博士論文

Nd/Na 異種 2 核金属触媒の新規調製法の開発とフロー反応への適用

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略語表

Ac	acetyl
Am	amyl (*n*-pentyl)
Ar	argon
aq.	aqueous
BINOL	1,1′-bi-2,2′-naphthol
Boc	*t*-butoxycarbonyl
Bn	benzyl
bp	boiling point
Bu	butyl
c	cyclo
cat.	catalytic
conc.	concentrated
conv.	conversion
COPD	chronic obstructive pulmonary disease
Cp	cyclopentadienyl
CPME	cyclopentyl methyl ether
d	doublet
DIPEA	*N*,*N* -diisopropylethylamine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDS	energy dispersive X-ray spectrometry
EtOAc	ehyl acetate
ee	enantiomeric excess
eq	equivalent(s)
EELS	electron energy-loss spectroscopy
ESI	electrospray ionization
Et	ethyl
Et_2O	diethyl ether
h	hour(s)
Hex	hexyl
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HPLC	high performance liquid chromatography
i	iso

IR	infrared spectroscopy
m	multiplet
m	meta
M	molar
Me	methyl
2-MeTHF	2-methyltetrahydrofurane
min	minute(s)
mp	melting point
MS	mass spectrometry or molecular sieves
MTBE	methyl *t*-butyl ether
MWNT	multi-walled carbon nanotube
n	normal
NaHMDS	sodium hexamethyldisilazide
NEt_3	triethylamine
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
ppm	parts per million
Pr	propyl
quant.	quantitative
rac	racemic
Rf	retention factor in chromatography
rt	room temperature
s	singlet
sat.	saturated
SEM	2-(trimethylsily)ethoxymethyl
SM	starting material
STEM	scanning transmission electron microscope
SWNT	single-walled carbon nanotube
t	triplet
t	tertiary
TBAI	tetra-*n*-butylammonium iodide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography

TON	turnover number
UV	ultraviolet
XRD	x-ray diffraction

序論

優れた不斉触媒反応の開発は有機合成化学における至上命題のひとつである。なぜならば、不斉触媒反応は光学活性物質が多く認められる生物活性物質あるいは機能性物質の効率的な合成を最小限の廃棄物で実現する強力な手段となり得るからである。特に有機合成化学の基盤ともいえる炭素–炭素結合形成反応を触媒的かつ立体選択的に実現する手法を開発する要求は高く、世界中で広く研究され多くの精良な触媒反応が開発されている。1895 年に Henry らによって開発されたニトロアルドール反応（Henry 反応）は代表的な炭素–炭素形成結合反応のひとつである。本反応はニトロアルカンとアルデヒドあるいはケトンからβニトロアルコールを形成する反応であり、原理上プロトン移動のみによって進行し得るアトムエコノミーに優れた反応である。ニトロ基は多様な官能基に変換可能なため、ニトロアルドール反応成績体は重要な合成中間体となり得る。とりわけ生成するβニトロアルコールから容易に変換可能なβアミノアルコールは多くの天然物や医薬品にみられる部分構造であるため、ニトロアルドール反応はこれら生物活性物質の部分構造を構築する有用な手段のひとつとなる。βアミノアルコールユニットを有する多くの生物活性物質は光学活性化合物であるが、ニトロアルドール反応成績体は *syn*/*anti* 体および各々のエナンチオマーの計 4 つの立体異性体が生じる可能性があり、これらの立体化学を如何に制御するかが光学活性化合物を合成する上で重要となる。ニトロアルドール反応が見出されて以降、触媒的かつ立体選択的な手法が模索されてきたが、長年に亘りそうした手法は実現されることはなかった。柴﨑らは元来生体系が備える高い立体認識能に着目し、多点認識型触媒というコンセプトの基、独自に創製した不斉希土類含有触媒を用いて 1995 年に世界で初めての直接的な *syn* 選択的触媒的不斉ニトロアルドール反応を実現し世界に衝撃を与えた。一方 *anti* 選択的不斉ニトロアルドール反応の開発は困難を極めた。なぜならば、一般的にニトロアルドール反応のキレーションモデル遷移状態では優先的に *syn* 体が生成するためである。1978 年以降 Seebach らによってシリルニトロネートを用いる *anti* 選択的ニトロアルドールが精力的に研究されたものの、当該反応は基質の事前調製を必要とし、またシリル由来の廃棄物が生じるという本質的課題を有していたため、アトムエコノミーに優れた真に効率的な反応の開発が待ち望まれた。このような背景の基、2007 年に大井らは *P*-スピロ型テトラアミノホスホニウム塩を用いた方法により世界で初めて触媒的な *anti* 選択的不斉ニトロアルドール反応を報告した。そして翌年柴﨑らも予てから研究していた多核不斉認識触媒のコンセプトを展開させ、Nd/Na 異種 2 核金属触媒を用いる方法を報告した。$NdO_{1/5}(O^iPr)_{13/5}$、NaHMDS、アミド型配位子およびニトロエタンから調製される本触媒は自己組織化により不均一系触媒を形成する特徴を呈し、幅広い基質に対して優れた収率および立体選択性を示した。ところで近年グリーンケミストリーの関心の高まりからフロー反応が注目を集めており、特に触媒担持型カラムによるフロー反応はグリーンケミストリーの観点からはより好ましく、産業界を含めて盛んに研究が進められている。先述した *anti* 選択的不斉ニトロアルドール反応に用いられる Nd/Na 異種 2 核金属触媒は同形式の他の反応と比してトッ

プクラスの触媒性能を示すことに加え、本触媒の自己組織化し不均一系触媒を形成する特徴を活かし、バッチ反応に加えて多層カーボンナノチューブ（MWNT）上に触媒を固定化することによって触媒の再利用および連続フロー反応への適用を実現している。しかしながら、本触媒系の Nd 源である $NdO_{1/5}(O^iPr)_{13/5}$ は高価かつ大量入手困難であり、不活性ガス雰囲気下での取り扱いを必要とするため、実用性および利便性に問題が残されていた。

こうした背景を踏まえて私は、第 1 章において Nd/Na 異種 2 核金属触媒の実用性および利便性を高めることを目的として、より安価で入手容易かつ空気中で取扱い可能な Nd 源を利用可能な新たな触媒調製法の開発に着手した。入手容易な Nd 塩は概して中性の塩であり、また有機溶媒に溶けにくく有機合成反応への適用は不適とされる。だが触媒調製法に工夫を重ねた結果、価格・入手性・安定性の全てをクリアした Nd 塩を用いて所望の Nd/Na 異種 2 核金属触媒を調製する方法を見出した。続いて第 2 章では、第 1 章で得られた Nd/Na 異種 2 核金属触媒の触媒能を探求し、触媒系の実践的有用性の実証を目指しフロー反応を活用した医薬品候補化合物の鍵中間体の合成に取り組んだ。反応条件を最適化することにより、フロー反応における同反応形式では他に類を見ない程長時間に亘る触媒活性と高い触媒回転数（TON）を示し所望のニトロアルドール成績体を与えることを見出した。続く変換工程を経て、目的とする鍵中間体が効率的に合成可能であることを実証した。

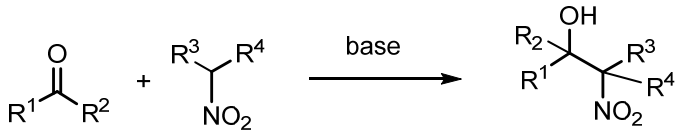
本研究が今後のバッチ反応およびフロー反応における不斉触媒反応の発展に寄与し、グリーンケミストリーに立脚した光学活性な生物活性物質の商用製造を進展させる手がかりとなることを願う。

本文

第 1 章　安定・安価な Nd 塩を用いる Nd/Na 異種 2 核金属触媒の新規調製法の開発

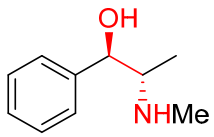
1-1.　背景

炭素–炭素結合形成反応は有機合成化学の基盤となる反応であり、代表的な反応の一つとして 1895 年に開発されたニトロアルドール（Henry）反応が挙げられる[1,2]（Scheme 1）。ニトロアルドール反応は塩基存在下、ニトロアルカンとアルデヒドまたはケトンからβニトロアルコールを生成する反応であり、原理上プロトン移動のみによって進行し得る原子効率の優れた反応である。

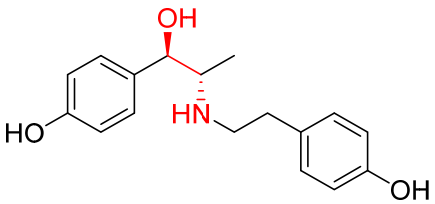


Scheme 1. Nitoroaldol (Henry) reaction

本反応は幅広い基質に適用可能であり、またニトロ基は Nef 反応によって対応するアルデヒド、ケトンあるいはカルボン酸に[3]、あるいは接触還元等によって対応するアミノ基へと変換可能であるため[4]、ニトロアルドール反応成績体は重要な合成中間体となり得る。特にβニトロアルコールから容易に得られるβアミノアルコールは多くの天然物や医薬品、生物活性物質、配位子等にみられる部分構造であることからその有用性は高い[5]。例えば、アルカロイドの一種であり交感神経興奮剤である Ephedrine、切迫流産・切迫早産治療薬の Ritodrine、抗がん剤治療薬の Paclitaxel、抗マラリア化合物である Febrifugine、多剤耐性がん克服活性を有する Hapalosin、生体内のリン脂質の一種であるスフィンゴ脂質の構成成分である Sphingosine、不斉アルドール反応に用いられる不斉補助剤 Evans auxiliary 等が挙げられる（Figure 1）。



Ephedrine



Ritodrine

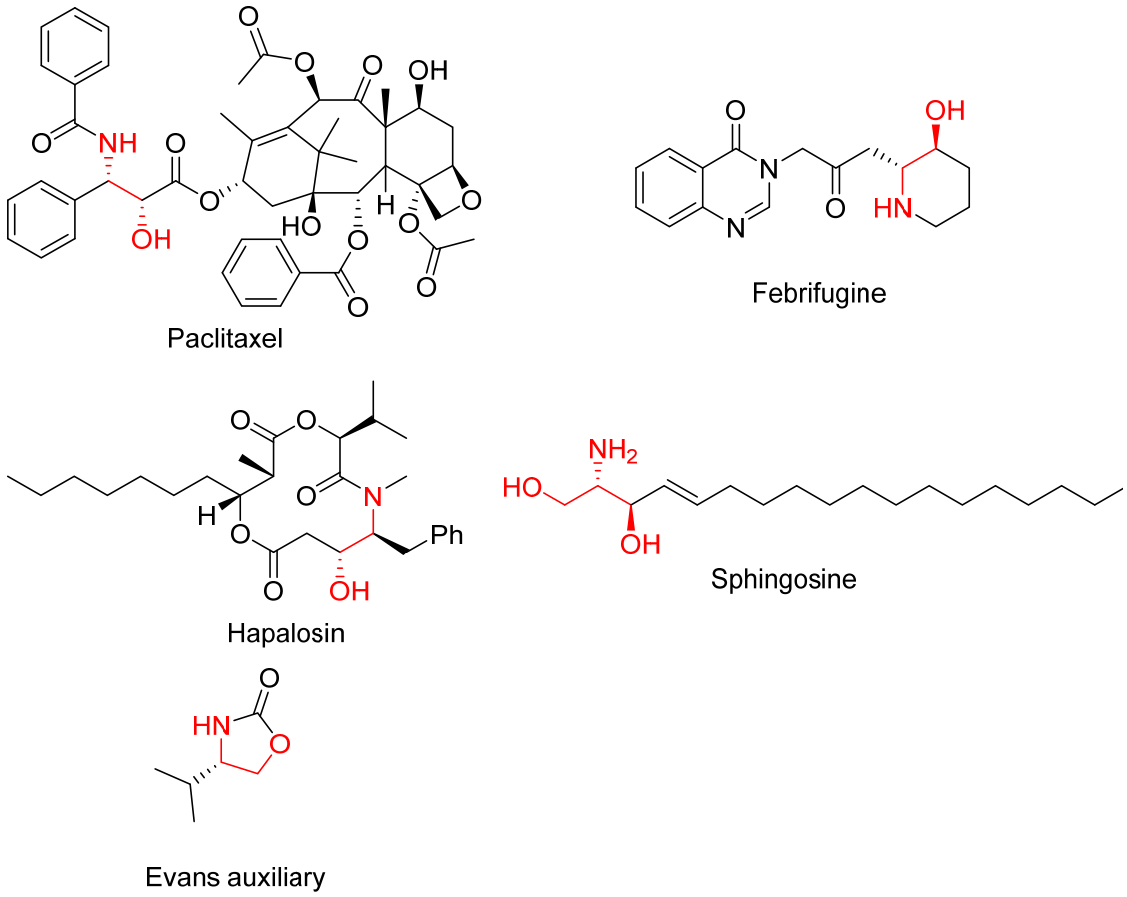
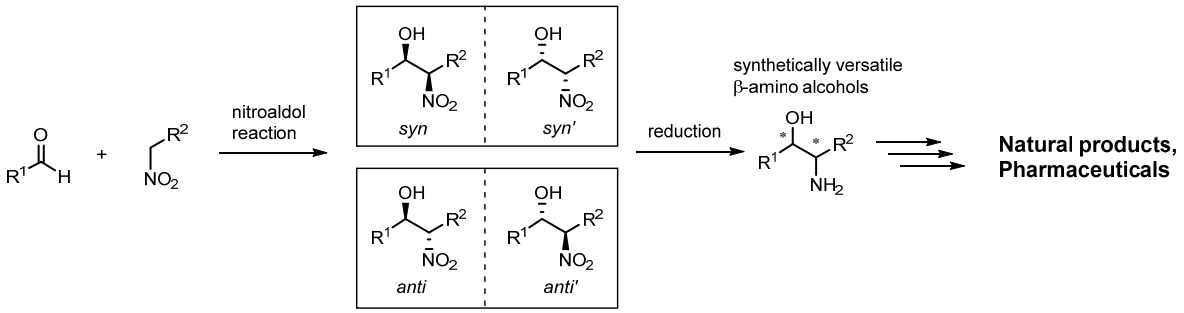


