a** 1.0 equiv　　**35aa**

entry	solvent	concentration (M)	**35aa** (%)	**33a** (%)	**34a** (%)
1	toluene	0.20	27	68	0
2	PhCl	0.20	33	59	0
3	**DCM**	**0.20**	**63**	**33**	**0**
4	DCE	0.20	62	31	0
5	THF	0.20	12	84	0
6	MeCN	0.20	50	45	0
7	DMF	0.20	5	77	—
8	DMSO	0.20	0	79	—
9	DCM	0.10	53	43	0
10	DCM	0.40	63	34	0
11	DCM	0.60	60	31	0
12	DCM	0.80	58	35	0
13	DCM	1.0	60	33	0

Yields were determined by ^{1}H NMR analysis using dibenzyl as an internal standard.

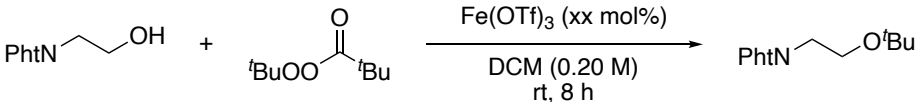
トルエンやクロロベンゼンを用いた条件では目的物の収率は低かった(entries 1,2)。ジクロロメタンや 1,2-ジクロロエタンを用いた条件が目的物の収率が最も良い条件であった。(entries 3,4)。極性が中程度以上の THF や DMF、DMSO を用いた条件では反応はほとんど進行しなかったものの、アセトニトリルを用いた際に中程度の収率で目的物が得られた(entries 5–8)。

次にジクロロメタンを用いて反応濃度の検討を行ったところ、0.40 M 以上の濃度では収率はほとんど一定であったものの、0.10 M の条件では目的物の収率は若干低下した(entries 9–13)。

3-3-4. 触媒量の検討

次に触媒量の検討を行った(Table 3-5)。

Table 3-5. Optimization of Catalyst Amount



33a 1.0 equiv　　**34a** 1.0 equiv　　**35aa**

entry	$Fe(OTf)_3$ (mol%)	**35aa** (%)	**33a** (%)	**34a** (%)
1	1	21	76	39
2	5	43	51	0
3	**10**	**63**	**33**	**0**
4	20	63	30	0

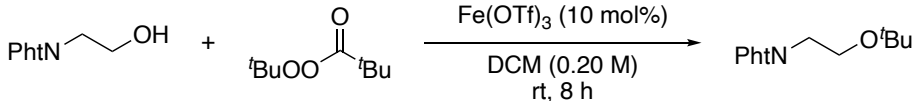
Yields were determined by ^{1}H NMR analysis using dibenzyl as an internal standard.

触媒量 1 mol%, 5 mol%, 10 mol%の条件では触媒量を増やすごとに目的物の収率は向上した(entries 1–3)。一方、触媒量を 20 mol%に増やしたところ、触媒量 10 mol%の条件と同様の結果となった(entry 4)。

3-3-5. 基質の当量の検討

次に基質の当量の検討を行った(Table 3-6)。

Table 3-6. Optimization of Substrate Amount



33a x mmol　　**34a** y mmol　　**35aa**

entry	**33a** (mmol)	**34a** (mmol)	**35aa** (mmol)	**33a** (mmol)	**34a** (mmol)
1	0.10	0.10	0.063 (63%)	0.033	0
2	0.20	0.10	0.077 (77%)	0.126	0
3	**0.30**	**0.10**	**0.087 (87%)**	**0.211**	**0**
4	0.10	0.20	0.057 (57%)	0.033	0.015

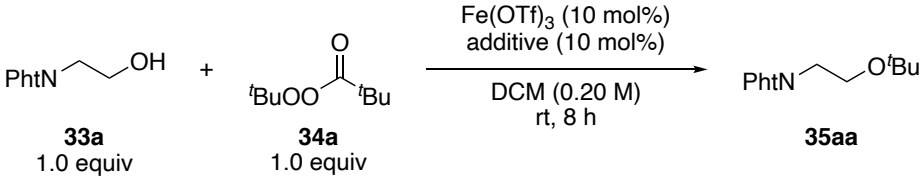
Yields were determined by ^{1}H NMR analysis using dibenzyl as an internal standard.

過酸化物 **34a** に対するアルコール **33a** の当量を増やすごとに目的物の収率は向上した(entries 1–3)。そして、アルコール **33a** に対して過酸化物 **34a** を 3 当量用いる条件で 87%の収率で目的物が得られた(entries 3)。一方で、アルコール **33a** に対する過酸化物 **34a** の当量を 2 当量に増加させた場合では、目的物の収率は 57%に低下した(entry 4)。

3-3-6. 添加剤の検討

本反応では過酸化物 **34a** から脱炭酸的にアルキルラジカルが生じ、続いて鉄触媒によるアルキルラジカルの酸化が起こることでアルキルカチオンが生じる機構を想定している。そこで、アルキルカチオン中間体の長寿命化により収率の改善が可能であると考え、添加剤として塩の検討を行った(Table 3-7)。

Table 3-7. Screening of Additive



33a 1.0 equiv　　**34a** 1.0 equiv　　**35aa**

entry	additive	**35aa** (%)	**33a** (%)	**34a** (%)
1	—	63	33	0
2	LiOTf	60	35	0
3	NaOTf	57	36	0
4	KOTf	57	35	0

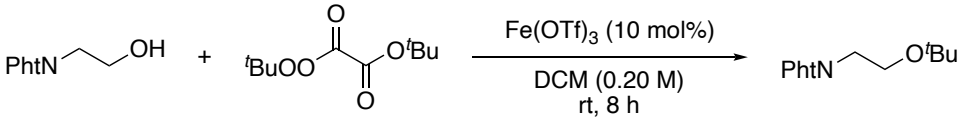
Yields were determined by ^{1}H NMR analysis using dibenzyl as an internal standard.

触媒としてトリフルオロメタンスルホン酸鉄を用いているため、対アニオンを統一するためにトリフルオロメタンスルホン酸塩を用いて種々の塩の検討を行った(entries 1–4)。その結果、いずれの塩を添加した条件においても添加剤を加えない条件を上回る結果を得ることはできなかった。

3-3-7. 基質の検討

低収率ではあったものの、オキサレートを基盤とした基質 **36a** を用いることでアルコールをアルキルカチオン源として利用することも可能であった(Scheme 3-5)。

Scheme 3-5. Application of alcohol-derived alkyl source



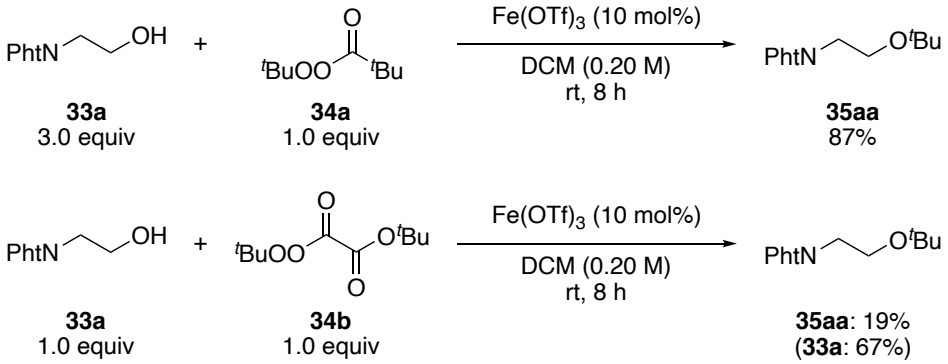
33a 1.0 equiv　　**36a** 1.0 equiv　　**35aa**: 19% (**33a**: 67%)

3-4. 結論

3-4-1. 結論

鉄触媒と過酸エステルを用いることで、電気・光・熱といった外部エネルギーを必要としない触媒的なカルボカチオン生成法の開発に成功した。本触媒系に求核剤としてアルコールを加えることで、S_N2 反応では困難な四置換炭素の構築が可能であった(Scheme 3-6)。また、オキサレートを基盤とした基質を用いることで、低収率ではあるもののアルコールをアルキルカチオン源として利用することも可能であった。

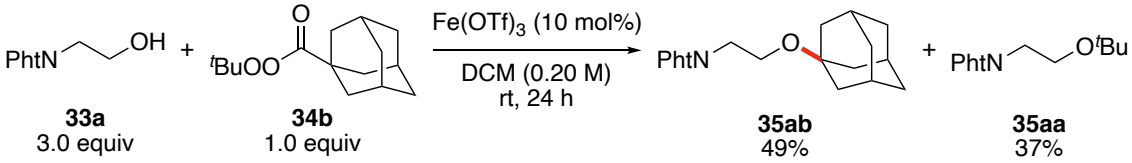
Scheme 3-6. Iron-Catalyzed Decarboxylative S_N1 Reaction



3-4-2. 今後の展望および課題

本反応の基質一般性の検討を行ったところ、共同研究者の古賀祐之介氏によってピバル酸以外のカルボン酸を由来とする過酸エステルを用いた際にもターシャリーブチル化反応が進行することが明らかとなった(Scheme 3-7)。本結果より本反応条件下では、副生成物であるターシャリーブチルアルコール由来のカルボカチオンが生成することが示唆されており、現在のところ本反応はターシャリーブチル化以外に適用することが困難である。一方で、本現象を利用することでより効率的な四置換炭素の形成が可能であると考えており、現在検討を進めている。

Scheme 3-7. Unexpected Generation of *tert*-Butyl Cation



総括

本研究では第 1 章、第 2 章に記すように、カルボン酸のエノラート化が可能な二種類の新規触媒系を開発した。これらの触媒系は Brønsted 塩基触媒によるカルボン酸のエノラート化を達成した世界初の触媒系であり、化学量論量の外部塩基による酸性プロトンの中和を必要としない。

第 1 章では、鉄とアルカリ金属が協働する新規エノラート化法の開発を行った。本触媒系ではラジカル機構によるカルボン酸の α 位官能基化が可能であり、ラジカル試薬として TEMPO を用いることで過剰酸化反応を抑制したカルボン酸の直接的触媒的 α-酸化反応を開発した。本反応はエステルやアミド、α-アルキルケトンの存在下においてもカルボン酸のみの α-酸化反応が可能であり、本触媒系が有するカルボン酸に対する高い化学選択性が明らかとなった。さらに、本反応生成物は合成化学的に有用な α-ヒドロキシエステルや α-ヒドロキシアミド、1,2-ケトエステル、1,2-ケトアミドに変換可能であった。本反応はラジカル機構によるカルボン酸の触媒的 α 位官能基化を達成した世界初の例であり、本触媒系を基盤として従来の二電子型反応では困難な β 位四級炭素構築反応等への展開が期待できる。

第 2 章では、第 1 章で課題となっていた基質適用範囲を拡大するために酸無水物触媒を用いた新規触媒系の開発を行い、脂肪族カルボン酸への基質適用範囲の拡大を達成した。本触媒系に重水素源を加えることで、カルボン酸の触媒的 α-重水素化反応を開発した。本反応はカルボキシ基を有する医薬品や天然物に対して高い化学選択性で late-stage での重水素導入が可能であった。また、また、生成物である α-重水素カルボン酸は重水素化率を維持したまま多様な構造に変換可能であることから、含重水素合成素子として複雑な重水素置換分子の合成に利用可能であると考えられる。第 2 章では開発した重水素化反応を利用して生物活性化合物の重水素置換体の合成を行い、化合物への重水素導入による代謝安定性の向上を確認した。

第 3 章では、第 1 章で開発した鉄とアルカリ金属の触媒系を用い、ラジカル機構によるカルボン酸の触媒的 α-アルキル化反応の開発を試みた。ラジカル機構での反応を開発することにより、S_N2 反応で困難な β 位四級炭素の構築が可能であると考えた。しかし、検討を行ったところ想定の α-アルキル化反応は進行せず、S_N1 反応によるエステル化が進行することが明らかとなった。本触媒系では電気・光・熱などの外部エネルギーを必要としないカルボカチオンの生成が可能であった。そこで、カルボン酸の代わりにアルコールを求核剤として用い、S_N1 反応によるかさ高いエーテル合成法として反応開発を行った。

Experimental Section

1. Catalytic α-Oxidation of Carboxylic Acids via Radical Process

1-1. General

All reactions were carried out using heat gun dried glassware under a positive pressure of dry argon unless otherwise noted. Catalytic reactions were run under argon atmosphere. Air- and moisture-sensitive liquids were transferred via a syringe and a stainless-steel needle. Reactions were magnetically stirred and monitored by thin layer chromatography using Merck Silica Gel 60 F254 plates. All work-up and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Flash chromatography was performed using silica gel 60N (spherical neutral, particle size 40–50μm) purchased from Kanto Chemical Co., Inc. For ICP-MS, Ultrapure Water (for Ultratrace Analysis) was purchased from Wako Pure Chemical Industries, Ltd., Nitric acid 1.42 (Ultrapur-100) was purchased from Kanto Chemical Co., Inc. and Multielement standard solution 5 for ICP TraceCERT®, in 10% nitric acid was purchased from Aldrich.

1-2. Instrumentation

NMR was recorded on 500 MHz Bruker Avance III. Chemical shifts for proton are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$: δ 7.26 ppm). For ^{13}C NMR, chemical shifts were reported in the scale relative to NMR solvent ($CDCl_3$: δ 77.0 ppm) as an internal reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: double doublet, dt: double triplet, ddd: double double doublet, t: triplet, q: qualtet, quin: quintet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. Infrared (IR) spectra were recorded on with Shimadzu IR Affinity-1S. High-resolution mass spectroscopy (HRMS) was obtained with Bruker MicrOTOF II. Inductively coupled Plasma-mass spectroscopy (ICP-MS) measurement was carried out with Agilent 7500c.

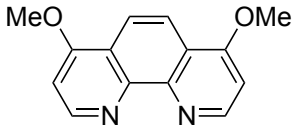
1-3. Materials

Commercially available carboxylic acids were used as received. THF (deoxidized, stabilizer free) was purchased from Kanto Chemical Co., Inc. and stored in a dry box. $Fe(OAc)_2$ (≥99.99% trace metals basis) was purchased from Aldrich and used as received and stored in a dry box. Molecular Sieves 4A was purchased from Nacalai Tesque, Inc. TEMPO was purchased from Oakwood Products, Inc.

1-4. Syntheses and Characterization

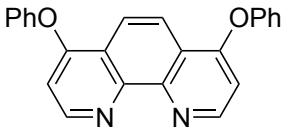
1-4-1. Synthesis of 1,10-Phenanthroline Derivatives

4,7-dimethoxy-1,10-phenanthroline (L7)[38]



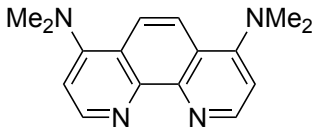
4,7-dichloro-1,10-phenanthroline (249 mg, 1.0 mmol) and sodium methoxide (432 mg, 8.0 mmol) were added followed by the addition dry methanol (5.0 mL, 0.20 M). The mixture was stirred under argon at 80 °C for 17.5 h. To the resultant mixture was added H_2O and extracted with CH_2Cl_2. After removal of solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (0%–3% MeOH in CH_2Cl_2 as eluent) to afford **L7**. (white solid, 86% yield); CAS Registry Number 92149-07-0; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (d, *J* = 5.5 Hz, 2H, Ar*H*), 8.18 (s, 2H, Ar*H*), 7.00 (d, *J* = 5.5 Hz, 2H, Ar*H*), 4.10 (s, 6H, OC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 151.2, 146.9, 121.0, 119.0, 102.8, 55.9.

4,7-diphenoxy-1,10-phenanthroline (L8)[38]



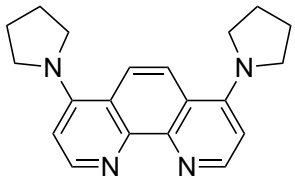
4,7-dichloro-1,10-phenanthroline (249 mg, 1.0 mmol), potassium hydroxide (281 mg, 5.0 mmol) and phenol (4.71 g, 50 mmol) were added. The mixture was stirred under argon at 120 °C for 24 h. To the resultant mixture was added 1 M KOH aq and extracted with CH_2Cl_2. After removal of solvent under reduced pressure, the resulting residue was purified by recrystallization after silica gel flash chromatography (3% MeOH in CH_2Cl_2 as eluent) to afford **L8**. (White solid, 70% yield); CAS Registry Number 95943-00-3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.95 (d, *J* = 5.5 Hz, 2H, Ar*H*), 8.40 (s, 2H, Ar*H*), 7.51 (t, *J* = 7.5 Hz, 4H, Ar*H*), 7.33 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.25 (d, *J* = 7.5 Hz, 4H, Ar*H*), 6.85 (d, *J* = 5.5 Hz, 2H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 154.5,151.1, 147.6, 130.4, 125.7, 121.5, 121.0, 119.6, 107.3.

N^4,N^4,N^7,N^7-tetramethyl-1,10-phenanthroline-4,7-diamine (L10)[39]



4,7-dichloro-1,10-phenanthroline (1.0 g, 4.0 mmol) was added followed by the addition dry DMF (10.0 mL, 0.40 M). The mixture was stirred under argon at 160 °C for 15 h. To the resultant mixture was added sat. $NaHCO_3$ aq and extracted with CH_2Cl_2. After removal of solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (10 % MeOH in CH_2Cl_2 to 20% MeOH and 1% Et_3N in CH_2Cl_2 as eluent) to afford **L10**. (beige solid, 54% yield); CAS Registry Number 169516-12-5; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (d, *J* = 5.5 Hz, 2H, Ar*H*), 7.97 (s, 2H, Ar*H*), 7.01 (d, *J* = 5.5 Hz, 2H, Ar*H*), 3.08 (s, 12H, N(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 150.0, 148.0, 122.1, 120.8, 109.7, 44.1.

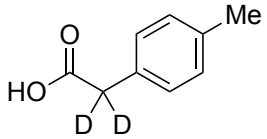
4,7-di(pyrrolidin-1-yl)-1,10-phenanthroline (L11)[40]



4,7-dichloro-1,10-phenanthroline (249 mg, 1.0 mmol) was added followed by the addition pyrrolidine (5.0 mL, 0.20 M). The mixture was stirred under argon at 130 °C for 1 h. To the resultant mixture was added sat. $NaHCO_3$ aq and extracted with CH_2Cl_2. After removal of solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (CH_2Cl_2 to 20% MeOH and 3% Et_3N in CH_2Cl_2 as eluent) to afford **L11**. (beige solid, 95% yield); CAS Registry Number 1422577-91-0; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 5.0 Hz, 2H, Ar*H*), 7.96 (s, 2H, Ar*H*), 6.72 (d, *J* = 5.0 Hz, 2H, Ar*H*), 3.70 (m, 8H, NC*H*$_2$CH$_2$), 2.06 (m, 8H, NCH$_2$C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 149.3, 148.4, 119.5, 119.4, 105.6, 52.3, 26.0.

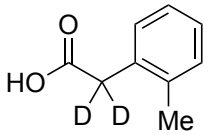
1-4-2. Synthesis of Substrates

2-(*p*-tolyl)acetic-2,2-d_2 acid (1a-d_2)[41]



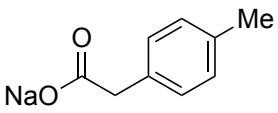
2-(*p*-tolyl)acetic acid (751 mg, 5 mmol) and sodium methoxide (1.08 g, 20 mmol) were added followed by the addition D_2O (5.0 mL, 1.0 M). The mixture was stirred under argon at 100 °C for 20 h. To the resultant mixture was added 1 M HCl aq and extracted with CH_2Cl_2. After removal of solvent under reduced pressure, the resulting residue was purified by silica short column and washed with EtOAc to afford **1a-d_2**. (white solid, 99% yield, 97% deuterated); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.14 (d, *J* = 8.0 Hz, 2H, Ar*H*), 2.33 (s, 3H, ArC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 137.0, 130.1, 129.4, 129.2, 39.9 (quin, *J* = 19.8 Hz), 21.1; IR (neat) 2920, 1692, 1518, 1408, 1287, 1234, 1209, 1047, 930, 910, 854, 748, 665, 505 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_9H_8D_2NaO_2$ $(M + Na)^+$ 175.0699, found 175.0699.

2-(*o*-tolyl)acetic-2,2-d_2 acid (1c-d_2)[41]



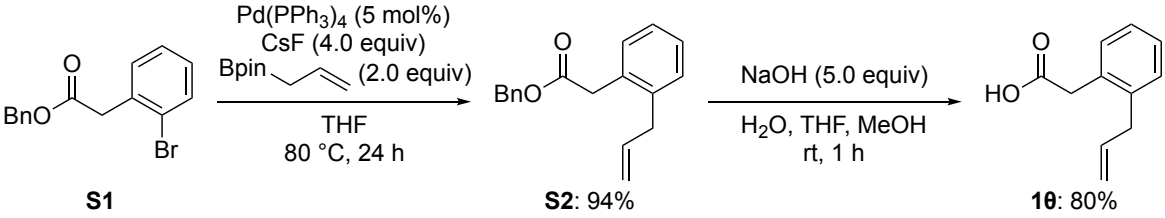
2-(*o*-tolyl)acetic acid (751 mg, 5 mmol) and sodium methoxide (1.08 g, 20 mmol) were added followed by the addition D_2O (5.0 mL, 1.0 M). The mixture was stirred under argon at 100 °C for 24 h. To the resultant mixture was added 1 M HCl aq and extracted with CH_2Cl_2. After removal of solvent under reduced pressure, the resulting residue was purified by silica short column and washed with EtOAc to afford **1c-d_2**. (white solid, 73% yield, 97% deuterated); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.15 (m, 4H, Ar*H*), 2.33 (s, 3H, ArC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 136.9, 131.9, 130.4, 130.2, 127.7, 126.2, 38.2 (quin, *J* = 19.7 Hz), 19.5; IR (neat) 3015, 1686, 1406, 1302, 1281, 1233, 1028, 943, 905, 849, 737, 665, 600, 417 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_9H_8D_2NaO_2$ $(M + Na)^+$ 175.0699, found 175.0699.

sodium 2-(*p*-tolyl)acetate (1a-Na)

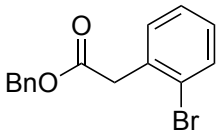


2-(*p*-tolyl)acetic acid (451 mg, 3 mmol) and sodium carbonate (159 mg, 1.5 mmol) were added followed by the addition H_2O (3.0 mL, 1.0 M). The mixture was stirred under argon at room temperature for 3 h. After removal of solvent under reduced pressure, the residual solid was gathered (**1a-Na**). (white solid, 58% yield, 299.0 mg); CAS Registry Number 25307-01-1; ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.10 (d, J = 8.0 Hz, 2H, Ar*H*), 7.00 (d, J = 8.0 Hz, 2H, Ar*H*), 3.16 (s, 2H, ArCH_2COONa), 2.24 (s, 3H, ArCH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.0, 137.4, 133.9, 129.5, 128.5, 46.2, 21.1.

Synthesis of 2-(2-allylphenyl)acetic acid (1θ)

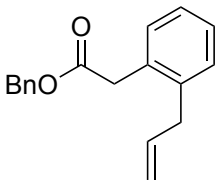


benzyl 2-(2-bromophenyl)acetate (S1)



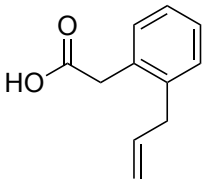
To a solution of 2-(2-bromophenyl)acetic acid **1f** (3.22 g, 15 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.31 g, 22.5 mmol) and DMAP (183.3 mg, 1.5 mmol) in dry CH_2Cl_2 (15 mL, 1.0 M) was added benzyl alcohol (2.32 mL, 22.5 mmol) under argon atmosphere. The reaction mixture was stirred for 17 h at room temperature. To the resultant mixture was added H_2O and extracted with CH_2Cl_2. After removal of solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (1–3% EtOAc in *n*-Hexane as eluent) to obtain benzyl 2-(2-bromophenyl)acetate (**S1**). (colorless liquid, 91% yield, 4.15 g); CAS Registry Number 892146-11-1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.5 Hz, 1H, Ar*H*), 7.37–7.27 (m, 7H, Ar*H*), 7.16–7.13 (m, 1H, Ar*H*), 5.17 (s, 2H, PhCH_2O), 3.84 (s, 2H, ArCH_2CO); ^{13}C NMR (125 MHz, $CDCl_3$) δ170.4, 135.8, 134.1, 132.8, 131.5, 128.9, 128.5, 128.2, 128.2, 127.6, 125.0, 66.8, 41.7.

benzyl 2-(2-allylphenyl)acetate (S2)[42]



To a mixture of $Pd(PPh_3)_4$ (780.1 mg, 0.68 mmol) and cesium fluoride (8.20 g, 54 mmol) in dry THF (185 mL) was added benzyl 2-(2-bromophenyl)acetate (4.12 g, 13.5 mmol) under argon atmosphere. After the reaction mixture was stirred for 15 min at room temperature, 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was added to the mixture. The reaction mixture was stirred for 16 h at 80 °C. Dry THF (50 mL) was added and the reaction mixture was stirred for 8 h at 80 °C. To the resultant mixture was added H_2O and extracted with CH_2Cl_2. After removal of solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (1–3% EtOAc in *n*-Hexane as eluent) to obtain benzyl 2-(2-allylphenyl)acetate (**S2**). (colorless liquid, 94% yield, 3.40 g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.29 (m, 5H, Ar*H*), 7.25–7.17 (m, 4H, Ar*H*), 5.95–5.87 (m, 1H, $ArCH_2C\mathit{H}{=}CH_2$), 5.12 (s, 2H, $PhC\mathit{H}_2O$), 5.04–5.01 (m, 1H, $ArCH_2CH{=}C\mathit{H}_2$), 4.97–4.92 (m, 1H, $ArCH_2CH{=}C\mathit{H}_2$), 3.70 (s, 2H, $ArC\mathit{H}_2CO$), 3.40 (d, J = 6.0 Hz, 2H, $ArC\mathit{H}_2CH{=}CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ171.4, 138.4, 136.5, 135.9, 132.6, 130.7, 129.9, 128.5, 128.2, 128.1, 127.6, 126.6, 116.0, 66.6, 38.6, 37.4; IR (neat) 1732, 1454, 1331, 1238, 1182, 1144, 993, 914, 735, 696, 594, 579, 492, 463 cm^{-1}.

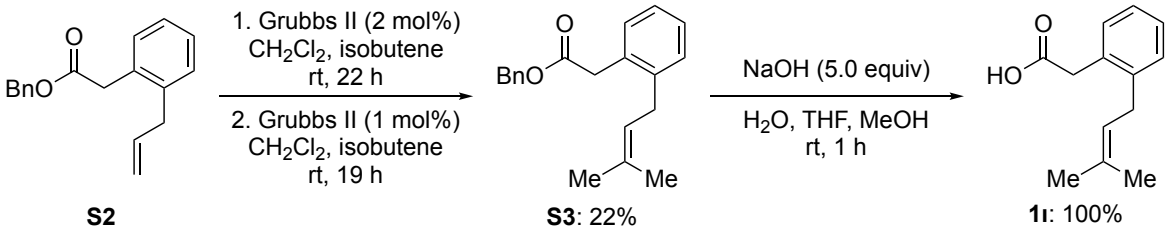
2-(2-allylphenyl)acetic acid (1θ)



To a solution of benzyl 2-(2-allylphenyl)acetate (266.3 mg, 1.0 mmol) in THF (5.0 mL) and MeOH (2.0 mL) was added 1.0 M NaOH aq (5.0 mL). The mixture was stirred at room temperature for 1 h. To the resultant mixture was added 1 M HCl aq and extracted with CH_2Cl_2. After removal of solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent) to obtain 2-(2-allylphenyl)acetic acid (**1θ**). (colorless liquid, 80% yield, 141.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.19 (m, 4H, Ar*H*), 5.97–5.89 (m, 1H, $ArCH_2C\mathit{H}{=}CH_2$), 5.07–5.05 (m, 1H, $ArCH_2CH{=}C\mathit{H}_2$), 5.00–4.97 (m, 1H, $ArCH_2CH{=}C\mathit{H}_2$), 3.69 (s, 2H, $ArC\mathit{H}_2CO$), 3.42 (d, J = 6.0 Hz, 2H, $ArC\mathit{H}_2CH{=}CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ176.9, 138.5,

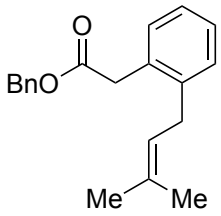
136.4, 132.0, 130.7, 130.0, 127.9, 126.7, 116.2, 38.2, 37.4; IR (neat) 1697, 1408, 1287, 1234, 1211, 1177, 1163, 912, 758, 725, 681, 625, 615, 442, 419 cm^{-1}.

Synthesis of 2-(2-(3-methylbut-2-en-1-yl)phenyl)acetic acid (1ι)



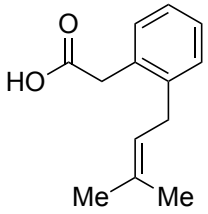
S2 **S3**: 22% **1ι**: 100%

benzyl 2-(2-(3-methylbut-2-en-1-yl)phenyl)acetate (S3)[43]



To a solution of benzyl 2-(2-allylphenyl)acetate (537.0 mg, 2.0 mmol) in CH_2Cl_2 (5.0 mL) was added a solution of Grubbs II (34.0 mg, 0.04 mmol) in CH_2Cl_2 (5.0 mL). After bubbling isobutene, the mixture was stirred under argon at room temperature for 22 h. After removal of solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (1–3% EtOAc in *n*-hexane as eluent). After the mixture was performed under the same reaction using Grubbs II (17.0 mg, 0.02 mmol), the resulting residue was purified by silica gel flash chromatography (1–3% EtOAc in *n*-hexane as eluent) to obtain benzyl 2-(2-(3-methylbut-2-en-1-yl)phenyl)acetate (**S3**). (colorless liquid, 22% yield, 131.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.29 (m, 5H, Ar*H*), 7.23–7.14 (m, 4H, Ar*H*), 5.19–5.15 (m, 1H, $ArCH_2CH$=$C(CH_3)_2$), 5.13 (s, 2H, $PhCH_2O$), 3.70 (s, 2H, $ArCH_2CO$), 3.33 (d, J = 7.0 Hz, 2H, $ArCH_2CH$=$C(CH_3)_2$), 1.70 (s, 3H, $ArCH_2CH$=$C(CH_3)_2$), 1.67 (s, 3H, $ArCH_2CH$=$C(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ171.5, 140.3, 135.9, 132.8, 132.3, 130.6, 129.4, 128.5, 128.2, 128.1, 127.6, 126.2, 122.4, 66.5, 38.7, 32.0, 25.7, 17.8; IR (neat) 1732, 1493, 1452, 1375, 1331, 1236, 1180, 1142, 1086, 978, 920, 746, 696, 579, 447 cm^{-1}.

2-(2-(3-methylbut-2-en-1-yl)phenyl)acetic acid (1ι)



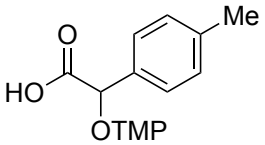
To a solution of benzyl 2-(2-(3-methylbut-2-en-1-yl)phenyl)acetate (124.4 mg, 0.42 mmol) in THF (5.0 mL) and MeOH (2.0 mL) was added 1.0 M NaOH aq (5.0 mL). The mixture was stirred at room temperature for 1 h. the resultant mixture was extracted with CH_2Cl_2 and the remained basic water layer was added 1 M HCl aq and extracted with CH_2Cl_2. After removal of solvent under reduced pressure, the residual liquid was gathered (**1ι**). (colorless liquid, 100% yield, 86.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.16 (m, 4H, Ar*H*), 5.20–5.16 (m, 1H, $ArCH_2CH{=}C(CH_3)_2$), 3.67 (s, 2H, $ArCH_2CO$), 3.35 (d, *J* = 7.0 Hz, 2H, $ArCH_2CH{=}C(CH_3)_2$), 1.71 (m, 6H, $ArCH_2CH{=}C(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ177.0, 140.4, 132.9, 131.7, 130.7, 129.5, 127.8, 126.3, 122.4, 38.2, 32.1, 25.6, 17.9; IR (neat) 2361, 2342, 1697, 1412, 1308, 1290, 1281, 1150, 951, 930, 750, 725, 631, 438 cm^{-1}.

1-5. General Procedure and Characterization of Products

General procedure for catalytic oxidative cross-coupling reaction

A 20 mL schlenk flask equipped with a magnetic stirring bar and 3-way glass stopcock was charged with 4A crushed molecular sieves (MS4A 100.0 mg) and flamed-dried under vacuum. After cooling down to room temperature, $Fe(OAc)_2$ (1.7 mg, 0.01 mmol), **L10** (2.7 mg, 0.01 mmol), carboxylic acid **1** (0.20 mmol) and TEMPO derivatives **2** (0.42 mmol) were added followed by the addition of THF (1.0 mL, 0.20 M). After stirring under argon at 60 °C for 24 h, the reaction mixture was added dehydrated MeOH (2.0 mL) and 2.0 M $TMSCHN_2$ in hexane (0.30 mL, 0.60 mmol). After stirring under argon at room temperature for 1 h, the reaction mixture was diluted with 10% AcOH in EtOAc (1.0 mL). The diluted solution was filtered through silica short column and washed with EtOAc. After evaporation of the organic solvent under reduced pressure, the resultant mixture was purified by silica gel flash chromatography to obtain methyl esterified cross-coupling product (**3aa**, **Me-3aa**–**Me-3ζa, Me-3yb**–**Me-3yd**).

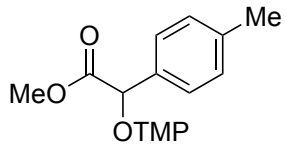
2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*p*-tolyl)acetic acid (3aa)



2-(*p*-tolyl)acetic acid **1a** (30.0 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. Without esterification, the resultant mixture was purified by silica gel flash chromatography (10%–20% EtOAc in *n*-Hexane as eluent) to afford the product **3aa**. (white solid, 95% yield, 59.0 mg); **gram scale synthesis:** A 300 mL two-necked flask equipped with a magnetic stirring bar and 3-way glass stopcock was charged with 4A crushed molecular sieves (MS4A 2.00 g) and flamed-dried under vacuum. After cooling down to room temperature, $Fe(OAc)_2$ (7.0 mg, 0.04 mmol), **L10** (10.7 mg, 0.04 mmol), carboxylic acid **1a** (601 mg, 4.0 mmol) and TEMPO **2a** (1.31 g, 8.4 mmol) were added followed by the addition of THF (20 mL, 0.20 M). After stirring under argon at 60 °C for 72 h, the reaction mixture was diluted with 10% AcOH in EtOAc. The diluted solution was filtered through silica short column and washed with EtOAc. After evaporation of the organic solvent under reduced pressure, the resultant mixture was purified by silica gel flash chromatography (10%–20% EtOAc in *n*-Hexane as eluent) to afford the product **3aa**. (white solid, 97% yield, 1.19 g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.18 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.38 (s, 1H, COC*H*), 2.35 (s, 3H, ArC*H*$_3$), 1.66 (m, 5H, *TMP*), 1.48 (br, 1H, *TMP*), 1.33–1.21 (m, 12H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 138.6, 133.4, 129.2, 128.7, 84.0, 62.7, 62.5, 39.6, 39.6, 31.9, 31.1, 21.3, 20.9, 20.9,

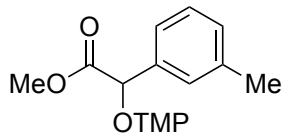
16.5; IR (neat) 2926, 1715, 1375, 1260, 1177, 1132, 1047, 957, 924, 816, 797, 714, 681, 613, 503 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{28}NO_3$ $(M + H)^+$ 306.2064, found 306.2063.

methyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*p*-tolyl)acetate (Me-3aa)



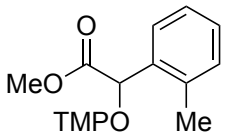
2-(*p*-tolyl)acetic acid **1a** (30.0 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3aa**. (white solid, 85% yield, 54.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.14 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.17 (s, 1H, COC*H*), 3.64 (s, 3H, COOC*H*$_3$), 2.33 (s, 3H, ArC*H*$_3$), 1.58–1.26 (m, 6H, *TMP*), 1.23 (s, 3H, *TMP*), 1.13 (s, 3H, *TMP*), 1.07 (s, 3H, *TMP*), 0.73 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 137.7, 135.2, 129.0, 126.8, 88.4, 59.9, 59.9, 51.8, 40.2, 40.1, 33.6, 32.9, 21.2, 20.2, 20.1, 17.1; IR (neat) 1749, 1366, 1261, 1198, 1155, 1134, 1063, 978, 957, 926, 820, 814, 797, 741, 501 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{30}NO_3$ $(M + H)^+$ 320.2220, found 320.2220.

methyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*m*-tolyl)acetate (Me-3ba)



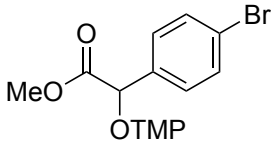
2-(*m*-tolyl)acetic acid **1b** (30.0 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ba**. (white solid, 88% yield, 56.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.20 (m, 3H, Ar*H*), 7.09 (d, *J* = 6.5 Hz, 1H, Ar*H*), 5.17 (s, 1H, COC*H*), 3.66 (s, 3H, COOC*H*$_3$), 2.35 (s, 3H, ArC*H*$_3$), 1.57–1.26 (m, 6H, *TMP*), 1.23 (s, 3H, *TMP*), 1.13 (s, 3H, *TMP*), 1.08 (s, 3H, *TMP*), 0.73 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 138.0, 138.0, 128.7, 128.2, 127.4, 124.0, 88.6, 59.9, 59.9, 51.8, 40.2, 40.1, 33.6, 32.9, 21.5, 20.2, 20.2, 17.1; IR (neat) 1742, 1439, 1333, 1192, 1173, 1167, 1150, 1134, 1061, 800, 737, 729, 692, 434 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{30}NO_3$ $(M + H)^+$ 320.2220, found 320.2229.

methyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*o*-tolyl)acetate (Me-3ca)



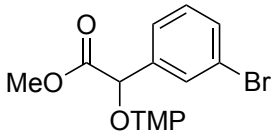
$Fe(OAc)_2$ (3.5 mg, 0.02 mmol), **L10** (5.3 mg, 0.02 mmol), 2-(*o*-tolyl)acetic acid **1c** (30.0 mg, 0.20 mmol) and TEMPO **2a** (125.0 mg, 0.80 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ca**. (colorless liquid, 86% yield, 55.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 7.5 Hz, 1H, Ar*H*), 7.23–7.16 (m, 2H, Ar*H*), 7.11 (d, J = 7.5 Hz, 1H, Ar*H*), 5.41 (s, 1H, COC*H*), 3.65 (s, 3H, COOCH_3), 2.41 (s, 3H, ArCH_3), 1.56–1.28 (m, 6H, *TMP*), 1.24 (s, 3H, *TMP*), 1.15 (s, 3H, *TMP*), 1.04 (s, 3H, *TMP*), 0.66 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 137.0, 135.3, 130.1, 127.7, 127.5, 126.1, 85.7, 59.9, 59.8, 51.7, 40.2, 40.0, 32.8, 32.8, 20.2, 20.2, 19.5, 17.1; IR (neat) 2924, 1746, 1360, 1260, 1192, 1157, 1134, 1105, 1057, 1045, 957, 928, 795, 737, 447 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{30}NO_3$ $(M + H)^+$ 320.2220, found 320.2234.

methyl 2-(4-bromophenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3da)



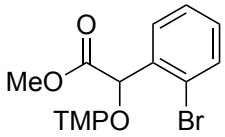
2-(4-bromophenyl)acetic acid **1d** (43.0 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3da**. (white solid, 80% yield, 61.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 8.5 Hz, 2H, Ar*H*), 7.32 (d, J = 8.5 Hz, 2H, Ar*H*), 5.17 (s, 1H, COC*H*), 3.66 (s, 3H, COOCH_3), 1.57–1.29 (m, 6H, *TMP*), 1.22 (s, 3H, *TMP*), 1.12 (s, 3H, *TMP*), 1.06 (s, 3H, *TMP*), 0.72 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 137.2, 131.6, 128.6, 122.1, 88.0, 60.0, 59.9, 52.0, 40.2, 40.1, 33.6, 32.8, 20.2, 20.1, 17.0; IR (neat) 2359, 2340, 1749, 1364, 1260, 1200, 1159, 1134, 1065, 1013, 926, 822, 760, 505 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{27}BrNO_3$ $(M + H)^+$ 384.1169, found 384.1169.

methyl 2-(3-bromophenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3ea)



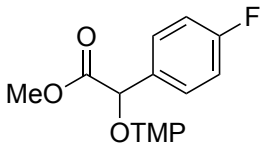
2-(3-bromophenyl)acetic acid **1e** (43.0 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ea**. (white solid, 88% yield, 68.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (t, *J* = 2.0 Hz, 1H, Ar*H*), 7.42 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar*H*), 7.37 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.21 (t, *J* = 8.0 Hz, 1H, Ar*H*), 5.18 (s, 1H, COC*H*), 3.67 (s, 3H, COOC*H*$_3$), 1.57–1.26 (m, 6H, *TMP*), 1.22 (s, 3H, *TMP*), 1.12 (s, 3H, *TMP*), 1.08 (s, 3H, *TMP*), 0.73 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 140.3, 131.1, 130.0, 129.8, 125.5, 122.5, 87.9, 60.0, 60.0, 52.0, 40.2, 40.1, 33.6, 32.8, 20.2, 20.2, 17.0; IR (neat) 1749, 1734, 1260, 1196, 1155, 1132, 1057, 920, 880, 802, 793, 768, 700, 689 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{27}BrNO_3$ $(M + H)^+$ 384.1169, found 384.1173.

methyl 2-(2-bromophenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3fa)



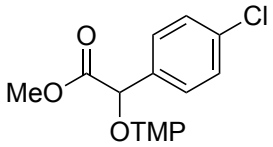
$Fe(OAc)_2$ (3.5 mg, 0.02 mmol), **L10** (5.3 mg, 0.02 mmol), 2-(2-bromophenyl)acetic acid **1f** (43.0 mg, 0.20 mmol) and TEMPO **2a** (125.0 mg, 0.80 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3fa**. (white solid, 93% yield, 71.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 7.51 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 7.34 (dt, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 7.15 (dt, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 5.67 (s, 1H, COC*H*), 3.68 (s, 3H, COOC*H*$_3$), 1.57–1.29 (m, 6H, *TMP*), 1.22 (s, 3H, *TMP*), 1.16 (s, 3H, *TMP*), 1.02 (s, 3H, *TMP*), 0.70 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 138.2, 132.4, 129.4, 129.3, 127.6, 122.6, 86.6, 60.0, 59.9, 51.9, 40.1, 39.9, 32.8, 32.8, 20.2, 20.1, 17.1; IR (neat) 1742, 1470, 1433, 1339, 1204, 1169, 1132, 1047, 1018, 995, 982, 922, 799, 745 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{27}BrNO_3$ $(M + H)^+$ 384.1169, found 384.1169.

methyl 2-(4-fluorophenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3ga)



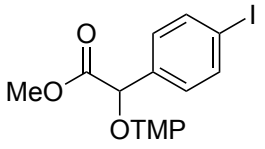
2-(4-fluorophenyl)acetic acid **1g** (30.8 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ga**. (white solid, 83% yield, 53.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.5, 5.5 Hz, 2H, Ar*H*), 7.02 (t, *J* = 8.5 Hz, 2H, Ar*H*), 5.18 (s, 1H, COC*H*), 3.66 (s, 3H, COOC*H*$_3$), 1.57–1.29 (m, 6H, *TMP*), 1.22 (s, 3H, *TMP*), 1.12 (s, 3H, *TMP*), 1.06 (s, 3H, *TMP*), 0.71 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 138.6, 133.4, 129.2, 128.7, 84.0, 62.7, 62.5, 39.6, 39.6, 31.9, 31.1, 21.3, 20.9, 20.9, 16.5; IR (neat) 1748, 1506, 1362, 1223, 1196, 1165, 1153, 1134, 1098, 1061, 926, 835, 812, 748, 536, 513 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{27}FNO_3$ $(M + H)^+$ 324.1969, found 324.1960.

methyl 2-(4-chlorophenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3ha)



2-(4-chlorophenyl)acetic acid **1h** (34.1 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ha**. (colorless liquid, 84% yield, 57.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.31 (d, *J* = 8.5 Hz, 2H, Ar*H*), 5.18 (s, 1H, COC*H*), 3.66 (s, 3H, COOC*H*$_3$), 1.58–1.29 (m, 6H, *TMP*), 1.22 (s, 3H, *TMP*), 1.12 (s, 3H, *TMP*), 1.06 (s, 3H, *TMP*), 0.71 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 136.7, 133.9, 128.6, 128.3, 87.9, 60.0, 59.9, 52.0, 40.2, 40.1, 33.6, 32.8, 20.2, 20.1, 17.0; IR (neat) 1744, 1439, 1362, 1261, 1200, 1159, 1132, 1088, 1051, 1015, 974, 930, 827, 764, 517, 434 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{27}ClNO_3$ $(M + H)^+$ 340.1674, found 340.1673.

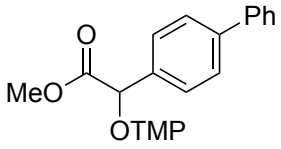
methyl 2-(4-iodophenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3ia)



2-(4-iodophenyl)acetic acid **1i** (52.4 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used.

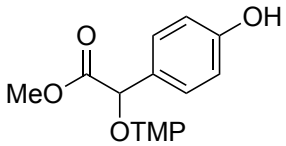
The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ia**. (white solid, 81% yield, 70.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.19 (d, *J* = 8.5 Hz, 2H, Ar*H*), 5.15 (s, 1H, COC*H*), 3.65 (s, 3H, COOC*H*$_3$), 1.57–1.29 (m, 6H, *TMP*), 1.22 (s, 3H, *TMP*), 1.11 (s, 3H, *TMP*), 1.06 (s, 3H, *TMP*), 0.72 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 137.8, 137.5, 128.8, 93.8, 88.1, 60.0, 60.0, 52.0, 40.2, 40.1, 33.6, 32.8, 20.2, 20.1, 17.0; IR (neat) 1744, 1260, 1200, 1153, 1132, 1067, 1049, 1011, 974, 926, 818, 754, 735, 501 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{27}INO_3$ $(M + H)^+$ 432.1030, found 432.1030.

methyl 2-([1,1'-biphenyl]-4-yl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3ja)



2-([1,1'-biphenyl]-4-yl)acetic acid **1j** (42.5 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (2% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ja**. (white solid, 75% yield, 57.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.56 (m, 4H, Ar*H*), 7.50 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.43 (t, *J* = 7.0 Hz, 2H, Ar*H*), 7.33 (t, *J* = 7.0 Hz, 1H, Ar*H*), 5.26 (s, 1H, COC*H*), 3.68 (s, 3H, COOC*H*$_3$), 1.56–1.30 (m, 6H, *TMP*), 1.25 (s, 3H, *TMP*), 1.15 (s, 3H, *TMP*), 1.10 (s, 3H, *TMP*), 0.77 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 140.8, 140.7, 137.1, 128.7, 127.3, 127.3, 127.1, 127.1, 88.4, 59.9, 59.9, 51.9, 40.2, 40.1, 33.7, 32.9, 20.2, 20.2, 17.1; IR (neat) 1742, 1431, 1362, 1196, 1163, 1132, 1055, 974, 957, 928, 837, 756, 741, 729, 700, 691 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{24}H_{32}NO_3$ $(M + H)^+$ 382.2377, found 382.2377.

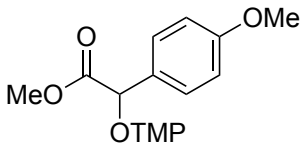
methyl 2-(4-hydroxyphenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3ka)



2-(4-acetoxyphenyl)acetic acid **Ac-1k** (38.8 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. Esterification was conducted for 24 h stirring at room temperature. The resultant mixture was purified by silica gel flash chromatography (10% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ka**. (White solid, 50% yield, 32.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.5 Hz, 2H, Ar*H*), 6.79 (d, *J* = 7.5 Hz, 2H, Ar*H*), 5.13 (s, 1H, COC*H*), 4.98 (br, 1H, ArO*H*),

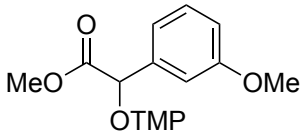
3.66 (s, 3H, COOC*H*$_3$), 1.64–1.26 (m, 6H, *TMP*), 1.21 (s, 3H, *TMP*), 1.12 (s, 3H, *TMP*), 1.05 (s, 3H, *TMP*), 0.73 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 155.4, 130.5, 128.5, 115.5, 88.1, 59.9, 59.8, 51.8, 40.2, 40.1, 33.7, 32.9, 20.2, 20.1, 17.1; IR (neat) 3406, 2938, 1703, 1510, 1275, 1261, 1223, 1165, 1051, 1015, 841, 623, 538, 527 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{28}NO_4$ $(M + H)^+$ 322.2013, found 322.2018.

methyl 2-(4-methoxyphenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3la)



2-(4-methoxyphenyl)acetic acid **1l** (33.2 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (3% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3la**. (white solid, 86% yield, 57.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.86 (d, *J* = 8.5 Hz, 2H, Ar*H*), 5.14 (s, 1H, COC*H*), 3.80 (s, 3H, OC*H*$_3$), 3.65 (s, 3H, COOC*H*$_3$), 1.58–1.28 (m, 6H, *TMP*), 1.22 (s, 3H, *TMP*), 1.13 (s, 3H, *TMP*), 1.06 (s, 3H, *TMP*), 0.73 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 159.3, 130.4, 128.2, 113.7, 88.1, 59.9, 59.8, 55.2, 51.8, 40.2, 40.1, 33.7, 32.9, 20.2, 20.1, 17.1; IR (neat) 2359, 1753, 1510, 1244, 1202, 1159, 1132, 1057, 1030, 928, 833, 799, 789, 530 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{30}NO_4$ $(M + H)^+$ 336.2169, found 336.2185.

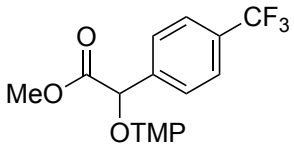
methyl 2-(3-methoxyphenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3ma)



2-(3-methoxyphenyl)acetic acid **1m** (33.2 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (3% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ma**. (white solid, 88% yield, 59.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.02–7.00 (m, 2H, Ar*H*), 6.83 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H, Ar*H*), 5.19 (s, 1H, COC*H*), 3.81 (s, 3H, OC*H*$_3$), 3.66 (s, 3H, COOC*H*$_3$), 1.58–1.29 (m, 6H, *TMP*), 1.23 (s, 3H, *TMP*), 1.13 (s, 3H, *TMP*), 1.09 (s, 3H, *TMP*), 0.75 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 159.6, 139.6, 129.3, 119.3, 113.7, 112.1, 88.5, 59.9, 59.9, 55.3, 51.9, 40.2, 40.1, 33.5, 32.8, 20.2, 20.2, 17.1; IR (neat) 1749, 1734, 1584, 1296, 1261, 1234, 1159, 1140, 1061, 1043, 1032, 795, 779, 741, 727, 694 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{30}NO_4$ $(M + H)^+$ 336.2169,

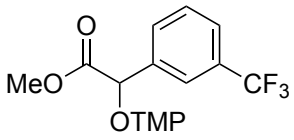
found 336.2161.

methyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(4-(trifluoromethyl)phenyl)acetate (Me-3na)



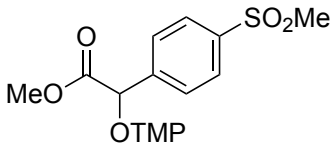
2-(4-(trifluoromethyl)phenyl)acetic acid **1n** (40.8 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3na**. (white solid, 81% yield, 60.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.56 (d, *J* = 8.5 Hz, 2H, Ar*H*), 5.28 (s, 1H, COC*H*), 3.67 (s, 3H, COOC*H*$_3$), 1.58–1.30 (m, 6H, *TMP*), 1.24 (s, 3H, *TMP*), 1.13 (s, 3H, *TMP*), 1.08 (s, 3H, *TMP*), 0.70 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 142.0, 130.2 (q, *J* = 32.3 Hz), 127.1, 125.4 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 270.3 Hz), 88.1, 60.0, 60.0, 52.1, 40.2, 40.1, 33.5, 32.8, 20.2, 20.2, 17.0; IR (neat) 1748, 1323, 1202, 1159, 1128, 1109, 1067, 1059, 1020, 976, 928, 918, 837, 716 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{27}F_3NO_3$ $(M + H)^+$ 374.1938, found 374.1936.

methyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(3-(trifluoromethyl)phenyl)acetate (Me-3oa)



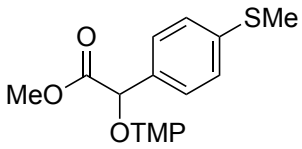
2-(3-(trifluoromethyl)phenyl)acetic acid **1o** (40.8 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3oa**. (colorless liquid, 84% yield, 62.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H, Ar*H*), 7.64 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.56 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.47 (t, *J* = 8.0 Hz, 1H, Ar*H*), 5.28 (s, 1H, COC*H*), 3.68 (s, 3H, COOC*H*$_3$), 1.58–1.29 (m, 6H, *TMP*), 1.24 (s, 3H, *TMP*), 1.14 (s, 3H, *TMP*), 1.08 (s, 3H, *TMP*), 0.68 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 139.2, 130.8 (q, *J* = 32.3 Hz), 130.2, 128.9, 124.9 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 270.3 Hz), 123.7 (q, *J* = 3.7 Hz), 88.0, 60.1, 60.0, 52.1, 40.2, 40.1, 33.6, 32.8, 20.2, 20.1, 17.0; IR (neat) 1753, 1740, 1331, 1261, 1242, 1161, 1125, 1099, 1074, 1018, 918, 800, 745, 700 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{27}F_3NO_3$ $(M + H)^+$ 374.1938, found 374.1938.

methyl 2-(4-(methylsulfonyl)phenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3pa)



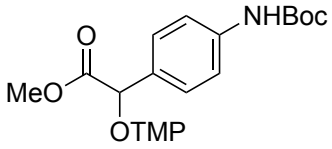
2-(4-(methylsulfonyl)phenyl)acetic acid **1p** (42.8 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (10%–20% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3pa**. (white solid, 79% yield, 60.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.66 (d, *J* = 8.5 Hz, 2H, Ar*H*), 5.32 (s, 1H, COC*H*), 3.68 (s, 3H, COOCH_3), 3.06 (s, 3H, SO_2CH_3), 1.57–1.26 (m, 6H, *TMP*), 1.24 (s, 3H, *TMP*), 1.13 (s, 3H, *TMP*), 1.08 (s, 3H, *TMP*), 0.69 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 144.2, 140.1, 127.7, 127.6, 88.0, 60.1, 60.1, 52.2, 44.5, 40.2, 40.0, 33.6, 32.8, 20.2, 20.2, 17.0; IR (neat) 1740, 1306, 1260, 1206, 1165, 1152, 1132, 1090, 1067, 955, 839, 793, 768, 746, 546, 532 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{30}NO_5S$ $(M + H)^+$ 384.1839, found 384.1839.

methyl 2-(4-(methylthio)phenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3qa)



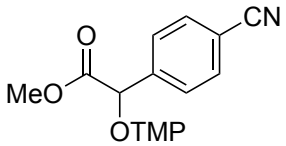
2-(4-(methylthio)phenyl)acetic acid **1q** (36.4 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3qa**. (white solid, 81% yield, 57.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.21 (d, *J* = 8.5 Hz, 2H, Ar*H*), 5.16 (s, 1H, COC*H*), 3.65 (s, 3H, COOCH_3), 2.48 (s, 3H, SCH_3), 1.56–1.28 (m, 6H, *TMP*), 1.22 (s, 3H, *TMP*), 1.12 (s, 3H, *TMP*), 1.06 (s, 3H, *TMP*), 0.73 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 138.3, 134.9, 127.4, 126.3, 88.2, 59.9, 59.9, 51.9, 40.2, 40.1, 33.7, 32.8, 20.2, 20.1, 17.1, 15.6; IR (neat) 2922, 1744, 1435, 1206, 1153, 1132, 1061, 976, 955, 926, 816, 764, 737, 694 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{30}NO_3S$ $(M + H)^+$ 352.1941, found 352.1941.

methyl 2-(4-((*tert*-butoxycarbonyl)amino)phenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3ra)



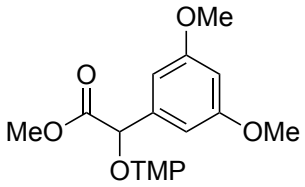
2-(4-((*tert*-butoxycarbonyl)amino)phenyl)acetic acid **1r** (50.3 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (5% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ra**. (white solid, 90% yield, 75.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.33 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.49 (br, 1H, N*H*) 5.15 (s, 1H, COC*H*), 3.64 (s, 3H, COOCH_3), 1.63–1.24 (m, 6H, *TMP*), 1.51 (s, 9H, NH*Boc*), 1.22 (s, 3H, *TMP*), 1.12 (s, 3H, *TMP*), 1.05 (s, 3H, *TMP*), 0.72 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 152.7, 138.1, 132.8, 127.7, 118.3, 88.2, 80.6, 59.9, 59.8, 51.8, 40.2, 40.1, 33.7, 32.9, 28.3, 20.2, 20.1, 17.1; IR (neat) 1728, 1713, 1522, 1412, 1366, 1314, 1233, 1207, 1153, 1134, 1051, 1016, 910, 837, 731, 529 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{23}H_{37}N_2O_5$ $(M + H)^+$ 421.2697, found 421.2696.

methyl 2-(4-cyanophenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3sa)



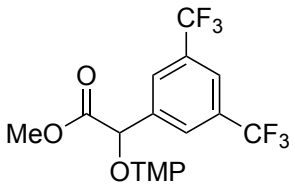
2-(4-cyanophenyl)acetic acid **1s** (32.2 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (5% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3sa**. (white solid, 55% yield, 36.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.56 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.27 (s, 1H, COC*H*), 3.67 (s, 3H, COOCH_3), 1.57–1.26 (m, 6H, *TMP*), 1.23 (s, 3H, *TMP*), 1.12 (s, 3H, *TMP*), 1.08 (s, 3H, *TMP*), 0.68 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 143.2, 132.3, 127.5, 118.6, 112.0, 88.0, 60.1, 60.1, 52.2, 40.2, 40.0, 33.5, 32.8, 20.2, 20.2, 17.0; IR (neat) 1742, 1362, 1261, 1242, 1202, 1186, 1159, 1132, 1061, 1018, 957, 914, 835, 733, 554 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{27}N_2O_3$ $(M + H)^+$ 331.2016, found 331.2016.

methyl 2-(3,5-dimethoxyphenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3ta)



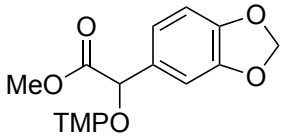
2-(3,5-dimethoxyphenyl)acetic acid **1t** (39.2 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (5% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ta**. (white solid, 82% yield, 59.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (d, *J* = 2.0 Hz, 2H, Ar*H*), 6.38 (t, *J* = 2.0 Hz, 1H, Ar*H*), 5.15 (s, 1H, COC*H*), 3.79 (s, 6H, (OC*H*$_3$)$_2$), 3.66 (s, 3H, COOC*H*$_3$), 1.59–1.29 (m, 6H, *TMP*), 1.23 (s, 3H, *TMP*), 1.11 (s, 3H, *TMP*), 1.10 (s, 3H, *TMP*), 0.79 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 160.6, 140.4, 104.8, 100.1, 88.5, 59.9, 59.9, 55.4, 55.4, 51.9, 40.2, 40.1, 33.5, 32.8, 20.2, 20.2, 17.1; IR (neat) 1748, 1732, 1593, 1454, 1431, 1325, 1204, 1159, 1132, 1067, 1045, 1011, 932, 845, 806, 706 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{20}H_{32}NO_5$ $(M + H)^+$ 366.2275, found 366.2287.

methyl 2-(3,5-bis(trifluoromethyl)phenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3ua)



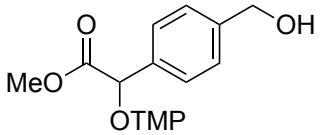
2-(3,5-bis(trifluoromethyl)phenyl)acetic acid **1u** (54.4 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ua**. (white solid, 67% yield, 59.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 2H, Ar*H*), 7.82 (s, 1H, Ar*H*), 5.35 (s, 1H, COC*H*), 3.70 (s, 3H, COOC*H*$_3$), 1.58–1.30 (m, 6H, *TMP*), 1.25 (s, 3H, *TMP*), 1.14 (s, 3H, *TMP*), 1.08 (s, 3H, *TMP*), 0.65 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 140.7, 131.8 (q, *J* = 33.3 Hz), 127.0, 123.2 (q, *J* = 271.1 Hz), 122.0 (q, *J* = 3.7 Hz), 87.4, 60.2, 60.1, 52.3, 40.2, 40.0, 33.6, 32.8, 20.2, 20.1, 17.0; IR (neat) 1748, 1377, 1277, 1204, 1163, 1140, 1117, 1109, 1065, 1045, 920, 893, 804, 739, 702, 681 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{20}H_{26}F_6NO_3$ $(M + H)^+$ 442.1811, found 442.1803.

methyl 2-(benzo[*d*][1,3]dioxol-5-yl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3va)



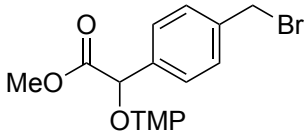
2-(benzo[*d*][1,3]dioxol-5-yl)acetic acid **1v** (36.0 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (3% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3va**. (white solid, 86% yield, 60.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, *J* = 1.5 Hz, 1H, Ar*H*), 6.87 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar*H*), 6.74 (d, *J* = 8.0 Hz, 1H, Ar*H*), 5.93 (m, 2H, OC*H*$_2$O), 5.10 (s, 1H, COC*H*), 3.65 (s, 3H, COOC*H*$_3$), 1.53–1.09 (m, 15H, *TMP*), 0.78 (br, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 147.7, 147.4, 132.2, 120.7, 108.0, 107.5, 101.0, 88.3, 59.9, 59.9, 51.6, 40.2, 40.2, 33.7, 32.8, 20.2, 20.2, 17.1; IR (neat) 1744, 1503, 1489, 1443, 1238, 1198, 1165, 1132, 1070, 1040, 932, 924, 918, 816, 750 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{28}NO_5$ $(M + H)^+$ 350.1962, found 350.1962.

methyl 2-(4-(hydroxymethyl)phenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3wa)



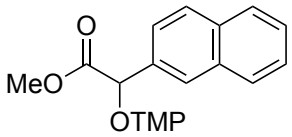
2-(4-(hydroxymethyl)phenyl)acetic acid **1w** (33.2 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (10%–20% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3wa**. (white solid, 79% yield, 52.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.34 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.22 (s, 1H, COC*H*), 4.69 (s, 2H, ArC*H*$_2$OH) 3.65 (s, 3H, COOC*H*$_3$), 1.68 (br, 1H, ArCH$_2$O*H*), 1.58–1.29 (m, 6H, *TMP*), 1.23 (s, 3H, *TMP*), 1.13 (s, 3H, *TMP*), 1.07 (s, 3H, *TMP*), 0.72 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 140.6, 137.6, 127.1, 127.0, 88.4, 65.1, 59.9, 59.9, 51.9, 40.2, 40.1, 33.6, 32.8, 20.2, 20.2, 17.1; IR (neat) 1748, 1314, 1202, 1169, 1059, 1018, 1007, 808, 802, 772, 704, 671, 637, 629 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{30}NO_4$ $(M + H)^+$ 336.2169, found 336.2181.

methyl 2-(4-(bromomethyl)phenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3xa)



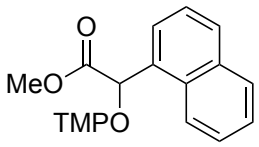
2-(4-(bromomethyl)phenyl)acetic acid **1x** (45.8 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3xa**. (white solid, 36% yield, 28.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.36 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.21 (s, 1H, COC*H*), 4.48 (s, 2H, ArC*H*$_2$Br), 3.66 (s, 3H, COOC*H*$_3$), 1.56–1.26 (m, 6H, *TMP*), 1.23 (s, 3H, *TMP*), 1.12 (s, 3H, *TMP*), 1.07 (s, 3H, *TMP*), 0.72 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 138.4, 137.4, 129.1, 127.3, 88.3, 59.9, 59.9, 51.9, 40.2, 40.1, 33.6, 33.2, 32.8, 20.2, 20.2, 17.1; IR (neat) 2930, 1744, 1335, 1261, 1229, 1209, 1163, 1132, 1069, 914, 835, 737, 710, 691, 604 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{29}BrNO_3$ $(M + H)^+$ 398.1325, found 398.1333.

methyl 2-(naphthalen-2-yl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3ya)



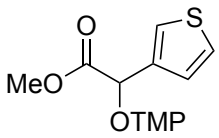
2-(naphthalen-2-yl)acetic acid **1y** (37.2 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ya**. (white solid, 91% yield, 64.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H, Ar*H*), 7.86–7.81 (m, 3H, Ar*H*), 7.59 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar*H*), 7.49–7.45 (m, 2H, Ar*H*), 5.38 (s, 1H, COC*H*), 3.65 (s, 3H, COOC*H*$_3$), 1.58–1.39 (m, 6H, *TMP*), 1.28 (s, 3H, *TMP*), 1.18 (s, 3H, *TMP*), 1.09 (s, 3H, *TMP*), 0.71 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 135.6, 133.1, 133.1, 128.2, 128.2, 127.7, 126.1, 126.1, 126.0, 124.7, 88.7, 60.0, 59.9, 51.9, 40.3, 40.1, 33.7, 32.9, 20.3, 20.2, 17.1; IR (neat) 1746, 1738, 1196, 1175, 1163, 1132, 1059, 860, 818, 748, 733, 721, 478, 473 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{22}H_{30}NO_3$ $(M + H)^+$ 356.2220, found 356.2220.

methyl 2-(naphthalen-1-yl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3za)



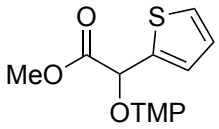
$Fe(OAc)_2$ (3.5 mg, 0.02 mmol), **L10** (5.3 mg, 0.02 mmol), 2-(naphthalen-1-yl)acetic acid **1z** (37.2 mg, 0.20 mmol) and TEMPO **2a** (125.0 mg, 0.80 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3za**. (colorless liquid, 92% yield, 65.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (d, J = 8.5 Hz, 1H, Ar*H*), 7.84 (d, J = 8.0 Hz, 1H, Ar*H*), 7.80 (d, J = 8.0 Hz, 1H, Ar*H*), 7.70 (d, J = 7.0 Hz, 1H, Ar*H*), 7.53 (dt, J = 7.0, 1.5 Hz, 1H, Ar*H*), 7.47 (m, 2H, Ar*H*), 5.86 (s, 1H, COC*H*), 3.61 (s, 3H, COOC*H*$_3$), 1.56–1.52 (m, 3H, *TMP*), 1.37–1.31 (m, 6H, *TMP*), 1.24 (s, 3H, *TMP*), 1.01 (s, 3H, *TMP*), 0.52 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 134.6, 133.7, 130.6, 128.6, 128.5, 126.2, 126.2, 125.6, 125.3, 124.8, 87.2, 60.1, 60.0, 51.9, 40.2, 40.0, 33.2, 32.9, 20.3, 20.2, 17.1; IR (neat) 1749, 1734, 1261, 1238, 1157, 1132, 1082, 1057, 1047, 1016, 804, 787, 773, 741, 718 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{22}H_{30}NO_3$ $(M + H)^+$ 356.2220, found 356.2220.

methyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(thiophen-3-yl)acetate (Me-3αa)



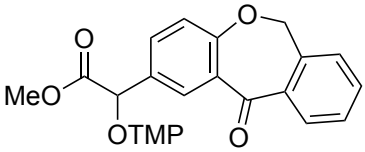
2-(thiophen-3-yl)acetic acid **1α** (28.4 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3αa**. (white solid, 82% yield, 50.9 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (ddd, J = 3.0, 1.0, 0.5 Hz, 1H, Ar*H*), 7.27 (dd, J = 5.0, 3.0 Hz, 1H, Ar*H*), 7.14 (dd, J = 5.0, 1.0 Hz, 1H, Ar*H*), 5.31 (s, 1H, COC*H*), 3.68 (s, 3H, COOC*H*$_3$), 1.58–1.26 (m, 6H, *TMP*), 1.21 (s, 3H, *TMP*), 1.12 (s, 3H, *TMP*), 1.07 (s, 3H, *TMP*), 0.80 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 138.5, 126.4, 125.7, 122.7, 85.2, 60.0, 59.9, 51.9, 40.2, 40.1, 33.3, 32.9, 20.2, 20.1, 17.1; IR (neat) 1744, 1277, 1209, 1163, 1144, 1132, 1053, 1013, 841, 810, 797, 775, 714, 671 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{26}NO_3S$ $(M + H)^+$ 312.1628, found 312.1637.

methyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(thiophen-2-yl)acetate (Me-3βa)



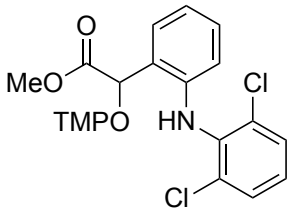
2-(thiophen-2-yl)acetic acid **1β** (28.4 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3βa**. (white solid, 40% yield, 24.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 5.0, 1.0 Hz, 1H, Ar*H*), 7.05 (d, *J* = 3.5 Hz, 1H, Ar*H*), 6.96 (dd, *J* = 5.0, 3.5 Hz, 1H, Ar*H*), 5.45 (s, 1H, COC*H*), 3.71 (s, 3H, COOC*H*$_3$), 1.57–1.26 (m, 6H, *TMP*), 1.20 (s, 3H, *TMP*), 1.11 (s, 3H, *TMP*), 1.09 (s, 3H, *TMP*), 0.86 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 140.1, 126.4, 126.0, 125.9, 84.6, 60.1, 60.1, 52.1, 40.2, 40.2, 33.4, 32.9, 20.2, 19.9, 17.1; IR (neat) 1728, 1263, 1209, 1175, 1132, 1036, 1011, 989, 959, 920, 862, 812, 729, 704, 646 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{26}NO_3S$ $(M + H)^+$ 312.1628, found 312.1628.

methyl 2-(11-oxo-10,11-dihydrodibenzo[*b*,*f*]oxepin-2-yl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3γa)



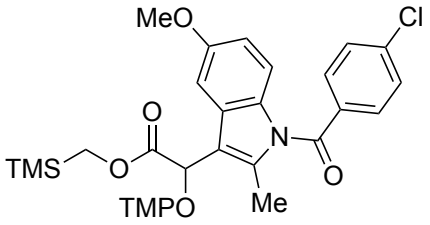
2-(11-oxo-10,11-dihydrodibenzo[*b*,*f*]oxepin-2-yl)acetic acid **1γ** (53.7 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (5% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3γa**. (white solid, 85% yield, 74.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.90 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.64 (dd, *J* = 7.5, 2.0 Hz, 1H, Ar*H*), 7.56 (dt, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.47 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.36 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.06 (d, *J* = 8.5 Hz, 1H, Ar*H*), 5.25 (s, 1H, COC*H*), 5.19 (s, 2H, ArOC*H*$_2$Ar), 3.67 (s, 3H, COOC*H*$_3$), 1.60–1.29 (m, 6H, *TMP*), 1.23 (s, 3H, *TMP*), 1.14 (s, 3H, *TMP*), 1.07 (s, 3H, *TMP*), 0.74 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.7, 172.2, 161.0, 140.5, 135.4, 133.8, 132.7, 132.1, 130.5, 129.5, 129.3, 127.8, 124.9, 121.1, 87.6, 73.6, 60.0, 60.0, 51.9, 40.2, 40.0, 33.8, 32.9, 20.2, 20.2, 17.1; IR (neat) 1732, 1639, 1296, 1275, 1256, 1240, 1219, 1192, 1144, 1119, 1063, 1009, 993, 768, 698, 631 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{26}H_{32}NO_5$ $(M + H)^+$ 438.2275, found 438.2275.

methyl 2-(2-((2,6-dichlorophenyl)amino)phenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3δa)



MS4A (50.0 mg), $Fe(OAc)_2$ (3.5 mg, 0.02 mmol), **L10** (5.3 mg, 0.02 mmol), 2-(2-((2,6-dichlorophenyl)amino)phenyl)acetic acid **1δ** (29.6 mg, 0.10 mmol), TEMPO **2a** (62.5 mg, 0.40 mmol) and THF (0.50 mL, 0.20 M) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3δa**. (white solid, 74% yield, 34.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.34 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.13 (dt, *J* = 7.5, 1.5 Hz, 1H, Ar*H*), 7.01–6.96 (m, 2H, Ar*H*), 6.74 (s, 1H, ArN*H*Ar), 6.46 (d, *J* = 8.0 Hz, 1H, Ar*H*), 5.62 (s, 1H, COC*H*), 3.73 (s, 3H, COOCH_3), 1.56–1.28 (m, 6H, *TMP*), 1.27 (s, 3H, *TMP*), 1.20 (s, 3H, *TMP*), 1.14 (s, 3H, *TMP*), 0.78 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 140.6, 137.0, 130.0, 128.9, 128.4, 128.2, 127.0, 124.3, 121.2, 116.8, 85.6, 60.2, 59.9, 52.2, 40.4, 40.2, 33.4, 32.8, 20.4, 20.3, 17,1; IR (neat) 1753, 1504, 1447, 1198, 1167, 1155, 1101, 1059, 781, 770, 748, 714, 667, 482, 457 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{24}H_{31}Cl_2N_2O_3$ $(M + H)^+$ 465.1706, found 465.1727.