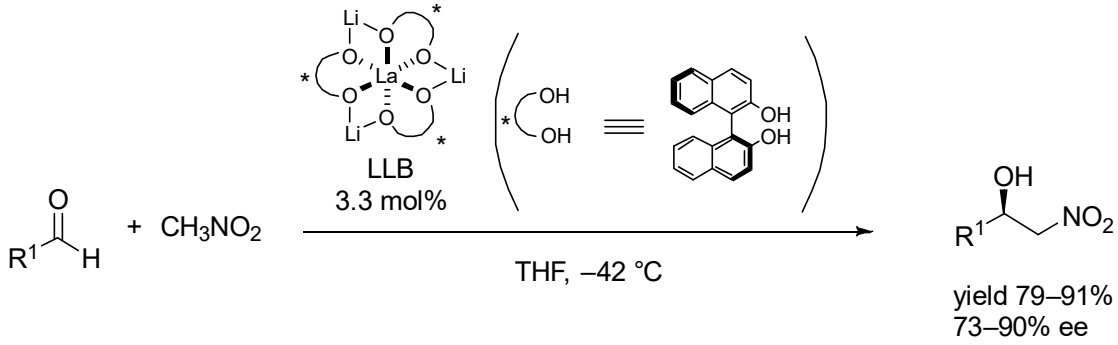
Figure 1. Structure of molecules containing a β-amino alcohol

ニトロアルドール反応は多くの生物活性物質の部分構造を構築する有用な手段の一つとなるが、ニトロアルドール反応成績体は *syn*/*anti* 体および各々のエナンチオマーの計 4 つの立体異性体が生じる可能性がある。一方、β アミノアルコールユニットを有する多くの生物活性物質は光学活性化合物であるため、光学活性化合物を合成する上でニトロアルドール反応によって生成し得る立体化学を如何に制御するかが重要となる（Scheme 2）。



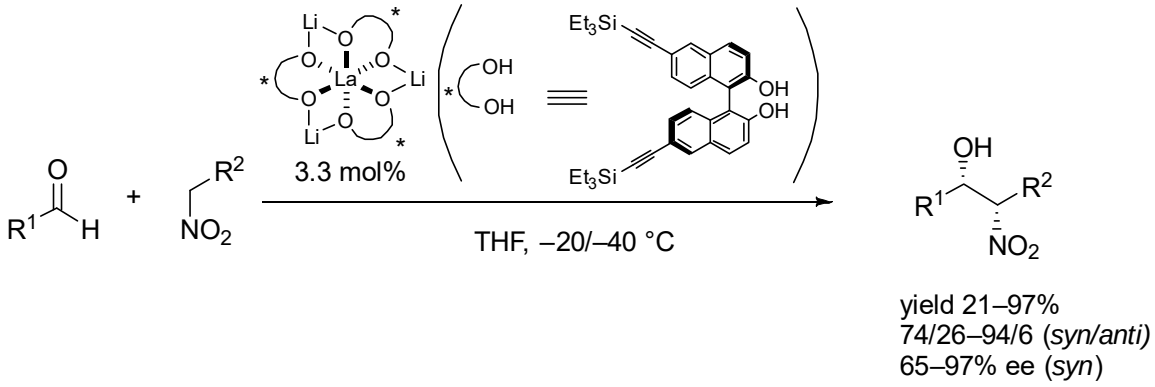
Scheme 2. Nitroalcol reaction for the expedious stereoselective access to β-amino alcohol

1895 年のニトロアルドール反応報告以来、長年に亘り立体選択的な触媒的不斉ニトロアルドール反応の報告がされることはなかったが、1992 年柴﨑らは世界で初めて直接的な触媒的不斉ニトロアルドール反応を達成した（Scheme 3）[6]。本反応は一つの分子上に Lewis 酸性と Brønsted 塩基性を有する多点認識型触媒というコンセプトから創製された不斉希土類含有触媒の一種である LLB (LaLi$_3$ tris(binaphthoxide) complex)がニトロアルカンとアルデヒド各々を活性化させるとともに配向性を制御し不斉反応場を構築することにより、高収率かつ良好なエナンチオ選択的ニトロアルドール反応が実現された。



Scheme 3. Asymmetric nitroaldol reaction by lanthanum-based catalyst

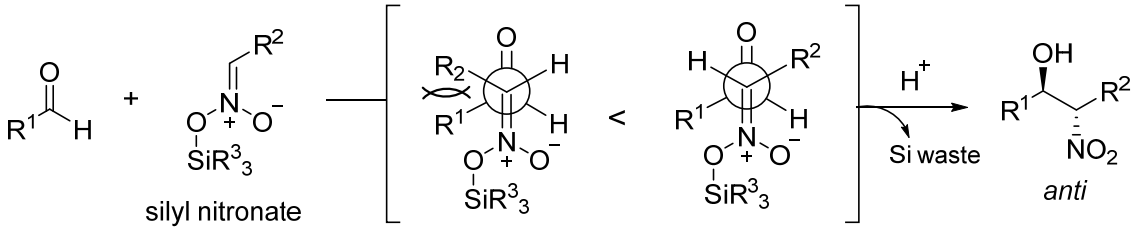
柴﨑らは上記触媒を改良し、1995 年にはより複雑なニトロアルカンを基質として用いた系において高収率かつ *syn* 選択的な触媒的不斉ニトロアルドール反応を開発した [7]（Scheme 4）。



Scheme 4. *syn*-Selective asymmetric nitroaldol reaction by lanthanum-lithium-6,6′-disubstituted BINOL complex

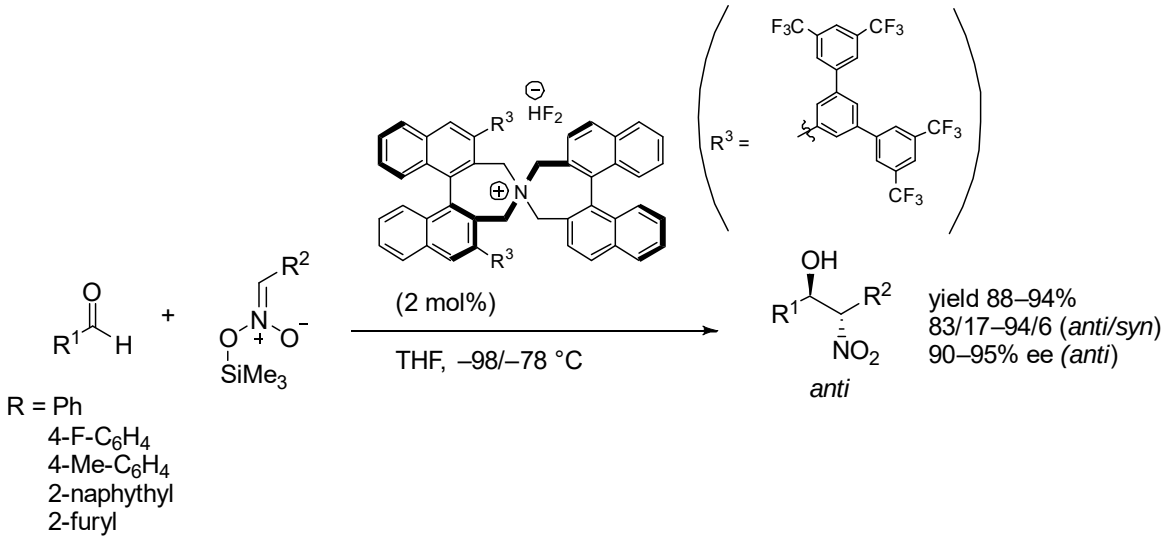
これらの報告を契機に世界中の研究グループによって多くの精良な触媒が創製され、*syn* 選択的な触媒的不斉ニトロアルドール反応が報告されるようになった [8]。

一方、*anti* 選択的不斉ニトロアルドール反応の開発は困難を極めた。Seebach らはシリルニトロネートを用いる *anti* 選択的ニトロアルド―ル反応を精力的に研究し、高い立体選択性が得られることを報告した[9]。一般的に単純なキレーションモデルでは *syn* 選択性が優先するが、事前に活性化されたシリルニトロネートを用いた場合はシリルニトロネートとアルデヒドがアンチペリプラナー遷移状態を取ることによって *anti* 体の生成が有利となる（Scheme 5）。本反応はフッ素イオン源を共存させることで不可逆的にニトロアルドール反応が進行する。



Scheme 5. *anti*-Selective nitroaldol reaction using silyl nitrate

上記コンセプトを背景に丸岡らは独自に開発した光学活性な 4 級アンモニウムフッ化水素塩を用いることでシリルニトロネートとアルデヒドの高収率かつ *anti* 選択的な不斉ニトロアルドール反応を開発した[10]（Scheme 6）。

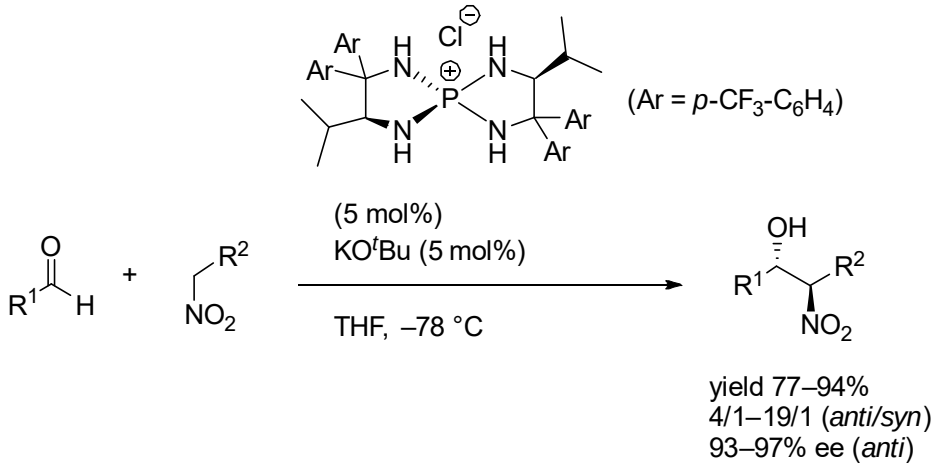


Scheme 6. Chiral quaternary ammonium bifluorides for asymmetric nitroaldol reaction of silyl nitronates with aromatic aldehydes

しかしながら、これらシリルニトロネートを用いる手法は事前にシリルニトロネートを合成する必要があり、またシリル由来の廃棄物が生じるという本質的課題を有していた。アトムエコノミーの観点からは基質の事前調製を必要とせず、かつプロトン移動のみによって

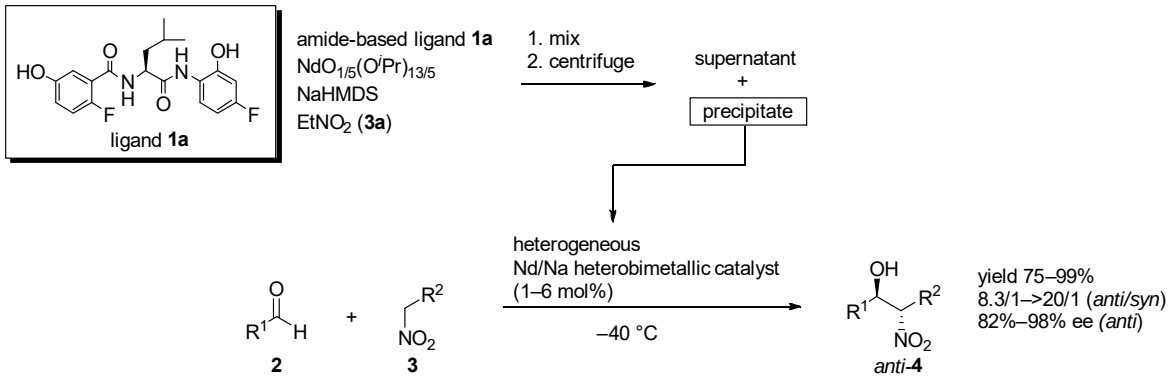
進行し得る原子効率100%の直接的な*anti*選択的触媒的不斉ニトロアルドール反応の開発が待ち望まれた。

大井らは有機イオン対触媒を分子触媒に活用するという研究戦略から独自に開発した *P*-スピロ型テトラアミノホスホニウム塩を用いて2007年にアルデヒドとニトロエタンとの直接的な*anti*選択的触媒的不斉ニトロアルドール反応を世界で初めて報告した[11](Scheme 7)。



Scheme 7. Asymmetric nitroaldol reaction by chiral tetraaminophosphonium salt

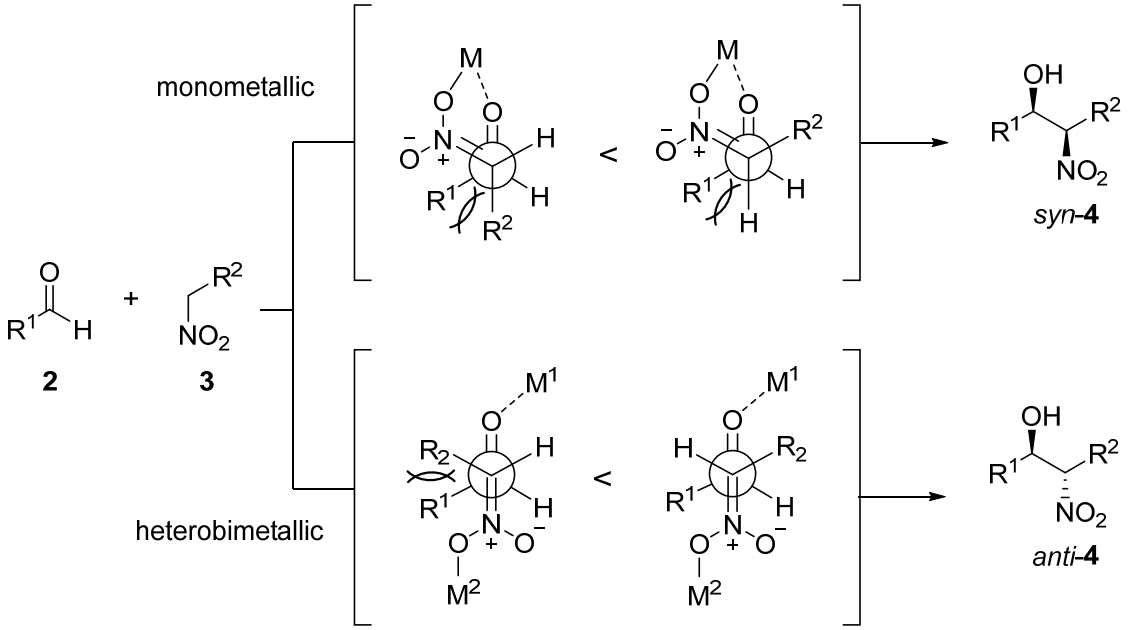
翌年柴﨑らは、予てから研究していた多核不斉金属触媒というコンセプトに基づき創製されたNd/Na異種2核金属触媒を用いる新しい*anti*選択的な触媒的不斉ニトロアルドール反応を報告した[12]。本触媒は巧みに設計されたアミド型配位子 **1a** [13] と $NdO_{1/5}(O^iPr)_{13/5}$[14] および NaHMDS、ニトロエタン **3a** から調製され、自己組織化により不均一系触媒を形成する特徴を呈し、幅広い基質に対して高収率かつ高立体選択なニトロアルドール反応を可能とする（Scheme 8）。