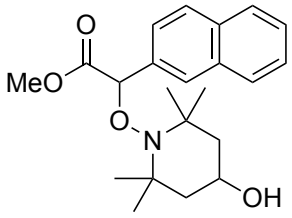
(trimethylsilyl)methyl 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (TMSCH_2-3εa)



$Fe(OAc)_2$ (3.5 mg, 0.02 mmol), **L10** (5.3 mg, 0.02 mmol), 2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid **1ε** (71.6 mg, 0.20 mmol) and TEMPO **2a** (125.0 mg, 0.80 mmol) were used. The product **3εa** was obtained in 61% yield determined by ^{1}H NMR analysis using dibenzyl as an internal standard. Then, esterification was conducted without MeOH because deacylation progressed when MeOH was added. The resultant mixture was purified by silica gel flash chromatography (1–3% EtOAc in *n*-Hexane as eluent) to afford the (trimethylsilyl)methyl esterified

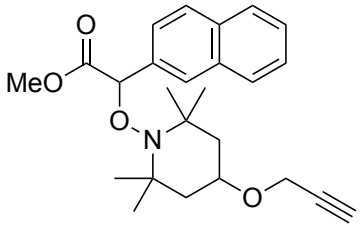
product **TMSCH$_2$-3εa**. (yellow liquid); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.46 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.39 (br, 1H, Ar*H*), 6.84 (d, *J* = 9.0 Hz, 1H, Ar*H*), 6.66 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 5.47 (s, 1H, COC*H*), 3.85 (s, 3H, ArOC*H*$_3$), 3.76 (m, 2H, COOC*H*$_2$TMS), 2.44 (s, 3H, ArC*H*$_3$), 1.54–1.31 (m, 6H, *TMP*), 1.28 (s, 3H, *TMP*), 1.20 (s, 3H, *TMP*), 1.01 (s, 3H, *TMP*), 0.82 (s, 3H, *TMP*), -0.05 (s, 9H, *TMS*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 168.4, 155.8, 139.4, 135.1, 133.9, 131.2, 130.1, 129.1, 129.0, 117.4, 114.5, 112.2, 103.7, 83.3, 60.0, 59.8, 57.9, 55.6, 40.1, 39.9, 33.0, 33.0, 20.4, 20.3, 17.1, 13.6, -3.2; IR (neat) 1686, 1476, 1362, 1312, 1260, 1250, 1225, 1088, 1070, 1015, 856, 841, 756, 731 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{32}H_{44}ClN_2O_5Si$ $(M + H)^+$ 599.2703, found 599.2703.

methyl 2-((4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(naphthalen-2-yl)acetate (Me-3yb)



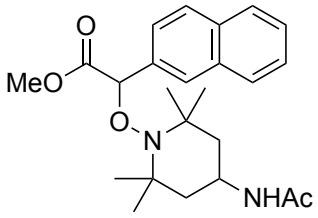
MS4A (50.0 mg), $Fe(OAc)_2$ (1.7 mg, 0.01 mmol), **L10** (2.7 mg, 0.01 mmol), 2-(naphthalen-2-yl)acetic acid **1y** (18.6 mg, 0.10 mmol), 4-hydroxy-TEMPO **2b** (36.2 mg, 0.21 mmol) and THF (0.50 mL, 0.20 M) were used. The resultant mixture was purified by silica gel flash chromatography (10%–20% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3yb**. (white solid, 89% yield, 33.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88-7.82 (m, 4H, Ar*H*), 7.57 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar*H*), 7.49–7.48 (m, 2H, Ar*H*), 5.37 (s, 1H, COC*H*), 4.00–3.95 (m, 1H, C*H*OH) 3.66 (s, 3H, COOC*H*$_3$), 1.87–1.85 (m, 1H, *TMP*), 1.77–1.74 (m, 1H, *TMP*), 1.58 (br, 1H, CHO*H*), 1.52–1.47 (m, 1H, *TMP*), 1.43–1.38 (m, 1H, *TMP*), 1.33 (s, 3H, *TMP*), 1.22 (s, 3H, *TMP*), 1.14 (s, 3H, *TMP*), 0.74 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 135.4, 133.1, 133.1, 128.3, 128.2, 127.7, 126.2, 126.2, 124.6, 88.8, 63.1, 60.4, 60.4, 52.0, 48.6, 48.5, 33.7, 32.9, 21.2, 21.2, 14.2; IR (neat) 1742, 1362, 1260, 1194, 1173, 1165, 1040, 1032, 953, 901, 818, 748, 735, 721, 478 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{22}H_{30}NO_4$ $(M + H)^+$ 372.2169, found 372.2172.

methyl 2-(naphthalen-2-yl)-2-((2,2,6,6-tetramethyl-4-(prop-2-yn-1-yloxy)piperidin-1-yl)oxy)acetate (Me-3yc)



MS4A (50.0 mg), $Fe(OAc)_2$ (1.7 mg, 0.01 mmol), **L10** (2.7 mg, 0.01 mmol), 2-(naphthalen-2-yl)acetic acid **1y** (18.6 mg, 0.10 mmol), 4-propargyloxy-TEMPO **2c** (44.2 mg, 0.21 mmol) and THF (0.50 mL, 0.20 M) were used. The resultant mixture was purified by silica gel flash chromatography (5% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3yc**. (white solid, 90% yield, 36.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H, Ar*H*), 7.85–7.80 (m, 3H, Ar*H*), 7.57 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar*H*), 7.48–7.44 (m, 2H, Ar*H*), 5.37 (s, 1H, COC*H*), 4.14 (d, *J* = 2.5 Hz, 2H, OCH_2CCH), 3.84–3.78 (m, 1H, C*H*OCH$_2$CCH) 3.65 (s, 3H, COOCH_3), 2.38 (t, *J* = 2.5 Hz, 1H, OCH$_2$CC*H*), 1.92–1.90 (m, 1H, *TMP*), 1.81–1.79 (m, 1H, *TMP*), 1.49–1.38 (m, 2H, *TMP*), 1.35 (s, 3H, *TMP*), 1.23 (s, 3H, *TMP*), 1.15 (s, 3H, *TMP*), 0.75 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 135.4, 133.2, 133.2, 128.2, 128.1, 127.7, 126.2, 126.1, 126.1, 124.6, 88.8, 80.2, 73.9, 69.6, 60.4, 60.3, 55.3, 51.8, 45.2, 45.0, 33.8, 33.0, 21.2, 21.2; IR (neat) 1746, 1364, 1192, 1173, 1161, 1082, 1053, 978, 953, 862, 818, 752, 729, 654, 476 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{25}H_{32}NO_4$ $(M + H)^+$ 410.2326, found 410.2326.

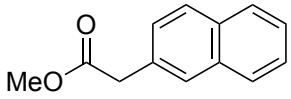
methyl 2-((4-acetamido-2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(naphthalen-2-yl)acetate (Me-3yd)



MS4A (50.0 mg), $Fe(OAc)_2$ (1.7 mg, 0.01 mmol), **L10** (2.7 mg, 0.01 mmol), 2-(naphthalen-2-yl)acetic acid **1y** (18.6 mg, 0.10 mmol), 4-acetamido-TEMPO **2d** (44.8 mg, 0.21 mmol) and THF (0.50 mL, 0.20 M) were used. The resultant mixture was purified by silica gel flash chromatography (5–67% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3yd** and methyl esterified starting material **Me-1y**. (white solid, 62% yield, 25.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H,

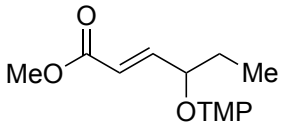
Ar*H*), 7.86–7.81 (m, 3H, Ar*H*), 7.57 (dd, *J* = 8.5, 1.5 Hz, 1H, Ar*H*), 7.50–7.46 (m, 2H, Ar*H*), 5.35 (s, 1H, COC*H*), 5.14 (br, 1H, CHN*H*Ac), 4.18–4.10 (m, 1H, C*H*NHAc), 3.66 (s, 3H, COOC*H*$_3$), 1.93 (s, 3H, NHCOC*H*$_3$), 1.85–1.83 (m, 1H, *TMP*), 1.76–1.72 (m, 1H, *TMP*), 1.37 (s, 3H, *TMP*), 1.36–1.31 (m, 1H, *TMP*), 1.27–1.24 (m, 1H, *TMP*), 1.20–1.19 (m, 6H, *TMP*), 0.73 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 169.3, 135.3, 133.1, 133.1, 128.3, 128.1, 127.7, 126.2, 126.2, 126.1, 124.5, 88.8, 60.2, 60.2, 52.0, 46.1, 46.0, 41.0, 33.6, 32.8, 23.5, 20.9, 20.8; IR (neat) 1746, 1651, 1634, 1557, 1375, 1364, 1314, 1244, 1192, 1173, 1061, 976, 816, 750, 725, 474 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{24}H_{33}N_2O_4$ $(M + H)^+$ 413.2435, found 413.2428.

methyl 2-(naphthalen-2-yl)acetate (Me-1y)



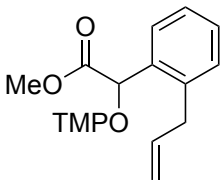
(colorless liquid, 21% yield, 4.3 mg); CAS Registry Number 2876-71-3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.79 (m, 3H, Ar*H*), 7.73 (s, 1H, Ar*H*), 7.47–7.45 (m, 2H, Ar*H*), 7.41 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar*H*), 3.80 (s, 2H, COC*H*$_2$), 3.71 (s, 3H, COOC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 133.5, 132.5, 131.5, 128.3, 128.0, 127.7, 127.7, 127.3, 126.2, 125.8, 52.1, 41.4.

methyl (*E*)-4-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hex-2-enoate (Me-3ζa)



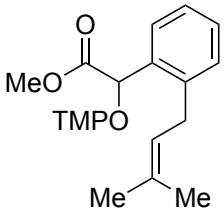
(*E*)-hex-2-enoic acid **1ζ** (24 μL, 0.2 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ζa**. (colorless liquid, 58% yield, 32.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (dd, *J* = 15.5, 8.0 Hz, 1H, COCHC*H*CH), 5.87 (dd, *J* = 15.5, 1.0 Hz, 1H, COC*H*CHCH), 4.23 (m, 1H, COCHCHC*H*), 3.75 (s, 3H, COOC*H*$_3$), 1.82–1.74 (m, 1H, CHC*H*$_2$CH$_3$), 1.63–1.55 (m, 2H, CHC*H*$_2$CH$_3$ + *TMP*), 1.42 (m, 4H, *TMP*), 1.31 (m, 1H, *TMP*), 1.17 (s, 3H, *TMP*), 1.12 (s, 3H, *TMP*), 1.08 (s, 3H, *TMP*), 1.06 (s, 3H, *TMP*), 0.87 (t, 3H, *J* = 8.0 Hz, CHCH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 150.5, 120.9, 84.5, 60.2, 59.6, 51.5, 40.2, 40.2, 34.7, 34.1, 26.7, 20.4, 20.3, 17.2, 9.4; IR (neat) 2932, 1726, 1435, 1375, 1360, 1302, 1267, 1238, 1171, 1132, 1005, 982, 972, 957 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{30}NO_3$ $(M + H)^+$ 284.2220, found 284.2230.

methyl 2-(2-allylphenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3θa)



$Fe(OAc)_2$ (3.5 mg, 0.02 mmol), **L10** (5.3 mg, 0.02 mmol), 2-(2-allylphenyl)acetic acid **1θ** (35.2 mg, 0.20 mmol) and TEMPO **2a** (125.0 mg, 0.80 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3θa**. (colorless liquid, 76% yield, 52.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.56 (m, 1H, Ar*H*), 7.25–7.21 (m, 2H, Ar*H*), 7.17–7.15 (m, 1H, Ar*H*), 6.00–5.91 (m, 1H, $ArCH_2CH{=}CH_2$), 5.47 (s, 1H, COC*H*), 5.10–5.09 (m, 1H, $ArCH_2CH{=}CH_2$), 5.07–5.06 (m, 1H, $ArCH_2CH{=}CH_2$), 3.64 (s, 3H, $COOCH_3$), 3.59 (dd, *J* = 16.0, 6.5 Hz, 1H, $ArCH_2CH{=}CH_2$), 3.51 (dd, *J* = 16.0, 6.5 Hz, 1H, $ArCH_2CH{=}CH_2$), 1.57–1.28 (m, 6H, *TMP*), 1.24 (s, 3H, *TMP*), 1.14 (s, 3H, *TMP*), 1.04 (s, 3H, *TMP*), 0.65 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 137.2, 136.9, 136.6, 129.3, 127.9, 127.9, 126.4, 116.1, 85.4, 60.0, 59.8, 51.7, 40.2, 40.1, 36.6, 33.2, 32.9, 20.2, 20.2, 17.1; IR (neat) 1753, 1736, 1362, 1260, 1240, 1194, 1157, 1132, 1043, 1018, 993, 957, 914, 795, 745 cm^{-1}.

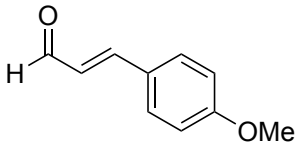
methyl 2-(2-(3-methylbut-2-en-1-yl)phenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (Me-3ιa)



$Fe(OAc)_2$ (1.7 mg, 0.01 mmol), **L10** (2.7 mg, 0.01 mmol), 2-(2-(3-methylbut-2-en-1-yl)phenyl)acetic acid **1ι** (20.4 mg, 0.10 mmol) and TEMPO **2a** (62.5 mg, 0.40 mmol) were used. The resultant mixture was purified by silica gel flash chromatography (1% EtOAc in *n*-Hexane as eluent) to afford the methyl esterified product **Me-3ιa**. (colorless liquid, 51% yield, 19.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.55 (m, 1H, Ar*H*), 7.23–7.19 (m, 2H, Ar*H*), 7.14–7.13 (m, 1H, Ar*H*), 5.48 (s, 1H, COC*H*), 5.27–5.24 (m, 1H, $ArCH_2CH{=}C(CH_3)_2$), 3.65 (s, 3H, $COOCH_3$), 3.58 (dd, *J* = 16.0, 8.0 Hz, 1H, $ArCH_2CH{=}C(CH_3)_2$), 3.38 (dd, *J* = 16.0, 6.5 Hz, 1H, $ArCH_2CH{=}C(CH_3)_2$), 1.75 (s, 3H, $ArCH_2CH{=}C(CH_3)_2$), 1.74 (s, 3H, $ArCH_2CH{=}C(CH_3)_2$), 1.56–1.26 (m, 6H, *TMP*), 1.24 (s, 3H, *TMP*), 1.14 (s, 3H, *TMP*), 1.05 (s, 3H, *TMP*), 0.64 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 138.7,

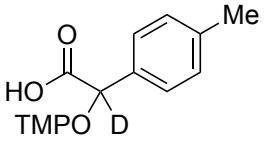
136.8, 132.5, 128.9, 127.9, 127.6, 126.1, 122.8, 85.0, 59.9, 59.7, 51.7, 40.2, 40.1, 33.1, 32.9, 31.3, 25.8, 20.2, 20.2, 17.9, 17.1; IR (neat) 2928, 1753, 1734, 1375, 1362, 1260, 1240, 1192, 1155, 1132, 1043, 1018, 924, 795, 745 cm^{-1}.

(*E*)-3-(4-methoxyphenyl)acrylaldehyde (1η')



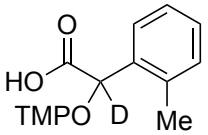
4-(4-methoxyphenyl)butanoic acid **1η** (38.8 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were used. (colorless liquid, 43% yield); CAS Registry Number 24680-50-0; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (d, *J* = 8.0 Hz, 1H, C*H*O), 7.53 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.43 (d, *J* = 16.0 Hz, 1H, ArC*H*), 6.95 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.62 (d, *J* = 16.0, 8.0 Hz, 1H, C*H*CHO), 3.86 (s, 3H, ArOCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7, 162.2, 152.7, 130.3, 126.8, 126.6, 114.6, 55.5.

2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*p*-tolyl)acetic-2-*d* acid (3aa-*d*)



(white solid, 87% D); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.19 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.39 (s, 0.13H, COC*H*), 2.36 (s, 3H, ArCH_3), 1.67 (m, 5H, *TMP*), 1.49 (br, 1H, *TMP*), 1.33–1.21 (m, 12H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 138.6, 133.4, 129.2, 128.6, 84.1, 62.6, 62.4, 39.6, 39.6, 31.9, 31.1, 21.3, 20.8, 20.8, 16.5; IR (neat) 1713, 1375, 1260, 1242, 1207, 1132, 1072, 957, 922, 816, 795, 775, 731, 683, 606, 503 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{27}DNO_3$ $(M + H)^+$ 307.2126, found 307.2130.

2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*o*-tolyl)acetic-2-*d* acid (3ca-*d*)



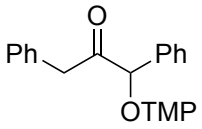
(white solid, 94% D); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.5, 2.0 Hz, 1H, Ar*H*), 7.25–7.17 (m, 3H, Ar*H*), 5.66 (s, 0.06H, COC*H*), 2.43 (s, 3H, ArCH_3), 1.65 (m, 5H, *TMP*), 1.47 (br, 1H, *TMP*), 1.29–1.18 (m, 12H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ174.2, 136.8, 135.4, 130.3, 128.4, 128.3, 126.1, 81.7, 62.0, 61.9, 39.6, 39.6, 31.8, 31.5, 20.7, 20.6, 19.5, 16.6; IR (neat) 1713, 1375, 1360, 1260,

1242, 1209, 1132, 1070, 1045, 957, 922, 797, 752, 733, 617, 449 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{27}DNO_3$ $(M + H)^+$ 307.2126, found 307.2126.

Procedure for chemoselective cross-coupling experiments

A 20 mL schlenk flask equipped with a magnetic stirring bar and 3-way glass stopcock was charged with 4A crushed molecular sieves (MS4A 100.0 mg) and flamed-dried under vacuum. After cooling down to room temperature, $Fe(OAc)_2$ (1.7 mg, 0.01 mmol), **L10** (2.7 mg, 0.01 mmol), 2-(*p*-tolyl)acetic acid **1a** (30.0 mg, 0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were added followed by the addition of THF (1.0 mL, 0.20 M) and carbonyl compound **4** (0.20 mmol). The mixture was stirred under argon at 60 °C for 24 h and diluted with 10% AcOH in EtOAc. The diluted solution was filtered through silica short column and washed with EtOAc. The diluted solution was filtered through silica short column and washed with EtOAc. After evaporation of the organic solvent under reduced pressure, yields were determined by ^1H NMR analysis using 2-methoxynaphthalene as an internal standard.

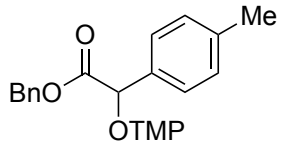
1,3-diphenyl-1-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)propan-2-one (5aa)



(white solid); ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.0 Hz, 2H, Ar*H*), 7.35 (t, *J* = 7.0 Hz, 2H, Ar*H*), 7.30 (m, 1H, Ar*H*), 7.24–7.18 (m, 3H, Ar*H*), 6.98 (d, *J* = 7.0 Hz, 2H, Ar*H*), 5.28 (s, 1H, COC*H*), 3.89 (d, *J* = 16.5 Hz, 1H, COCH_2), 3.72 (d, *J* = 16.5 Hz, 1H, COCH_2), 1.47–1.37 (m, 4H, *TMP*), 1.28 (m, 4H, *TMP*), 1.13 (m, 4H, *TMP*), 1.05 (m, 3H, *TMP*), 0.67 (m, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 137.7, 133.7, 129.8, 128.6, 128.3, 128.0, 127.2, 126.7, 95.3, 60.1, 59.7, 44.3, 40.3, 40.3, 33.7, 33.4, 20.3, 20.3, 17.0; IR (neat) 1713, 1452, 1360, 1134, 1018, 989, 955, 939, 768, 714, 696, 590, 567, 488, 474 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{24}H_{32}NO_2$ $(M + H)^+$ 366.2428, found 366.2428.

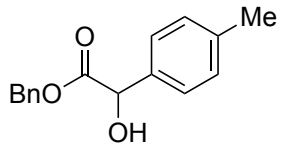
1-6. Transformation of the Product

benzyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*p*-tolyl)acetate (6)



To a solution of 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*p*-tolyl)acetic acid **3aa** (153 mg, 0.50 mmol), *N*,*N*′-Dicyclohexylcarbodiimide (155 mg, 0.75 mmol) and DMAP (6.1 mg, 0.05 mmol) in dry CH_2Cl_2 (1.0 mL, 0.50 M) was added benzyl alcohol (80 μL, 0.77 mmol) at 0 °C under argon atmosphere. The cooling bath was removed and the reaction mixture was stirred for 6 h at room temperature. To the resultant mixture was added H_2O and extracted with CH_2Cl_2. After removal of solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (3% Et_2O in *n*-Hexane as eluent) to obtain **6**. (white solid, 85% yield, 167.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.30–7.28 (m, 3H, Ar*H*), 7.24–7.22 (m, 2H, Ar*H*), 7.13 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.21 (s, 1H, COC*H*), 5.11 (d, *J* = 12.5 Hz, 1H, PhC*H*$_2$OCO), 5.03 (d, *J* = 12.5 Hz, 1H, PhC*H*$_2$OCO), 2.33 (s, 3H, ArC*H*$_3$), 1.57–1.26 (m, 6H, *TMP*), 1.20 (s, 3H, *TMP*), 1.08 (s, 3H, *TMP*), 1.06 (s, 3H, *TMP*), 0.72 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 137.6, 135.7, 135.2, 129.0, 128.4, 128.0, 128.0, 126.9, 88.6, 66.3, 59.9, 59.8, 40.2, 40.1, 33.7, 32.9, 21.2, 20.2, 20.1, 17.1; IR (neat) 1742, 1260, 1152, 1132, 1040, 955, 947, 924, 822, 752, 739, 696, 598, 509 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{25}H_{34}NO_3$ $(M + H)^+$ 396.2533, found 396.2533.

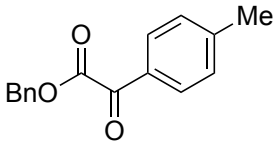
benzyl 2-hydroxy-2-(*p*-tolyl)acetate (7)[44]



To a solution of benzyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*p*-tolyl)acetate **6** (39.6 mg, 0.10 mmol) and zinc dust (262 mg, 4.0 mmol) in AcOH (0.60 ml) and THF (0.20 ml) was stirred for 2 h at 60 °C and diluted with EtOAc. The diluted solution was filtered through silica short column and washed with EtOAc. After evaporation of the organic solvent under reduced pressure, the resultant mixture was purified by silica gel flash chromatography (10%–20% EtOAc in *n*-Hexane as eluent) to obtain **7**. (white solid, 97% yield); CAS Registry Number 887641-38-5; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.28 (m, 5H, Ar*H*), 7.22–7.20 (m, 2H, Ar*H*), 7.16 (d, *J* = 7.5 Hz, 2H, Ar*H*), 5.25 (d, *J* = 12.5 Hz, 1H, PhC*H*$_2$), 5.18 (d, *J* = 5.5 Hz, 1H, COC*H*), 5.12 (d, *J* = 12.5 Hz, 1H, PhC*H*$_2$), 3.35 (d, *J* = 5.5 Hz, 1H, O*H*), 2.35 (s, 3H, ArC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.7, 138.3, 135.3, 135.1, 129.3,

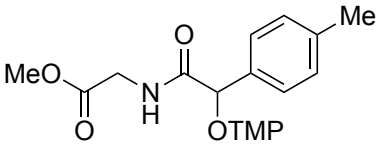
128.6, 128.4, 128.0, 126.5, 72.8, 67.6, 21.2.

benzyl 2-oxo-2-(*p*-tolyl)acetate (8)[45]



To a solution of benzyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*p*-tolyl)acetate **6** (39.6 mg, 0.10 mmol) in CH_2Cl_2 (0.50 mL) was added dropwise a solution of 0.24 M 3-chloroperoxidebenzoic acid in CH_2Cl_2 (0.50 mL, 0.12 mmol) at 0 °C under argon atmosphere. The cooling bath was removed and the reaction mixture was stirred for 4 h at room temperature. To the resultant mixture was added sat. $NaHCO_3$ aq and extracted with CH_2Cl_2. After removal of solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (3%–5% Et_2O in *n*-Hexane as eluent) to obtain **8**. (white solid, 98% yield); CAS Registry Number 887641-60-3; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.44 (dd, *J* = 8.0, 1.5 Hz, 2H, Ar*H*), 7.41–7.36 (m, 3H, Ar*H*), 7.28 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.41 (s, 2H, PhCH_2), 2.43 (s, 3H, ArCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 163.9, 146.3, 134.6, 130.2, 130.0, 129.6, 128.8, 128.7, 128.6, 67.7, 21.9.

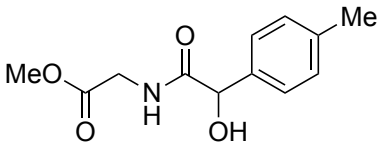
methyl (2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*p*-tolyl)acetyl)glycinate (9)



To a solution of 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*p*-tolyl)acetic acid **3aa** (153 mg, 0.50 mmol), glycine methyl ester hydrochloride (94.2 mg, 0.75 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (144 mg, 0.75 mmol) and DMAP (6.1 mg, 0.05 mmol) in dry CH_2Cl_2 (1.0 mL, 0.50 M) was added trimethylamine (110 μL, 0.80 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 24 h at room temperature. To the resultant mixture was added sat. $NaHCO_3$ aq and extracted with CH_2Cl_2. After removal of solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (10%–20% EtOAc in *n*-Hexane as eluent) to obtain **9**. (white solid, 67% yield, 125.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.5 Hz, 2H, Ar*H*), 7.13–7.11 (m, 3H, Ar*H* + CH_2N*H*CO), 5.08 (s, 1H, COC*H*), 4.19 (dd, *J* = 18.5, 6.0 Hz, 1H, COCH_2NH), 3.98 (dd, *J* = 18.5, 5.0 Hz, 1H, COCH_2NH), 3.77 (s, 3H, COOCH_3), 2.31 (s, 3H, ArCH_3), 1.57–1.10 (m, 15H, *TMP*), 0.56 (br, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 170.3, 137.7, 136.4, 129.1, 127.2, 90.0, 60.4, 59.6, 52.3, 40.8, 40.4, 40.4, 34.0, 32.9, 21.2, 20.3, 20.3, 17.0; IR (neat)

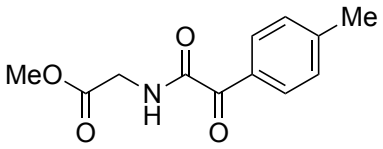
1757, 1649, 1560, 1441, 1368, 1200, 1177, 1134, 1045, 1032, 924, 824, 799, 687, 519 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{21}H_{33}N_2O_4$ $(M + H)^+$ 377.2435, found 377.2453.

methyl (2-hydroxy-2-(*p*-tolyl)acetyl)glycinate (10)[44]



To a solution of methyl (2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*p*-tolyl)acetyl)glycinate **9** (18.8 mg, 0.05 mmol) and zinc dust (131 mg, 2.0 mmol) in AcOH (0.30 ml) and THF (0.10 ml) was stirred for 2 h at 60 °C and diluted with EtOAc. The diluted solution was filtered through silica short column and washed with EtOAc. After evaporation of the organic solvent under reduced pressure, the resultant mixture was purified by silica gel flash chromatography (50% EtOAc in *n*-Hexane as eluent) to obtain **10**. (colorless liquid, 95% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.19 (d, *J* = 8.0 Hz, 2H, Ar*H*), 6.71 (br, 1H, N*H*), 5.08 (s, 1H, NHCOC*H*), 4.11–3.99 (m, 2H, MeOCOCH_2), 3.75 (s, 3H, COOCH_3), 3.42 (br, 1H, O*H*), 2.35 (s, 3H, ArCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 170.0, 138.7, 136.0, 129.6, 126.9, 74.1, 52.4, 41.1, 21.2.; IR (neat) 3364, 1744, 1655, 1526, 1512, 1437, 1368, 1206, 1180, 1061, 1020, 583, 503 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{12}H_{15}NNaO_4$ $(M + Na)^+$ 260.0893, found 260.0894.

methyl (2-oxo-2-(*p*-tolyl)acetyl)glycinate (11)[45]

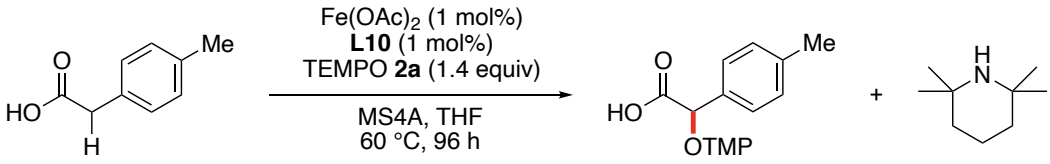


To a solution of methyl (2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*p*-tolyl)acetyl)glycinate **9** (37.6 mg, 0.10 mmol) in CH_2Cl_2 (0.50 mL) was added dropwise a solution of 0.24 M 3-chloroperoxidebenzoic acid in CH_2Cl_2 (0.50 mL, 0.12 mmol) at 0 °C under argon atmosphere. The cooling bath was removed and the reaction mixture was stirred for 4 h at room temperature. To the resultant mixture was added sat. $NaHCO_3$ aq and extracted with CH_2Cl_2. After removal of solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (10%–20% EtOAc in *n*-Hexane as eluent) to obtain **11**. (white solid, 82% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.53 (br, 1H, CON*H*), 7.28 (d, *J* = 8.5 Hz, 2H, Ar*H*), 4.18 (d, *J* = 5.5 Hz, 2H, MeOCOCH_2), 3.81 (s, 3H, COOCH_3), 2.43 (s, 3H, ArCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.2, 169.4, 162.0, 145.8, 131.4, 130.6, 129.3, 52.6, 41.1, 21.9.; IR (neat) 3377, 1738, 1661, 1603,

1504, 1261, 1196, 1171, 932, 787, 623, 505, 482 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{12}H_{13}NNaO_4$ $(M + Na)^+$ 258.0737, found 258.0727.

1-7. Mechanistic Study

1-7-1. Detection of 2,2,6,6-tetramethylpiperidine 12



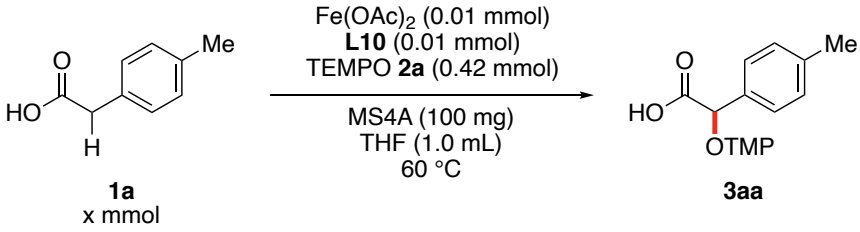
1a 4.0 mmol | **3aa** 90% | **12** 0.58 mmol

A flask equipped with a magnetic stirring bar and 3-way glass stopcock was charged with 4A crushed molecular sieves (MS4A 2.0 g) and flamed-dried under vacuum. After cooling down to room temperature, $Fe(OAc)_2$ (7.0 mg, 0.04 mmol), **L10** (10.7 mg, 0.04 mmol), 2-(*p*-tolyl)acetic acid **1a** (601 mg, 4.0 mmol) and TEMPO **2a** (875 mg, 5.6 mmol) were added followed by the addition of THF (20 mL, 0.20 M). The mixture was stirred under argon at 60 °C for 96 h and diluted with 10 % AcOH in EtOAc (8.0 mL). The diluted solution was filtered through silica short column and washed with EtOAc to obtain the product **3aa**, then washed with 3% Et_3N in acetone to another flask to obtain 2,2,6,6-tetramethylpiperidine **12**. After evaporation of the organic solvent under reduced pressure, the resultant mixture was purified by silica gel flash chromatography (10% EtOAc in *n*-Hexane as eluent) to afford the product **3aa** in 90% yield (1.10 g scale). The yield of 2,2,6,6-tetramethylpiperidine **12** was determined by ^{1}H NMR analysis using 2-methoxynaphthalene as an internal standard.

1-7-2. Initial Kinetic Studies

Initial Rates of Varying Concentrations of 1a

$Fe(OAc)_2$ (1.7 mg, 0.01 mmol), **L10** (2.7 mg, 0.01 mmol), TEMPO **2a** (65.6 mg, 0.42 mmol), pre-dried 4A crushed molecular sieves (MS4A 100.0 mg) and 2-methoxynaphthalene (9.5 mg, 0.06 mmol) as an internal standard were added followed by the addition of THF (0.75 mL). The mixture was stirred under argon at 60 °C for 30 min. Then 0.48, 0.64, 0.80, 0.96 M 2-(*p*-tolyl)acetic acid **1a** in THF (0.25 mL, 0.12, 0.16, 0.20, 0.24 mmol) was added to the reaction mixture. At the specified period, 0.10 mL of reaction mixture was extracted via a syringe filled by 10% AcOH in EtOAc 0.20 mL with a stainless-steel needle. The diluted solution was filtered through silica short column and washed with EtOAc. After evaporation of the volatiles under reduced pressure, the crude mixture was analyzed by ^{1}H NMR to determine chemical yield by the integration value of a peak at 5.38 ppm (**3aa**: COC*H*) and 3.93 ppm (2-methoxynaphthalene: ArOCH_3). The results were summarized in Figures 1-7-1.

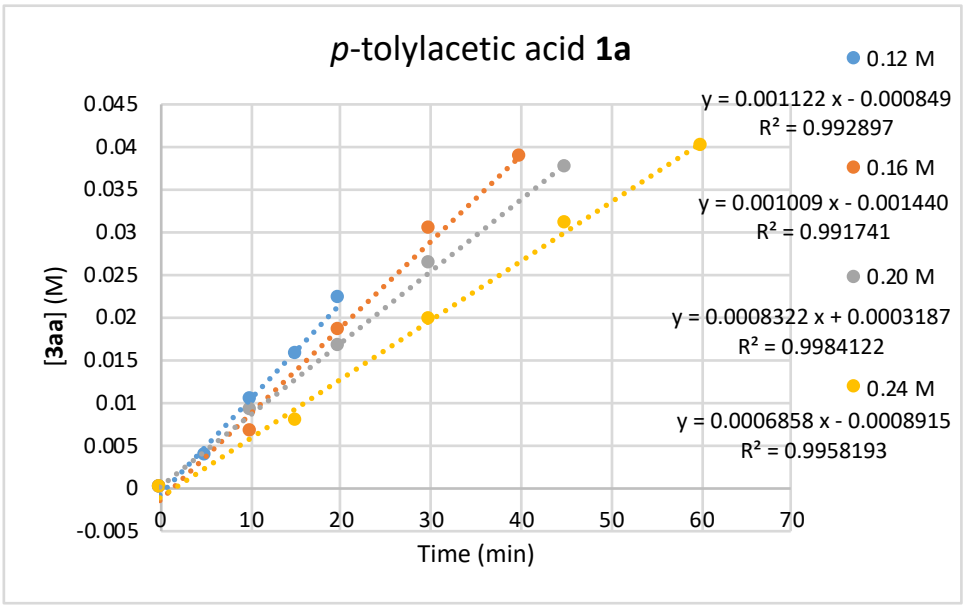


1a
x mmol

3aa

1a (mmol)	[**1a**] (M)	ln[**1a**]	*d* [**3aa**]/*d* t (M/min)	ln(*d* [**3aa**]/*d* t)
0.12	0.12	-2.12	0.001122	-6.793
0.16	0.16	-1.83	0.001009	-6.899
0.20	0.20	-1.61	0.0008322	-7.091
0.24	0.24	-1.43	0.0006858	-7.285

(a)



(b)

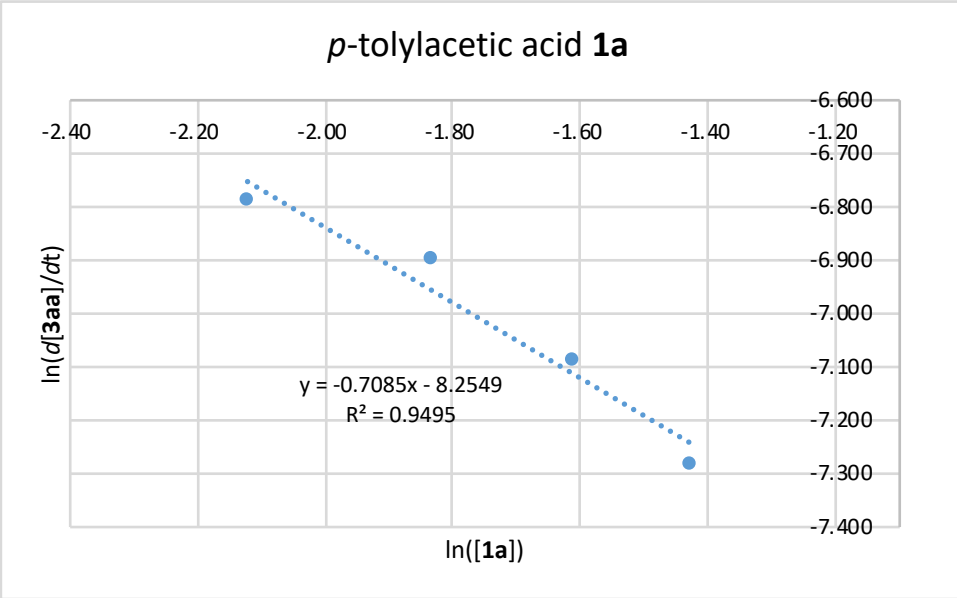
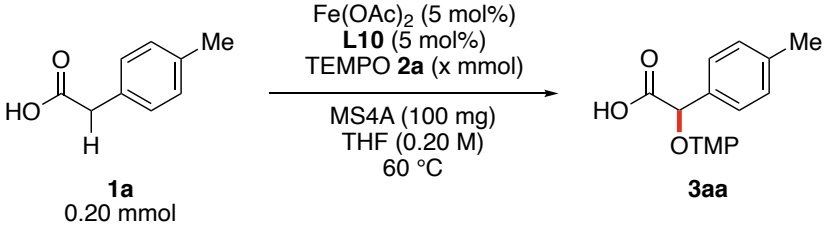


Figure 1-7-1. (a) Initial Rate Kinetic Experiments for 2-(*p*-tolyl)acetic acid **1a**

(b) Plot of ln(*d*[**3aa**]/*d*t) versus ln([**1a**])

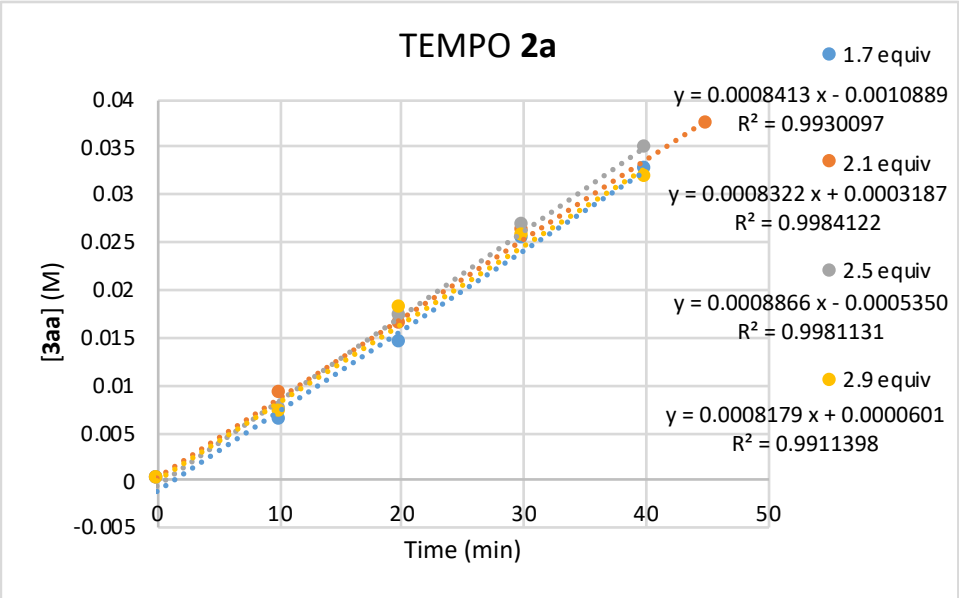
Initial Rates of Varying Concentrations of TEMPO 2a

$Fe(OAc)_2$ (1.7 mg, 0.01 mmol), **L10** (2.7 mg, 0.01 mmol), TEMPO **2a** (0.34, 0.42, 0.50, 0.58 mmol), pre-dried 4A crushed molecular sieves (MS4A 100.0 mg) and 2-methoxynaphthalene (9.5 mg, 0.06 mmol) as an internal standard were added followed by the addition of THF (0.75 mL). The mixture was stirred under argon at 60 °C for 30 min. Then 0.80 M 2-(*p*-tolyl)acetic acid **1a** in THF (0.25 mL, 0.20 mmol) was added to the reaction mixture. At the specified period, 0.10 mL of reaction mixture was extracted via a syringe filled by 10% AcOH in EtOAc 0.20 mL with a stainless-steel needle. The diluted solution was filtered through silica short column and washed with EtOAc. After evaporation of the volatiles under reduced pressure, the crude mixture was analyzed by ^{1}H NMR to determine chemical yield by the integration value of a peak at 5.38 ppm (**3aa**: COC*H*) and 3.93 ppm (2-methoxynaphthalene: ArOCH_3). The results were summarized in Figures 1-7-2.



2a (equiv)	[**2a**] (M)	ln([**2a**])	*d* [**3aa**]/*d* t (M/min)	ln(*d* [**3aa**]/*d* t)
1.7	0.34	-1.08	0.0008413	-7.081
2.1	0.42	-0.87	0.0008322	-7.091
2.5	0.50	-0.69	0.0008866	-7.028
2.9	0.58	-0.54	0.0008179	-7.109

(a)



(b)

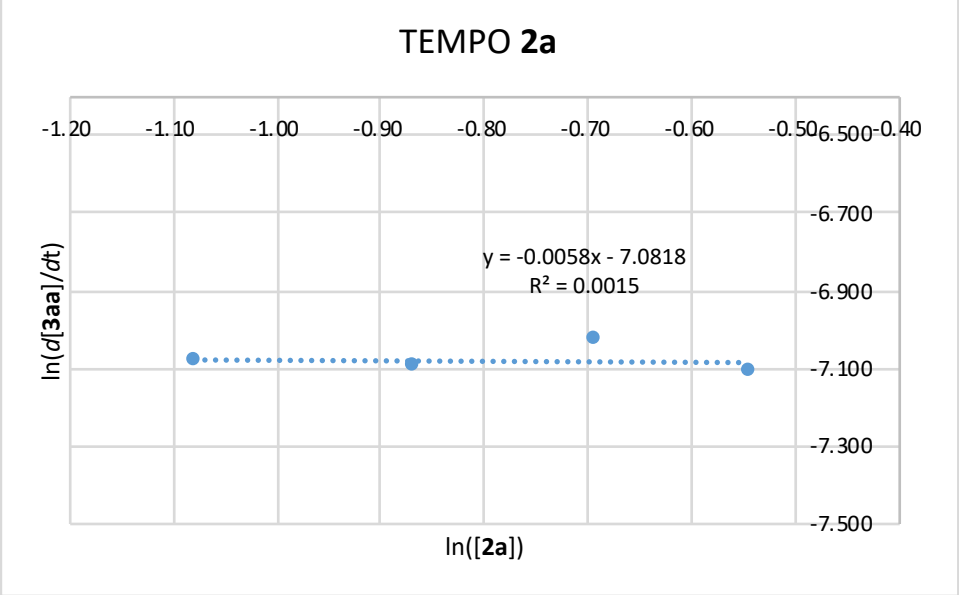
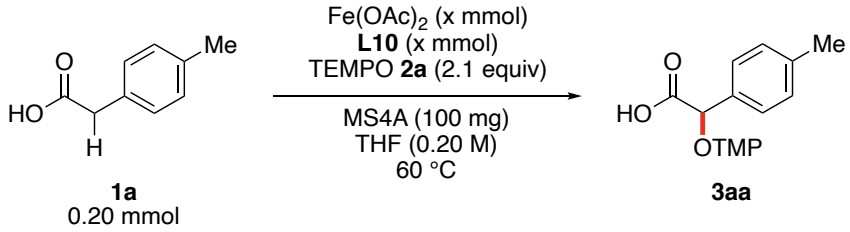


Figure 1-7-2. (a) Initial Rate Kinetic Experiments for TEMPO **2a**

(b) Plot of ln(*d*[**3aa**]/*d*t) versus ln([**2a**])

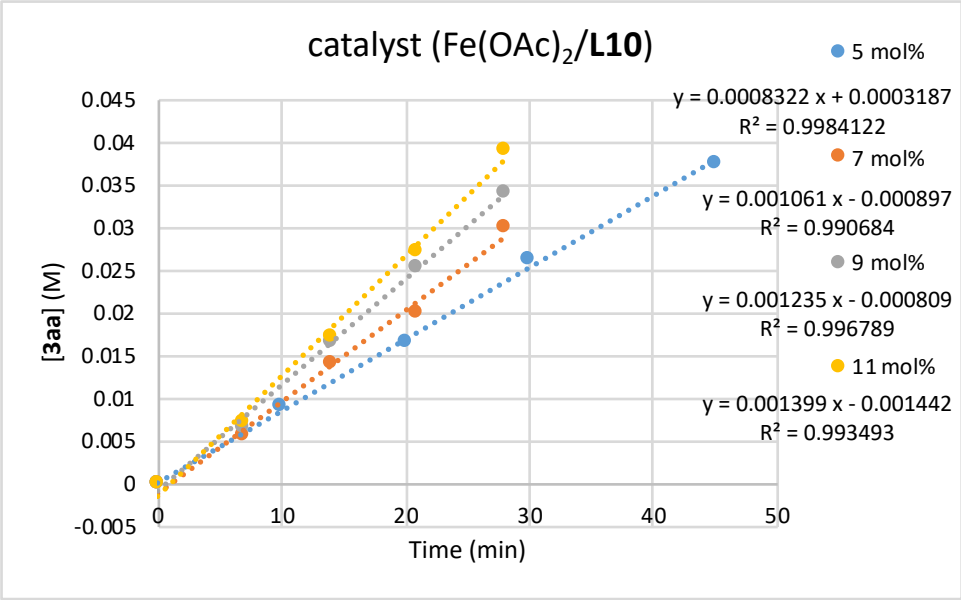
Initial Rates of Varying Concentrations of Catalyst ($Fe(OAc)_2$/L10)

$Fe(OAc)_2$ (0.010, 0.014, 0.018, 0.022 mmol), **L10** (0.010, 0.014, 0.018, 0.022 mmol), TEMPO **2a** (65.6 mg, 0.42 mmol), pre-dried 4A crushed molecular sieves (MS4A 100.0 mg) and 2-methoxynaphthalene (9.5 mg, 0.06 mmol) as an internal standard were added followed by the addition of THF (0.75 mL). The mixture was stirred under argon at 60 °C for 30 min. Then 0.80 M 2-(*p*-tolyl)acetic acid **1a** in THF (0.25 mL, 0.20 mmol) was added to the reaction mixture. At the specified period, 0.10 mL of reaction mixture was extracted via a syringe filled by 10% AcOH in EtOAc 0.20 mL with a stainless-steel needle. The diluted solution was filtered through silica short column and washed with EtOAc. After evaporation of the volatiles under reduced pressure, the crude mixture was analyzed by ^{1}H NMR to determine chemical yield by the integration value of a peak at 5.38 ppm (**3aa**: COC*H*) and 3.93 ppm (2-methoxynaphthalene: ArOCH_3). The results were summarized in Figures 1-7-3.



catalyst (mol%)	[catalyst] (M)	ln([catalyst])	*d* [**3aa**]/*d* t (M/min)	ln(*d* [**3aa**]/*d* t)
5	0.010	-4.61	0.0008322	-7.091
7	0.014	-4.27	0.001061	-6.849
9	0.018	-4.02	0.001235	-6.697
11	0.022	-3.82	0.001399	-6.572

(a)



(b)

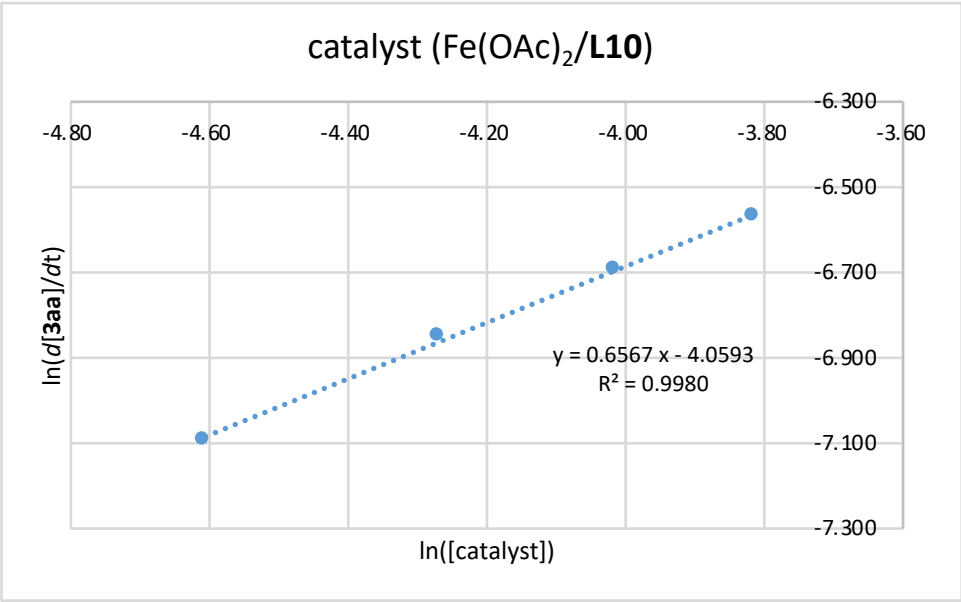


Figure 1-7-3. (a) Initial Rate Kinetic Experiments for Catalyst

(b) Plot of ln(*d*[**3aa**]/*d*t) versus Catalyst

1-7-3. Kinetic Isotope Effect Experiments

1a/1a-d_2 with L10 (k_H/k_D = 2.01)

$Fe(OAc)_2$ (1.7 mg, 0.01 mmol), **L10** (2.7 mg, 0.01 mmol), TEMPO **2a** (65.6 mg, 0.42 mmol), pre-dried 4A crushed molecular sieves (MS4A 100.0 mg) and 1,2,4,5-tetramethylbenzene (13.4 mg, 0.10

mmol) as an internal standard were added followed by the addition of THF (0.75 mL). The mixture was stirred under argon at 60 °C for 30 min. Then 0.80 M 2-(*p*-tolyl)acetic acid **1a** or 2-(*p*-tolyl)acetic acid-d_2 **1a-*d*$_2$** in THF (0.25 mL, 0.20 mmol) was added to the reaction mixture. At the specified period, 0.10 mL of reaction mixture was extracted via a syringe filled by 10% AcOH in EtOAc 0.20 mL with a stainless-steel needle. The diluted solution was filtered through silica short column and washed with EtOAc. After evaporation of the volatiles under reduced pressure, the crude mixture was analyzed by ^{1}H NMR using DMSO-d_6 as a solvent to determine chemical yield by the integration value of a peak at 7.27 ppm (**3aa** or **3aa-*d***: Ar*H*) and 6.88 ppm (1,2,4,5-tetramethylbenzene: Ar*H*). The results were summarized in Figure 1-7-4.

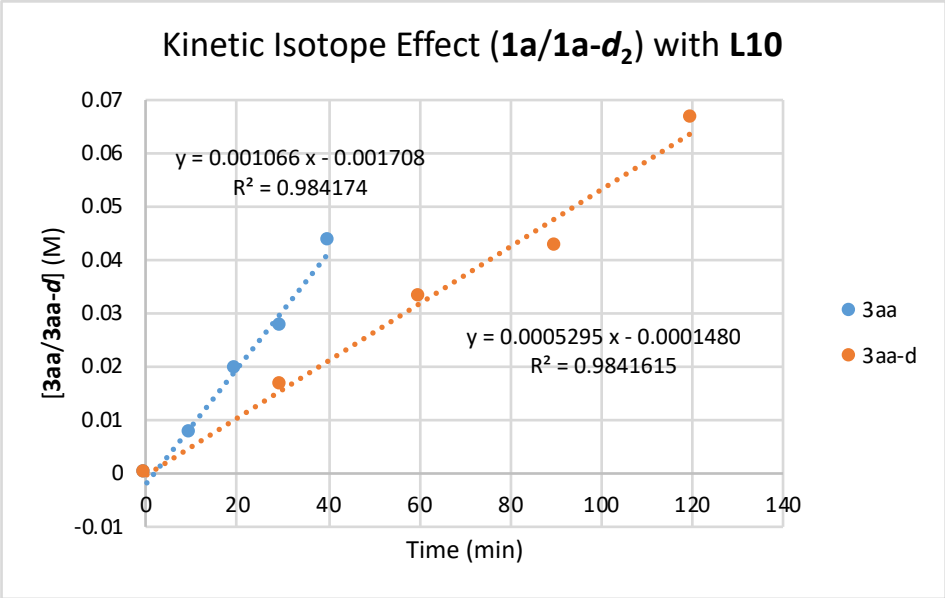


Figure 1-7-4. Kinetic Isotope Effect Experiments using **1a**/**1a-*d*$_2$** with **L10**

1a/1a-*d*$_2$ without L10 (k_H/k_D = 1.36)

$Fe(OAc)_2$ (1.7 mg, 0.01 mmol), TEMPO **2a** (65.6 mg, 0.42 mmol), pre-dried 4A crushed molecular sieves (MS4A 100.0 mg) and 1,2,4,5-tetramethylbenzene (13.4 mg, 0.10 mmol) as an internal standard were added followed by the addition of THF (0.75 mL). The mixture was stirred under argon at 60 °C for 30 min. Then 0.80 M 2-(*p*-tolyl)acetic acid **1a** or 2-(*p*-tolyl)acetic acid-d_2 **1a-*d*$_2$** in THF (0.25 mL, 0.20 mmol) was added to the reaction mixture. At the specified period, 0.10 mL of reaction mixture was extracted via a syringe filled by 10% AcOH in EtOAc 0.20 mL with a stainless-steel needle. The diluted solution was filtered through silica short column and washed with EtOAc. After evaporation of the volatiles under reduced pressure, the crude mixture was analyzed by ^{1}H NMR using DMSO-d_6 as a solvent to determine chemical yield by the integration value of a peak at 7.27 ppm (**3aa** or **3aa-*d***:

Ar*H*) and 6.88 ppm (1,2,4,5-tetramethylbenzene: Ar*H*). The results were summarized in Figure 1-7-5.

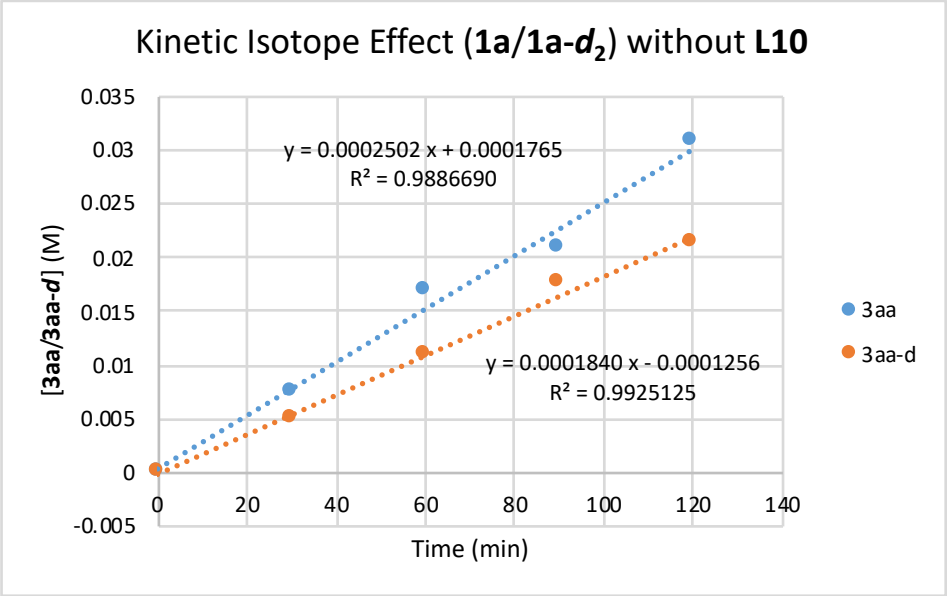


Figure 1-7-5. Kinetic Isotope Effect Experiments using **1a**/**1a-*d*$_2$** without **L10**

1c/1c-*d*$_2$ (k_H/k_D = 1.78)

$Fe(OAc)_2$ (1.7 mg, 0.01 mmol), **L10** (2.7 mg, 0.01 mmol), TEMPO **2a** (65.6 mg, 0.42 mmol), pre-dried 4A crushed molecular sieves (MS4A 100.0 mg) and 2-methoxynaphthalene (9.5 mg, 0.06 mmol) as an internal standard were added followed by the addition of THF (0.75 mL). The mixture was stirred under argon at 60 °C for 30 min. Then 0.80 M 2-(*o*-tolyl)acetic acid **1c** or 2-(*o*-tolyl)acetic acid-d_2 **1c-*d*$_2$** in THF (0.25 mL, 0.20 mmol) was added to the reaction mixture. At the specified period, 0.10 mL of reaction mixture was extracted via a syringe filled by 10% AcOH in EtOAc 0.20 mL with a stainless-steel needle. The diluted solution was filtered through silica short column and washed with EtOAc. After evaporation of the volatiles under reduced pressure, the crude mixture was analyzed by ^{1}H NMR using $CDCl_3$ as a solvent to determine chemical yield by the integration value of a peak at 2.43 ppm (**3ca** or **3ca-*d***: ArCH_3) and 3.93 ppm (2-methoxynaphthalene: ArOCH_3). The results were summarized in Figure 1-7-6.

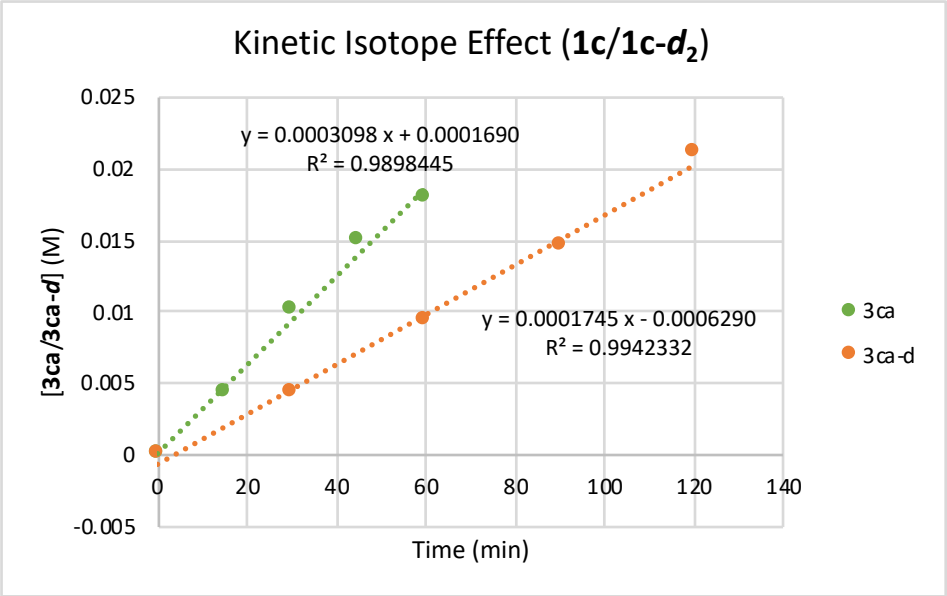


Figure 1-7-6. Kinetic Isotope Effect Experiments using **1c**/**1c-d_2**

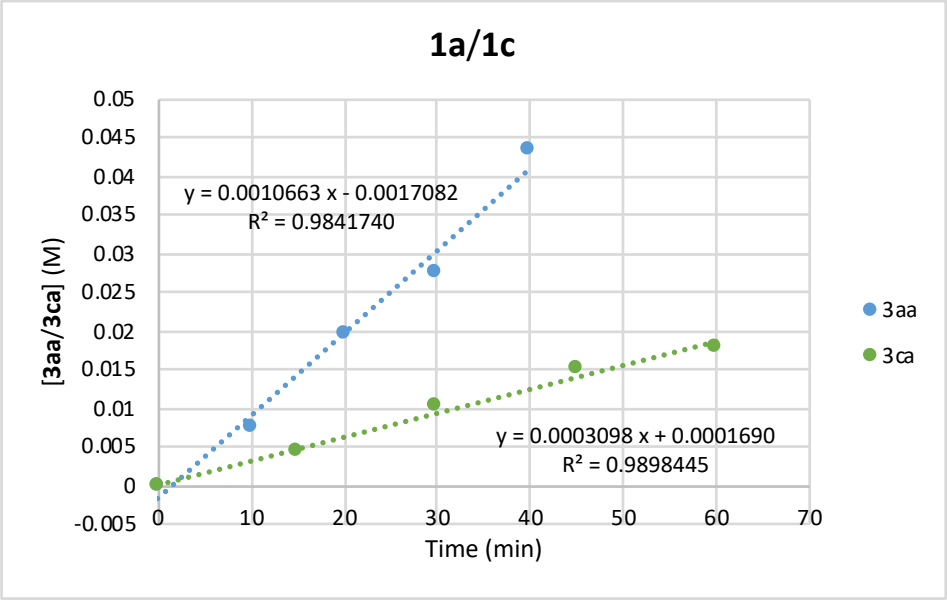
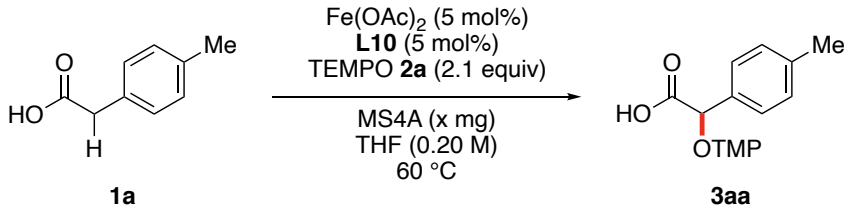


Figure 1-7-7. Comparing Reaction Rates between **1a** and **1c**

1-7-4. Dependency on Molecular Sieves

$Fe(OAc)_2$ (1.7 mg, 0.01 mmol), **L10** (2.7 mg, 0.01 mmol), TEMPO **2a** (65.6 mg, 0.42 mmol), pre-dried 4A crushed molecular sieves (MS4A 25.0, 50.0, 75.0, 100.0 mg) and 2-methoxynaphthalene (9.5 mg, 0.06 mmol) as an internal standard were added followed by the addition of THF (0.75 mL). The mixture was stirred under argon at 60 °C for 30 min. Then 0.80 M 2-(*p*-tolyl)acetic acid **1a** in

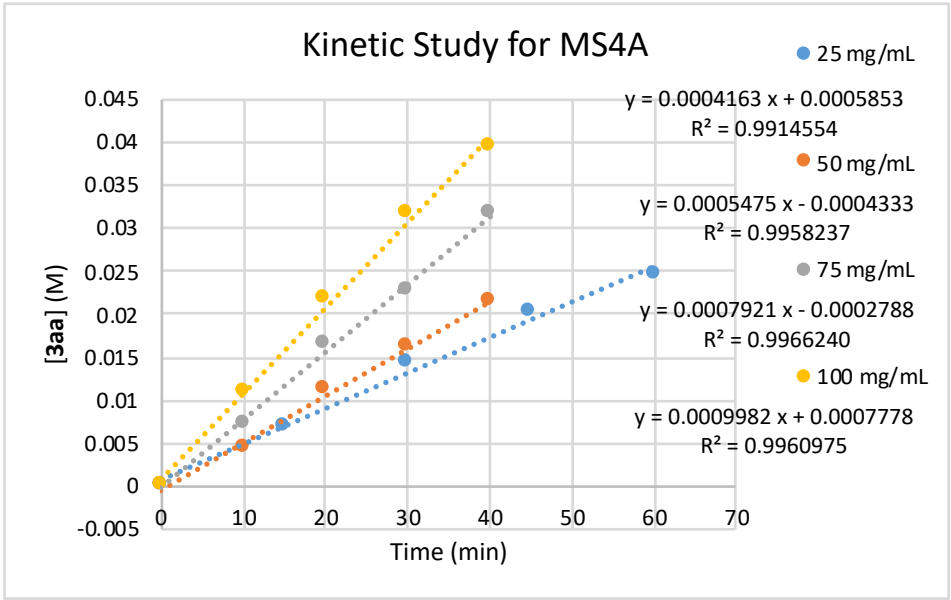
THF (0.25 mL, 0.20 mmol) was added to the reaction mixture. At the specified period, 0.10 mL of reaction mixture was extracted via a syringe filled by 10% AcOH in EtOAc 0.20 mL with a stainless-steel needle. The diluted solution was filtered through silica short column and washed with EtOAc. After evaporation of the volatiles under reduced pressure, the crude mixture was analyzed by ^{1}H NMR to determine chemical yield by the integration value of a peak at 5.38 ppm (**3aa**: COC*H*) and 3.93 ppm (2-methoxynaphthalene: ArOCH_3). The results were summarized in Figures 1-7-8.



1a **3aa**

MS4A (mg/mL)	*d* [**3aa**]/*d* t (M/min)
25	0.0004163
50	0.0005475
75	0.0007921
100	0.0009982

(a)



(b)

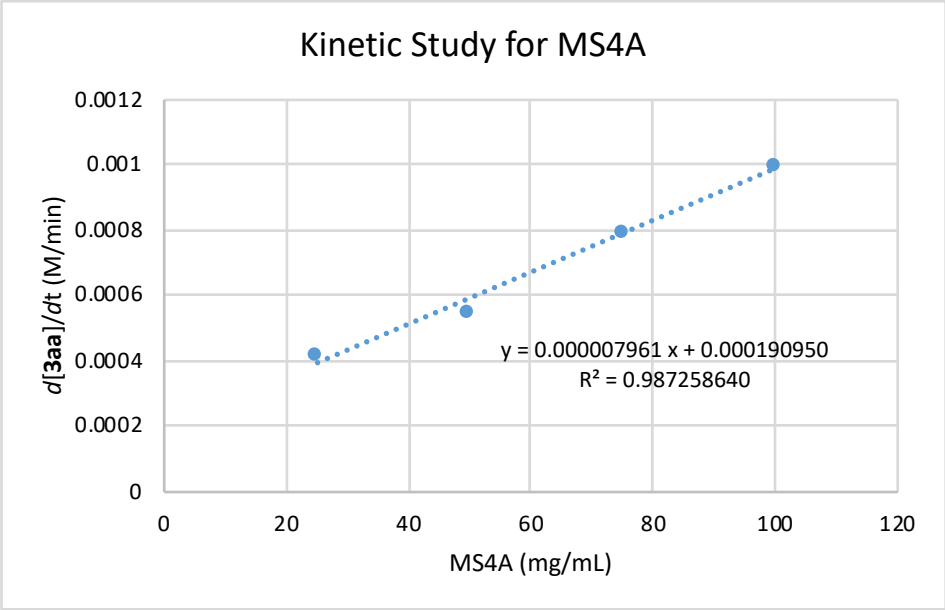
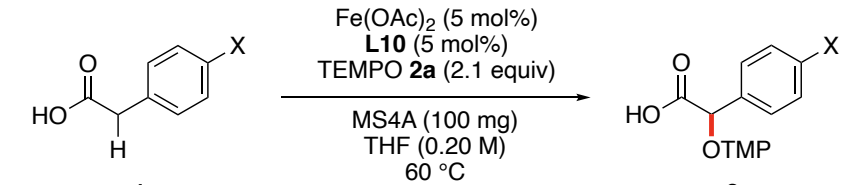


Figure 1-7-8. (a) Initial Rate Kinetic Experiments for MS4A.

(b) Plot of *d*[**3aa**]/*d*t versus MS4A.

1-7-5. Hammett Plot



1

X = Me, Ph, Cl, CF_3, NO_2

3

X	σ_p^-	*d* [**3**]/*d* t (M/min)	log(*d* [**3**]/*d* t)
Me	-0.14	0.0009982	-3.00
Ph	0.08	0.001371	-2.86
Cl	0.24	0.001260	-2.90
CF_3	0.62	0.0007846	-3.11
NO_2	1.25	0.001848	-2.73

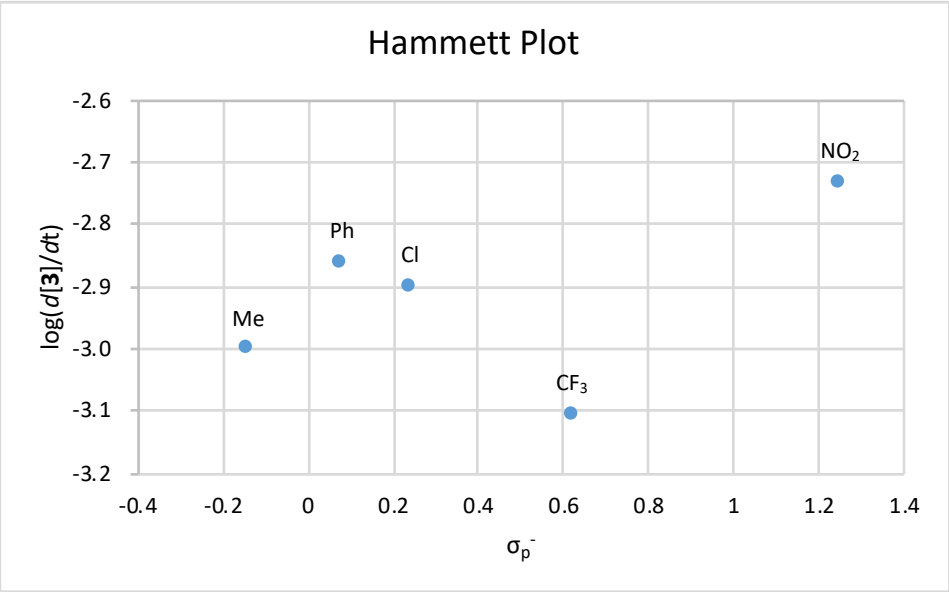
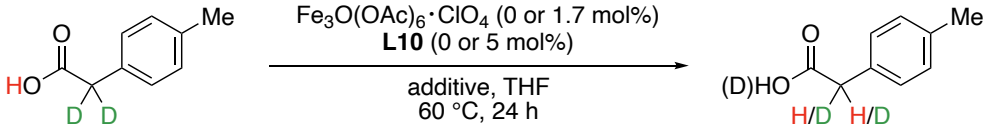


Figure 1-7-9. Hammett Plot

1-7-6. Metal Cation Effect on Enolization



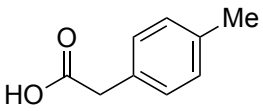
1a-*d*$_2$ (97% D)
0.20 mmol

1a/1a-*d*/1a-*d*$_2$

A 20 mL schlenk flask equipped with a magnetic stirring bar and 3-way glass stopcock was charged with 4A crushed molecular sieves (MS4A 0 or 100.0 mg) and flamed-dried under vacuum. After cooling down to room temperature, $Fe_3O(OAc)_6{\cdot}ClO_4$ (0 mmol or 2.3 mg, 0.0033 mmol), **L10** (0 mmol or 2.7 mg, 0.01 mmol), 2-(*p*-tolyl)acetic acid-d_2 **1a-*d*$_2$** (30.4 mg, 0.20 mmol) and NaOAc (0 mmol or 3.3 mg, 0.04 mmol) were added followed by the addition of THF (1.0 mL, 0.20 M). The mixture was stirred under argon at 60 °C for 24 h and diluted with 10% AcOH in EtOAc (2.0 mL). The diluted solution was filtered through silica short column and washed with EtOAc. After evaporation of the organic solvent under reduced pressure, protonated rates were determined by ^{1}H NMR analysis.