Scheme 8. Asymmetric nitroaldol reaction promoted by Nd/Na heterobimetallic catalyst

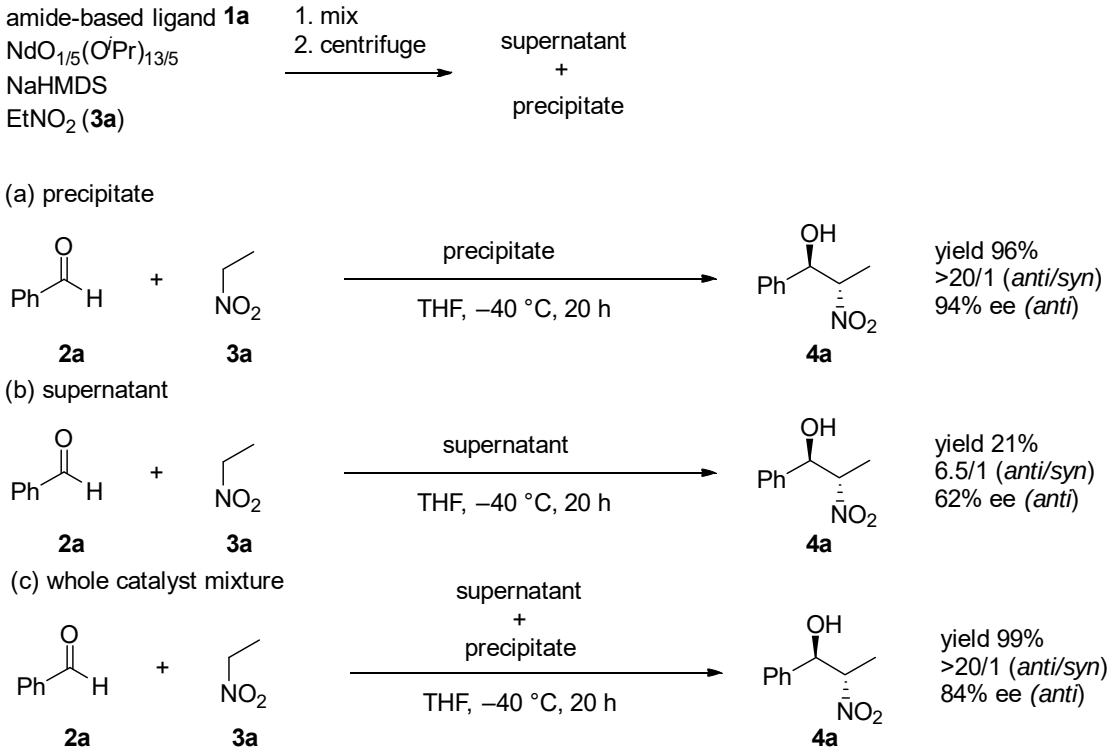
一般的にニトロアルドール反応において単一金属種を用いた場合、遷移状態は金属を介し

た環状遷移状態を取り得るため *syn* 体の生成が優先する（Scheme 9）。一方、2 種異核金属触媒を用いた場合、2 種類の金属が各々Lewis 酸/Brønsted 塩基として働き、アルデヒドの活性化/金属ニトロネートを形成し、アンチペリプラナー型遷移状態を取ることによって *anti* 体の生成が優先することにより立体選択性が発現すると考えられている。



Scheme 9. Diastereoselectivity in nitroaldol reactions

本触媒系で調製される不均一系触媒は優れた立体選択性を示す一方、触媒調製時の上澄み液が存在すると立体選択性が低下することから、自己組織化により生じる集積型不均一系金属触媒が緻密な不斉反応場を構築していることが示唆された（Scheme 10）。



Scheme 10. Nitroaldol reaction with separated precipitate or supernatant

これまでに Nd/Na 異種 2 核金属触媒を用いた *anti* 選択的不斉ニトロアルドール反応を活用することにより Zanamivir[16] や Anacerapib[17a]、AZD5423[17c] といった医薬品あるいは医薬品候補化合物の効率的不斉合成が達成されている（Figure 2）。

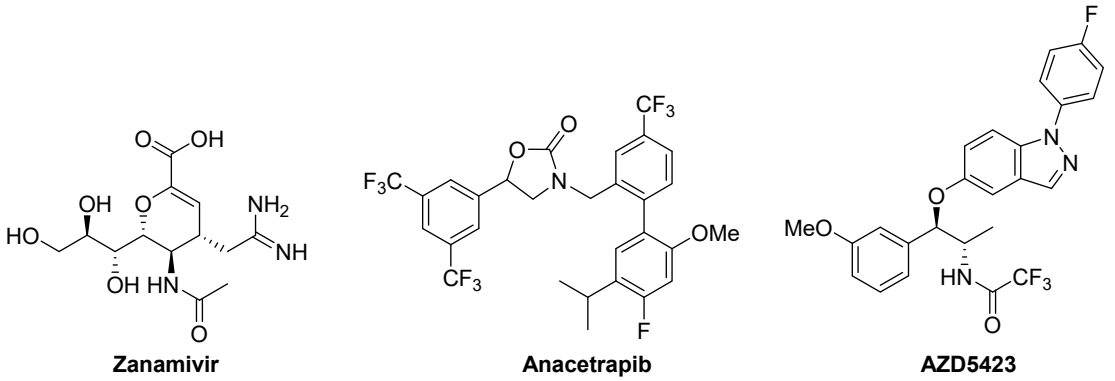
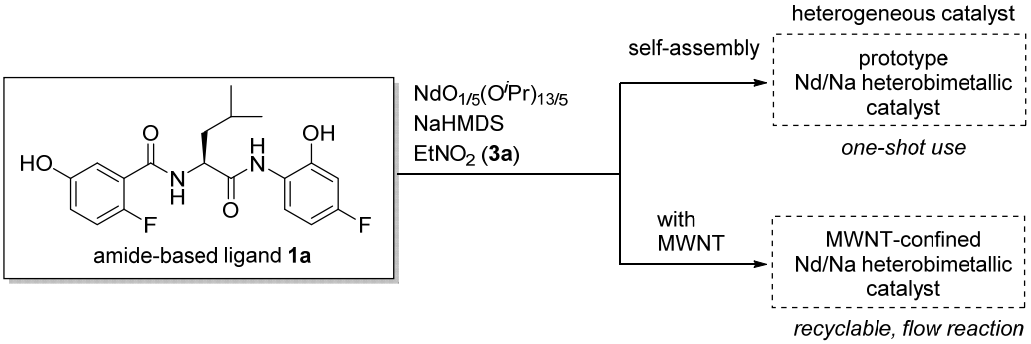


Figure 2. Structure of Zanamivir, Anacetrapib and AZD5423

大井、柴﨑の報告以降、多くの研究者らにより精緻な触媒設計に基づく *anti* 選択的不斉ニトロアルドール反応が報告され、今尚研究対象としての関心は尽きない[15]。

近年グリーンケミストリーへの関心の高まりから、多くの研究者がフロー反応の活用に関心を向けつつある[21]。前述の通りニトロアルドール反応は触媒促進による原子効率の優れた反応であるため、触媒を固定相としたフロー反応は反応効率の向上と反応混合物の簡便

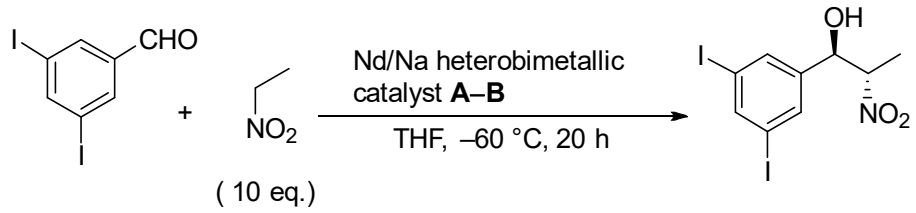
な分離精製を可能にする。柴﨑らは Nd/Na 異種 2 核金属触媒が自己組織化し不均一系触媒を形成する特徴を活かし、多層カーボンナノチューブ（MWNT: multi-walled carbon nanotube）上に本触媒を固定化させ、触媒の再利用およびフロー反応への適用を実現している[17]（Scheme 11）。MWNT 上には共有結合ではなく分子間相互作用等によって固定化されているため不斉環境への影響は最小限であると考えられ、また固定化に際して事前の反応等が必要ないため簡便である[19]。



Scheme 11. Overview of the previously developed Nd/Na heterobimetallic heterogeneous catalysts for *anti*-selective nitroaldol reaction

3,5-ジヨードベンズアルデヒドとニトロエタンとの *anti* 選択的な不斉ニトロアルドール反応において、MWNT 固定型触媒は通常よりも高い触媒活性を示した[17a]（Table 1）。使用される MWNT の一種である Baytube C 70P は高いアスペクト比を有し、網目状の三次元構造をとっているため、このような MWNT 存在下では触媒の自己組織化は微小な網目内で進行し、MWNT 非存在下よりも微小な集積型金属触媒が形成される。その結果、触媒の総面積が増大し、通常よりも触媒活性が高くなると考えられる。

Table 1. *anti*-Selective catalytic asymmetric nitroaldol reaction promoted by self-assembled heterobimetallic catalysts **A**-**B**



Entry	Catalyst (mol%)	t [h]	Yield [%]	*anti/syn*	ee [%] (*anti*)
1	**A** (3)	1	98	98/2	99
2	**A** (1)	20	24	98/2	98
3	**B** (1)	20	99	98/2	99

A: Self-assembled catalyst without MWNT
B: Self-assembled catalyst confined in MWNT

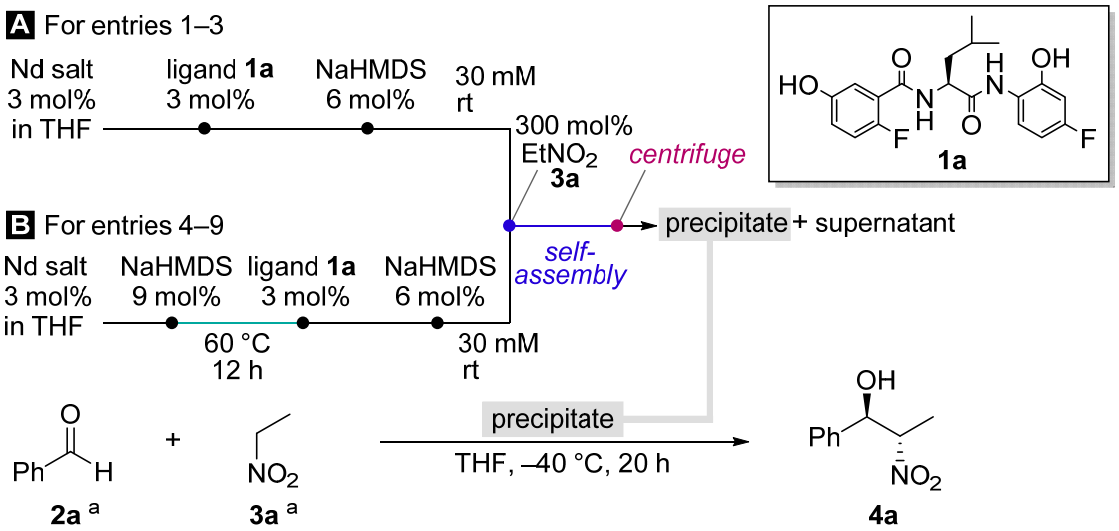
先に記載した通り、多くの生物活性物質に認められる光学活性なβアミノアルコールユニットを構築する反応手法は重要であり、Nd/Na 異種 2 核金属触媒は *anti* 選択的不斉ニトロアルドール反応の優れた触媒として機能するが、本触媒系で使用される $NdO_{1/5}(O^iPr)_{13/5}$ は非常に高価であり、供給メーカーが限定的かつ受注生産のため入手性が乏しく[18]、また空気中の水分に不安定なため不活性ガス雰囲気下での取り扱いが必要であり、実用性に問題が残されていた。私は本触媒の実用性および利便性を高めることを目的とし、より安価で入手容易、かつ空気中で取扱い可能な Nd 源が利用可能な新たな触媒調製法の開発を行った。さらに本触媒をフロー反応へ適用することによって医薬品候補化合物中間体の効率的合成が可能であることを明らかにしたので、ここに報告する。

1-2. Nd 塩および Na 塩の探索

一般的に多くの Nd 塩は有機溶媒に不溶であるため、有機合成反応に用いるのは不向きとされる。例外的に $NdO_{1/5}(O^iPr)_{13/5}$ は有機溶媒への溶解度が非常に高く、溶解性と塩基性の観点から $NdO_{1/5}(O^iPr)_{13/5}$ の代替品としては $Nd(HMDS)_3$[20] が挙げられた。実際、操作手順 A において $Nd(HMDS)_3$ から調製した触媒は、ベンズアルデヒド **2a** とニトロエタン **3a** のニトロアルドール反応において、$NdO_{1/5}(O^iPr)_{13/5}$ から調製した触媒と同等の収率および立体選択性を示した（Table 2, entry 1, 2）。より安価な塩基性 Nd 塩として $Nd(OH)_3$ を検討したが、得られた触媒の活性は非常に低く反応の進行はほとんどみられなかった（entry 3）。触媒調製時の反応溶液は終始スラリー状であり、$Nd(OH)_3$ の溶解性の低さが問題であると推察された。続いて中性 Nd 塩の探索を進め、塩基性補完を目的とし使用する NaHMDS を Nd 塩に対して 5 当量(3 当量 +2 当量)に増量した操作手順 B にて検討を行った。$Nd(NO_3)_3\cdot 6H_2O$, $Nd(OAc)_3\cdot H_2O$, NdF_3 を用いた場合は反応がほとんど進行せず、立体選択性も乏しい

結果となった（entry 4–6）。一方、$NdCl_3$ を用いた場合は $NdO_{1/5}(O^iPr)_{13/5}$ 使用時と同程度の収率および立体選択性を示したが（entry 7）、その水和物塩 $NdCl_3 \cdot 6H_2O$ を用いた場合は反応がほとんど進行しなかった（entry 8）。$NdCl_3$ は類似する $NdBr_3$ に比して有意に高い収率および立体選択性を示した（entry 7 vs. entry 9）。

Table 2. Screening of Nd salts



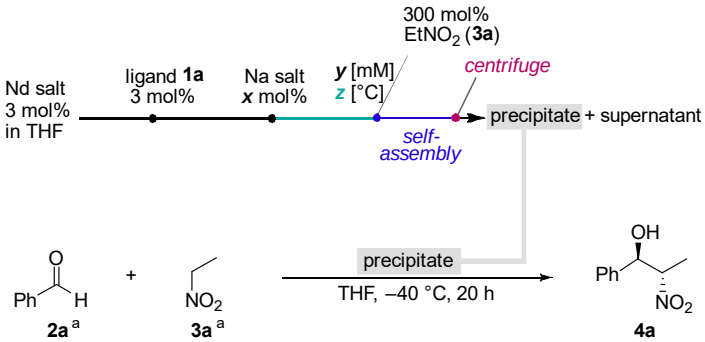
Entry	Nd salt	€/g Nd	preparation	Yield [%][b]	*anti/syn*[c]	ee [%][d]
1[e]	$NdO_{1/5}(O^iPr)_{13/5}$	239	A	99	>20/1	92
2	$Nd(HMDS)_3$	240	A	>99	>20/1	94
3	$Nd(OH)_3$	17	A	<5	1.7/1	nd[f]
4	$Nd(NO_3)\cdot 6H_2O$	3.3	B	<5	2.7/1	nd[f]
5	$Nd(OAc)_3\cdot H_2O$	1.8	B	<5	1.7/1	nd[f]
6	NdF_3	0.9	B	<5	1.2/1	nd[f]
7	$NdCl_3$	11	B	99	>20/1	93
8	$NdCl_3\cdot 6H_2O$	1.6	B	<5	1.9/1	nd[f]
9	$NdBr_3$	40	B	42	6.8/1	33

[a] **2a**: 0.4 mmol, **3a**: 4.0 mmol
[b] Determined by ^{1}H NMR analysis of the crude mixture with DMF as an internal standard.
[c] Determined by ^{1}H NMR analysis of the crude mixture.
[d] Ee of *anti* diastereomer. Determined by chiral stationary phase HPLC analysis.
[e] Data from ref. 3. Nd salt in THF was mixed into ligand **1a**/THF.
[f] nd: not determined

上記検討の結果、$NdCl_3$ が優れた結果を示したが、より安価、入手容易かつ空気中で取扱い可能な水和物塩 $NdCl_3 \cdot 6H_2O$ を用いるべく検討を行った。前述の $NdCl_3$ における，entry 7 で示した触媒調製法は塩基である NaHMDS を分割して添加する方法であったが、より簡便に一括して添加する方法でも所望の触媒形成は可能であった。すなわち $NdCl_3$ お

よび配位子 **1a** の THF 溶液に、Nd 塩に対して 6 当量の NaHMDS を室温にて加えて得られる触媒も優れた触媒活性を示した（**Table 3**, entry 1）。塩基は NaHMDS よりも安価な NaO^{t}Bu を用いても同等の結果を与えた（entry 2）。本触媒調製法においては、水和物塩 $NdCl_3 \cdot 6H_2O$ を用いても良好な結果を与えることを見出した（entry 3）。$NdCl_3 \cdot 6H_2O$ 使用時は試薬の添加順序が所望の触媒形成に肝要であり、Nd 塩および配位子存在下にて塩基続くニトロエタン **3a** を加えることで触媒形成が促される（**Table 3**, entry 3）。一方、配位子非存在下にて塩基を加えると Nd 塩は速やかに不活性な凝集体となるため所望の触媒形成が不能となる（**Table 2**, entry 8）。しかしながら、$NdCl_3 \cdot 6H_2O$ を用いた反応成績はバッチ間のばらつきが大きく、触媒調製法を改善する必要があった。配位子 **1a** 添加後の反応溶液を観察すると、反応成績が良好なときはほぼ均一系であるのに対し、反応成績が芳しくないときは $NdCl_3 \cdot 6H_2O$ とみられる不溶物の残存が確認された。溶解性向上を目論み、$NdCl_3 \cdot 6H_2O$ 塩を事前に粉砕し、配位子 **1a** および塩基を添加時の温度を 60 ℃に昇温することで再現性が確保できることを見出した。さらに、触媒調製時の溶液濃度を上昇させることで（30 mM から 40 mM）より速やかに自己組織化が進行することを確認した。以上の改良調製法によって得られた触媒は再現性良く優れた反応成績を与えた（entry 4）。NaO^{t}Bu の当量を増加した場合も同等な反応性成績を与える一方、NaO^{t}Bu の当量を減じた場合は収率の大幅な低下がみられた（entry 5, 6）。塩基としては他のナトリウムアルコキシドを用いた場合でも良好な結果を与えた（entry 7–9）。また、Nd/Na 異種 2 核金属触媒の自己組織化を MWNT 存在下にて行うことにより調製される MWNT 担持型触媒を当該ニトロアルドール反応に用いても良好な結果を与えた（entry 10）。

Table 3. Screening of Na salts



Entry	Nd salt	€/g Nd	Na salt	x	€/g Na	Preparation y	Preparation z	Yield [%][b]	*anti/syn*[c]	ee [%][d]
1	$NdCl_3$	11	NaHMDS	18	35	30	rt	93	>20/1	93
2	$NdCl_3$	11	NaO^{t}Bu	18	0.6	30	rt	90	>20/1	92
3	$NdCl_3$•$6H_2O$	1.6	NaO^{t}Bu	18	0.6	30	rt	98	>20/1	93
4	$NdCl_3$•$6H_2O$	1.6	NaO^{t}Bu	18	0.6	40	60	98	>20/1	93
5	$NdCl_3$•$6H_2O$	1.6	NaO^{t}Bu	21	0.6	40	60	>99	>20/1	94
6	$NdCl_3$•$6H_2O$	1.6	NaO^{t}Bu	12	0.6	40	60	40	>20/1	95
7	$NdCl_3$•$6H_2O$	1.6	NaOMe	18	0.2	40	60	93	>20/1	94
8	$NdCl_3$•$6H_2O$	1.6	NaOEt	18	0.3	40	60	>99	>20/1	93
9	$NdCl_3$•$6H_2O$	1.6	NaO^{t}Am	18	2.7	40	60	98	>20/1	94
10[e]	$NdCl_3$•$6H_2O$	1.6	NaO^{t}Bu	18	0.6	40	60	97	>20/1	93

[a] **2a**: 0.4 mmol, **3a**: 4.0 mmol

[b] Determined by ^{1}H NMR analysis of the crude mixture with DMF as an internal standard.

[c] Determined by ^{1}H NMR analysis of the crude mixture.

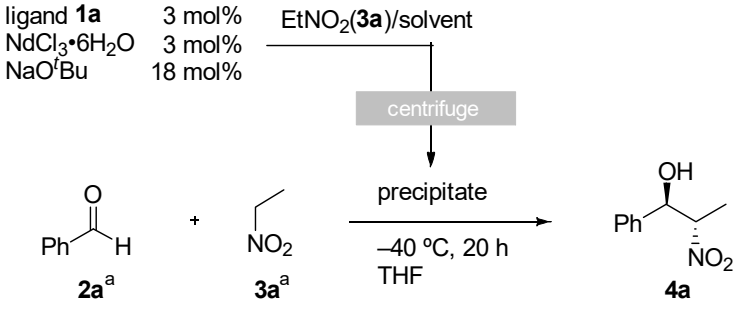
[d] Ee of *anti* diastereomer. Determined by chiral stationary phase HPLC analysis.

[e] 18 mg of MWNT was added before adding $EtNO_2$ (**3a**).

1-3. 触媒調製法の最適化

反応溶媒は THF に固定し、触媒調製時の溶媒を各種検討した（Table 4）。従来通り THF 溶媒にて調製した触媒は優れた反応成績を与える一方、トルエンや他のエーテル系溶媒にて調製した触媒を用いた場合はベンズアルデヒド **2a** とニトロエタン **3a** とのニトロアルドール反応は進行しなかった（entry 1–6）。一方、トルエンあるいは CPME と THF の混合溶媒中にて調製した触媒は原型と同等の反応性を呈したことから、所望の触媒生成機構には THF が関与していることが示唆された（entry 7, 8）。

Table 4. Solvent screening for preparation of Nd/Na heterobimetallic catalyst



Entry	Solvent	Yield [%][b]	*anti*/*syn*[c]	ee [%][d]
1	THF	97	>20/1	93
2	toluene	nd	nd	nd
3	DME	nd	nd	nd
4	1,4-dioxane	nd	nd	nd
5	CPME	nd	nd	nd
6	MTBE	nd	nd	nd
7	toluene/THF=1/1	98	>20/1	95
8	CPME/THF=1/1	99	>20/1	93

[a] **2a**: 0.4 mmol, **3a**: 4.0 mmol
[b] Determined by ^{1}H NMR analysis of the crude mixture with DMF as an internal standard.
[c] Determined by ^{1}H NMR analysis of the crude mixture.
[d] Ee of *anti* diastereomer. Determined by chiral stationary phase HPLC analysis.

続いて触媒の自己組織化挙動を確認するために触媒調製時における上澄み液中の配位子 **1a** の経時的な濃度変化を測定した（Figure 3）。$NdO_{1/5}(O^iPr)_{13/5}$ を用いる従来の方法では速やかに析出を伴う自己組織化が進行し、上澄み液中の配位子濃度は 2 時間程で平衡に達した。一方、$NdCl_3\cdot 6H_2O$ および NaO^tBu を用いる方法では自己組織化は従来法と比して緩やかな挙動を示し、上澄み中の配位子濃度が平衡に達するまでに室温にて 8 時間程度必要であることが明らかとなった。触媒調製法と組成の差違が所望とする触媒の自己組織化速度に影響を与えていることが窺えた。

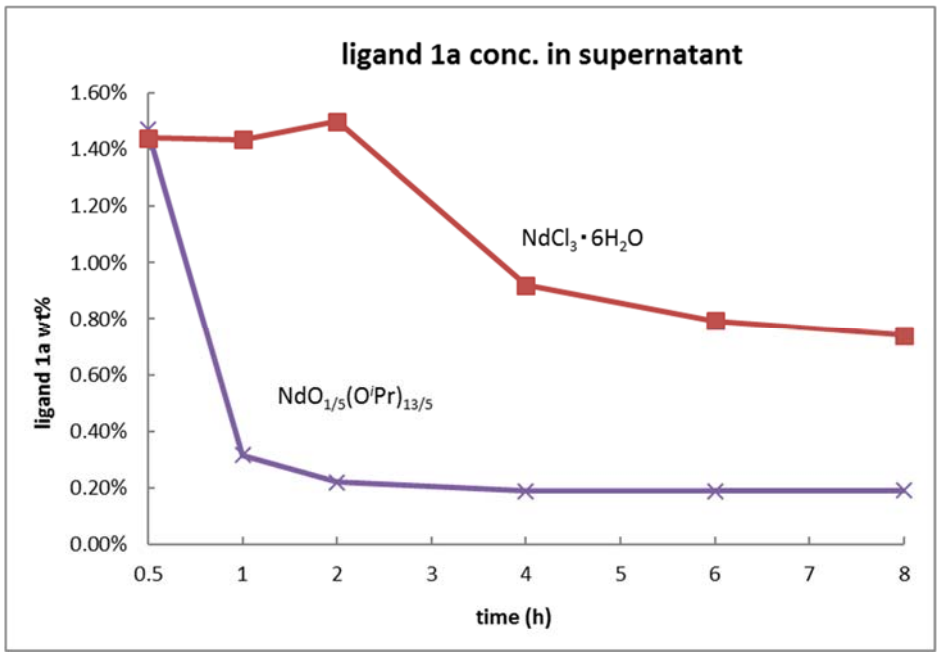
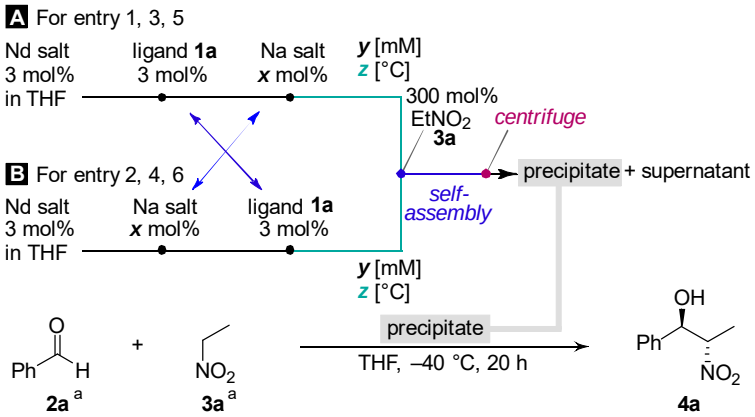


Figure 3. Comparison of self-assembly behavior between original protocol and new protocol for Nd/Na heterobimetallic catalyst preparation

続いて試薬の添加順を検証した（**Table 5**）。Nd 塩として $NdO_{1/5}(O^iPr)_{13/5}$ または $NdCl_3$ を用いた場合、添加順 A あるいは B いずれの場合でも良好な収率および立体選択性を示した（entry 1–4）。一方、$NdCl_3 \cdot 6H_2O$ を用いた場合、添加順 A では優れた結果を与えるのに対し（entry 5）、添加順 B の場合は反応が進行しなかった（entry 6）。詳細については明らかではないが、Nd 塩が水和物であることが原因であると推察された。すなわち手順 B において配位子非存在下にて $NdCl_3 \cdot 6H_2O$ と NaO^tBu が混合され $Nd(OH)_3$ 等の不活性な沈殿が速やかに生じるため、後の配位子添加による触媒形成が阻害されたと考えられる。沈殿物中の配位子含量は反応の成否により顕著な差がみられ、触媒の自己組織化過程が重要であることが窺えた（entry 1–5 vs. entry 6）。

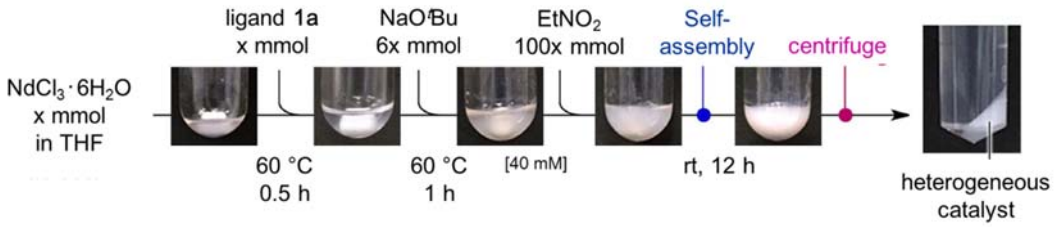
Table 5. Investigation of the addition order of reagents



Entry	Nd salt	Na salt	x	Preparation	y	z	Yield [%] [b]	*anti/syn* [c]	ee [%] [d]	Ligand **1a** in precipitate [%] [e]
1	$NdO_{1/5}(O^iPr)_{13/5}$	NaHMDS	6	A	30	rt	95	>20/1	85	90
2	$NdO_{1/5}(O^iPr)_{13/5}$	NaHMDS	6	B	30	rt	94	>20/1	86	90
3	$NdCl_3$	NaO^tBu	18	A	40	60	99	>20/1	88	93
4	$NdCl_3$	NaO^tBu	18	B	40	60	99	>20/1	80	93
5	$NdCl_3 \cdot 6H_2O$	NaO^tBu	18	A	40	60	98	>20/1	93	94
6	$NdCl_3 \cdot 6H_2O$	NaO^tBu	18	B	40	60	<5	1.6/1	1.3	11

[a] **2a**: 0.4 mmol, **3a**: 4.0 mmol
[b] Determined by ^{1}H NMR analysis of the crude mixture with DMF as an internal standard.
[c] Determined by ^{1}H NMR analysis of the crude mixture.
[d] Ee of *anti* diastereomer. Determined by chiral stationary phase HPLC analysis.
[e] Caluculated based on quantitative analysis of ligand **1a** in supernatant.