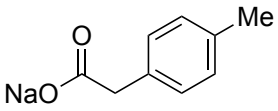
1-7-7. NMR Experiments

2-(*p*-tolyl)acetic acid (1a)



^{1}H NMR (500 MHz, methanol-d_4) δ 7.15 (d, J = 8.0 Hz, 2H, Ar*H*), 7.11 (d, J = 8.0 Hz, 2H, Ar*H*), **3.537 (s, 2H, ArC*H*$_2$COOH)**, 2.30 (s, 3H, ArCH_3).

sodium 2-(*p*-tolyl)acetate (1a-Na)



^{1}H NMR (500 MHz, methanol-d_4) δ 7.18 (d, J = 8.0 Hz, 2H, Ar*H*), 7.05 (d, J = 8.0 Hz, 2H, Ar*H*), **3.414 (s, 2H, ArC*H*$_2$COONa)**, 2.28 (s, 3H, ArCH_3).

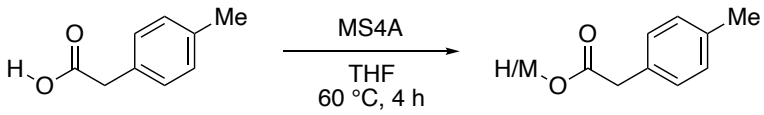
2-(*p*-tolyl)acetic acid (1a) and sodium 2-(*p*-tolyl)acetate (1a-Na) 1:1 mixture

^{1}H NMR (500 MHz, methanol-d_4) δ 7.17 (d, J = 8.0 Hz, 2H, Ar*H*), 7.08 (d, J = 8.0 Hz, 2H, Ar*H*), **3.478 (s, 2H, ArC*H*$_2$COOH/Na)**, 2.29 (s, 3H, ArCH_3).

2-(*p*-tolyl)acetic acid (1a) and sodium trifluoromethanesulfonate 1:1 mixture

^{1}H NMR (500 MHz, methanol-d_4) δ 7.17 (d, J = 8.0 Hz, 2H, Ar*H*), 7.13 (d, J = 8.0 Hz, 2H, Ar*H*), **3.555 (s, 2H, ArC*H*$_2$COOH)**, 2.32 (s, 3H, ArCH_3).

Procedure for mixing of 2-(*p*-tolyl)acetic acid 1a and MS4A



1a

A 20 mL schlenk flask equipped with a magnetic stirring bar and 3-way glass stopcock was charged with 4A crushed molecular sieves (MS4A 100.0 mg) and flamed-dried under vacuum. After cooling down to room temperature, 2-(*p*-tolyl)acetic acid **1a** (30.0 mg, 0.20 mmol) was added followed by the addition of THF (1.0 mL, 0.20 M). The mixture was stirred under argon at 60 °C for 24 h and diluted with methanol. The diluted solution was filtered through celite and washed with methanol. After evaporation of the organic solvent under reduced pressure, the residual solid was gathered.: ^{1}H NMR

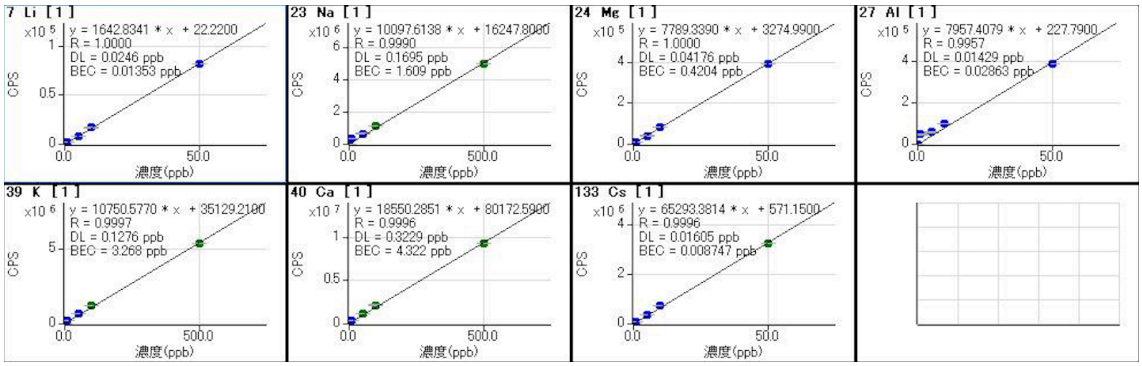
(500 MHz, methanol-d_4) δ 7.16 (d, J = 8.0 Hz, 2H, ArH), 7.10 (d, J = 8.0 Hz, 2H, ArH), **3.514 (s, 2H, ArCH_2COOH/Na)**, 2.30 (s, 3H, ArCH_3).

1-7-8. ICP-MS Measurement

Quantification of each elements was performed three times using above sample in 0.7% HNO_3 aq (100 ppb) as a sample.

(ppb)	Li	Na	K	Cs	Mg	Ca	Al
1	0.016	18.040	17.664	0.099	0.000	10.158	5.772
2	0.018	18.464	17.921	0.100	0.040	10.584	6.033
3	0.016	18.518	17.915	0.100	0.000	10.494	5.903
average	0.017	18.341	17.833	0.100	0.013	10.412	5.903

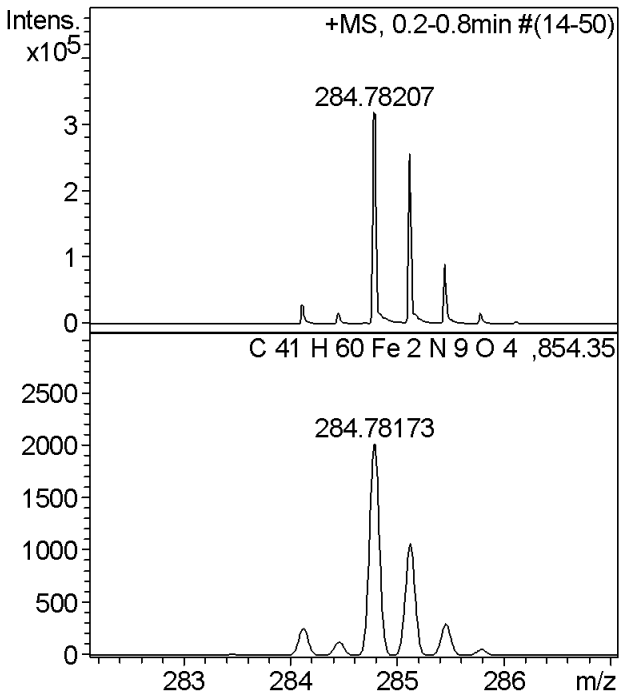
Calibration Curve

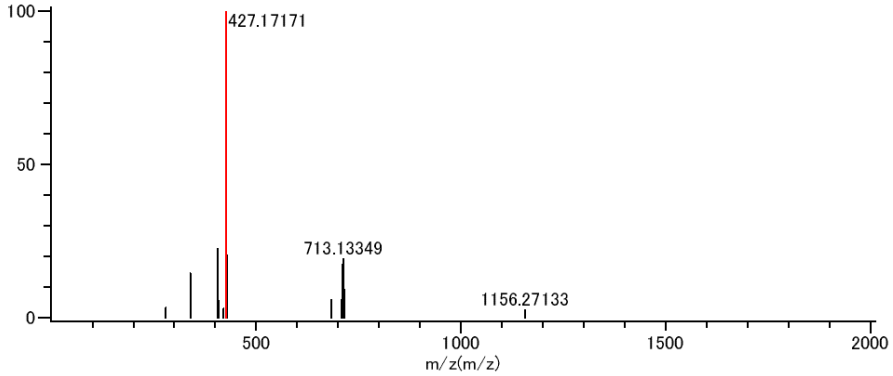


1-7-9. CSI-MS Measurement

Preparation of the iron complex ($Fe(OAc)_2$ + L10 + TEMPO)

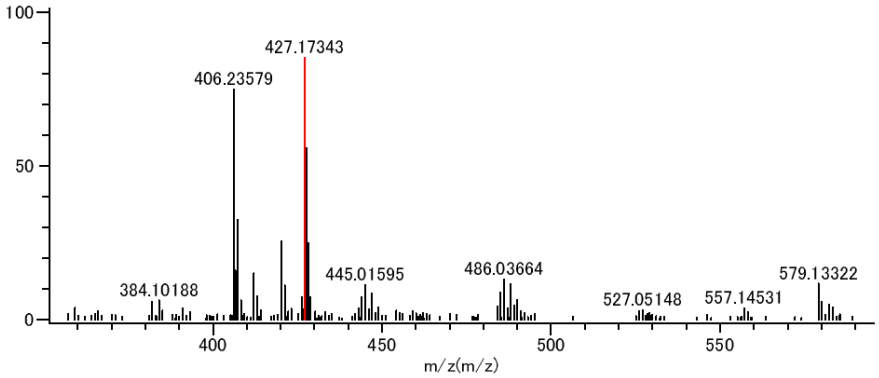
To a 4 mL vial equipped with a magnetic stirring bar, $Fe(OAc)_2$ (1.7 mg, 0.01 mmol), **L10** (2.7 mg, 0.01 mmol), and TEMPO **2a** (1.6 mg, 0.01 mmol) were added followed by the addition of THF (0.50 mL, 0.02 M) and stirred under argon at 60 °C for 1 h. After removal of solvent, to the residue was added CH_3CN and the resulting CH_3CN solution was subjected to the CSI-MS analysis.





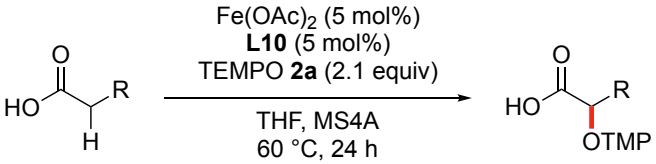
Preparation of the iron complex ($Fe_3O(OAc)_6 \cdot ClO_4$ + L10 + 2,2,6,6-tetramethylpiperidine)

To a 4 mL vial equipped with a magnetic stirring bar, $Fe_3O(OAc)_6 \cdot ClO_4$ (2.3 mg, 0.0033 mmol), **L10** (2.7 mg, 0.01 mmol), and 2,2,6,6-tetramethylpiperidine (3.4 μL, 0.02 mmol) were added followed by the addition of THF (0.50 mL, 0.02 M) and stirred under argon at 60 °C for 1 h. After removal of solvent, to the residue was added CH_3CN and the resulting CH_3CN solution was subjected to the CSI-MS analysis.

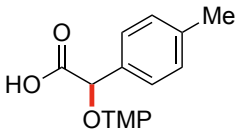

100
50
0
427.17343
406.23579
384.10188
445.01595
486.03664
527.05148
557.14531
579.13322
400
450
500
550
m/z(m/z)

1-8. Substrate Scope Isolated as Carboxylic Acids

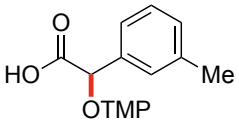
Table S1-1. Substrate Scope Isolated as Carboxylic Acids



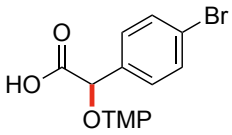
1 **3**



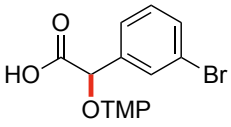
3aa: 95%



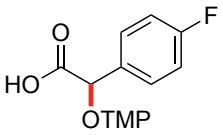
3ba: 82%



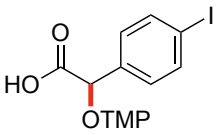
3da: 90%



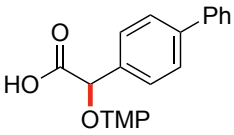
3ea: 97%



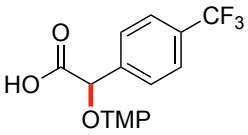
3ga: 92%



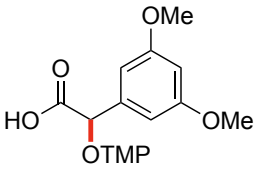
3ia: 85%



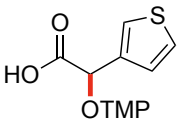
3ja: 89%



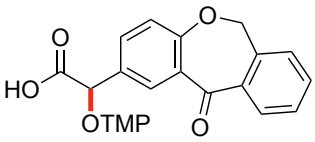
3na: 95%



3ta: 88%



3αa: 77%

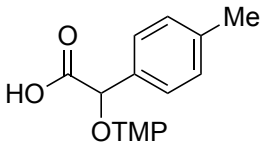


3γa: 82%

General procedure for catalytic oxidative cross-coupling reaction

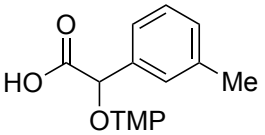
A 20 mL schlenk flask equipped with a magnetic stirring bar and 3-way glass stopcock was charged with 4A crushed molecular sieves (MS4A 100.0 mg) and flamed-dried under vacuum. After cooling down to room temperature, $Fe(OAc)_2$ (1.7 mg, 0.01 mmol), **L10** (2.7 mg, 0.01 mmol), carboxylic acid **1** (0.20 mmol) and TEMPO **2a** (65.6 mg, 0.42 mmol) were added followed by the addition of THF (1.0 mL, 0.20 M). After stirring under argon at 60 °C for 24 h, the reaction mixture was diluted with 10% AcOH in EtOAc (2.0 mL). The diluted solution was filtered through silica short column and washed with EtOAc. After evaporation of the organic solvent under reduced pressure, the resultant mixture was purified by silica gel flash chromatography to obtain cross-coupling product (**3aa**, **3ba**, **3da**, **3ea**, **3ga**, **3ia**, **3ja**, **3na**, **3ta**, **3αa**, **3γa**).

2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*p*-tolyl)acetic acid (3aa)



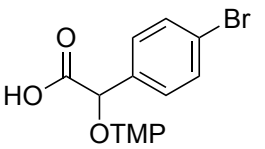
2-(*p*-tolyl)acetic acid **1a** (30.0 mg, 0.20 mmol) was used. The resultant mixture was purified by silica gel flash chromatography (10–20% EtOAc in *n*-Hexane as eluent) to afford the product **3aa**. (white solid, 95% yield, 59.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.18 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.38 (s, 1H, COC*H*), 2.35 (s, 3H, ArC*H*$_3$), 1.66 (m, 5H, *TMP*), 1.48 (br, 1H, *TMP*), 1.33–1.21 (m, 12H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.0, 138.6, 133.4, 129.2, 128.7, 84.0, 62.7, 62.5, 39.6, 39.6, 31.9, 31.1, 21.3, 20.9, 20.9, 16.5; IR (neat) 2926, 1715, 1375, 1260, 1177, 1132, 1047, 957, 924, 816, 797, 714, 681, 613, 503 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{28}NO_3$ $(M + H)^+$ 306.2064, found 306.2063.

2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(*m*-tolyl)acetic acid (3ba)



2-(*m*-tolyl)acetic acid **1b** (30.0 mg, 0.20 mmol) was used. The resultant mixture was purified by silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent) to afford the product **3ba**. (white solid, 82% yield, 50.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.25 (m, 1H, Ar*H*), 7.22–7.21 (m, 2H, Ar*H*), 7.17–7.15 (m, 1H, Ar*H*), 5.37 (s, 1H, COC*H*), 2.36 (s, 3H, ArC*H*$_3$), 1.66 (m, 5H, *TMP*), 1.48 (br, 1H, *TMP*), 1.33–1.21 (m, 12H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 138.1, 136.4, 129.4, 129.3, 128.4, 125.6, 84.7, 62.4, 62.3, 39.6, 39.6, 32.0, 31.3, 21.5, 20.8, 20.8, 16.6; IR (neat) 1717, 1375, 1362, 1260, 1242, 1182, 1132, 1045, 957, 922, 799, 775, 708, 694, 635, 438 cm^{-1}.

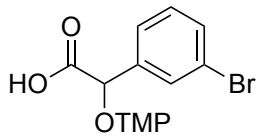
2-(4-bromophenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetic acid (3da)



2-(4-bromophenyl)acetic acid **1d** (43.0 mg, 0.20 mmol) was used. The resultant mixture was purified by silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent) to afford the product **3da**. (white solid, 90% yield, 66.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.30 (d, *J* = 8.5 Hz, 2H, Ar*H*), 5.35 (s, 1H, COC*H*), 1.65 (m, 5H, *TMP*), 1.47 (br, 1H, *TMP*), 1.28–1.21 (m, 12H,

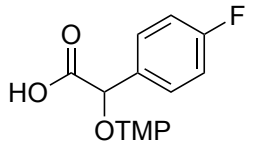
TMP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 135.7, 131.6, 130.0, 122.8, 84.2, 62.4, 62.4, 39.6, 39.6, 32.1, 31.3, 20.7, 20.7, 16.6; IR (neat) 1485, 1375, 1362, 1167, 1132, 1069, 1011, 991, 957, 920, 820, 750, 729, 638 cm^{-1}.

2-(3-bromophenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetic acid (3ea)



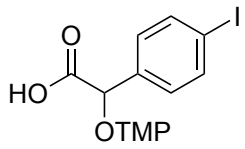
2-(3-bromophenyl)acetic acid **1e** (43.0 mg, 0.20 mmol) was used. The resultant mixture was purified by silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent) to afford the product **3ea**. (white solid, 97% yield, 71.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (t, *J* = 1.5 Hz, 1H, Ar*H*), 7.47 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.37 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.24 (t, *J* = 8.0 Hz, 1H, Ar*H*), 5.35 (s, 1H, COC*H*), 1.65 (m, 5H, *TMP*), 1.46 (br, 1H, *TMP*), 1.30–1.21 (m, 12H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 139.0, 131.6, 131.3, 130.0, 126.9, 122.4, 84.4, 62.3, 62.3, 39.7, 39.7, 32.2, 31.4, 20.8, 20.8, 16.6; IR (neat) 1470, 1375, 1362, 1242, 1207, 1175, 1132, 1055, 922, 797, 758, 727, 691, 662, 633, 434 cm^{-1}.

2-(4-fluorophenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetic acid (3ga)



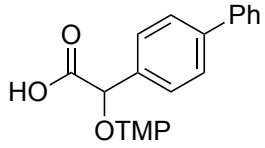
2-(4-fluorophenyl)acetic acid **1g** (30.8 mg, 0.20 mmol) was used. The resultant mixture was purified by silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent) to afford the product **3ga**. (white solid, 92% yield, 56.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 8.5, 5.5 Hz, 2H, Ar*H*), 7.05 (t, *J* = 8.5 Hz, 2H, Ar*H*), 5.38 (s, 1H, COC*H*), 1.65 (m, 5H, *TMP*), 1.47 (br, 1H, *TMP*), 1.29–1.21 (m, 12H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 162.8 (d, *J* = 247.4 Hz), 132.6, 130.3 (d, *J* = 8.6 Hz), 115.4 (d, *J* = 21.6 Hz), 84.1, 62.4, 62.4, 39.6, 39.6, 32.0, 31.3, 20.7, 20.7, 16.6; IR (neat) 1715, 1506, 1261, 1219, 1180, 1063, 1047, 924, 837, 810, 737, 723, 534, 513 cm^{-1}.

2-(4-iodophenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetic acid (3ia)



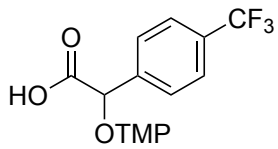
2-(4-iodophenyl)acetic acid **1i** (52.4 mg, 0.20 mmol) was used. The resultant mixture was purified by silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent) to afford the product **3ia**. (white solid, 85% yield, 70.9 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.17 (d, *J* = 8.5 Hz, 2H, Ar*H*), 5.35 (s, 1H, COC*H*), 1.66 (m, 5H, *TMP*), 1.48 (br, 1H, *TMP*), 1.29–1.19 (m, 12H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 137.6, 136.4, 130.2, 94.5, 84.4, 62.4, 62.3, 39.6, 39.6, 32.1, 31.4, 20.7, 20.7, 16.6; IR (neat) 1481, 1375, 1360, 1242, 1207, 1167, 1132, 1059, 1007, 991, 957, 920, 876, 818, 731, 635 cm^{-1}.

2-([1,1'-biphenyl]-4-yl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetic acid (3ja)



2-([1,1'-biphenyl]-4-yl)acetic acid **1j** (42.5 mg, 0.20 mmol) was used. The resultant mixture was purified by silica gel flash chromatography (1–1.5% MeOH in CH_2Cl_2 as eluent) to afford the product **3ja**. (white solid, 89% yield, 65.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.58 (m, 4H, Ar*H*), 7.49 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.44 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.35 (t, *J* = 7.5 Hz, 1H, Ar*H*), 5.47 (s, 1H, COC*H*), 1.69 (m, 5H, *TMP*), 1.50 (br, 1H, *TMP*), 1.37–1.25 (m, 12H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 141.5, 140.7, 135.5, 129.0, 128.8, 127.4, 127.2, 127.2, 84.3, 62.6, 62.5, 39.6, 39.6, 32.0, 31.2, 20.9, 20.9, 16.6; IR (neat) 1719, 1375, 1360, 1207, 1132, 1007, 991, 957, 922, 835, 756, 731, 696, 627 cm^{-1}.

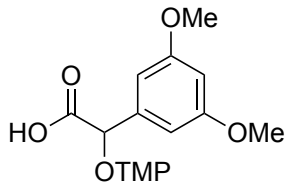
2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(4-(trifluoromethyl)phenyl)acetic acid (3na)



2-(4-(trifluoromethyl)phenyl)acetic acid **1n** (40.8 mg, 0.20 mmol) was used. The resultant mixture was purified by silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent) to afford the product **3na**. (colorless liquid, 95% yield, 68.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.56 (d, *J* = 8.0 Hz, 2H, Ar*H*), 5.42 (s, 1H, COC*H*), 1.63–1.61 (m, 5H, *TMP*), 1.45–1.43 (br,

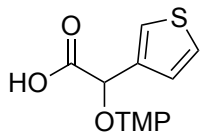
1H, *TMP*), 1.28–1.23 (m, 9H, *TMP*), 1.12 (s, 3H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 141.1, 130.4 (q, J = 32.3 Hz), 128.3, 125.3 (q, J = 3.7 Hz), 124.0 (q, J = 272.2 Hz), 85.4, 62.0, 62.0, 39.7, 39.7, 32.4, 31.6, 20.6, 20.6, 16.6; IR (neat) 1377, 1321, 1261, 1242, 1163, 1123, 1065, 1018, 991, 957, 908, 835, 731, 714, 642 cm^{-1}.

2-(3,5-dimethoxyphenyl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetic acid (3ta)



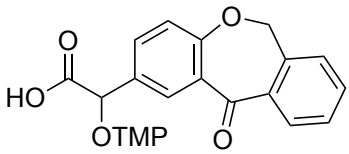
2-(3,5-dimethoxyphenyl)acetic acid **1t** (39.2 mg, 0.20 mmol) was used. The resultant mixture was purified by silica gel flash chromatography (1.5% MeOH in CH_2Cl_2 as eluent) to afford the product **3ta**. (white solid, 88% yield, 61.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (d, J = 2.0 Hz, 2H, Ar*H*), 6.44 (t, J = 2.0 Hz, 1H, Ar*H*), 5.32 (s, 1H, COC*H*), 3.79 (s, 6H, ArOCH_3), 1.64 (m, 5H, *TMP*), 1.46 (br, 1H, *TMP*), 1.32–1.23 (m, 12H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 160.6, 138.9, 106.3, 100.7, 85.1, 62.0, 62.0, 55.4, 39.7, 39.7, 32.2, 31.5, 20.7, 20.7, 16.6; IR (neat) 1595, 1458, 1427, 1321, 1294, 1204, 1153, 1132, 1045, 957, 918, 835, 804, 694 cm^{-1}.

2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-2-(thiophen-3-yl)acetic acid (3αa)



2-(thiophen-3-yl)acetic acid **1α** (28.4 mg, 0.20 mmol) was used. The resultant mixture was purified by silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent) to afford the product **3αa**. (white solid, 77% yield, 45.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (m, 1H, Ar*H*), 7.32 (dd, J = 5.0, 3.0 Hz, 1H, Ar*H*), 7.18 (dd, J = 5.0, 1.5 Hz, 1H, Ar*H*), 5.54 (s, 1H, COC*H*), 1.71–1.69 (m, 5H, *TMP*), 1.52 (br, 1H, *TMP*), 1.35–1.24 (m, 12H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 136.6, 127.2, 125.8, 124.7, 79.0, 63.0, 62.8, 39.3, 39.3, 31.3, 30.6, 20.9, 20.9, 16.4; IR (neat) 2936, 2924, 1703, 1275, 1206, 1159, 1059, 924, 841, 799, 781, 772, 723, 692 cm^{-1}.

2-(11-oxo-10,11-dihydrodibenzo[*b*,*f*]oxepin-2-yl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetic acid (3γa)



2-(11-oxo-10,11-dihydrodibenzo[*b*,*f*]oxepin-2-yl)acetic acid **1γ** (53.7 mg, 0.20 mmol) was used. The resultant mixture was purified by silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent) to afford the product **3γa**. (white solid, 82% yield, 69.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.90 (dd, *J* = 7.5, 1.0 Hz, 1H, Ar*H*), 7.58–7.55 (m, 2H, Ar*H*), 7.48 (dt, *J* = 7.5, 1.0 Hz, 1H, Ar*H*), 7.37 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.08 (d, *J* = 7.5 Hz, 1H, Ar*H*), 5.46 (s, 1H, COC*H*), 5.21 (s, 2H, ArOCH_2Ar), 1.69 (m, 5H, *TMP*), 1.50 (br, 1H, *TMP*), 1.37–1.23 (m, 12H, *TMP*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.6, 173.2, 161.5, 140.5, 135.4, 135.2, 132.8, 132.8, 130.6, 129.5, 129.3, 127.9, 124.9, 121.2, 83.7, 73.6, 62.7, 62.6, 39.6, 39.6, 32.0, 32.0, 20.9, 20.8, 16.5; IR (neat) 1647, 1485, 1298, 1258, 1202, 1136, 1119, 1013, 995, 910, 760, 727, 635, 619 cm^{-1}.

2. Catalytic α-Deuteration of Carboxylic Acids

2-1. General

All reactions were carried out using heat gun dried glassware under a positive pressure of dry argon unless otherwise noted. Catalytic reactions were run under an argon atmosphere. Air- and moisture-sensitive liquids were transferred via a syringe and a stainless-steel needle. Reactions were magnetically stirred and monitored by thin-layer chromatography using Merck Silica Gel 60 F254 plates. All work-up and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Flash chromatography was performed using silica gel 60N (spherical neutral, particle size 40–50μm) purchased from Kanto Chemical Co., Inc.

2-2. Instrumentation

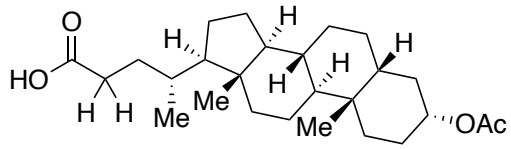
NMR was recorded on 500 MHz Bruker Avance III. Chemical shifts for proton are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$: δ 7.26 ppm). For ^{13}C NMR, chemical shifts were reported in the scale relative to NMR solvent ($CDCl_3$: δ 77.0 ppm) as an internal reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: double doublet, dt: double triplet, t: triplet, q: quartet, quin: quintet, sext: sextet, sep: septet, m: multiplet, br: broad signal), coupling constants (Hz), and integration. Infrared (IR) spectra were recorded with Shimadzu IR Affinity-1S. High-resolution mass spectroscopy (HRMS) was obtained with Bruker MicrOTOF II.

2-3. Materials

Commercially available carboxylic acids were used as received. K_2CO_3 was purchased from FUJIFILM Wako Pure Chemical Corporation and stored in a dry box. Pivalic anhydride was purchased from Kanto Chemical Co., Inc. and used as received. DMAP was purchased from Chem-Impex Int'l. Inc. and stored in a dry box. Acetone-d_6 (99.9% D) was purchased from Cambridge Isotope Laboratories, Inc. and used as received. Dimethyl sulfoxide was purchased from Nacalai Tesque, Inc. and dried over molecular sieves 4A before use. *N*,*N*-Dimethylformamide (super dehydrated) was purchased from Wako Pure Chemical Industries, Ltd. and stored in a dry box. D_2O (99.8% D) was purchased from Kanto Chemical Co., Inc. and used as received.

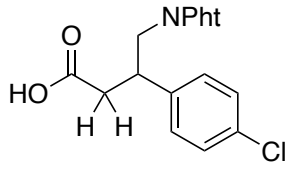
2-4. Substrate Synthesis and Characterization

(*R*)-4-((3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanoic acid (13c)



Lithocholic acid (1.13 g, 3.0 mmol) was added followed by the addition of acetic anhydride (5.0 mL, 0.60 M) and sulfuric acid (1 drop). After the mixture was stirred under argon at room temperature for 3 h, H_2O was added to the mixture and stirring at room temperature for 3 h. The resultant mixture was added 1 M HCl aq and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the resulting residue was washed by H_2O. The obtained solid was purified by silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent) to afford **13c**. (white solid, 50% yield, 623.0 mg).; CAS Registry Number 4057-84-5; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75–4.69 (m, 1H, AcOC*H*), 2.53–2.46 (m, 1H, C*H*$_2$COOH), 2.39–2.33 (m, 1H, C*H*$_2$COOH), 2.03 (s, 3H, OCOC*H*$_3$), 1.97–1.95 (m, 1H, *Alkyl*), 1.87–1.80 (m, 5H, *Alkyl*), 1.70–1.67 (m, 1H, *Alkyl*), 1.59–1.58 (m, 1H, *Alkyl*), 1.43–1.00 (m, 18H, *Alkyl*), 0.93–0.92 (m, 6H, CC*H*$_3$ + CHC*H*$_3$), 0.65 (s, 3H, CC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.1, 74.4, 56.5, 56.0, 42.8, 41.9, 40.4, 40.2, 35.8, 35.2, 35.0, 34.6, 32.3, 30.3, 30.2, 28.2, 27.0, 26.7, 26.3, 24.2, 23.3, 21.5, 20.8, 18.3, 12.1.

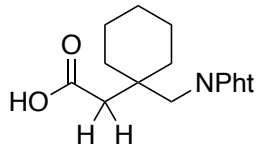
3-(4-chlorophenyl)-4-(1,3-dioxoisoindolin-2-yl)butanoic acid (13e)



4-amino-3-(4-chlorophenyl)butanoic acid (427 mg, 2.0 mmol) and phthalic anhydride (296 mg, 2.0 mmol) were added followed by the addition of dry toluene (8.0 mL, 0.25 M) and triethylamine (0.31 mL, 2.2 mmol). The reaction mixture was stirred under argon at 100 °C for 7 h. The resultant mixture was added 1 M HCl aq and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the resulting residue was purified by recrystallization after silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent) to afford **13e**. (white solid, 54% yield, 386.9 mg); CAS Registry Number 78131-01-8; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.79 (m, 2H, Ar*H*), 7.70–7.68 (m, 2H, Ar*H*), 7.24 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.19 (d, *J* = 8.5 Hz, 2H, Ar*H*), 3.90–3.82 (m, 2H, NC*H*$_2$), 3.69 (quin, *J* = 7.5 Hz, 1H, ArC*H*), 2.76–2.66 (m, 2H, C*H*$_2$COOH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.5, 168.1, 138.5, 134.1,

133.2, 131.7, 129.1, 128.9, 123.4, 42.8, 39.9, 37.8.

2-(1-((1,3-dioxoisoindolin-2-yl)methyl)cyclohexyl)acetic acid (13h)



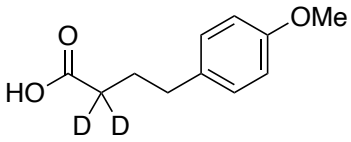
2-(1-(aminomethyl)cyclohexyl)acetic acid (514 mg, 3.0 mmol) and phthalic anhydride (1.11 g, 7.5 mmol) were added followed by the addition of dry toluene (1.0 mL, 0.30 M) and triethylamine (0.46 mL, 3.3 mmol). The reaction mixture was stirred under argon at 100 °C for 18 h. The resultant mixture was added 1 M HCl aq and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (2% MeOH in CH_2Cl_2 as eluent) to afford **13h**. (white solid, 82% yield, 738.2mg); CAS Registry Number 1554303-64-8; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.86 (m, 2H, Ar*H*), 7.76–7.74 (m, 2H, Ar*H*), 3.80 (s, 2H, NCH_2), 2.46 (s, 2H, CH_2COOH), 1.66–1.31 (m, 10H, *Alkyl*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 169.7, 134.3, 131.8, 123.5, 46.2, 39.7, 38.1, 33.7, 25.7, 21.4.

2-5. General Procedure and Characterization of the Products

General procedure for anhydride-mediated α–deuteration of carboxylic acids

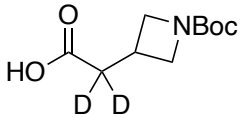
To a 4 mL vial equipped with a magnetic stirring bar, carboxylic acid **13** (0.20 mmol), K_2CO_3 (2.8 mg, 0.02 mmol) and DMAP (2.4 mg, 0.02 mmol) was added followed by the addition of acetone-d_6 (0.50 mL, 6.8 mmol, 0.40 M) and pivalic anhydride (8 μL, 0.04 mmol). The reaction mixture was stirred under argon at 40 °C for 48 h. After the reaction mixture was added D_2O (0.10 mL), stirring at room temperature for 1 h. The reaction mixture was added 1 M HCl aq and extracted with CH_2Cl_2, and the solvent was removed under reduced pressure. Then, 2.0 mL of CH_2Cl_2/formic acid = 4/1 was added to the residue, and evaporation was carried out for the removal of pivalic acid. This azeotropic operation was performed three times. the residue was purified by silica gel flash chromatography if necessary.

4-(4-methoxyphenyl)butanoic-2,2-d_2 acid (13a-d_2)



4-(4-methoxyphenyl)butanoic acid **13a** (38.8 mg, 0.20 mmol) was used as a substrate. The product **13a-d_2** was obtained without silica gel flash chromatography. (white solid, 94% deuterated, 98% yield, 38.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, J = 9.0 Hz, 2H, Ar*H*), 6.83 (d, J = 9.0 Hz, 2H, Ar*H*), 3.79 (s, 3H, ArOC*H*$_3$), 2.62 (t, J = 7.5 Hz, 2H, ArC*H*$_2$), 2.33 (m, 0.12H, C*H*$_2$COOH, 94% D), 1.92 (t, J = 7.5 Hz, 2H, C*H*$_2$CD$_2$COOH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 157.9, 133.3, 129.4, 113.8, 55.3, 34.0, 32.7, 26.3; IR (neat) 1695, 1510, 1412, 1300, 1277, 1242, 1182, 1175, 1026, 947, 831, 814, 557, 525, 403 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{12}D_2NaO_3$ $(M + Na)^+$ 219.0961, found 219.0978.

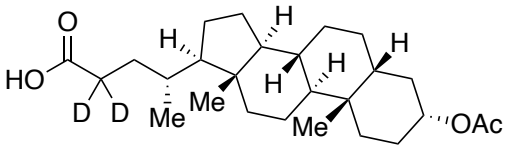
2-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)acetic-2,2-d_2 acid (13b-d_2)



2-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)acetic acid **13b** (43.0 mg, 0.20 mmol) was used as a substrate. The product **13b-d_2** was obtained without silica gel flash chromatography. (white solid, 98% deuterated, 90% yield, 38.9 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09 (dd, J = 8.5, 8.5 Hz, 2H, N(C*H*$_2$)$_2$), 3.63 (dd, J = 8.5, 5.5 Hz, 2H, N(C*H*$_2$)$_2$), 2.89–2.84 (m, 1H, C*H*CD$_2$COOH), 2.65 (m, 0.05H, C*H*$_2$COOH, 98% D), 1.43 (s, 9H, NCOOC(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 156.5, 79.7,

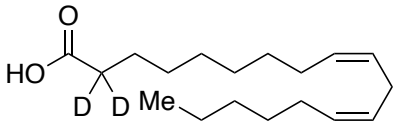
54.2, 38.0, 28.4, 24.9; IR (neat) 1721, 1641, 1422, 1396, 1366, 1341, 1254, 1221, 1063, 968, 856, 818, 768, 635, 561 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{10}H_{15}D_2NNaO_4$ $(M + Na)^+$ 240.1175, found 240.1170.

(*R*)-4-((3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanoic-2,2-d_2 acid (13c-d_2)



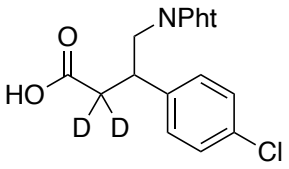
(*R*)-4-((3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-acetoxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanoic acid **13c** (83.7 mg, 0.20 mmol) was used as a substrate and DMSO (0.50 mL) was used as a co-solvent. The product **13c-d_2** was obtained after silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent). (white solid, 90% deuterated, 91% yield, 76.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75–4.69 (m, 1H, AcOC*H*), 2.40–2.23 (m, 0.19H, CH_2COOH, 90% D), 2.03 (s, 3H, OCOCH_3), 1.98–1.95 (m, 1H, *Alkyl*), 1.87–1.80 (m, 5H, *Alkyl*), 1.69–1.67 (m, 1H, *Alkyl*), 1.58–1.53 (m, 1H, *Alkyl*), 1.43–1.00 (m, 18H, *Alkyl*), 0.93–0.92 (m, 6H, CCH_3 + CHCH_3), 0.65 (s, 3H, CCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.5, 170.8, 74.5, 56.5, 56.0, 42.8, 41.9, 40.4, 40.2, 35.8, 35.3, 35.0, 34.6, 32.2, 30.7, 30.5, 28.2, 27.0, 26.6, 26.3, 24.2, 23.3, 21.5, 20.8, 18.3, 12.1; IR (neat) 2359, 1734, 1707, 1412, 1294, 1254, 1026, 669, 617, 426, 419 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{26}H_{40}D_2NaO_4$ $(M + Na)^+$ 443.3101, found 443.3101.

(9*Z*,12*Z*)-octadeca-9,12-dienoic-2,2-d_2 acid (13d-d_2)



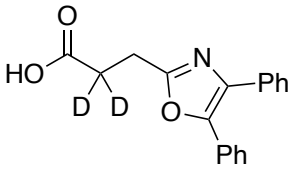
(9*Z*,12*Z*)-octadeca-9,12-dienoic acid **13d** (62.5 μL, 0.20 mmol) was used as a substrate. The reaction was performed at 60 °C. The product **13d-d_2** was obtained without silica gel flash chromatography. (colorless liquid, 97% deuterated, 103% yield, 58.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.41–5.30 (m, 4H, *vinyl*), 2.77 (t, *J* = 6.5 Hz, 2H, CH=CHCH_2CH=CH), 2.35–2.32 (m, 0.06H, CH_2COOH, 97% D), 2.07–2.03 (m, 4H, CH=CHCH_2CH_2), 1.64–1.61 (m, 2H, CH_2CD_2COOH), 1.39–1.27 (m, 14H, *Alkyl*), 0.89 (t, *J* = 7.0 Hz, 3H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.3, 130.2, 130.0, 128.1, 127.9, 33.5, 31.5, 29.6, 29.4, 29.2, 29.1, 29.0, 27.2, 27.2, 25.6, 24.6, 22.6, 14.1; IR (neat) 3007, 2924, 2855, 1705, 1464, 1410, 1377, 1294, 1171, 1125, 945, 723, 436, 415, 409 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{30}D_2NaO_2$ $(M + Na)^+$ 305.2420, found 305.2420.

3-(4-chlorophenyl)-4-(1,3-dioxoisoindolin-2-yl)butanoic-2,2-*d*$_2$ acid (13e-*d*$_2$)



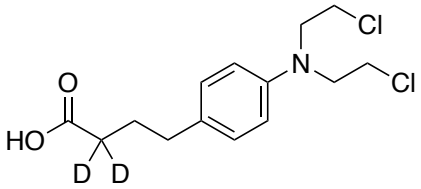
3-(4-chlorophenyl)-4-(1,3-dioxoisoindolin-2-yl)butanoic acid **13e** (72.2 mg, 0.20 mmol) was used as a substrate and DMSO (0.50 mL) was used as a co-solvent. The product **13e-*d*$_2$** was obtained after silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent). (white solid, 98% deuterated, 93% yield, 67.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.79 (m, 2H, Ar*H*), 7.70–7.69 (m, 2H, Ar*H*), 7.25 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.20 (d, *J* = 8.0 Hz, 2H, Ar*H*), 3.91–3.83 (m, 2H, NC*H*$_2$), 3.69 (t, *J* = 8.0 Hz, 1H, ArC*H*), 2.70 (m, 0.04H, C*H*$_2$COOH, 98% D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 168.1, 138.5, 134.1, 133.2, 131.7, 129.1, 128.9, 123.4, 42.8, 39.8, 37.3; IR (neat) 1728, 1688, 1398, 1358, 1229, 1053, 997, 887, 835, 816, 721, 710, 650, 552, 530 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{12}D_2ClNNaO_4$ $(M + Na)^+$ 368.0629, found 368.0625.

3-(4,5-diphenyloxazol-2-yl)propanoic-2,2-*d*$_2$ acid (13f-*d*$_2$)



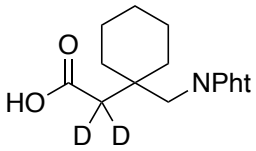
3-(4,5-diphenyloxazol-2-yl)propanoic acid **13f** (58.7 mg, 0.20 mmol) was used as a substrate and DMSO (0.50 mL) was used as a co-solvent. The product **13f-*d*$_2$** was obtained after silica gel flash chromatography (2% MeOH in CH_2Cl_2 as eluent). (white solid, 99% deuterated, 96% yield, 56.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.61 (m, 2H, Ar*H*), 7.58–7.56 (m, 2H, Ar*H*), 7.38–7.31 (m, 6H, Ar*H*), 3.19 (s, 2H, ArC*H*$_2$), 2.96–2.93 (m, 0.03H, C*H*$_2$COOH, 99% D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 161.9, 145.6, 134.9, 132.1, 128.8, 128.7, 128.6, 128.6, 128.2, 128.0, 126.5, 30.4, 23.1; IR (neat) 1717, 1308, 1256, 1219, 1206, 1059, 966, 922, 766, 756, 727, 704, 694, 675, 523 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{13}D_2NNaO_3$ $(M + Na)^+$ 318.1070, found 318.1079.

4-(4-(bis(2-chloroethyl)amino)phenyl)butanoic-2,2-*d*$_2$ acid (13g-*d*$_2$)



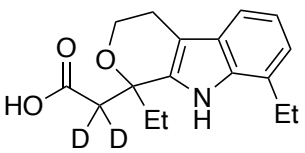
4-(4-(bis(2-chloroethyl)amino)phenyl)butanoic acid **13g** (60.8 mg, 0.20 mmol) was used as a substrate. The product **13g-*d*$_2$** was obtained without silica gel flash chromatography. (white solid, 95% deuterated, 97% yield, 59.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.63 (d, *J* = 8.5 Hz, 2H, Ar*H*), 3.71–3.69 (m, 4H, C*H*$_2$CH$_2$), 3.63–3.60 (m, 4H, C*H*$_2$CH$_2$), 2.58 (t, *J* = 7.5 Hz, 2H, ArC*H*$_2$), 2.35 (m, 0.11H, C*H*$_2$COOH, 95% D), 1.91 (t, *J* = 7.5 Hz, 2H, ArCH$_2$C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 144.4, 130.4, 129.7, 112.2, 53.6, 40.5, 33.8, 32.7, 26.3; IR (neat) 1713, 1614, 1520, 1358, 1292, 1275, 1244, 1177, 1140, 947, 804, 741, 725, 557, 544 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{14}H_{18}D_2Cl_2NO_2$ $(M + H)^+$ 306.0991, found 306. 0998.

2-(1-((1,3-dioxoisoindolin-2-yl)methyl)cyclohexyl)acetic-2,2-*d*$_2$ acid (13h-*d*$_2$)



2-(1-((1,3-dioxoisoindolin-2-yl)methyl)cyclohexyl)acetic acid **13h** (63.7 mg, 0.20 mmol) was used as a substrate and DMSO (0.50 mL) was used as a co-solvent. The reaction was performed at 60 °C. The product **13h-*d*$_2$** was obtained after silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent). (white solid, 97% deuterated, 93% yield, 59.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88–7.86 (m, 2H, Ar*H*), 7.76–7.74 (m, 2H, Ar*H*), 3.80 (s, 2H, NC*H*$_2$), 2.44 (m, 0.05H, C*H*$_2$COOH, 97% D), 1.66–1.33 (m, 10H, *Alkyl*);^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 169.5, 134.1, 131.9, 123.4, 46.1, 39.2, 38.0, 33.6, 25.7, 21.4; IR (neat) 2359, 2340, 1709, 1686, 1402, 1391, 1373, 1362, 1346, 1288, 1229, 718, 710, 669, 530 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{17}D_2NNaO_4$ $(M + Na)^+$ 326.1332, found 326.1332.

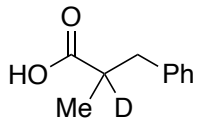
2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic-2,2-*d*$_2$ acid (13i-*d*$_2$)



2-(1,8-diethyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-1-yl)acetic acid **13i** (57.5 mg, 0.20 mmol) was

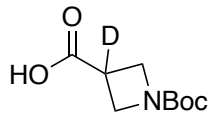
used as a substrate and DMSO (0.50 mL) was used as a co-solvent. The reaction was performed at 60 °C. The product **13i-*d*$_2$** was obtained after silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent). (white solid, 92% deuterated, 88% yield, 50.9 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (br, 1H, N*H*), 7.36 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.07 (dd, *J* = 7.5, 7.5 Hz, 1H, Ar*H*), 7.00 (d, *J* = 7.5 Hz, 1H, Ar*H*), 4.14–4.09 (m, 1H, OC*H*$_2$), 4.07–4.02 (m, 1H, OC*H*$_2$), 3.05–3.02 (m, 0.15H, C*H*$_2$COOH, 92% D), 2.86–2.78 (m, 4H, ArC*H*$_2$CH$_2$ + ArC*H*$_2$CH$_3$), 2.17–2.09 (m, 1H, CC*H*$_2$CH$_3$), 2.07–2.00 (m, 1H, CC*H*$_2$CH$_3$), 1.32 (t, *J* = 7.5 Hz, 3H, CH$_2$C*H*$_3$), 0.88 (t, *J* = 7.5 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.7, 134.7, 134.6, 126.7, 126.1, 120.7, 119.9, 116.0, 108.6, 75.1, 60.9, 42.2, 30.9, 24.0, 22.2, 13.7, 7.7; IR (neat) 1744, 1701, 1302, 1250, 1227, 1072, 1036, 905, 783, 746, 739, 590, 556, 519, 484 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{19}D_2NNaO_3$ $(M + Na)^+$ 312.1539, found 312.1552.

2-methyl-3-phenylpropanoic-2-*d* acid (13j-*d*)



2-methyl-3-phenylpropanoic acid **13j** (32.8 mg, 0.20 mmol) was used as a substrate. The reaction was performed at 80 °C. The product **13j-*d*** was obtained without silica gel flash chromatography. (white solid, 83% deuterated, 92% yield, 30.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.23–7.18 (m, 3H, Ar*H*), 3.07 (d, *J* = 14.0 Hz, 1H, PhC*H*$_2$), 2.81–2.74 (m, 0.17H, C*H*COOH, 83% D), 2.67 (d, *J* = 14.0 Hz, 1H, PhC*H*$_2$), 1.18 (s, 3H, CDC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.5, 139.0, 129.0, 128.4, 126.4, 40.9, 39.2, 16.4; IR (neat) 1686, 1450, 1310, 1288, 1217, 1092, 962, 910, 781, 739, 725, 702, 604, 515, 474 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{10}H_{11}DNaO_2$ $(M + Na)^+$ 188.0792, found 188.0792.

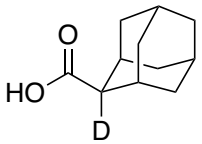
1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic-3-*d* acid (13k-*d*)



1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid **13k** (40.2 mg, 0.20 mmol) was used as a substrate. The reaction was performed at 60 °C. The product **13k-*d*** was obtained without silica gel flash chromatography. (white solid, 99% deuterated, 83% yield, 33.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (s, 4H, N(C*H*$_2$)$_2$), 3.38 (m, 0.01H, C*H*COOH, 99% D), 1.44 (s, 9H, NCOOC(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 156.3, 80.3, 51.5, 31.7, 28.3; IR (neat) 1719, 1638, 1477, 1458, 1395,

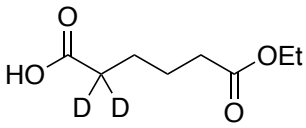
1366, 1250, 1153, 1130, 895, 870, 854, 768, 694, 563 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_9H_{14}DNNaO_4$ $(M + Na)^+$ 225.0956, found 225.0950.

(1*R*,3*S*,5*r*,7*r*)-adamantane-2-carboxylic-2-*d* acid (13l-*d*)



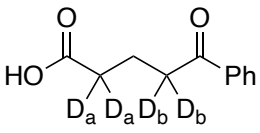
(1*R*,3*S*,5*r*,7*r*)-adamantane-2-carboxylic acid **13l** (36.0 mg, 0.20 mmol) was used as a substrate and DMSO (0.50 mL) was used as a co-solvent. The reaction was performed at 80 °C. The product **13l-*d*** was obtained after the additional azeotropic operation with toluene three times, without silica gel flash chromatography. (white solid, 80% deuterated, 90% yield, 32.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.68 (s, 0.20H, C*H*COOH, 80% D), 2.35 (br, 2H, *Alkyl*), 1.94–1.85 (m, 6H, *Alkyl*), 1.78–1.75 (m, 4H, *Alkyl*), 1.66–1.64 (m, 2H, *Alkyl*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.2, 49.0, 38.0, 37.3, 33.5, 29.4, 29.3, 27.4; IR (neat) 2916, 2897, 2849, 1682, 1454, 1414, 1292, 1279, 1105, 949, 939, 766, 735, 511, 407 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{15}DNaO_2$ $(M + Na)^+$ 204.1105, found 204.1105.

6-ethoxy-6-oxohexanoic-2,2-d_2 acid (13m-d_2)



6-ethoxy-6-oxohexanoic acid **13m** (32.0 μL, 0.20 mmol) was used as a substrate. The product **13m-d_2** was obtained without silica gel flash chromatography. (colorless liquid, 96% deuterated, 88% yield, 31.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.13 (q, J = 7.0 Hz, 2H, $COOCH_2CH_3$), 2.34–2.31 (m, 2.08H, CH_2COOH + CH_2COOEt, 96% D), 1.68–1.67 (m, 4H, $CD_2CH_2CH_2CH_2$), 1.26 (t, J = 7.0 Hz, 3H, $COOCH_2CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.5, 173.4, 60.4, 33.9, 33.1, 24.3, 24.0, 14.2; IR (neat) 411, 438, 451, 746, 945, 1028, 1086, 1117, 1167, 1252, 1344, 1373, 1703, 1730, 2938 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_8H_{12}D_2NaO_4$ $(M + Na)^+$ 199.0910, found 199.0915.

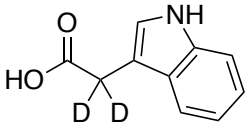
5-oxo-5-phenylpentanoic-2,2,4,4-d_4 acid (13n-d_4)



5-oxo-5-phenylpentanoic acid **13n** (38.4 mg, 0.20 mmol) was used as a substrate. The product **13n-d_4**

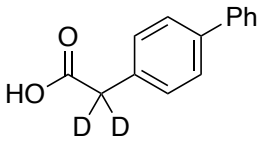
was obtained without silica gel flash chromatography. (white solid, D_a: 93% deuterated, D_b: 96% deuterated, 76% yield, 30.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.0 Hz, 2H, Ar*H*), 7.57 (t, *J* = 7.0 Hz, 1H, Ar*H*), 7.46 (t, *J* = 7.0 Hz, 2H, Ar*H*), 3.08 (m, 0.08H, C*H*$_2$COPh, 96% D), 2.49 (m, 0.14H, C*H*$_2$COOH, 93% D), 2.07 (s, 2H, C*H*$_2$CD$_2$COOH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 179.4, 136.8, 133.2, 128.6, 128.0, 36.6, 32.5, 18.8; IR (neat) 1690, 1668, 1304, 1273, 1126, 991, 947, 910, 837, 766, 756, 723, 691, 665, 652 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_8D_4NaO_3$ $(M + Na)^+$ 219.0930, found 219.0942.

2-(1*H*-indol-3-yl)acetic-2,2-*d*$_2$ acid (13o-*d*$_2$)



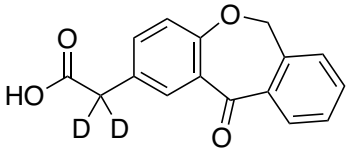
2-(1*H*-indol-3-yl)acetic acid **13o** (35.0 mg, 0.20 mmol) was used as a substrate and DMSO (0.50 mL) was used as a co-solvent. The product **13o-*d*$_2$** was obtained after silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent). (white solid, 98% deuterated, 71% yield, 25.0 mg); ^{1}H NMR (500 MHz, methanol-*d*$_4$) δ 7.44 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.24 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.06 (s, 1H, Ar*H*), 7.01–6.97 (m, 1H, Ar*H*), 6.92–6.89 (m, 1H, Ar*H*), 3.61 (m, 0.04H, C*H*$_2$COOH, 98% D); ^{13}C NMR (125 MHz, methanol-*d*$_4$) δ 175.1, 136.6,127.3, 123.2, 121.0, 118.4, 118.1, 110.8, 107.4, 30.0; IR (neat) 2513, 1452, 1342, 1331, 1312, 1190, 1001, 947, 922, 741, 664, 610, 575, 426, 419 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{10}H_7D_2NNaO_2$ $(M + Na)^+$ 200.0651, found 200.0651.

2-([1,1'-biphenyl]-4-yl)acetic-2,2-*d*$_2$ acid (13p-*d*$_2$)



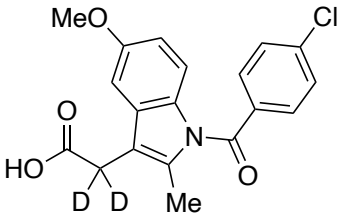
2-([1,1'-biphenyl]-4-yl)acetic acid **13p** (42.4 mg, 0.20 mmol) was used as a substrate and DMSO (0.50 mL) was used as a co-solvent. The reaction was performed at 60 °C. The product **13p-*d*$_2$** was obtained after silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent). (white solid, 97% deuterated, 84% yield, 36.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.56 (m, 4H, Ar*H*), 7.43 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.38–7.33 (m, 3H, Ar*H*), 3.69 (m, 0.06H, C*H*$_2$COOH, 97% D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 140.7, 140.4, 132.2, 129.8, 128.8, 127.4, 127.3, 127.1, 40.1; IR (neat) 1684, 1487, 1406, 1323, 1242, 1049, 1007, 928, 858, 760, 739, 696, 660, 432, 419 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{14}H_{10}D_2NaO_2$ $(M + Na)^+$ 237.0855, found 237.0855.

2-(11-oxo-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetic-2,2-d_2 acid (13q-d_2)



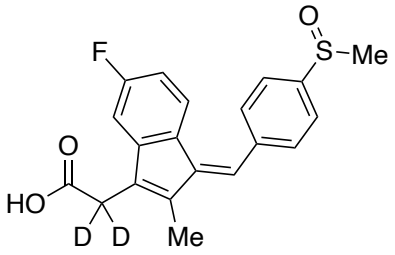
2-(11-oxo-6,11-dihydrodibenzo[*b*,*e*]oxepin-2-yl)acetic acid **13q** (53.7 mg, 0.20 mmol) was used as a substrate and DMSO (0.50 mL) was used as a co-solvent. The reaction was performed at 60 °C. The product **13q-d_2** was obtained after silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent). (white solid, 90% deuterated, 88% yield, 47.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.5 Hz, 1H, Ar*H*), 7.89 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.56 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.47 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.42 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar*H*), 7.36 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.04 (d, *J* = 8.5 Hz, 1H, Ar*H*), 5.19 (s, 2H, ArOCH_2), 3.66 (m, 0.21H, CH_2COOH, 90% D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.9, 177.4, 160.6, 140.4, 136.3, 135.5, 132.8, 132.6, 129.5, 129.3, 127.8, 127.0, 125.2, 121.2, 73.6, 39.5; IR (neat) 1709, 1641, 1493, 1402, 1300, 1287, 1223, 1204, 1142, 1123, 1018, 827, 756, 669, 638 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{10}D_2NaO_4$ $(M + Na)^+$ 293.0753, found 293.0757.

2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic-2,2-d_2 acid (13r-d_2)



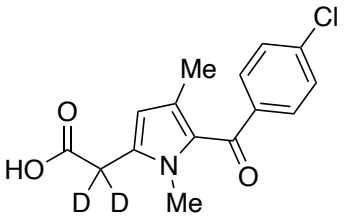
2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetic acid **13r** (71.6 mg, 0.20 mmol) was used as a substrate and DMSO (0.50 mL) was used as a co-solvent. The product **13r-d_2** was obtained after silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent). (white solid, 94% deuterated, 84% yield, 60.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.47 (d, *J* = 8.0 Hz, 2H, Ar*H*), 6.95 (d, *J* = 2.5 Hz, 1H, Ar*H*), 6.85 (d, *J* = 9.0 Hz, 1H, Ar*H*), 6.67 (dd, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 3.83 (s, 3H, ArOCH_3), 3.68 (m, 0.12H, CH_2COOH, 94% D), 2.39 (s, 3H, ArCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 168.3, 156.1, 139.3, 136.3, 133.8, 131.2, 130.8, 130.4, 129.1, 115.0, 111.8, 111.7, 101.3, 55.7, 29.5, 13.3; IR (neat) 1674, 1477, 1352, 1329, 1300, 1287, 1225, 1213, 1163, 1094, 1038, 999, 847, 810, 733 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{14}D_2ClNNaO_4$ $(M + Na)^+$ 382.0786, found 382.0800.

(*Z*)-2-(5-fluoro-2-methyl-1-(4-(methylsulfinyl)benzylidene)-1*H*-inden-3-yl)acetic-2,2-d_2 acid (13s-d_2)



(*Z*)-2-(5-fluoro-2-methyl-1-(4-(methylsulfinyl)benzylidene)-1*H*-inden-3-yl)acetic acid **13s** (71.3 mg, 0.20 mmol) was used as a substrate and DMSO (0.50 mL) was used as a co-solvent. The reaction was performed at 60 °C. The product **13s-d_2** was obtained after silica gel flash chromatography (5% MeOH in CH_2Cl_2 as eluent). (yellow solid, 98% deuterated, 72% yield, 51.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.64 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.15 (s, 1H, C=C*H*), 7.11 (dd, *J* = 8.5, 5.0 Hz, 1H, Ar*H*), 6.89 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar*H*), 6.54 (dt, *J* = 9.0, 2.5 Hz, 1H, Ar*H*), 3.57 (m, 0.03H, CH_2COOH, 98% D), 2.83 (s, 3H, SOCH_3), 2.21 (s, 3H, ArCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 163.3 (d, *J* = 246.7 Hz), 146.7 (d, *J* = 8.7 Hz), 144.4, 141.7, 139.9, 138.3, 131.6, 130.3, 129.5 (d, *J* = 2.8 Hz), 128.1, 124.0, 123.6 (d, *J* = 8.9 Hz), 110.8 (d, *J* = 22.8 Hz), 106.2 (d, *J* = 23.8 Hz), 43.4, 31.0, 10.5; IR (neat) 1713, 1599, 1464, 1246, 1184, 1022, 1005, 959, 881, 851, 814, 727, 577, 538, 438 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{20}H_{15}D_2FNaO_3S$ $(M + Na)^+$ 381.0900, found 381.0901.

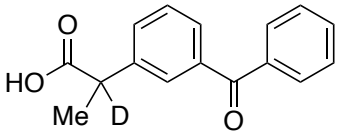
2-(5-(4-chlorobenzoyl)-1,4-dimethyl-1*H*-pyrrol-2-yl)acetic-2,2-d_2 acid (13t-d_2)



sodium 2-(5-(4-chlorobenzoyl)-1,4-dimethyl-1*H*-pyrrol-2-yl)acetate **13t-Na** (62.7 mg, 0.20 mmol) was used as a substrate and DMSO (0.50 mL) was used as a co-solvent without the addition of K_2CO_3. The reaction was performed at 60 °C. The product **13t-d_2** was obtained after silica gel flash chromatography (2% MeOH in CH_2Cl_2 as eluent). (white solid, 98% deuterated, 83% yield, 48.9 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.42 (d, *J* = 9.0 Hz, 2H, Ar*H*), 5.97 (s, 1H, Ar*H*), 3.75 (m, 3.03H, NCH_3 + CH_2COOH, 98% D), 1.75 (s, 3H, ArCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.6, 174.3, 139.1, 138.1, 132.2, 130.6, 129.9, 129.1, 128.7, 112.7, 33.1, 31.8, 14.4; IR (neat) 1611, 1593, 1449, 1396, 1379, 1265, 1184, 1169, 1088, 934, 791, 754, 735, 698, 652 cm^{-1};

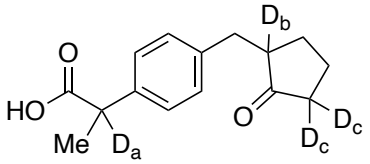
HRMS (ESI) *m/z* calc'd for $C_{15}H_{12}D_2ClNNaO_3$ $(M + Na)^+$ 316.0680, found 316.0692.

2-(3-benzoylphenyl)propanoic-2-*d* acid (13u-*d*)



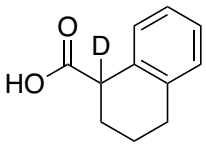
2-(3-benzoylphenyl)propanoic acid **13u** (50.9 mg, 0.20 mmol) was used as a substrate and DMSO (0.50 mL) was used as a co-solvent. The product **13u-*d*** was obtained after silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent). (white solid, 98% deuterated, 99% yield, 50.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80–7.78 (m, 3H, Ar*H*), 7.70–7.68 (m, 1H, Ar*H*), 7.60–7.56 (m, 2H, Ar*H*), 7.49–7.43 (m, 3H, Ar*H*), 3.83 (q, *J* = 7.0 Hz, 0.02H, C*H*COOH, 98% D), 1.55 (s, 3H, CDC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.5, 180.1, 140.0, 137.9, 137.4, 132.5, 131.6, 130.1, 129.3, 129.3, 128.6, 128.3, 44.8, 18.0; IR (neat) 2361, 2342, 1651, 1283, 1138, 962, 937, 924, 716, 700, 689, 669, 642, 602, 438 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{13}DNaO_3$ $(M + Na)^+$ 278.0898, found 278.0909.

2-(4-((2-oxocyclopentyl-1,3,3-*d*$_3$)methyl)phenyl)propanoic-2-*d* acid (13v-*d*$_4$)



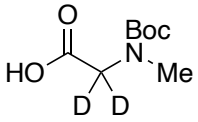
2-(4-((2-oxocyclopentyl-1,3,3-*d*$_3$)methyl)phenyl)propanoic acid **13v** (49.3 mg, 0.20 mmol) was used as a substrate and DMSO (0.50 mL) was used as a co-solvent. The product **13v-*d*$_4$** was obtained after silica gel flash chromatography (1% MeOH in CH_2Cl_2 as eluent). (colorless liquid, D_a: 98% deuterated, D_b: 78% deuterated, D_c: 83% deuterated, 96% yield, 47.9 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.12 (d, *J* = 8.5 Hz, 2H, Ar*H*), 3.71 (q, *J* = 7.0 Hz, 0.03H, C*H*COOH, 98% D), 3.11 (d, *J* = 14.0 Hz, 1H, ArC*H*$_2$), 2.50 (d, *J* = 14.0 Hz, 1H, ArC*H*$_2$), 2.32–2.30 (m, 0.33H, COC*H*$_2$, 83% D), 2.09–2.06 (m, 1.22H, C*H*$_2$CH$_2$ + COC*H*, 78% D), 1.96–1.92 (m, 1H, C*H*$_2$CH$_2$), 1.75–1.69 (m, 1H, C*H*$_2$CH$_2$), 1.57–1.50 (m, 1H, C*H*$_2$CH$_2$), 1.49 (s, 3H CDC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.6, 139.2, 137.6, 129.2, 127.6, 50.5, 44.6, 37.7, 35.1, 29.1, 20.3, 18.0; IR (neat) 1730, 1701, 1512, 1287, 1209, 1130, 1092, 939, 910, 864, 837, 731, 569, 509, 405 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{14}D_4NaO_3$ $(M + Na)^+$ 273.1399, found 273.1406.

1,2,3,4-tetrahydronaphthalene-1-carboxylic-1-*d* acid (13w-*d*)



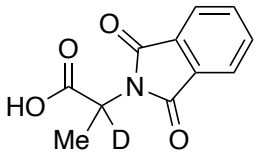
1,2,3,4-tetrahydronaphthalene-1-carboxylic acid **13w** (35.2 mg, 0.20 mmol) was used as a substrate. The product **13w-*d*** was obtained without silica gel flash chromatography. (white solid, 99% deuterated, 100% yield, 35.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.10 (m, 4H, Ar*H*), 3.85 (t, *J* = 6.0 Hz, 0.01H, C*H*COOH, 99% D), 2.87–2.81 (m, 1H, ArCH_2), 2.79–2.73 (m, 1H, ArCH_2), 2.21–2.17 (m, 1H, *Alkyl*), 2.05–1.94 (m, 2H, *Alkyl*), 1.83–1.75 (m, 1H, *Alkyl*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.5, 137.3, 132.4, 129.6, 129.5, 127.1, 125.8, 44.1, 29.1, 26.4, 20.4; IR (neat) 2357, 1684, 1495, 1402, 1290, 1279, 1219, 1184, 951, 926, 735, 702, 677, 484, 434 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{11}DNaO_2$ $(M + Na)^+$ 200.0792, found 200.0792.

***N*-(*tert*-butoxycarbonyl)-*N*-methylglycine-2,2-d_2 (13x-d_2)**



N-(*tert*-butoxycarbonyl)-*N*-methylglycine **13x** (37.8 mg, 0.20 mmol) was used as a substrate. The reaction was performed at 60 °C. The product **13x-d_2** was obtained without silica gel flash chromatography. (white solid, 91% deuterated, 68% yield, 26.1 mg); ^{1}H NMR (500 MHz, $CDCl_3$) (***rotamer mixture)*** δ 2.94 (s, 3H, NCH_3), 2.68 (m, 0.18H, CH_2COOH, 91% D), 1.47–1.44 (m, 9H, NCOOC(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) (***rotamer mixture)*** δ 175.1, 174.6, 156.5, 155.5, 80.6, 80.5, 50.2, 35.6, 35.4, 28.3, 28.2; IR (neat) 1744, 1638, 1449, 1396, 1368, 1223, 1159, 1092, 1049, 1020, 853, 831, 822, 766, 673 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_8H_{13}D_2NNaO_4$ $(M + Na)^+$ 214.1019, found 214.1026.

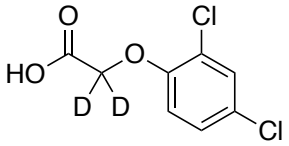
2-(1,3-dioxoisoindolin-2-yl)propanoic-2-*d* acid (13y-*d*)



2-(1,3-dioxoisoindolin-2-yl)propanoic acid **13y** (43.8 mg, 0.20 mmol) was used as a substrate. The product **13y-*d*** was obtained without silica gel flash chromatography. (white solid, 98% deuterated, 93% yield, 40.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–7.86 (m, 2H, Ar*H*), 7.74–7.73 (m, 2H, Ar*H*),

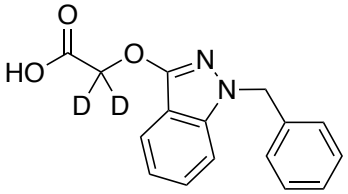
5.04 (q, J = 7.5 Hz, 0.02H, C*H*COOH, 98% D), 1.72 (s, 3H, CDC*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 167.4, 134.2, 131.8, 123.6, 47.0, 14.9; IR (neat) 2359, 2342, 1707, 1389, 1306, 1190, 961, 916, 745, 718, 706, 692, 669, 625, 529 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_8DNNaO_4$ $(M + Na)^+$ 243.0487, found 243.0493.

2-(2,4-dichlorophenoxy)acetic-2,2-d_2 acid (13z-d_2)



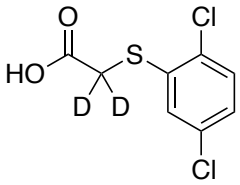
2-(2,4-dichlorophenoxy)acetic acid **13z** (44.2 mg, 0.20 mmol) was used as a substrate and DMF (0.50 mL) was used as a co-solvent. The reaction was performed at 60 °C. The product **13z-d_2** was obtained after silica gel flash chromatography (5% MeOH in CH_2Cl_2 as eluent). (white solid, 87% deuterated, 93% yield, 41.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, J = 2.5 Hz, 1H, Ar*H*), 7.19 (dd, J = 9.0, 2.5 Hz, 1H, Ar*H*), 6.82 (d, J = 9.0 Hz, 1H, Ar*H*), 4.72 (m, 0.27H, C*H*$_2$COOH, 87% D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 152.0, 130.5, 127.7, 127.6, 124.3, 114.9, 65.5; IR (neat) 1722, 1477, 1288, 1248, 1233, 1130, 1103, 1057, 872, 827, 793, 708, 677, 638, 438 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_8H_4D_2Cl_2NaO_3$ $(M + Na)^+$ 244.9712, found 244.9715.

2-((1-benzyl-1*H*-indazol-3-yl)oxy)acetic-2,2-d_2 acid (13α-d_2)



2-((1-benzyl-1*H*-indazol-3-yl)oxy)acetic acid **13α** (56.5 mg, 0.20 mmol) was used as a substrate and DMF (0.50 mL) was used as a co-solvent. The reaction was performed at 60 °C. The product **13α-d_2** was obtained after silica gel flash chromatography (2% MeOH in CH_2Cl_2 as eluent). (white solid, 91% deuterated, 82% yield, 46.6 mg); ^{1}H NMR (500 MHz, methanol-d_4) δ 7.71 (d, J = 8.0 Hz, 1H, Ar*H*), 7.38–7.33 (m, 2H, Ar*H*), 7.29–7.26 (m, 2H, Ar*H*), 7.24–7.21 (m, 1H, Ar*H*), 7.18 (d, J = 7.5 Hz, 2H, Ar*H*), 7.09–7.06 (m, 1H, Ar*H*), 5.43 (s, 2H, NC*H*$_2$Ph), 4.95 (m, 0.19H, C*H*$_2$COOH, 91% D); ^{13}C NMR (125 MHz, methanol-d_4) δ 171.1, 154.8, 141.9, 137.6, 128.1, 127.3, 127.1, 126.7, 119.4, 119.2, 112.3, 108.9, 64.3, 51.5; IR (neat) 2361, 1719, 1707, 1701, 1522, 1352, 1190, 1128, 748, 741, 700, 669, 656, 648, 623 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{12}D_2N_2NaO_3$ $(M + Na)^+$ 307.1022, found 307.1022.