一連の触媒調製手順およびその触媒溶液の外観を示す（Scheme 12）。室温において $NdCl_3 \cdot 6H_2O$ は THF に不溶であるが、配位子存在下 60 ℃に加熱するとほぼ均一な溶液となる。続いて NaO^tBu を加えると速やかに白濁し、1 時間同温にて撹拌後室温に冷却してニトロエタンを加えると徐々に白色沈殿（Nd/Na 異種 2 核金属触媒）が生成し、12 時間後に遠心することで不均一系触媒として利用可能となる。



Scheme 12. Schematic representation of new preparation protocol of the Nd/Na heterogeneous catalyst. The solid white object is a magnetic stirring bar.

1-4. 触媒の評価

新規触媒調製法（$NdCl_3$･$6H_2O$ + NaO^tBu）で得られた Nd/Na 異種 2 核金属触媒と原型（$NdO_{1/5}(O^iPr)_{13/5}$ + NaHMDS）の触媒の粉末 XRD（X 線回折）解析を行った（Figure 4）。その結果、有意なピークは共通することから両触媒は同等の微細構造を有していることが示唆された。加えて新規調製法から得られた触媒を MWNT に固定化した MWNT 担持型触媒を STEM（走査型透過電子顕微鏡）と EDS（エネルギー分散型 X 線分光）により精査した。EDS マッピングによって F（配位子 **1a** 由来）、Cl、Nd は高アスペクト比の MWNT の網目状構造体中に捕捉されている様子が確認された（Figure 5）。Cl は従来法（$NdO_{1/5}(O^iPr)_{13/5}$ + NaHMDS）には存在しない新規触媒調製法の $NdCl_3$･$6H_2O$ に由来する元素種であるが、触媒活性には特に影響しないことが明らかとなった。Na のピークは Nd の M 線と重なるため Na の EDS 分析は不可能であったが、EELS（電子エネルギー損失分光法）分析によって Na の有無を確認した結果、触媒像が存在する任意測定した 4 点（Figure 6 (a)）の全点から Na が検出され、Nd/Na 異種 2 核金属触媒が形成されていることが強く示唆された（Figure 6 (b)）。

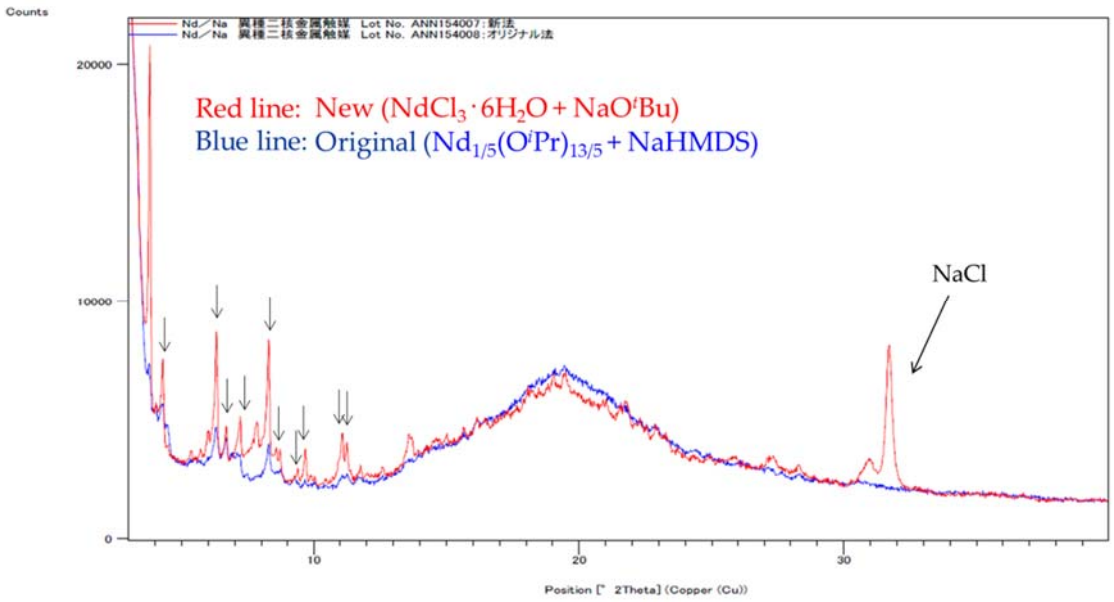


Figure 4. XRD analysis of Nd/Na heterobimetallic catalysts

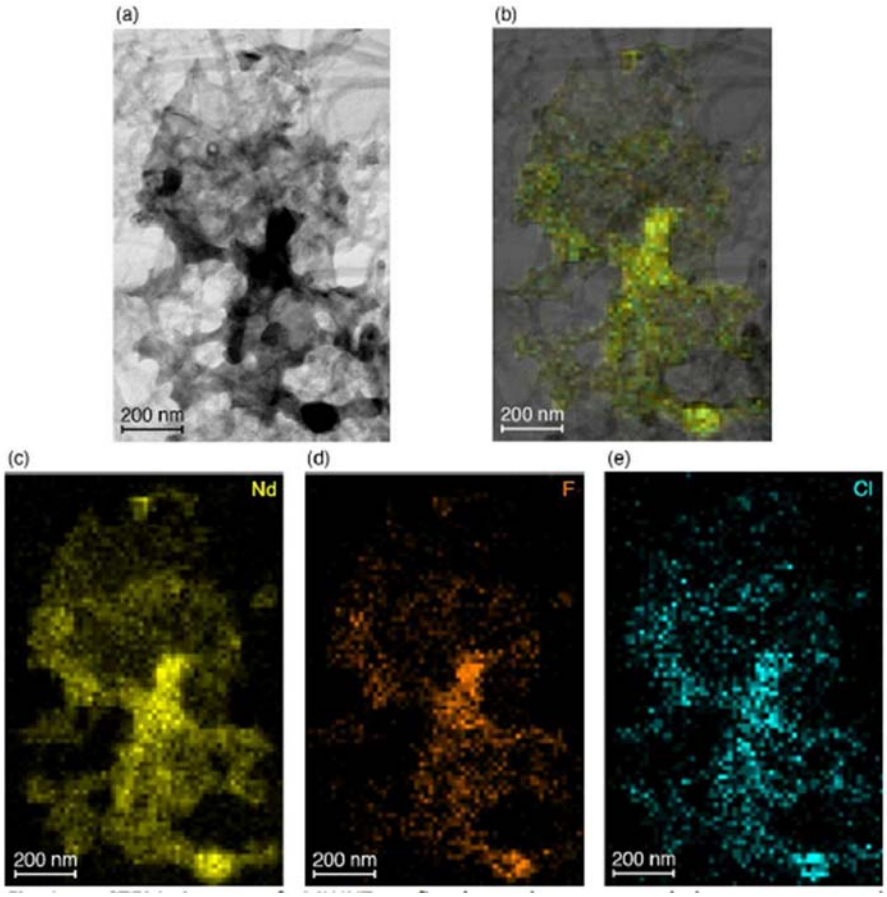


Figure 5. STEM, EDS mapping of MWNT-confined Nd/Na heterobimetallic catalyst

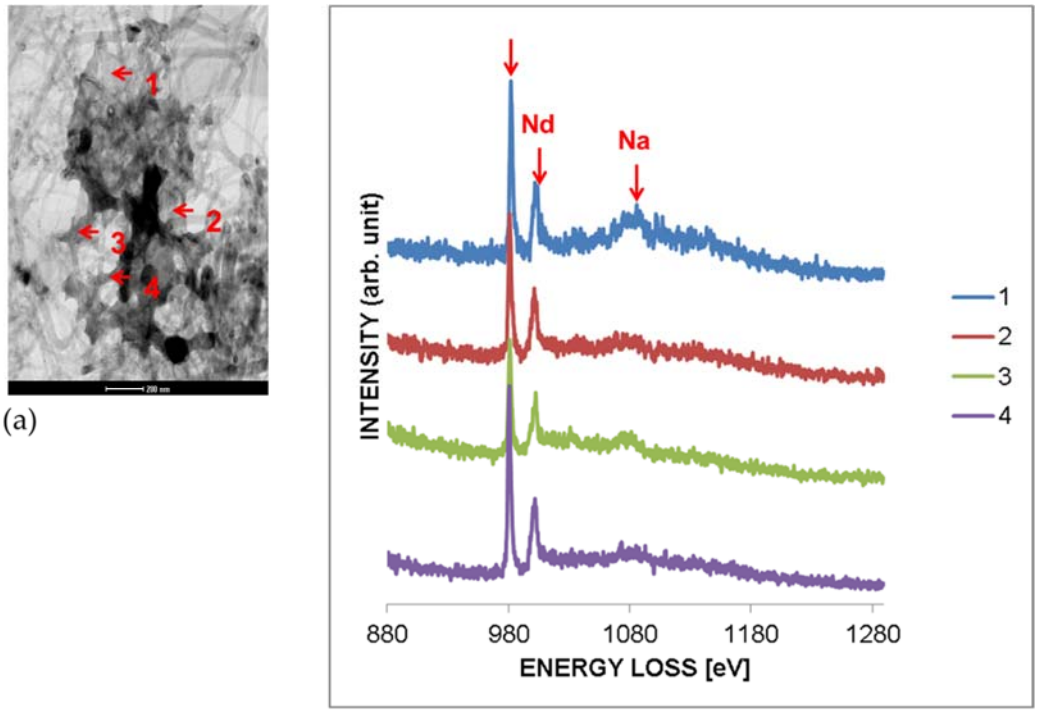


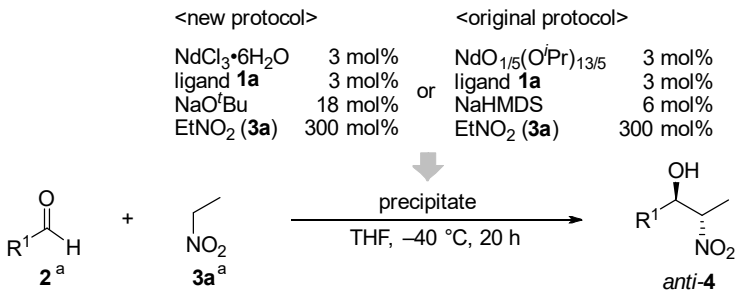
Figure 6. (a) STEM image and (b) EELS analysis of MWNT-confined Nd/Na heterobimetallic catalyst; EELS analysis was conducted at arbitrary 4 points (as described 1-4 in (a)).

1-5.　基質一般性と原型との比較

新規調製法から得られた触媒を用いて種々のアルデヒド **2** とニトロエタン **3a** とのニトロアルドール反応を評価し、その結果を原型の触媒を用いた場合と比較した（Table 6）。オルト位に置換基を有するアルデヒド、パラ位に電子吸引基、電子供与基が置換したアルデヒドに対して良好な結果を示した（entry 2–5）。パラ位にニトロ基を有するアルデヒドは従来法と同様に他の芳香環基質と比べて若干の dr および ee の低下が認められた（entry 6）。シンナムアルデヒドは優れた収率および立体選択性を示した（entry 7）。脂肪族アルデヒドは芳香族アルデヒドと比して dr および ee が低下する傾向がみられたがいずれも良好な立体選択性を呈した（entry 8–10）。各種分析結果ならびに反応性から両触媒は同等の触媒構造を有していることが強く示唆された。

以上、安価、入手容易かつ空気中で取扱い可能な $NdCl_3 \cdot 6H_2O$ および NaO^tBu を用いた Nd/Na 異種 2 核金属触媒の新規調製法を開発した。

Table 6. Substrate generality of the nitroaldol reaction promoted by the Nd/Na heterobimetallic catalyst *via* new protocol ($NdCl_3 \cdot 6H_2O/NaO^tBu$) or original protocol ($NdO_{1/5}(O^iPr)_{13/5}/NaHMDS$)



Entry	Aldehyde **2**		**4**	Yield [%] [b]		*anti/syn* [c]		ee [%] [d]	
	R^1 =			new	original [e]	new	original [e]	new	original [e]
1	Ph	**2a**	**4a**	96	99	>20/1	>20/1	93	92
2	2,4-MeC_6H_3	**2b**	**4b**	95	99	>20/1	>20/1	99	98
3	4-$BnOC_6H_4$	**2c**	**4c**	87	89	>20/1	>20/1	99	97
4	4-NCC_6H_4	**2d**	**4d**	91	88	19/1	15/1	97	94
5 [f]	4-$MeO_2CC_6H_4$	**2e**	**4e**	92	99	>20/1	>20/1	96	96
6	4-$NO_2C_6H_4$	**2f**	**4f**	92	99	6.5/1	5.7/1	88	86
7	(*E*)-PhCH=CH	**2g**	**4g**	95	96	>20/1	>20/1	98	97
8 [g, h]	^{c}Hex	**2h**	**4h**	90	92	6.8/1	8.3/1	94	95
9 [g]	$PhCH_2CH_2$	**2i**	**4i**	94	99	4.4/1	4.9/1	82	77
10 [g]	$^nC_8H_{17}$	**2j**	**4j**	90	93	3.3/1	3.4/1	85	87

[a] **2**: 0.4 mmol, **3a**: 4.0 mmol

[b] Isolated yield of diastereomixture.