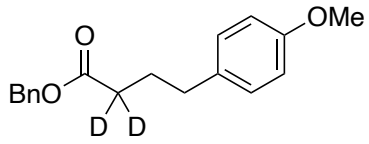
2-((2,5-dichlorophenyl)thio)acetic-2,2-*d*$_2$ acid (13β-*d*$_2$)



2-((2,5-dichlorophenyl)thio)acetic acid **13β** (47.4 mg, 0.20 mmol) was used as a substrate. The reaction was performed at 60 °C. The product **13β-*d*$_2$** was obtained without silica gel flash chromatography. (white solid, 97% deuterated, 98% yield, 47.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.32 (d, *J* = 8.5 Hz, 1H, Ar*H*), 7.15 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar*H*), 3.93 (m, 0.06H, C*H*$_2$COOH, 97% D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 135.6, 133.2, 132.2, 130.7, 129.0, 127.8, 34.2; IR (neat) 2361, 1701, 1447, 1283, 1101, 1034, 1016, 885, 841, 804, 681, 644, 575, 544, 407 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_8H_4D_2Cl_2NaO_2S$ $(M + Na)^+$ 260.9483, found 260.9483.

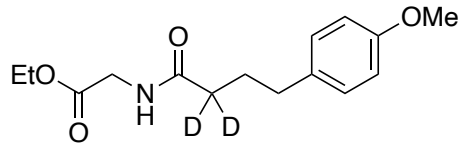
2-6. Transformation of the Products

benzyl 4-(4-methoxyphenyl)butanoate-2,2-d_2 (14-d_2)



4-(4-methoxyphenyl)butanoic-2,2-d_2 acid **13a-d_2** (39.2 mg, 0.20 mmol, 94% deuterated), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (57.5 mg, 0.30 mmol) and DMAP (2.4 mg, 0.02 mmol) were added followed by the addition of CH_2Cl_2 (1.0 mL, 0.20 M) and benzyl alcohol (31 μL, 0.30 mmol). The reaction mixture was stirred for 6 h at room temperature. The resultant mixture was added 1 M HCl aq and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (5% EtOAc in *n*-hexane as eluent) to obtain **14-d_2**. (colorless liquid, 94% deuterated, 86% yield, 49.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.30 (m, 5H, Ar*H*), 7.06 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar*H*), 5.11 (s, 2H, PhC*H*$_2$), 3.78 (s, 3H, ArOC*H*$_3$), 2.58 (t, *J* = 7.5 Hz, 2H, ArC*H*$_2$), 2.34 (m, 0.12H, C*H*$_2$COOCH$_2$Ph, 94% D), 1.93 (t, *J* = 7.5 Hz, 2H, ArCH$_2$C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 157.9, 136.1, 133.4, 129.4, 128.6, 128.2, 128.2, 113.8, 66.1, 55.2, 34.1, 33.0, 26.6; IR (neat) 1730, 1510, 1454, 1300, 1242, 1175, 1113, 1061, 1034, 972, 829, 748, 735, 696, 519 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{18}D_2NaO_3$ $(M + Na)^+$ 309.1430, found 309.1447.

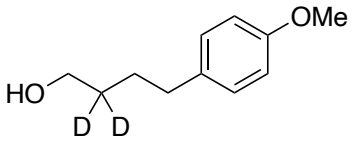
ethyl (4-(4-methoxyphenyl)butanoyl-2,2-d_2)glycinate (15-d_2)



4-(4-methoxyphenyl)butanoic-2,2-d_2 acid **13a-d_2** (19.6 mg, 0.10 mmol, 94% deuterated), glycine methyl ester hydrochloride (20.9 mg, 0.15 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (28.8 mg, 0.15 mmol) and DMAP (1.2 mg, 0.01 mmol) were added followed by the addition of CH_2Cl_2 (0.50 mL, 0.20 M) and triethylamine (25 μL, 0.18 mmol). The reaction mixture was stirred for 15 h at room temperature. The resultant mixture was added H_2O and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (33% EtOAc in *n*-hexane as eluent) to obtain **15-d_2**. (white solid, 97% deuterated, 80% yield, 22.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.83 (d, *J* = 8.5 Hz, 2H, Ar*H*), 5.88 (br, 1H, N*H*), 4.22 (q, *J* = 7.0 Hz, 2H, COOC*H*$_2$CH$_3$), 4.03 (d, *J* = 5.0 Hz, 2H, NHC*H*$_2$COOEt), 3.79 (s, 3H, ArOC*H*$_3$), 2.61 (t, *J* = 7.5 Hz, 2H, ArC*H*$_2$), 2.22 (m, 0.07H,

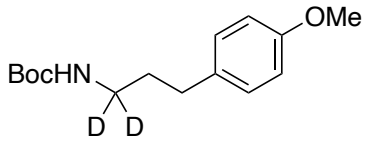
C*H*$_2$CONH, 97% D), 1.94 (t, *J* = 7.5 Hz, 2H, C*H*$_2$CD$_2$CONH), 1.29 (t, *J* = 7.0 Hz, 3H, COOCH$_2$C*H*$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 170.1, 157.9, 133.5, 129.4, 113.8, 61.5, 55.3, 41.3, 34.8, 34.1, 27.0, 14.1; IR (neat) 1755, 1746, 1638, 1611, 1512, 1420, 1377, 1244, 1182, 1111, 1032, 1015, 833, 694, 567 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{19}D_2NNaO_4$ $(M + Na)^+$ 304.1488, found 304.1500.

4-(4-methoxyphenyl)butan-2,2-*d*$_2$-1-ol (16-*d*$_2$)



4-(4-methoxyphenyl)butanoic-2,2-*d*$_2$ acid **13a-*d*$_2$** (19.6 mg, 0.10 mmol, 94% deuterated) and lithium aluminum hydride (9.5 mg, 0.25 mmol) were added followed by the addition of THF (1.0 mL, 0.10 M). After the reaction mixture was stirred for 19 h at room temperature, the reaction mixture was diluted with EtOAc 1.0 mL and MeOH 2.0 mL. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (20% EtOAc in *n*-hexane as eluent) to obtain **16-*d*$_2$**. (colorless liquid, 96% deuterated, 68% yield, 12.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.82 (d, *J* = 8.5 Hz, 2H, Ar*H*), 3.79 (s, 3H, ArOC*H*$_3$), 3.65 (s, 2H, C*H*$_2$OH), 2.59 (t, *J* = 7.5 Hz, 2H, ArC*H*$_2$), 1.67–1.64 (m, 2.09H, ArCH$_2$C*H*$_2$ + C*H*$_2$CH$_2$OH, 96% D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 134.4, 129.3, 113.7, 62.7, 55.3, 34.7, 31.5, 27.6; IR (neat) 2922, 1611, 1510, 1441, 1300, 1242, 1177, 1111, 1034, 829, 745, 700, 557, 476, 442 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{14}D_2NaO_2$ $(M + Na)^+$ 205.1168, found 205.1168.

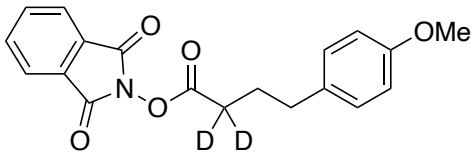
***tert*-butyl (3-(4-methoxyphenyl)propyl-1,1-*d*$_2$)carbamate (17-*d*$_2$)**



4-(4-methoxyphenyl)butanoic-2,2-*d*$_2$ acid **13a-*d*$_2$** (19.6 mg, 0.10 mmol, 94% deuterated) was added followed by the addition of *tert*-butyl alcohol (0.50 mL, 0.20 M), triethylamine (20 μL, 0.14 mmol) and diphenylphosphoryl azide (25 μL, 0.12 mmol). The reaction mixture was stirred for 25 h at 85 °C. The resultant mixture was added sat. $NaHCO_3$ aq and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (3%–5% EtOAc in *n*-hexane as eluent) to obtain **17-*d*$_2$**. (white solid, 97% deuterated, 69% yield, 18.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.82 (d, *J* = 8.5 Hz, 2H, Ar*H*), 4.49 (br, 1H, N*H*), 3.78 (s, 3H, ArOC*H*$_3$), 3.12 (m, 0.06H, C*H*$_2$NHBoc, 97% D), 2.58 (t, *J* = 7.5 Hz, 2H,

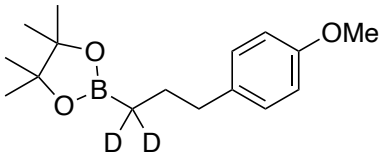
ArC*H*$_2$), 1.76 (t, *J* = 7.5 Hz, 2H, C*H*$_2$CD$_2$NHBoc), 1.44 (s, 9H, NHCOOC(C*H*$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 156.0, 133.6, 129.2, 113.9, 79.1, 55.3, 39.6, 32.1, 31.7, 28.4; IR (neat) 2361, 2342, 1686, 1522, 1508, 1364, 1273, 1242, 1165, 1061, 1028, 835, 669, 652, 521 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{15}H_{21}D_2NNaO_3$ $(M + Na)^+$ 290.1696, found 290.1705.

1,3-dioxoisoindolin-2-yl 4-(4-methoxyphenyl)butanoate-2,2-*d*$_2$ (18-*d*$_2$)



4-(4-methoxyphenyl)butanoic-2,2-*d*$_2$ acid **13a-*d*$_2$** (588 mg, 3.0 mmol, 94% deuterated), *N*-hydroxyphthalimide (734 mg, 4.5 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (863 mg, 4.5 mmol) and DMAP (36.7 mg, 0.30 mmol) were added followed by the addition of CH_2Cl_2 (10 mL, 0.30 M) at 0 °C. The cooling bath was removed and the reaction mixture was stirred for 21 h at room temperature. The resultant mixture was added 1 M HCl aq and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (10%–20% EtOAc in *n*-hexane as eluent) to obtain **18-*d*$_2$**. (white solid, 96% deuterated, 81% yield, 832.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.89 (m, 2H, Ar*H*), 7.80–7.79 (m, 2H, Ar*H*), 7.14 (d, *J* = 8.0 Hz, 2H, Ar*H*), 6.86 (d, *J* = 8.0 Hz, 2H, Ar*H*), 3.80 (s, 3H, ArOC*H*$_3$), 2.72 (t, *J* = 7.5 Hz, 2H, ArC*H*$_2$), 2.64 (m, 0.08H, COC*H*$_2$, 96% D), 2.07 (t, *J* = 7.5 Hz, 2H, ArCH$_2$C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 162.0, 158.1, 134.8, 132.7, 129.5, 129.0, 124.0, 114.0, 55.3, 33.6, 29.6, 26.4; IR (neat) 1784, 1738, 1514, 1254, 1177, 1130, 1049, 1032, 970, 874, 804, 789, 694, 517, 486 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{19}H_{15}D_2NNaO_5$ $(M + Na)^+$ 364.1124, found 364.1132.

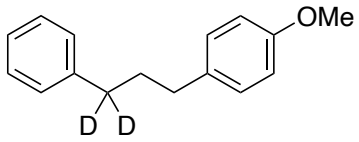
2-(3-(4-methoxyphenyl)propyl-1,1-*d*$_2$)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (19-*d*$_2$)[28]



1,3-dioxoisoindolin-2-yl 4-(4-methoxyphenyl)butanoate-2,2-*d*$_2$ **18-*d*$_2$** (34.1 mg, 0.10 mmol), bis(catecholato)diboron (29.7 mg, 0.13 mmol) were added followed by the addition of *N*,*N*-dimethylacetamide (1.0 mL, 0.10 M). The reaction mixture was stirred and irradiated using a 40 W blue LED lamp (3 cm away, with a cooling fan to keep the reaction at room temperature) for 18 h. After the addition of pinacol (47.3 mg, 0.40 mmol) and triethylamine (0.34 mL, 2.5 mmol), the

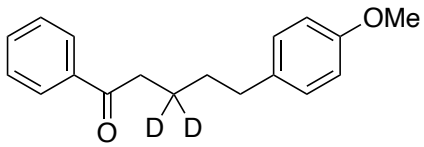
reaction mixture was stirred for 1 h at room temperature. The resultant mixture was added sat. NH_4Cl aq and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (5% EtOAc in *n*-hexane as eluent) to obtain **19-*d*$_2$**. (colorless liquid, 97% deuterated, 59% yield, 16.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.5 Hz, 2H, Ar*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar*H*), 3.78 (s, 3H, ArOC*H*$_3$), 2.54 (t, *J* = 7.5 Hz, 2H, ArC*H*$_2$), 1.68 (t, *J* = 7.5 Hz, 2H, ArCH$_2$C*H*$_2$), 1.24 (s, 12H, *Bpin*), 0.78 (m, 0.06H, C*H*$_2$Bpin, 97% D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 134.9, 129.4, 113.6, 82.9, 55.3, 37.6, 26.2, 24.8, 10.2; IR (neat) 2361, 1510, 1389, 1352, 1306, 1267, 1242, 1175, 1165, 1144, 1038, 964, 862, 827, 669 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{23}D_2BNaO_3$ $(M + Na)^+$ 301.1914, found 301.1906.

1-methoxy-4-(3-phenylpropyl-3,3-*d*$_2$)benzene (20-*d*$_2$)[29]



1,3-dioxoisoindolin-2-yl 4-(4-methoxyphenyl)butanoate-2,2-*d*$_2$ **18-*d*$_2$** (34.1 mg, 0.10 mmol), $NiBr_2$ diglyme complex (2.5 mg, 0.007 mmol), 4,4′-di-*tert*-butyl-2,2′-bipyridyl (1.9 mg, 0.007 mmol) and Zn dust (13.1 mg, 0.20 mmol) were added followed by the addition of *N*,*N*-dimethylacetamide (0.50 mL, 0.20 M) and phenyl iodide (15 μL, 0.13 mmol). The reaction mixture was stirred for 25 h at room temperature. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (1% Et_2O in *n*-hexane as eluent) to obtain **20-*d*$_2$**. (colorless liquid, 95% deuterated, 68% yield, 15.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.19–7.17 (m, 3H, Ar*H*), 7.10 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.83 (d, *J* = 9.0 Hz, 2H, Ar*H*), 3.79 (s, 3H, ArOC*H*$_3$), 2.61–2.58 (m, 2.11H, ArC*H*$_2$ + ArC*H*$_2$, 95% D), 1.91 (t, *J* = 7.5 Hz, 2H, C*H*$_2$CD$_2$Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 142.3, 134.4, 129.3, 128.4, 128.3, 125.7, 113.7, 55.3, 34.6, 34.5, 33.0; IR (neat) 1611, 1510, 1495, 1464, 1454, 1447, 1300, 1242, 1177, 1036, 827, 735, 698, 546, 517 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{16}D_2NaO$ $(M + Na)^+$ 251.1375, found 251.1375.

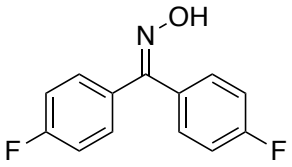
5-(4-methoxyphenyl)-1-phenylpentan-1-one-3,3-*d*$_2$ (21-*d*$_2$)[30]



1,3-dioxoisoindolin-2-yl 4-(4-methoxyphenyl)butanoate-2,2-*d*$_2$ **18-*d*$_2$** (34.1 mg, 0.10 mmol), triphenylphosphine (5.2 mg, 0.02 mmol) and sodium iodide (22.5 mg, 0.15 mmol) were added

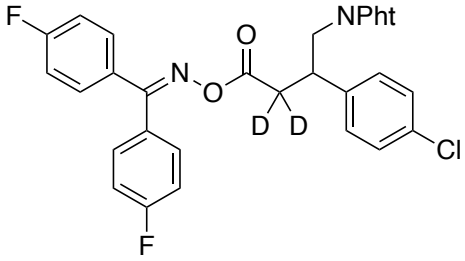
followed by the addition of acetonitrile (1.0 mL, 0.10 M) and 1-phenyl-1-trimethylsilyloxyethylene (40 μL, 0.20 mmol). After degassed by sparging with argon for 1 min, the reaction mixture was stirred and irradiated using a 40 W blue LED lamp (3 cm away, with a cooling fan to keep the reaction at room temperature) for 24 h. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (5% EtOAc in *n*-hexane as eluent) to obtain **21-*d*$_2$**. (white solid, 92% deuterated, 61% yield, 16.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.55 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.45 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.10 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.82 (d, *J* = 9.0 Hz, 2H, Ar*H*), 3.78 (s, 3H, ArOC*H*$_3$), 2.97 (s, 2H, PhCOC*H*$_2$), 2.61 (t, *J* = 7.5 Hz, 2H, ArC*H*$_2$), 1.76 (m, 0.17H, PhCOCH$_2$C*H*$_2$, 92% D), 1.67 (t, *J* = 7.5 Hz, 2H, ArCH$_2$C*H*$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 157.7, 137.1, 134.4, 132.9, 129.3, 128.6, 128.0, 113.7, 55.3, 38.2, 34.8, 31.1, 23.2; IR (neat) 1678, 1508, 1236, 1221, 1177, 1032, 831, 818, 770, 748, 731, 691, 650, 631, 557 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{18}D_2NaO_2$ $(M + Na)^+$ 293.1481, found 293.1482.

bis(4-fluorophenyl)methanone oxime (S4)



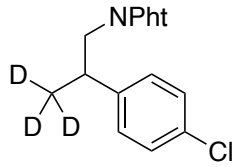
4,4'-difluorobenzophenone (1.09 g, 5.0 mmol), hydroxylamine hydrochloride (0.56 g, 8.0 mmol) and sodium acetate (0.82 g, 10 mmol) were added followed by the addition of EtOH (10 mL) and H_2O (2.5 mL). The mixture was stirred under argon at 80 °C for 23 h. The resultant mixture was added H_2O and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the residual solid was gathered as **S4**. (white solid, 95% yield, 1.11 g); CAS Registry Number 363-02-0; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (br, 1H, O*H*), 7.44 (dd, *J* = 8.5, 5.5 Hz, 2H, Ar*H*), 7.40 (dd, *J* = 8.5, 5.5 Hz, 2H, Ar*H*), 7.16 (dd, *J* = 8.5, 8.5 Hz, 2H, Ar*H*), 7.03 (dd, *J* = 8.5, 8.5 Hz, 2H, Ar*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7 (d, *J* = 249.8 Hz), 163.0 (d, *J* = 249.4 Hz), 156.4, 132.3 (d, *J* = 3.0 Hz), 131.4 (d, *J* = 8.3 Hz), 129.7 (d, *J* = 8.4 Hz), 128.2 (d, *J* = 3.6 Hz), 115.4 (d, *J* = 21.8 Hz), 115.4 (d, *J* = 21.8 Hz).

2-(4-(((bis(4-fluorophenyl)methylene)amino)oxy)-2-(4-chlorophenyl)-4-oxobutyl-3,3-*d*$_2$)isoindoline-1,3-dione (22-*d*$_2$)



3-(4-chlorophenyl)-4-(1,3-dioxoisoindolin-2-yl)butanoic acid **13e** (289 mg, 0.80 mmol), K_2CO_3 (11.1 mg, 0.08 mmol) and DMAP (9.8 mg, 0.08 mmol) were added followed by the addition of acetone-d_6 (2.0 mL, 27 mmol), DMSO (2.0 mL) and pivalic anhydride (32 μL, 0.16 mmol). The reaction mixture was stirred under argon at 40 °C for 48 h. After the reaction mixture was added D_2O (0.50 mL), stirring at room temperature for 1 h. The reaction mixture was added 1 M HCl aq and extracted with CH_2Cl_2, and the solvent was removed under reduced pressure. Then, 2.0 mL of CH_2Cl_2/formic acid = 4/1 was added to the residue, and evaporation was carried out for the removal of pivalic acid. This azeotropic operation was performed three times. After the additional azeotropic operation with toluene three times, the residual solid **13e-*d*$_2$** was used in the next step without further purification. To the gathered solid, bis(4-fluorophenyl)methanone oxime **S4** (187 mg, 0.80 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (184 mg, 0.96 mmol) and DMAP (9.8 mg, 0.08 mmol) were added followed by the addition of CH_2Cl_2 (8.0 mL, 0.10 M). The reaction mixture was stirred for 14 h at room temperature. The resultant mixture was added H_2O and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (20% EtOAc in *n*-hexane as eluent) to obtain **22-*d*$_2$**. (white solid, 96% deuterated, 89% yield, 397.9 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.79 (m, 2H, Ar*H*), 7.70–7.69 (m, 2H, Ar*H*), 7.48 (dd, *J* = 9.0, 5.5 Hz, 2H, Ar*H*), 7.21 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.17–7.15 (m, 4H, Ar*H*), 7.11 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.02 (dd, *J* = 8.5, 8.5 Hz, 2H, Ar*H*), 3.91–3.81 (m, 2H, NC*H*$_2$), 3.70 (t, *J* = 8.0 Hz, 1H, ArC*H*), 2.74–2.64 (m, 0.09H, C*H*$_2$COOH, 96% D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 168.0, 164.6 (d, *J* = 252.4 Hz), 163.3 (d, *J* = 250.8 Hz), 163.0, 138.3, 134.1, 133.2, 131.7, 131.1 (d, *J* = 8.7 Hz), 131.0 (d, *J* = 8.3 Hz), 130.6 (d, *J* = 3.4 Hz), 129.1, 128.9, 128.0 (d, *J* = 3.6 Hz), 123.4, 115.6 (d, *J* = 21.8 Hz), 115.6 (d, *J* = 21.9 Hz), 42.7, 40.1, 36.8; IR (neat) 1767, 1709, 1506, 1395, 1358, 1319, 1221, 1155, 1126, 1090, 980, 841, 719, 594, 530 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{31}H_{19}D_2ClF_2N_2NaO_4$ $(M + Na)^+$ 583.1176, found 583.1174.

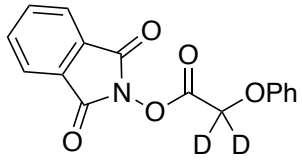
2-(2-(4-chlorophenyl)propyl-3,3,3-*d*$_3$)isoindoline-1,3-dione (23-*d*$_3$)[31]



2-(4-(((bis(4-fluorophenyl)methylene)amino)oxy)-2-(4-chlorophenyl)-4-oxobutyl-3,3-*d*$_2$)isoindoline-1,3-dione **22-*d*$_2$** (56.1 mg, 0.10 mmol) and (Ir[dF(CF$_3$)ppy]$_2$(dtbbpy))PF$_6$ (1.1 mg, 0.001 mmol) were added followed by the addition of $CDCl_3$ (1.0 mL, 0.10 M). After degassed by sparging with argon for 1 min, the reaction mixture was stirred and irradiated using a 40 W blue LED lamp (3 cm away, with a cooling fan to keep the reaction at room temperature) for 15 h. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (10% EtOAc in *n*-hexane as eluent) to obtain **23-*d*$_3$**. (yellow solid, 91% deuterated, 48% yield, 14.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.79 (m, 2H, Ar*H*), 7.70–7.68 (m, 2H, Ar*H*), 7.23 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.19 (d, *J* = 8.5 Hz, 2H, Ar*H*), 3.84 (dd, *J* = 13.5, 8.0 Hz, 1H, NC*H*$_2$), 3.75 (dd, *J* = 13.5, 8.0 Hz, 1H, NC*H*$_2$), 3.33 (t, *J* = 8.0 Hz, 1H, ArC*H*), 1.27–1.25 (m, 0.27H, ArCHC*H*$_3$ (+ ethyl acetate), 91% D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 141.7, 134.0, 132.4, 131.8, 128.7, 128.6, 123.3, 44.6, 37.8, 18.3; IR (neat) 1703, 1491, 1431, 1412, 1395, 1350, 1121, 1088, 1040, 972, 831, 810, 719, 708, 529 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{17}H_{11}D_3ClNNaO_2$ $(M + Na)^+$ 325.0794, found 325.0794.

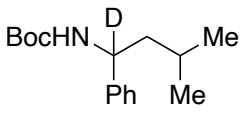
2-7. Total Synthesis of Deuterated EP3 Antagonist[32]

1,3-dioxoisoindolin-2-yl 2-phenoxyacetate-d_2 (24-d_2)



phenoxyacetic acid (761 mg, 5.0 mmol), K_2CO_3 (69.1 mg, 0.50 mmol) and DMAP (61.1 mg, 0.50 mmol) were added followed by the addition of acetone-d_6 (7.4 mL, 100 mmol), DMF (7.4 mL) and pivalic anhydride (0.20 mL, 1.0 mmol). The reaction mixture was stirred under argon at 60 °C for 48 h. After the reaction mixture was added D_2O (1.0 mL), stirring at room temperature for 1 h. The reaction mixture was added 1 M HCl aq and extracted with CH_2Cl_2, and the solvent was removed under reduced pressure. Then, 2.0 mL of CH_2Cl_2/formic acid = 4/1 was added to the residue, and the azeotropic evaporation was carried out for the removal of pivalic acid. The additional azeotropic operation using toluene was performed. The above operation was repeated because the deuterated ratio was 86%. After the second operation, the deuterated ratio was increased to 96% and the residual solid was used in the next step without further purification. To the gathered solid, *N*-hydroxyphthalimide (979 mg, 6.0 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.15 g, 6.0 mmol) were added followed by the addition of CH_2Cl_2 (25 mL, 0.20 M). The reaction mixture was stirred for 12 h at room temperature. The resultant mixture was added H_2O and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (20% EtOAc in *n*-hexane as eluent) to obtain **24-d_2**. (white solid, 95% deuterated, 63% yield, 944.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.90 (m, 2H, Ar*H*), 7.82–7.80 (m, 2H, Ar*H*), 7.34 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.05 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.00 (d, *J* = 7.5 Hz, 2H, Ar*H*), 5.04 (m, 0.10H, CH_2OPh, 95% D); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 161.5, 157.3, 134.9, 129.7, 128.8, 124.1, 122.4, 114.8, 62.9; IR (neat) 1740, 1736, 1495, 1238, 1180, 1092, 1080, 1024, 980, 872, 748, 692, 685, 517, 507 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_9D_2NNaO_5$ $(M + Na)^+$ 322.0655, found 322.0654.

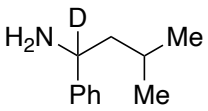
***tert*-butyl (3-methyl-1-phenylbutyl-1-*d*)carbamate (S5-*d*)**



lithium bis(trimethylsilyl)amide (920 mg, 5.5 mmol) was added followed by the addition of THF (20

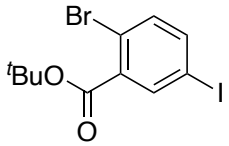
mL, 0.25 M) and ethyl phenylacetate (0.80 mL, 5.0 mmol) were added. After stirring for 1 h at room temperature, 1-iodo-2-methylpropane (0.86 mL, 7.5 mmol) was added to the reaction mixture. The reaction mixture was stirred for 20 h at room temperature. The resultant mixture was added sat. NH_4Cl aq and extracted with CH_2Cl_2. Then, the combined organic layer was added sat. $NaHCO_3$ aq and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the resultant residue was conducted short pad column with EtOAc. The obtained liquid was used in the next step without further purification. To the gathered liquid, THF (5.0 mL), MeOH (5.0 mL), H_2O (5.0 mL) and NaOH (1.0 g, 25 mmol) were added at 0 °C. The cooling bath was removed and the mixture was stirred for 3 h at room temperature. The resultant mixture was added 1 M HCl aq and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the residual solid was used in the next step without further purification. To the gathered solid, K_2CO_3 (69.1 mg, 0.50 mmol) and DMAP (61.1 mg, 0.50 mmol) were added followed by the addition of acetone-d_6 (7.4 mL, 100 mmol) and pivalic anhydride (0.20 mL, 1.0 mmol). The reaction mixture was stirred under argon at 40 °C for 48 h. After the reaction mixture was added D_2O (1.0 mL), stirring at room temperature for 1 h. The reaction mixture was added 1 M HCl aq and extracted with CH_2Cl_2, and the solvent was removed under reduced pressure. Then, 2.0 mL of CH_2Cl_2/formic acid = 4/1 was added to the residue, and the azeotropic evaporation was carried out for the removal of pivalic acid. The above operation was repeated because the deuterated ratio was 88%. After the second operation, the deuterated ratio was increased to 98% and the residual solid was used in the next step without further purification. To the gathered solid, *tert*-butyl alcohol (25 mL, 0.20 M), triethylamine (0.97 mL, 7.0 mmol) and diphenylphosphoryl azide (1.29 mL, 6.0 mmol) were added. The reaction mixture was stirred for 16 h at 80 °C. The resultant mixture was added sat. $NaHCO_3$ aq and extracted with EtOAc. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (3% EtOAc in *n*-hexane as eluent) to obtain **S5-*d***. (white solid, 95% deuterated, 64% yield, 847.9 mg); ^{1}H NMR (500 MHz, $CDCl_3$) (***rotamer mixture)*** δ 7.33–7.30 (m, 2H, Ar*H*), 7.27–7.22 (m, 3H, Ar*H*), 5.24 (m, 0.05H, ArC*H*, 95% D), 4.74 (br, 1H, N*H*), 1.62–1.55 (m, 3H, ArCDCH_2 + ArCDCH$_2$C*H*), 1.41 (br, 9H, NCOOC(CH_3)$_3$), 0.94–0.92 (m, 6H, CH(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) (***rotamer mixture)*** δ 155.7, 155.1, 143.4, 141.9, 128.8, 128.5, 127.6, 127.1, 126.4, 126.3, 79.3, 53.4, 52.7, 46.2, 45.3, 28.4, 24.9, 22.6, 22.6, 22.5, 22.3; IR (neat) 1680, 1506, 1464, 1449, 1366, 1250, 1169, 1067, 999, 746, 700, 617, 596, 579, 557 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{16}H_{24}DNNaO_2$ $(M + Na)^+$ 287.1840, found 287.1840.

3-methyl-1-phenylbutan-1-*d*-1-amine (25-*d*)



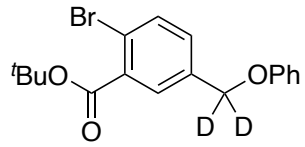
tert-butyl (3-methyl-1-phenylbutyl-1-*d*)carbamate **S5-*d*** (264 mg, 1.0 mmol) was added followed by the addition of 4 M HCl in 1,4-dioxane (5.0 mL, 0.20 M). The reaction mixture was stirred for 2 h at room temperature. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (2–10% MeOH in CH_2Cl_2 as eluent). The obtained solid was added sat. $NaHCO_3$ aq and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the residual liquid was gathered as **25-*d***. (yellow liquid, 98% deuterated, 95% yield, 156.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.30 (m, 4H, Ar*H*), 7.25–7.22 (m, 1H, Ar*H*), 3.95 (t, *J* = 7.5 Hz, 0.02H, ArC*H*, 98% D), 1.57–1.50 (m, 3H, ArCDCH_2 + ArCDCH$_2$C*H*), 0.93–0.89 (m, 6H, CH(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.0, 128.5, 126.8, 126.3, 53.7, 48.8, 25.1, 22.8, 22.5; IR (neat) 2953, 2926, 2866, 1491, 1466, 1447, 1366, 858, 829, 754, 698, 604, 583, 546, 536 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{11}H_{17}DN$ $(M + H)^+$ 165.1497, found 165.1497.

***tert*-butyl 2-bromo-5-iodobenzoate (27)**[33]



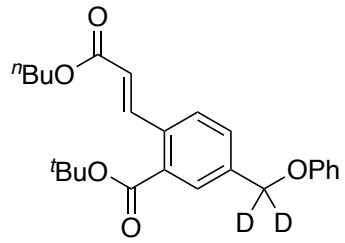
2-bromo-5-iodobenzoic acid **26** (1.63 g, 5.0 mmol) and DMAP (61.1 mg, 0.50 mmol) were added followed by the addition of *tert*-butyl alcohol (10 mL, 0.50 M) and di-*tert*-butyl dicarbonate (2.30 mL, 10 mmol). The mixture was stirred under argon at 80 °C for 5 h. The resultant mixture was added sat. $NaHCO_3$ aq and extracted with CH_2Cl_2. Then, the combined organic layer was added 1 M HCl aq and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the residual liquid was gathered as **27**. (brown liquid, 93% yield, 1.77 g); CAS Registry Number 1854600-90-0; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.57 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar*H*), 7.33 (d, *J* = 8.5 Hz, 1H, Ar*H*), 1.60 (s, 9H, COOC(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 140.7, 139.3, 136.1, 135.6, 120.8, 91.7, 83.3, 28.1.

***tert*-butyl 2-bromo-5-(phenoxymethyl-d_2)benzoate (28-d_2)**[29]



1,3-dioxoisoindolin-2-yl 2-phenoxyacetate-d_2 **24-d_2** (898 mg, 3.0 mmol, 95% deuterated), $NiBr_2$ diglyme complex (74.1 mg, 0.21 mmol), 4,4′-di-*tert*-butyl-2,2′-bipyridyl (56.4 mg, 0.21 mmol) and Zn dust (392 mg, 6.0 mmol) were added followed by the addition of *N*,*N*-dimethylacetamide (3.4 mL, 0.88 M) and *tert*-butyl 2-bromo-5-iodobenzoate **27** (0.78 mL, 3.6 mmol). The reaction mixture was stirred for 17 h at room temperature. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (2% EtOAc in *n*-hexane as eluent) to obtain **28-d_2**. (pale yellow solid, 95% deuterated, 82% yield, 899.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 2.5 Hz, 1H, Ar*H*), 7.62 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.36 (dd, *J* = 8.0, 2.5 Hz, 1H, Ar*H*), 7.30 (dd, *J* = 8.5, 7.5 Hz, 2H, Ar*H*), 6.99–6.94 (m, 3H, Ar*H*), 5.03–5.02 (m, 0.10H, CH_2OPh, 95% D), 1.62 (s, 9H, COOC(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 158.4, 136.4, 134.5, 134.3, 130.7, 129.7, 129.6, 121.3, 120.3, 114.8, 82.8, 68.1, 28.2; IR (neat) 1728, 1487, 1371, 1250, 1231, 1161, 1136, 1115, 1101, 1086, 1024, 839, 799, 758, 692 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{18}H_{17}D_2BrNaO_3$ $(M + Na)^+$ 387.0535, found 387.0535.

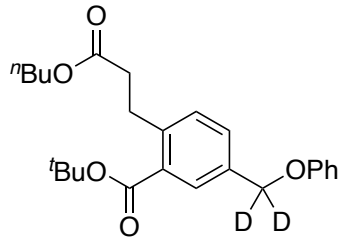
***tert*-butyl (*E*)-2-(3-butoxy-3-oxoprop-1-en-1-yl)-5-(phenoxymethyl-d_2)benzoate (29-d_2)**



tert-butyl 2-bromo-5-(phenoxymethyl-d_2)benzoate **28-d_2** (781 mg, 2.1 mmol), $Pd(OAc)_2$ (47.1 mg, 0.21 mmol) and triphenylphosphine (110 mg, 0.42 mmol) were added followed by the addition of toluene (10.7 mL, 0.20 M), *n*-butyl acrylate (0.61 mL, 4.3 mmol) and triethylamine (0.36 mL, 2.6 mmol). The reaction mixture was stirred for 24 h at 120 °C. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (5%–10% EtOAc in *n*-hexane as eluent) to obtain **29-d_2**. (white solid, 95% deuterated, 39% yield, 346.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 16.0 Hz, 1H, CH=C*H*), 7.93 (s, 1H, Ar*H*), 7.58 (m, 2H, Ar*H* + Ar*H*), 7.30 (t, *J* = 8.0 Hz, 2H, Ar*H*), 6.99–6.96 (m, 3H, Ar*H*), 6.28 (d, *J* = 16.0 Hz, 1H, CH=C*H*), 5.10–5.08 (m, 0.10H, CH_2OPh, 95% D), 4.42 (t, *J* = 7.0 Hz, 2H, COOCH_2), 1.69 (quin, *J* = 7.0 Hz, 2H,

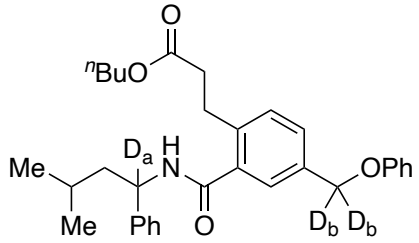
$COOCH_2CH_2$), 1.62 (s, 9H, $COOC(CH_3)_3$), 1.69 (sext, J = 7.0 Hz, 2H, $COOCH_2CH_2CH_2$), 0.96 (t, J = 7.0 Hz, 3H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 166.1, 158.5, 143.8, 138.5, 135.2, 132.4, 130.5, 129.6, 129.4, 128.1, 121.3, 120.6, 114.8, 82.5, 68.4, 64.5, 30.8, 28.2, 19.2, 13.7; IR (neat) 1713, 1701, 1495, 1321, 1250, 1233, 1202, 1161, 1140, 1076, 970, 851, 791, 754, 692 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{25}H_{28}D_2NaO_5$ $(M + Na)^+$ 435.2111, found 435.2100.