[c] Determined by ^1H NMR analysis of the crude mixture.

[d] Ee of *anti* diastereomer. Determined by chiral stationary phase HPLC analysis.

[e] Data are cited from ref. 12b.

[f] Run for 14 h

[g] DME was used as solvent with 6 mol% of catalyst.

[h] Run for 22 h.

第 2 章　Nd/Na 異種 2 核金属触媒担持型フロー反応を活用した AZD7594 の鍵中間体の合成

2-1. 背景

数十年に亘り石油化学の世界では生産性や安全性、品質を実現する手法として連続フロー反応が取り入れられ、評価されてきた。一方、ファインケミカル分野や製薬業界においては未だバッチ反応が主流であり、フロー反応の活用は限定的である。しかしながら、近年フロー反応特有の利点を追及すべく多くの研究者がその活用に関心を向けつつあり、またグリーンケミストリーの要求の高まりもフロー反応を後押しする一因となっている。環境に配慮するなどの観点から Anastas らによってグリーンケミストリーの基本的な考え方として以下の 12 原則が提唱されている [22]。

1. Prevention
   It is better to prevent waste than to treat or clean up waste after it has been created.
2. Atom Economy
   Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. Less Hazardous Chemical Syntheses
   Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Designing Safer Chemicals
   Chemical products should be designed to affect their desired function while minimizing their toxicity.
5. Safer Solvents and Auxiliaries
   The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. Design for Energy Efficiency
   Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7. Use of Renewable Feedstocks
   A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. Reduce Derivatives
   Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

9. Catalyst

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Design for Degradation

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. Real-time analysis for Pollution Prevention

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Inherently Safer Chemistry for Accident Prevention

Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

第 1 章で述べた優れた触媒反応の開発はグリーンケミストリーを実現する手法の一つである一方、フロー反応もグリーンケミストリーを実現する強力なツールのひとつとして捉えられている。またフロー反応はバッチ反応と比較して環境面のみならず化学合成の観点からも以下の優れた特性を多く備えている。

フロー反応の利点

- 基質同士の混合効率、フロー反応容器の熱交換率が高いため反応時間が短縮される
- 収率や純度が高くなる傾向にある
- 高圧、高温、極低温が可能
- リアルタイム分析機器との相性が良い
- スケールアップが容易
- 毒物等の作業者への暴露リスクが低い
- 爆発物等使用時の安全性リスクが低い
- 省エネルギー
- 省スペース
- 光反応やマイクロ波反応との相性が良い
- 再現性が高い
- 多段階反応が適応可能
- 自動化しやすい

こうしたフロー反応の特性は特に大量合成を必要とする産業界からの関心が高く、医薬品の合成に適用する試みが盛んに研究されている[23]。

小林らはフロー反応を 4 種類に分類することを提唱している[24] (Figure 7)。すなわち分類 I は基質 A および B を通液することで反応が進行する系であり、目的とする生成物 C が留

出するが同時に未反応の基質 A あるいは B、または不純物が混入し得る。分類 II は反応剤 B を担持したカラムに基質 A を通液することでカラム内にて反応が進行する系（例えば固相に担持されたトリアセトキシボロヒドリドを用いた還元的アミノ化反応等）であり、未反応の A あるいは B の混入は防げるが、反応剤 B は徐々に消費されるためカラムの交換が必要となる。また反応系によっては過剰反応が進行し得る。分類 III は基質 A、B および均一系触媒を通液することで反応が進行する系であり、反応は完結するが留出液に触媒が混入する。分類 IV は触媒を担持したカラムに基質 A および B を通液し、カラム内にて反応が進行する系であり、触媒を担持する操作が必要となるが、留出液に触媒は混入しない。グリーンケミストリーの観点からは分類 III あるいは分類 IV が好ましく、生成物から触媒を分離する必要がない分類 IV がより望ましいといえる。

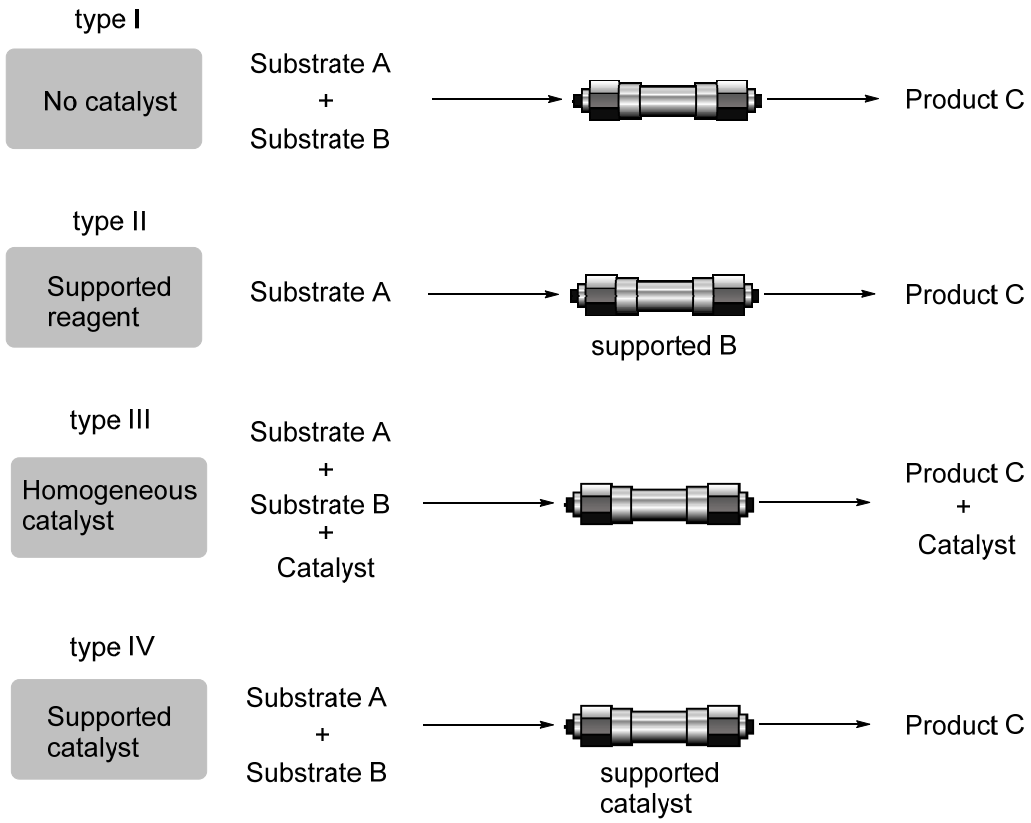


Figure 7. Types of flow system

グリーンケミストリーの要求の高まりから、近年では特に不均一系触媒によるフロー反応（分類 IV）への関心が高まりつつあり、例えば小林らは不均一触媒を充填したカラムのみを用いた連続フロー合成を駆使し、医薬品の多段階合成を報告している[24]。その他多くの研究者らが不均一系触媒によるフロー反応を報告しているが[25]、炭素–炭素結合形成反応、とりわけ立体選択的な反応は発展途上にあり、多くの例の TON は低い傾向にある。

柴﨑らによって開発された Nd/Na 異種 2 核金属触媒は不均一系触媒という特徴を活か

し、MWNT への非共有結合による固定化、フロー化学への適用を実現している。フロー反応によって 2-メトキシベンズアルデヒドとニトロエタンとのニトロアルドール反応では優れた収率および立体選択性を示し、TON は 204 を示した。スケールアップも容易であり、10 g 以上のニトロアルドール成績体の合成を実現している[17c]（Figure 8）。

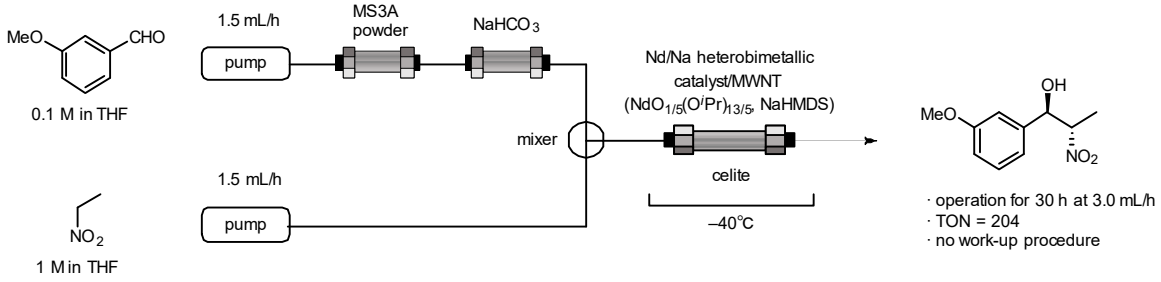
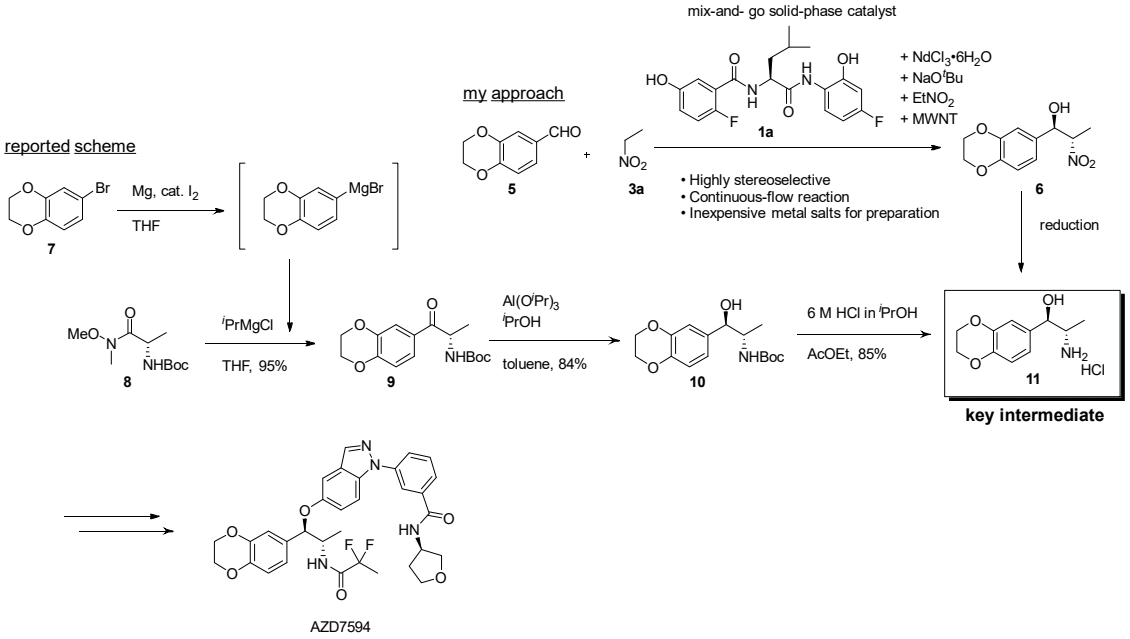


Figure 8. Continuous-flow platform by self-assembled asymmetric catalyst for the nitroaldol reaction

第 1 章にて報告した新規調製法から得られる Nd/Na 異種 2 核金属触媒は従来法と同等の触媒活性を示すことから、フロー反応においてもその反応促進特性が期待できる。そこで本章では、本触媒系の実践的有用性の実証を目指しフロー反応を活用した医薬品候補化合物 AZD7594 の鍵中間体の合成に着手したので報告する。

2-2. AZD7594 について

AZD7594 は喘息、COPD（慢性閉塞性肺疾患）を適応症とする、英アストラゼネカ社（AstraZeneca）によって臨床開発中の化合物である[26]。アラニン誘導体 **8** を出発物質として 3 工程経た後に得られるアミノアルコール体 **11** を中間体とし AZD7594 へと導く合成ルートが報告されている（Scheme 13）。鍵中間体であるアミノアルコール体 **11** の合成に対して、不均一系触媒の特長を生かしたフロー反応を活用した *anti* 選択的不斉ニトロアルドール反応が適用可能であればより効率的にアプローチできると考えた。すなわちアルデヒド **5** とニトロエタン **3a** との *anti* 選択的不斉ニトロアルドール反応から得られる成績体 **6** のニトロ基を還元し鍵中間体 **11** へ導くことを計画した。

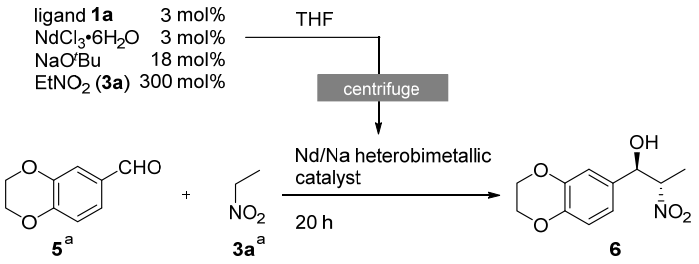


Scheme 13. Application of highly stereoselective nitroaldol reaction in a continuous flow platform to afford key intermediate of AZD7594

2-3. バッチ反応による最適化

新規触媒調製法（$NdCl_3 \cdot 6H_2O$ + NaO^tBu）から得られた Nd/Na 異種 2 核金属触媒を用い、バッチ法にて目的とする *anti* 選択的不斉ニトロアルドール反応の最適化条件を検討した（Table 7）。Entry 1–6 に示すエーテル系溶媒を用いた場合はいずれも良好な収率および立体選択性を示し、2-Me-THF が最も良好な結果を与えた（entry 6）。

Table 7. *anti*-Selective asymmetric nitroaldol reaction of aldehyde **5** promoted by heterogeneous catalyst prepared from $NdCl_3 \cdot 6H_2O$/NaO^tBu



Entry	Solvent	Temp [°C]	Yield [%][b]	*anti*/*syn*[c]	ee [%][d]
1	THF	–40	83	>20/1	95
2	Et_2O	–40	92	19/1	95
3	DME	–40	80	>20/1	94
4	CPME	–40	95	16/1	93
5	2-Me-THF	–30	92	14/1	94
6	2-Me-THF	–40	96	>20/1	96
7	toluene	–40	56	8.6/1	87

[a] **5**: 0.4 mmol, **3a**: 4.0 mmol
[b] Determined by ^{1}H NMR analysis of the crude mixture with DMF as an internal standard.
[c] Determined by ^{1}H NMR analysis of the crude mixture.
[d] Ee of *anti* diastereomer. Determined by chiral stationary phase HPLC analysis.

尚、新規調製法と従来法の触媒を用いた場合の反応挙動を観測した結果、両者は同等の反応性を示した（Figure 9）。

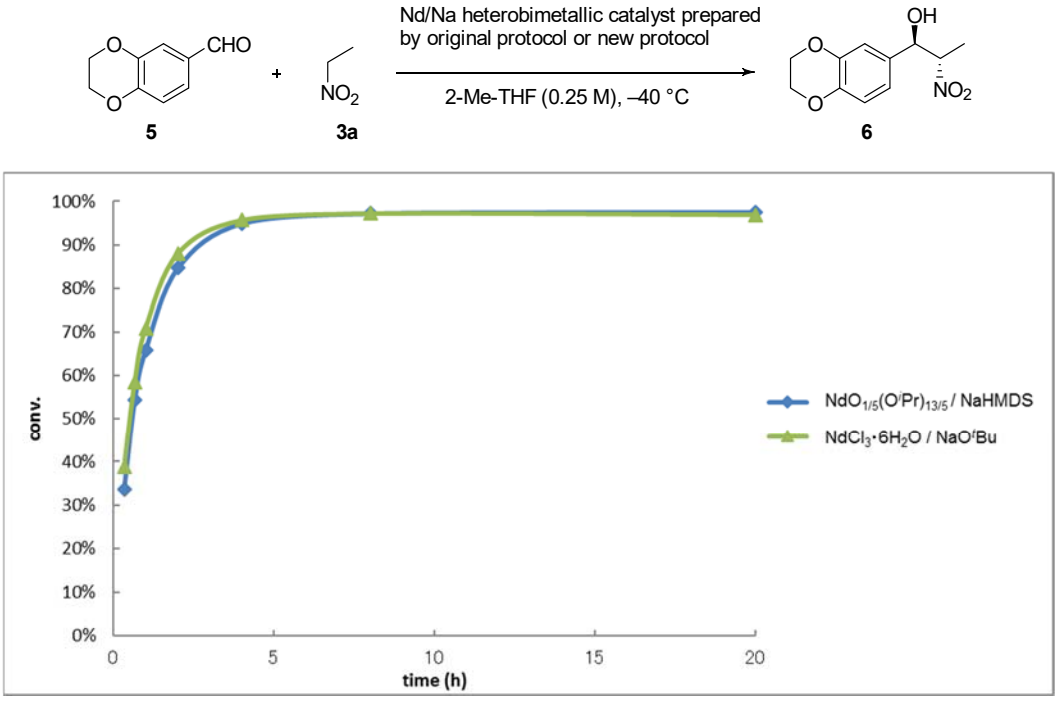


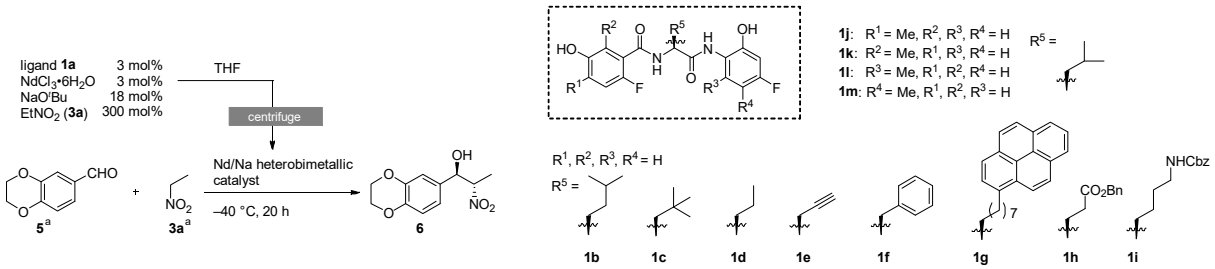
Figure 9. Comparison of the reaction profile promoted by the Nd/Na heterobimetallic catalys prepared by orginal protocol or new protocol

2-4. 配位子の探索

次に配位子の機能性付加を見据えた配位子の化学修飾を検討した（Table 8）。触媒活性の向上を目的としアミノ酸残基部位を種々変換した配位子（**1b–i**）を合成し、その触媒能を評価した。代表的な配位子の合成法を Scheme 14, Scheme 15 に示す。一炭素増炭した配位子

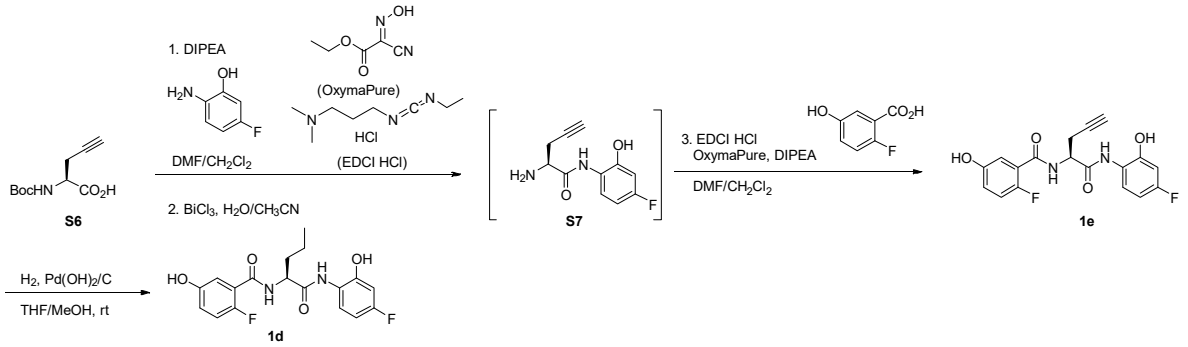
1b や **1c**、より立体障害の大きい **1f** を用いた場合は収率および立体選択性の低下がみられた一方（entry 1, 2, 5）、より立体障害が小さい配位子 **1d** は配位子 **1a** と同程度の収率および立体選択性を示した（entry 3）。また MWNT と親和的相互作用が期待されるピレン基[27]を含む配位子 **1g** は比較的良好な収率および立体選択性を示した（entry 6）。官能基化されたアミノ酸残基から調製した触媒を用いた場合は反応がほとんど進行しなかった（entry 7, 8）。一方、配位子の芳香環上の置換基については、過去の検討から 2 つのヒドロキシ基およびフッ素は反応性および立体選択性の発現に重要であるという知見が得られていたため、芳香環上の他の部位に Me 基を導入した配位子をモデル化合物として合成し、その置換基許容性を検討した（**1j–1m**）。その結果、いずれの置換パターンを有する配位子を用いた場合でも収率および立体選択性の低下がみられ（entry 9–12）、芳香環上への置換基導入は困難であることが窺えた。

Table 8. *anti*-Selective asymmetric nitroaldol reaction of aldehyde **5** promoted by heterogeneous catalyst prepared from $NdCl_3 \cdot 6H_2O$/NaO^tBu/modified ligand **1b–1m**

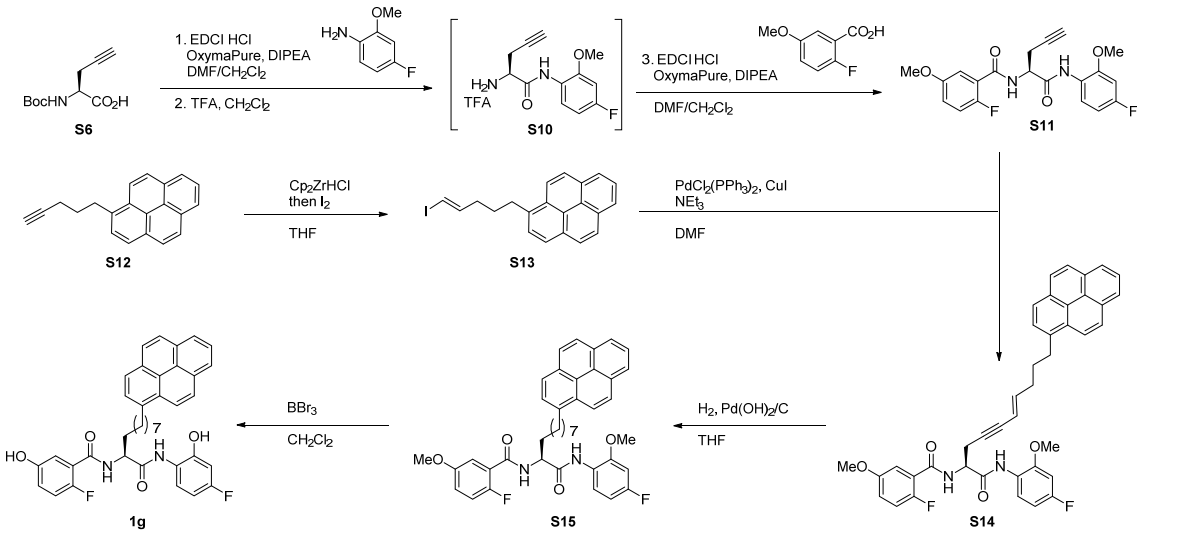


Entry	Ligand	Yield [%][b]	*anti*/*syn* [c]	ee [%][d]
1	**1b**	35	9.7/1	69
2	**1c**	<5	2.7/1	20
3	**1d**	89	>20/1	94
4	**1e**	29	12/1	80
5	**1f**	<5	3.8/1	11
6	**1g**	83	>20/1	90
7	**1h**	<5	2.4/1	0
8	**1i**	<5	5.1/1	32
9	**1j**	<5	1.4/1	<5
10	**1k**	<5	1.9/1	<5
11	**1l**	6.1	3.5/1	31
12	**1m**	68	14/1	57

[a] **5**: 0.4 mmol, **3a**: 4.0 mmol
[b] Determined by ^{1}H NMR analysis of the crude mixture with DMF as an internal standard.
[c] Determined by ^{1}H NMR analysis of the crude mixture.
[d] Ee of *anti* diastereomer. Determined by chiral stationary phase HPLC analysis.



Scheme 14. Synthetic route of ligand **1d**

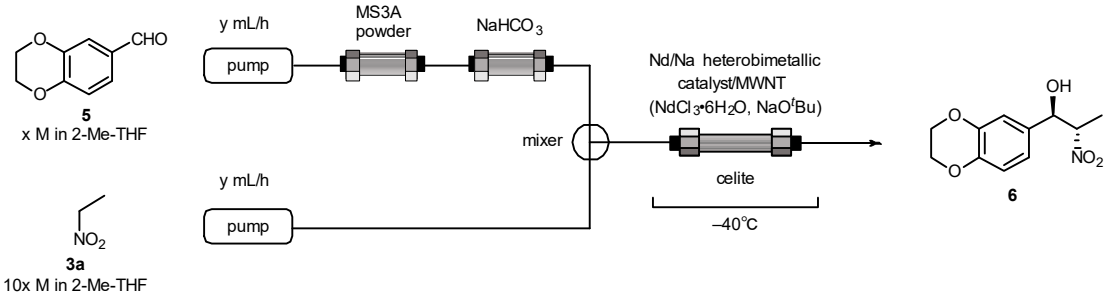


Scheme 15. Synthetic route of ligand **1g**

2-5. フロー反応の最適化と長期間運転

続いてバッチ反応検討で得られた最適化条件を基にしてフロー反応の最適化を図った。MWNT 共存下にて自己組織化させることで MWNT に固定化した Nd/Na 異種 2 核金属触媒をセライトとともにステンレスカラムに充填した。アルデヒド側の流路にはミキサー手前に水分除去を目的とした活性化した MS3A と酸性不純物の除去を目的とした炭酸水素ナトリウムを充填したプレカラムを直列に配置した。触媒を充填したカラムは–40℃に冷却し、アルデヒドおよびニトロエタンを一定時間通液し、得られた反応液の転化率および dr, ee を分析した (Table 9)。基質濃度は 0.3 M まで上げると dr の著しい低下がみられたため 0.2 M とした（entry 1 vs. entry 3)。カラムサイズや基質濃度、流速を検討した結果、流速を下げるほど変換率の向上がみられたため、最終的に流速は 0.6 mL/h と設定した（entry 8)。また MS3A と $NaHCO_3$ を定期的に新しいものに取り換えて系内の環境を保つことが触媒活性維持に重要であるという知見が得られた。

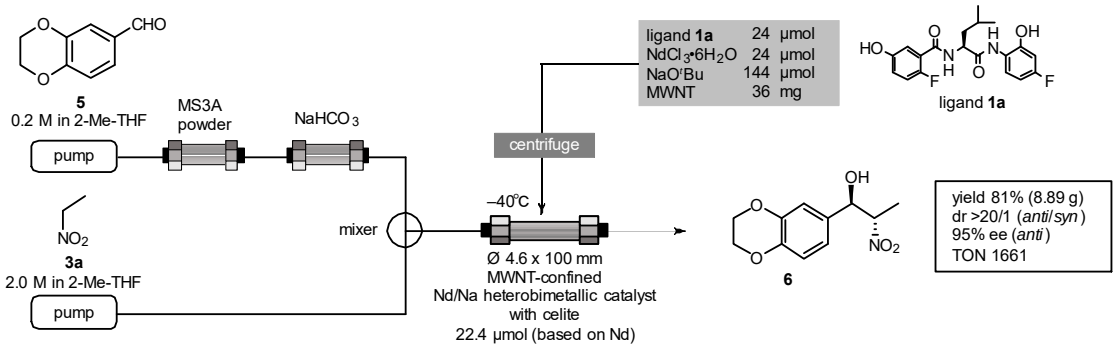
Table 9. Optimization of flow system for *anti*-selective nitroaldol reaction with aldehyde **5** and nitroethane **3a**



Entry	Column [mm][a]	x: Concentration (aldehyde) [M]	y: Flow rate (each pump) [mL/h]	Operation time [h]	Residence time [min]	Conv.[%][b] (avg.)	*anti*/*syn*[b] (avg.)	ee [%][c]
1	ø 4.6 x 100	0.2	1.500	19	33	73	>20/1	94
2	ø 8.0 x 30	0.2	1.500	17	30	61	20/1	94
3	ø 4.6 x 100	0.3	1.500	19	33	58	7.6/1	93
4	ø 4.6 x 100	0.2	1.125	25	44	75	>20/1	94
5	ø 4.6 x 100	0.2	0.750	35	66	83	>20/1	96
6	ø 10 x 30	0.2	0.750	28	94	77	>20/1	95
7	ø 4.6 x 100	0.2	0.720	15	69	88	>20/1	95
8	ø 4.6 x 100	0.2	0.600	100	83	87	>20/1	96

[a] Stainless column Ø (diameter) x (length) [mm]
[b] Determined by ^{1}H NMR analysis of the crude mixture.
[c] Ee of *anti* diastereomer. Determined by chiral stationary phase HPLC analysis.