***tert*-butyl 2-(3-butoxy-3-oxopropyl)-5-(phenoxymethyl-d_2)benzoate (30-d_2)**[32]



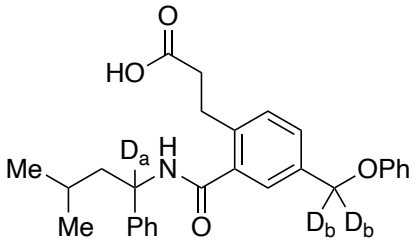
To *tert*-butyl (*E*)-2-(3-butoxy-3-oxoprop-1-en-1-yl)-5-(phenoxymethyl-d_2)benzoate **29-d_2** (337 mg, 0.82 mmol) in THF (2.1 mL), $NiCl_2$ hexahydrate (195 mg, 0.82 mmol), sodium borohydride (155 mg, 4.1 mmol) and MeOH (2.1 mL) were added at 0 °C. The cooling bath was removed and the reaction mixture was stirred for 1 h at room temperature. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (4% EtOAc in *n*-hexane as eluent) to obtain **30-d_2**. (colorless liquid, 95% deuterated, 73% yield, 302.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 2.0 Hz, 1H, Ar*H*), 7.47 (dd, J = 7.5, 2.0 Hz, 1H, Ar*H*), 7.31–7.27 (m, 3H, Ar*H*), 6.98–6.95 (m, 3H, Ar*H*), 5.04–5.03 (m, 0.10H, CH_2OPh, 95% D), 4.07 (t, J = 7.0 Hz, 2H, $COOCH_2$), 3.24 (t, J = 8.0 Hz, 2H, $ArCH_2CH_2$ or $ArCH_2CH_2$), 2.65 (t, J = 8.0 Hz, 2H, $ArCH_2CH_2$ or $ArCH_2CH_2$), 1.62–1.56 (m, 11H, $COOC(CH_3)_3$ + $COOCH_2CH_2CH_2$), 1.35 (sext, J = 7.5 Hz, 2H, $COOCH_2CH_2CH_2$), 0.92 (t, J = 7.5 Hz, 3H, CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 166.8, 158.7, 141.1, 135.2, 132.0, 131.3, 130.6, 129.8, 129.5, 121.1, 114.8, 81.7, 68.6, 64.3, 36.0, 30.7, 29.7, 28.2, 19.1, 13.7; IR (neat) 1732, 1711, 1597, 1495, 1368, 1292, 1231, 1161, 1140, 1078, 851, 810, 791, 752, 691 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{25}H_{30}D_2NaO_5$ $(M + Na)^+$ 437.2267, found 437.2267.

butyl 3-(2-((3-methyl-1-phenylbutyl-1-*d*)carbamoyl)-4-(phenoxymethyl-d_2)phenyl)propanoate (31-d_3)



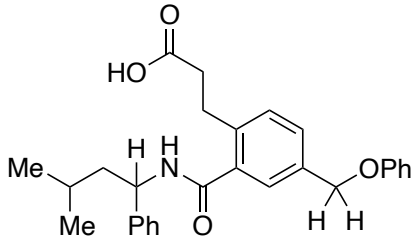
tert-butyl 2-(3-butoxy-3-oxopropyl)-5-(phenoxymethyl-d_2)benzoate **30-d_2** (105 mg, 0.25 mmol) was added followed by the addition of CH_2Cl_2 (1.27 mL) and trifluoroacetic acid (1.27 mL, 17 mmol). The reaction mixture was stirred for 2 h at room temperature. The resultant mixture was added 1 M HCl aq and extracted with CH_2Cl_2. The residual solid was used in the next step without further purification. To the gathered solid, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (71.9 mg, 0.38 mmol) and DMAP (3.1 mg, 0.03 mmol) were added followed by the addition of CH_2Cl_2 (1.0 mL, 0.25 M) and 3-methyl-1-phenylbutan-1-*d*-1-amine **25-*d*** (45.2 mg, 0.28 mmol). The reaction mixture was stirred for 14 h at room temperature. The resultant mixture was added 1 M HCl aq and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (20% EtOAc in *n*-hexane as eluent) to obtain **31-d_3**. (white solid, D_a: 99% deuterated, D_b: 95% deuterated, 83% yield, 107.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.24 (m, 10H, Ar*H*), 6.98–6.95 (m, 3H, Ar*H*), 6.61 (br, 1H, CON*H*), 5.25–5.23 (m, 0.01H, CONHC*H*, 99% D), 5.01–5.00 (m, 0.10H, CH_2OPh, 95% D), 4.02 (t, J = 7.0 Hz, 2H, COOCH_2), 3.01 (t, J = 7.0 Hz, 2H, ArCH_2CH$_2$ or ArCH$_2$CH_2), 2.71–2.60 (m, 2H, ArCH_2CH$_2$ or ArCH$_2$CH_2), 1.80 (dd, J = 13.5, 7.0 Hz, 1H, CONHCDCH_2), 1.70 (dd, J = 13.5, 7.0 Hz, 1H, CONHCDCH_2), 1.64–1.53 (m, 3H, COOCH$_2$CH_2 + CH(CH$_3$)$_2$), 1.33 (sext, J = 7.5 Hz, 2H, COOCH$_2$CH$_2$CH_2), 0.99–0.98 (m, 6H, CH(CH_3)$_2$), 0.91 (t, J = 7.5 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.3, 168.7, 158.6, 142.7, 138.1, 137.1, 135.2, 130.0, 129.5, 129.1, 128.7, 127.3, 126.6, 126.5, 121.1, 114.8, 68.6, 64.4, 51.8, 45.4, 35.2, 30.6, 27.6, 25.2, 22.7, 22.5, 19.1, 13.7; IR (neat) 1728, 1636, 1518, 1489, 1236, 1179, 1150, 1098, 1067, 800, 750, 698, 689, 669, 540 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{32}H_{36}D_3NNaO_4$ $(M + Na)^+$ 527.2960, found 527.2947.

3-(2-((3-methyl-1-phenylbutyl-1-*d*)carbamoyl)-4-(phenoxymethyl-d_2)phenyl)propanoic acid (32-d_3)



butyl 3-(2-((3-methyl-1-phenylbutyl-1-*d*)carbamoyl)-4-(phenoxymethyl-d_2)phenyl)propanoate **31-d_3** (69.5 mg, 0.14 mmol) was added followed by the addition of THF (0.46 mL), MeOH (0.46 mL) and 1.5 M NaOH aq (0.46 mL). The mixture was stirred for 2 h at room temperature. The resultant mixture was added 1 M HCl aq and extracted with CH_2Cl_2. After removal of the solvent under reduced pressure, the residual solid was gathered as **32-d_3**. (white solid, D_a: 99% deuterated, D_b: 95% deuterated, 98% yield, 60.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.41 (m, 2H, Ar*H*), 7.36–7.35 (m, 4H, Ar*H*), 7.32–7.27 (m, 4H, Ar*H*), 6.99–6.95 (m, 3H, Ar*H*), 6.35 (br, 1H, CON*H*), 5.24 (m, 0.01H, CONHC*H*, 99% D), 5.02–5.01 (m, 0.10H, C*H*$_2$OPh, 95% D), 3.07–2.97 (m, 2H, ArC*H*$_2$CH$_2$ or ArCH$_2$C*H*$_2$), 2.77–2.67 (m, 2H, ArC*H*$_2$CH$_2$ or ArCH$_2$C*H*$_2$), 1.79 (dd, *J* = 13.5, 7.0 Hz, 1H, CONHCDC*H*$_2$), 1.71 (dd, *J* = 13.5, 7.0 Hz, 1H, CONHCDC*H*$_2$), 1.60 (sep, *J* = 6.5 Hz, 1H, C*H*(CH$_3$)$_2$), 0.98 (d, *J* = 6.5 Hz, 6H, CH(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 168.9, 158.5, 142.4, 138.2, 136.5, 135.4, 130.3, 129.6, 129.4, 128.8, 127.4, 126.6, 126.3, 121.2, 114.8, 68.5, 51.9, 45.3, 35.2, 27.5, 25.2, 22.6, 22.5; IR (neat) 1636, 1599, 1522, 1493, 1447, 1412, 1296, 1238, 1088, 918, 797, 750, 691, 538, 513 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{28}H_{28}D_3NNaO_4$ $(M + Na)^+$ 471.2334, found 471.2321.

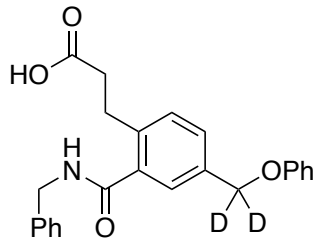
3-(2-((3-methyl-1-phenylbutyl)carbamoyl)-4-(phenoxymethyl)phenyl)propanoic acid (32)



With reference to the above procedure for synthesizing **32-d_3**, 3-(2-((3-methyl-1-phenylbutyl)carbamoyl)-4-(phenoxymethyl)phenyl)propanoic acid **32** was synthesized using corresponding starting materials. (white solid); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.41 (m, 2H, Ar*H*), 7.36–7.35 (m, 4H, Ar*H*), 7.32–7.27 (m, 4H, Ar*H*), 7.00–6.95 (m, 3H, Ar*H*), 6.35 (d, *J* = 8.0 Hz, 1H, CON*H*), 5.24 (q, *J* = 8.0 Hz, 1H, CONHC*H*), 5.03 (s, 2H, C*H*$_2$OPh), 3.07–2.97 (m, 2H, ArC*H*$_2$CH$_2$

or $ArCH_2CH_2$), 2.78–2.68 (m, 2H, $ArCH_2CH_2$ or $ArCH_2CH_2$), 1.83–1.77 (m, 1H, $CONHCHCH_2$), 1.74–1.69 (m, 1H, $CONHCHCH_2$), 1.60 (sep, J = 6.5 Hz, 1H, $CH(CH_3)_2$), 0.99 (d, J = 6.5 Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.5, 168.9, 158.5, 142.4, 138.2, 136.5, 135.5, 130.3, 129.6, 129.4, 128.8, 127.4, 126.6, 126.3, 121.2, 114.8, 69.2, 52.2, 45.4, 35.2, 27.5, 25.2, 22.6, 22.5; IR (neat) 1697, 1634, 1601, 1589, 1530, 1495, 1449, 1366, 1242, 943, 845, 748, 689, 550, 505 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{28}H_{31}NNaO_4$ $(M + Na)^+$ 468.2145, found 468.2153.

3-(2-(benzylcarbamoyl)-4-(phenoxymethyl-*d*$_2$)phenyl)propanoic acid (S6-*d*$_2$)



With reference to the above procedure for synthesizing **32-*d*$_3$**, 3-(2-(benzylcarbamoyl)-4-(phenoxymethyl-*d*$_2$)phenyl)propanoic acid **S6-*d*$_2$** was synthesized using corresponding starting materials. (white solid); ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 2.0 Hz, 1H, Ar*H*), 7.43 (dd, J = 8.0, 2.0 Hz, 1H, Ar*H*), 7.36–7.35 (m, 4H, Ar*H*), 7.31–7.27 (m, 4H, Ar*H*), 6.98–6.93 (m, 3H, Ar*H*), 6.41 (br, 1H, CON*H*), 5.02–5.00 (m, 0.10H, CH_2OPh, 95% D), 4.63 (d, J = 6.0 Hz, 2H, $CONHCH_2$), 3.11 (t, J = 7.5 Hz, 2H, $ArCH_2CH_2$ or $ArCH_2CH_2$), 2.80–2.77 (m, 2H, $ArCH_2CH_2$ or $ArCH_2CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 169.6, 158.5, 138.4, 137.8, 136.2, 135.4, 130.4, 129.6, 129.5, 128.8, 127.9, 127.7, 126.3, 121.2, 114.8, 68.5, 44.1, 35.4, 27.7; IR (neat) 2361, 2340, 1709, 1638, 1487, 1420, 1296, 1233, 1211, 1070, 760, 725, 692, 675, 669 cm^{-1}; HRMS (ESI) *m/z* calc'd for $C_{24}H_{21}D_2NNaO_4$ $(M + Na)^+$ 414.1645, found 414.1645.

2-8. Method of in vitro human microsomal stability assay

The reaction mixture consisted of 100 µl of 0.2 mg/ml human liver microsomes (VERITAS), 2 mM magnesium chloride, 100 mM potassium phosphate buffer (pH 7.4), NADPH regeneration system (Promega), 20 µM synthesized product of **32** or **32-*d*$_3$** was incubated at 37 ℃. Reactions were stopped by adding 200 µl of dichloromethane containing 1 µM **S6-*d*$_2$** as an internal standard and vortex mixing for 10 min. The mixtures were centrifuged at 15,000 × g at room temperature for 10 min. The 100 µl of underlayer was collected and drying under reduced pressure, and resolved by 50 µl of methanol. The amount of **32**, **32-*d*$_3$**, **S6-*d*$_2$** was analyzed by LC–MS/MS; Acquity ultra performance liquid chromatograph (UPLC) system (Waters) and Acquity Triple Quadrupole Detector (Waters).

The LC conditions were as follows: mobile phase, water containing 0.1% formic acid (solvent A) and acetonitrile containing 0.1% formic acid (solvent B); injection volume, 10 µL; flow rate, 0.4 mL/min; and column temperature, 40°C. The gradient conditions were as follows: 40% B, 0-1 min; 40%-100% B, 1-5 min; 100% B, 5-6 min. **32**, **32-*d*$_3$** and **S6-*d*$_2$** were detected in positive ion mode with the multiple reaction monitoring (MRM) transition set to (446.5 > 282), (449.5 > 284), and (392.2 > 91.1) respectively.

3. Iron-Catalyzed Decarboxylative S_N1 Reaction

3-1. General

All reactions were carried out using heat gun dried glassware under a positive pressure of dry argon unless otherwise noted. Catalytic reactions were run under an argon atmosphere. Air- and moisture-sensitive liquids were transferred via a syringe and a stainless-steel needle. Reactions were magnetically stirred and monitored by thin-layer chromatography using Merck Silica Gel 60 F254 plates. All work-up and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Flash chromatography was performed using silica gel 60N (spherical neutral, particle size 40–50μm) purchased from Kanto Chemical Co., Inc.

3-2. Instrumentation

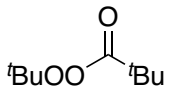
NMR was recorded on 500 MHz Bruker Avance III. Chemical shifts for proton are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CDCl_3$: δ 7.26 ppm). For ^{13}C NMR, chemical shifts were reported in the scale relative to NMR solvent ($CDCl_3$: δ 77.0 ppm) as an internal reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, t: triplet, m: multiplet), coupling constants (Hz), and integration. Infrared (IR) spectra were recorded with Shimadzu IR Affinity-1S. High-resolution mass spectroscopy (HRMS) was obtained with Bruker MicrOTOF II.

3-3. Materials

2-(2-hydroxyethyl)isoindoline-1,3-dione was purchased from Tokyo Chemical Industry Co., Ltd. and used as received. $Fe(OTf)_3$ was purchased from Ark Pharma Scientific, Ltd. and stored in a dry box. Dichloromethane was purchased from FUJIFILM Wako Pure Chemical Corporation and dried over molecular sieves 4A before use.

3-4. Substrate Synthesis and Characterization

***tert*-butyl 2,2-dimethylpropaneperoxoate (34a)**

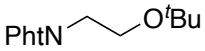


pivaloyl chloride (0.62 mL, 5 mmol), CH_2Cl_2 (25 mL, 0.20 M), pyridine (0.89 mL, 11 mmol) and 5.5 M nonane solution of 2-hydroperoxy-2-methylpropane (1.091 mL, 6 mmol) were added to a 100 mL flask. The mixture was stirred at 25 °C for 12 h. The crude mixture was quenched with *N*-methyl piperazine. To the resultant mixture was added 1 M HCl aq and extracted with CH_2Cl_2. After removal

of solvent under reduced pressure, the resulting residue was purified by flash silica gel column chromatography (9% EtOAc in *n*-hexane as eluent) to afford **34a**. (colorless liquid, 63% yield, 547.5mg); CAS Registry Number 927-07-1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 9H, OC(CH_3)$_3$), 1.26 (s, 9H, OCOC(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1, 83.4, 38.9, 27.3, 26.1.

3-5. Procedure and Characterization of the Product

2-(2-(*tert*-butoxy)ethyl)isoindoline-1,3-dione (35aa)



2-(2-hydroxyethyl)isoindoline-1,3-dione **33a** (117 mg, 0.61 mmol), $Fe(OTf)_3$ (10.3 mg, 0.02 mmol) and CH_2Cl_2 (1.0 mL) were added followed by the addition of *tert*-butyl 2,2-dimethylpropaneperoxoate **34a** (40.0 μL, 0.20 mmol). The mixture was stirred at 25 °C for 24 h. The diluted solution was filtered through silica short column and washed with EtOAc. After removal of the solvent under reduced pressure, the resulting residue was purified by silica gel flash chromatography (9% EtOAc in *n*-hexane as eluent) to obtain **35aa**. (white solid); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–7.83 (m, 2H, Ar*H*), 7.73–7.70 (m, 2H, Ar*H*), 3.85 (t, *J* = 6.5 Hz, 2H, NCH_2), 3.59 (t, *J* = 6.5 Hz, 2H, OCH_2), 1.12 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 133.9, 132.1, 123.2, 73.3, 58.8, 38.8, 27.4; IR (neat) 2970, 1775, 1707, 1389, 1321, 1190, 1090, 1078, 1030, 1011, 874, 802, 719, 619, 532 cm^{-1}; HRMS (ESI) m/z calc'd for $C_{14}H_{17}NNaO_3^+$ $(M + Na)^+$ 270.1101, found 270.1111.

Reference

(1) (a) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. *Science* **2014**, *345*, 437. (b) Patra, T.; Maiti, D. *Chem. Eur. J.* **2017**, *23*, 7382.

(2) (a) Tanaka, T.; Hashiguchi, K.; Tanaka, T.; Yazaki, R.; Ohshima, T. *ACS Catal.* **2018**, *8*, 8430. (b) Tanaka, T.; Tanaka, T.; Tsuji, T.; Yazaki, R.; Ohshima, T. *Org. Lett.* **2018**, *20*, 3541.

(3) (a) Hauser, C. R.; Chambers, W. J. *J. Am. Chem. Soc.* **1956**, *78*, 4942. (b) Creger, P. L. *J. Am. Chem. Soc.* **1967**, *89*, 2500.

(4) (a) Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2011**, *133*, 11936. (b) Ma, Y.; Stivala, C. E.; Wright, A. M.; Hayton, T.; Liang, J.; Keresztes, I.; Lobkovsky, E.; Collum, D. B.; Zakarian, A. *J. Am. Chem. Soc.* **2013**, *135*, 16853. (c) Lu, P.; Jackson, J. J.; Eickhoff, J. A.; Zakarian, A. *J. Am. Chem. Soc.* **2015**, *137*, 656. (d) Yu, K.; Lu, P.; Jackson, J. J.; Nguyen, T.-A. D.; Alvarado, J.; Stivala, C. E.; Ma, Y.; Mack, K. A.; Hayton, T. W.; Collum, D. B.; Zakarian, A. *J. Am. Chem. Soc.* **2017**, *139*, 527. (e) Ando, A.; Shioiri, T. *Chem. Commun.* **1987**, 656. (f) Matsuo, J.; Koga, K. *Chem. Pharm. Bull.* **1997**, *45*, 2122.

(5) (a) Tanaka, D.; Tanaka, S.; Mori, A. *Eur. J. Org. Chem.* **2014**, 4254. (b) Sha, S.-C.; Zhang, J.; Walsh, P. J. *Org. Lett.* **2015**, *17*, 410. (c) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. (d) Wu, G.-J.; Guan, J.; Han, F.-S.; Zhao, Y.-L. *ChemCatChem* **2014**, *6*, 1589.

(6) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(7) Morita, Y.; Yamamoto, T.; Nagai, H.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2015**, *137*, 7075.

(8) Kotani, S.; Yoshiwara, Y.; Ogasawara, M.; Sugiura, M.; Nakajima, M. *Angew. Chem., Int. Ed.* **2018**, *57*, 15877.

(9) Dinca, E.; Hartmann, P.; Smrček, J.; Dix, I.; Jones, P. G.; Jahn, U. *Eur. J. Org. Chem.* **2012**, 4461.

(10) (a) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319. (b) Davis, F. A.; Sheppard, A. C. *J. Org. Chem.* **1987**, *52*, 954.

(11) Chuang, G. J.; Wang, W.; Lee, E.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 1760.

(12) Liang, Y. F.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 548.

(13) Mabe, P. J.; Zakarian, A. *Org. Lett.* **2014**, *16*, 516.

(14) de la Torre, A.; Kaiser, D.; Maulide, N. *J. Am. Chem. Soc.* **2017**, *139*, 6578.

(15) Li, X.; Lin, F.; Huang, K.; Wei, J.; Li, X.; Wang, X.; Geng, X.; Jiao, N. *Angew. Chem., Int. Ed.* **2017**, *56*, 12307.

(16) Taninokuchi, S.; Yazaki, R.; Ohshima, T. *Org. Lett.* **2017**, *19*, 3187.

(17) Li, L.; Yu, Z.; Shen, Z. *Adv. Synth. Catal.* **2015**, *357*, 3495.

(18) Aldrich web site (https://www.sigmaaldrich.com/chemistry/chemical-synthesis/learning-

center/technical-bulletins/al-1430/molecular-sieves.html)

(19) Tanaka, T.; Yazaki, R.; Ohshima, T. *J. Am. Chem. Soc.* **2020**, *142*, 4517.

(20) (a) Gant, T. G. *J. Med. Chem.* **2014**, *57*, 3595. (b) Pirali, T.; Serafini, M.; Cargnin, S.; Genazzani, A. A. *J. Med. Chem.* **2019**, *62*, 5276. (c) Li, L.; Jakowski, J.; Do, C.; Hong, K. *Macromolecules* **2021**, *54*, 3555.

(21) (a) Schoenheimer, R.; Rittenberg, D. *Science* **1935**, *82*, 156. (b) De Feyter, H. M.; Behar, K. L.; Corbin, Z. A.; Fulbright, R. K.; Brown, P. B.; McIntyre, S.; Nixon, T. W.; Rothman, D. L.; De Graaf, R. A. *Sci. Adv.* **2018**, *4*, eaat7314. (c) Zhang, L.; Shi, L.; Shen, Y.; Miao, Y.; Wei, M.; Qian, N.; Liu, Y.; Min, W. *Nat. Biomed. Eng.* **2019**, *3*, 402.

(22) Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science* **2004**, *305*, 495.

(23) Gómez-Gallego, M.; Sierra, M. A. *Chem. Rev.* **2011**, *111*, 4857.

(24) (a) Atkinson, J. G.; Csakvary, J. J.; Herbert, G. T.; Stuart, R. S. *J. Am. Chem. Soc.* **1968**, *90*, 498. (b) Sajiki, H.; Aoki, F.; Esaki, H.; Maegawa, T.; Hirota, K. *Org. Lett.* **2004**, *6*, 1485. (c) Esaki, H.; Aoki, F.; Umemura, M.; Kato, M.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Chem. Eur. J.* **2007**, *13*, 4052. (d) Yamada, T.; Park, K.; Yasukawa, N.; Morita, K.; Monguchi, Y.; Sawama, Y.; Sajiki, H. *Adv. Synth. Catal.* **2016**, *358*, 3277. (e) Naruto, M.; Agrawal, S.; Toda, K.; Saito, S. *Sci. Rep.* **2017**, *7*, 3425. (f) Uttry, A.; Mal, S.; van Gemmeren, M. *J. Am. Chem. Soc.* **2021**, *143*, 10895.

(25) (a) Perkin, W. H. *J. Chem. Soc.* **1868**, *21*, 53. (b) Perkin, W. H. *J. Chem. Soc.* **1877**, *31*, 388.

(26) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed.* **1969**, *8*, 981.

(27) Morrill, L. C.; Smith, A. D. *Chem. Soc. Rev.* **2014**, *43*, 6214.

(28) Fawcett, A.; Pradeilles, J.; Wang, Y.; Mutsuga, T.; Myers, E. L.; Aggarwal, V. K. *Science* **2017**, *357*, 283.

(29) Huihui, K. M. M.; Caputo, J. A.; Melchor, Z.; Olivares, A. M.; Spiewak, A. M.; Johnson, K. A.; Dibenedetto, T. A.; Kim, S.; Ackerman, L. K. G.; Weix, D. J. *J. Am. Chem. Soc.* **2016**, *138*, 5016.

(30) Fu, M. C.; Shang, R.; Zhao, B.; Wang, B.; Fu, Y. *Science* **2019**, *363*, 1429.

(31) Patra, T.; Mukherjee, S.; Ma, J.; Strieth-Kalthoff, F.; Glorius, F. *Angew. Chem., Int. Ed.* **2019**, *131*, 10624.

(32) Asada, M.; Obitsu, T.; Nagase, T.; Tanaka, M.; Yamaura, Y.; Takizawa, H.; Yoshikawa, K.; Sato, K.; Narita, M.; Ohuchida, S.; Nakai, H.; Toda, M. *Bioorganic Med. Chem*. **2010**, *18*, 80.

(33) Kawajiri, T.; Kato, M.; Nakata, H.; Goto, R.; Aibara, S. Y.; Ohta, R.; Fujioka, H.; Sajiki, H.; Sawama, Y. *J. Org. Chem.* **2019**, *84*, 385.

(34) Xiang, J.; Shang, M.; Kawamata, Y.; Lundberg, H.; Reisberg, S. H.; Chen, M.; Mykhailiuk, P.; Beutner, G.; Collins, M. R.; Davies, A.; Del Bel, M.; Gallego, G. M.; Spangler, J. E.; Starr, J.; Yang,

S.; Blackmond, D. G.; Baran, P. S. *Nature* **2019**, *573*, 398.

(35) (a) Shibutani, S.; Kodo, T.; Takeda, M.; Nagao, K.; Tokunaga, N.; Sasaki, Y.; Ohmiya, H. *J. Am. Chem. Soc.* **2020**, *142*, 1211. (b) Shibutani, S.; Nagao, K.; Ohmiya, H. *Org. Lett.* **2021**, *23*, 1798. (c) Kobayashi, R.; Shibutani, S.; Nagao, K.; Ikeda, Z.; Wang, J.; Ibáñez, I.; Reynolds, M.; Sasaki, Y.; Ohmiya, H. *Org. Lett.* **2021**, *23*, 5415. (d) Nakagawa, M.; Nagao, K.; Ikeda, Z.; Reynolds, M.; Ibáñez, I.; Wang, J.; Tokunaga, N.; Sasaki, Y.; Ohmiya, H. *ChemCatChem* **2021**, *13*, 3930.

(36) (a) Webb, E. W.; Park, J. B.; Cole, E. L.; Donnelly, D. J.; Bonacorsi, S. J.; Ewing, W. R.; Doyle, A. G. *J. Am. Chem. Soc.* **2020**, *142*, 9493. (b) Leibler, I. N.-M.; Tekle-Smith, M. A.; Doyle, A. G. *Nat. Commun.* **2021**, *12*, 6950.

(37) (a) Jian, W.; Ge, L.; Jiao, Y.; Qian, B.; Bao, H. Angew. Chem., Int. Ed. 2017, 56, 3650. (b) Ge, L.; Jian, W.; Zhou, H.; Chen, S.; Ye, C.; Qian, B.; Li, Y.; Bao, H. *Chem. Asian J.* **2018**, *13*, 2522.

(38) Gooßen, L. J.; Rodríguez, N.; Linder, C.; Lange, P. P.; Fromm, A. *ChemCatChem* **2010**, *2*, 430.

(39) Wehman, P.; Kaasjager, V. E.; de Lange, W. G. J.; Hartl, F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3751.

(40) Edwards, A. C.; Geist, A.; Müllich, U.; Sharrad, C. A.; Pritchard, R. G.; Whitehead, R. C.; Harwood, L. M. *Chem. Commun.* **2017**, *53*, 8160.

(41) Wu, Q.; Wang, L.; Jin, R.; Kang, C.; Bian, Z.; Du, Z.; Ma, X.; Guo, H.; Gao, L. *Eur. J. Org. Chem.* **2016**, 5415.

(42) (a) Kotha, S.; Behera, M.; Shah, V. R. *Synlett* **2005**, 1877. (b) Scotson, J. L.; Andrews, B. I.; Laws, A. P.; Page, M. I. *Org. Biomol. Chem.* **2016**, *14*, 8301.

(43) Arredondo, V.; Roa, D. E.; Yan, S.; Liu-Smith, F.; Vranken, D. L. V. *Org. Lett.* **2019**, *21*, 1755.

(44) (a) Dinca, E.; Hartmann, P.; Smrček, J.; Dix, I.; Jones, P. G.; Jahn, U. *Eur. J. Org. Chem.* **2012**, 4461. (b) Taninokuchi, S.; Yazaki, R.; Ohshima, T. *Org. Lett.* **2017**, *19*, 3187.

(45) Li, L.; Yu, Z.; Shen, Z. *Adv. Synth. Catal.* **2015**, *357*, 3495.

研究業績

【学会発表】

1. 日本薬学会第 142 年会、2022 年 3 月、口頭、受理済み

2. Pacifichem 2021、2021 年 12 月、ポスター（英語）

3. 13th AFMC International Medecinal Chemistry Symposium、2021 年 11 月、ポスター（英語）

4. 第 1 回若手重水素研究会、2021 年 9 月、口頭、**若手優秀発表賞（浅野賞）**

5. 日本化学会第 101 年会 2021 年 3 月、口頭（英語）

6. 第 117 回有機合成シンポジウム、2020 年 10 月、口頭

7. 第 18 回次世代を担う有機化学シンポジウム、2020 年 8 月、口頭

8. 日本薬学会第 140 年会、2020 年 3 月、口頭

9. International Joint Symposium on Synthetic Organic Chemistry、2019 年 11 月、ポスター（英語）、**Poster Prize**

10. 第 10 回大津会議、2019 年 10 月、口頭（英語）

11. 第 36 回有機合成化学セミナー、2019 年 9 月、ポスター、**優秀ポスター賞**

12. The 1st International Symposium on Hybrid Catalysis for Enabling Molecular Synthesis on Demand、2019 年 5 月、ポスター（英語）

13. 第 2 回講演会、2018 年 11 月、口頭

14. 第 114 回有機合成シンポジウム、2018 年 11 月、口頭およびポスター

15. The 4th International Symposium on C–H Activation、2018 年 8 月、ポスター（英語）

16. 第 28 回万有福岡シンポジウム、2018 年 5 月、ポスター、**有機合成化学協会九州山口支部ポスター賞**

17. 日本薬学会第 138 年会、2018 年 3 月、口頭

18. IRCCS-JST CREST Joint Symposium、2018 年 1 月、ポスター（英語）

19. 第 34 回日本薬学会九州支部大会、2017 年 11 月、口頭

20. 第 29 回若手研究者のためのセミナー、2018 年 8 月、ポスター

21. 第 50 回有機金属若手の会 夏の学校、2017 年 8 月、ポスター

22. 第 54 回化学関連支部合同九州大会、2017 年 7 月、ポスター

【論文】

1. "α-Amino acid and peptide synthesis using catalytic cross-dehydrogenative coupling" Taro Tsuji, Kayoko Hashiguchi, Mana, Yoshida, Tetsu Ikeda, Yunosuke Koga, Yusaku Honda, Tsukushi Tanaka, Suyong Re, Kenji Mizuguchi, Daisuke Takahashi, Ryo Yazaki, Takashi Ohshima, *Nat. Synth.* just accepted.

2. "Chemoselective Catalytic α–Oxidation of Carboxylic Acids: Iron/Alkali Metal Cooperative Redox Active Catalysis" Tsukushi Tanaka, Ryo Yazaki, Takashi Ohshima, *J. Am. Chem. Soc.* **2020**, *142*, 4517.

3. "Catalytic Aerobic Cross-Dehydrogenative Coupling of Azlactones en Route to α,α-Disubstituted α-Amino Acids" Taro Tsuji, Takafumi Tanaka, Tsukushi Tanaka, Ryo Yazaki, Takashi Ohshima, *Org. Lett.* **2020**, *22*, 4164.

4. "Chemoselective Catalytic Dehydrogenative Cross-Coupling of 2-Acylimidazoles: Mechanistic Investigations and Synthetic Scope" Tsukushi Tanaka, Kayoko Hashiguchi, Takafumi Tanaka, Ryo Yazaki, Takashi Ohshima, *ACS Catal.* **2018**, *8*, 8430.

5. "Strategy for Catalytic Chemoselective Cross-Enolate Coupling Reaction via a Transient Homocoupling Dimer" Takafumi Tanaka, Tsukushi Tanaka, Taro Tsuji, Ryo Yazaki, Takashi Ohshima, *Org. Lett.* **2018**, *20*, 3541.

【書籍】

1. "ラジカル反応によるカルボン酸等価体およびカルボン酸の触媒的化学選択的 α 位官能基化" 田中 津久志、矢崎 亮、大嶋 孝志、*有機合成化学協会誌* **2021**, *79*, 417.

【特許】

1. "カルボン酸の触媒的重水素化反応" 大嶋 孝志、矢崎 亮、田中 津久志、特願 2021-147127.

【その他】

1. 第 10 回大津会議アワードフェロー、2019 年 10 月
2. 日本学術振興会特別研究員（DC1）、2019 年 4 月

謝辞

博士論文の執筆に際し、多くの方々のご指導、ご支援、ご厚意をいただきました。本論文に記載されている研究は九州大学大学院薬学研究院環境調和創薬化学分野の大嶋孝志教授、矢崎亮助教のご指導のもとで行われました。研究を行うにあたり、大嶋孝志教授は熱心なご指導やご助言だけでなく、自らの好奇心に従って研究に取り組める自由な環境を与えてくださいました。矢崎亮助教は日々の研究に関するディスカッションでお世話になっただけでなく、研究や人生に対する考え方など数多くのアドバイスを与えてくださいました。大嶋教授、矢崎助教に心から感謝の意を表します。森本浩之講師は研究に取り組んでいる中でなかなか気付けない新たな視点を常に与えてくださいました。森本講師に深く感謝いたします。研究室の日々の生活を支え、励ましてくださいました秘書の有村慎子さんにも多大なご協力をいただきました。

また、CSI-MS の測定でお世話になった九州大学の内田竜也先生、ICP-MS の測定でお世話になった九州大学の渡辺美登里先生、ヒトミクロソームを用いた代謝安定性試験を実施してくださった九州大学の鶴田朗人先生にこの場を借りて厚く御礼申し上げます。

時には狂気すら垣間見える研究生活を乗り越える上で、研究室のメンバーにも恵まれたことはとても幸運でした。研究室配属直後の右も左も分からなかった頃、実験手技から日々の生活に至るまでお世話になった田中尊書さんをはじめとする先輩方。苦楽を共にし、切磋琢磨しあった同期の近藤優太くん。共同研究者としてモチベーション高く研究に取り組んでくれた辻汰朗くんや古賀祐之介くんをはじめとする後輩諸氏。充実した研究生活を送れたことは研究室の皆様のおかげであり、大変感謝しています。また、1 ヶ月と短い期間でしたが、東北大学岩渕研究室から留学してくださった藤木翔吾さんにも大変刺激を受けました。

最後になりましたが、これまで長きに渡って私の生活を支え、成長を見守ってくださった家族に深く感謝いたします。