次に上記検討より見出された最適条件を基に長時間のフロー反応を実施した（Scheme 16）。触媒調製時に使用した Nd 塩（24 μmol）の 93.5%（22.4 μmol）が不均一系触媒を形成し、セライトに分散させてカラムに充填した。アルデヒド溶液中の微量の水分除去を目的とした MS3A 充填カラムおよび微量酸性成分の除去を目的とした $NaHCO_3$ 充填カラムをアルデヒド **5** の流路上流に設置し、アルデヒド **5**/2-Me-THF 溶液およびニトロエタン **3a**/2-Me-THF 溶液を 0.6 mL/h の流速にて–40 °C に冷却した触媒カラムに通液して所望の反応を実施した。その結果、時間の経過とともに転化率の緩やかな減少がみられたものの dr および ee は 400 時間以上高い値を示した（Figure 10）。最終的に 398 時間分の反応溶液の溶媒を留去し、シリカゲルカラムクロマトグラフィーによって精製することでニトロアルドール成績体 **6** が 8.89 g（*anti*/*syn* = >20/1, 95% ee）得られ、その触媒回転数（TON）は 1661 にまで達した。フロー反応を適用することでバッチ反応では 372 cm^3（0.1 M の場合）必要となる反応容積を 224 分の 1 の 1.66 cm^3 にダウンサイジングできたこととなる。一般的に反応スケールが上がるにつれて低温反応の厳密な制御は困難になるが、反応装置の大幅な省スペース化に伴い、厳密な温度制御が要求される反応を安定した条件下にて実施可能となる。



Scheme 16. *anti*-Selective catalytic asymmetric nitroaldol reaction in flow

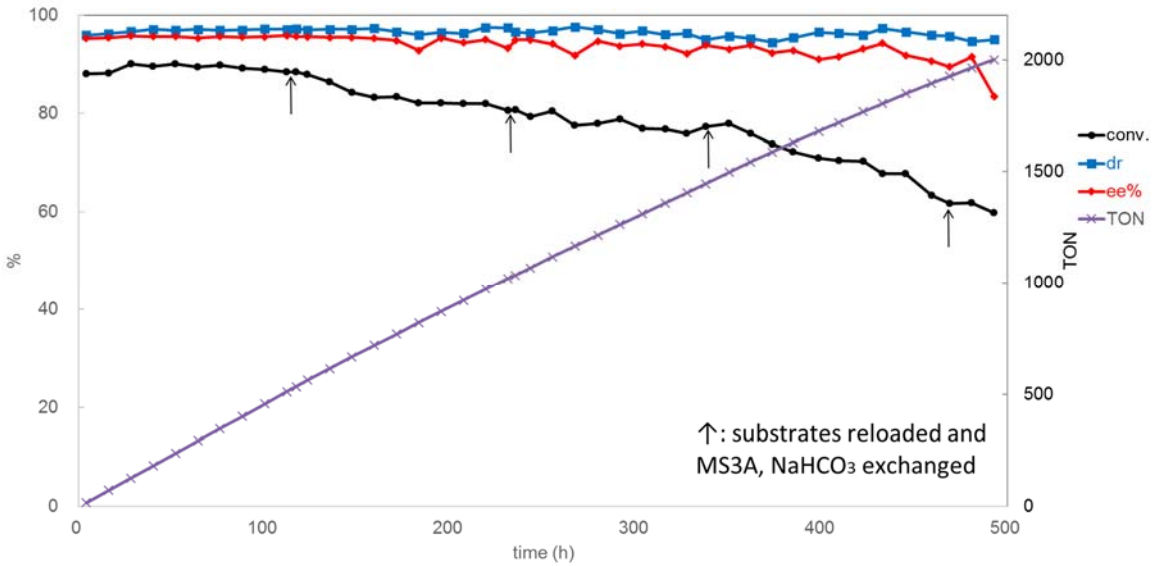
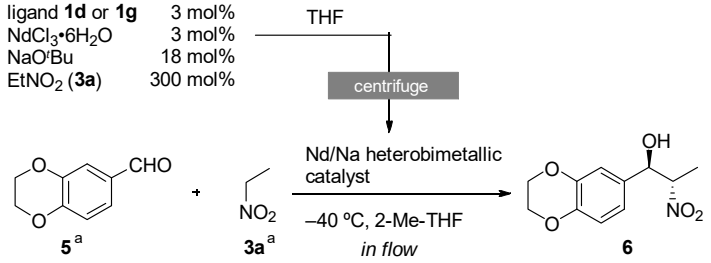


Figure 10. Reaction profile (conv., dr, ee, TON)

ピレン基を含む配位子 **1g** は MWNT との親和的相互作用が期待されるため、MWNT に対する吸着率を測定した。2-Me-THF 中にて配位子 **1a** あるい **1g** と MWNT の一種である Baytube C 70P 共存下、–40 ℃にて 2 h 撹拌した後の MWNT への配位子吸着率は **1a** の場合は 0%に対し、**1g** の場合 8%とわずかながら高い吸着率を示した。続いてバッチ法において良好な結果を示した配位子 **1d** および **1g** をフロー反応に適用したが、いずれも配位子 **1a** を用いた場合より低い転化率および立体選択性を与えた (Table 10, Figure 11, Figure 12)。

Table 10. Nitroaldol reaction between aldehyde **5** and nitroethane **3a** with ligand **1d** or ligand **1g** in flow



Entry	Ligand	Conv. [%] [a]	*anti*/*syn* [a]	ee [%] [b]
1	**1d**	68–75	>20/1	84–94
2	**1g**	29–34	11/1–18/1	83–88

[a] Determined by ^{1}H NMR analysis of the crude mixture.

[b] Ee of *anti* diastereomer. Determined by chiral stationary phase HPLC analysis.

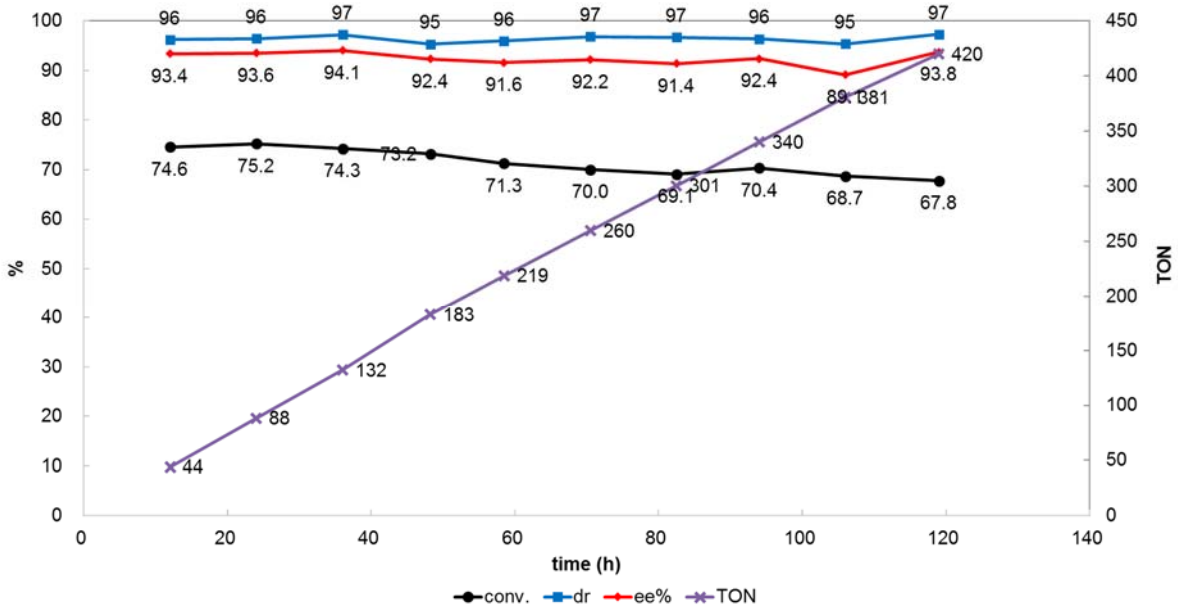


Figure 11. Reaction profile in flow (ligand **1d**)

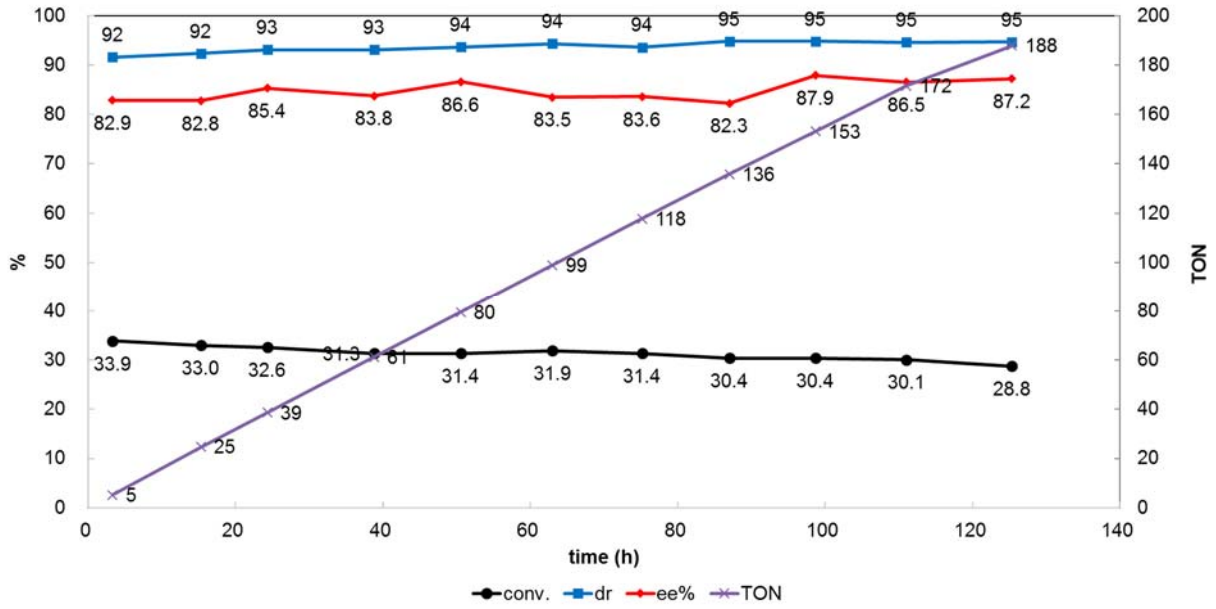
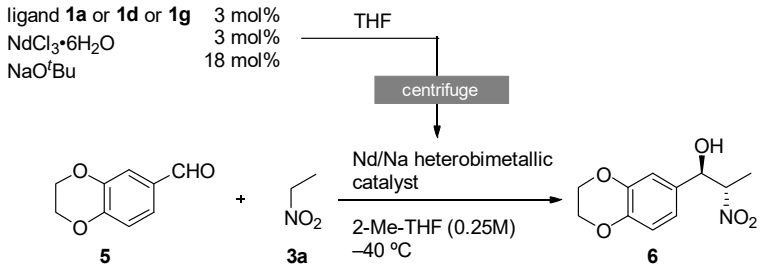


Figure 12. Reaction profile in flow (ligand **1g**)

配位子 **1a**, **1d**, **1g** のバッチ反応における反応挙動を比較した結果、配位子 **1a** と比較して **1d**, **1g** はいずれも反応性が劣るため、フロー反応においても乏しい結果を与えたと推察された（Figure 13）。より低流速にてフロー反応を実施することで転化率の向上が期待できるが、ポンプ性能や生産性の観点からこれ以上の流速低下は困難であると考えられた。



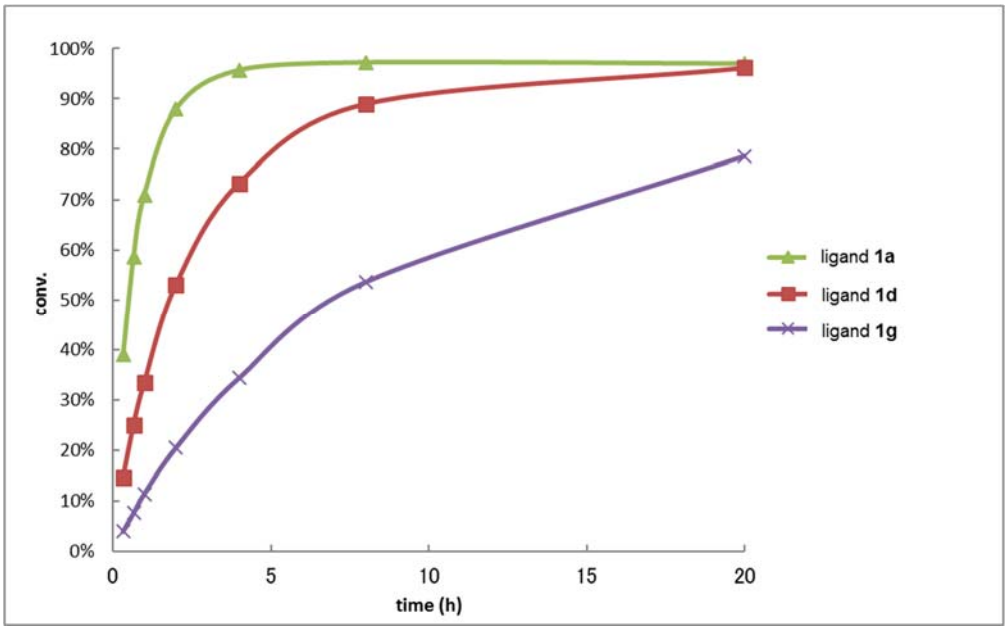


Figure 13. Reaction profile (ligand 1a vs. ligand 1d vs. ligand 1g) in batch condition

2-6. 固定化触媒の評価

配位子 **1g** はフロー反応には不適であったが、ピレン基とカーボンナノチューブを含む炭素シートの相互作用という特性に着目し、先に配位子を固定相に固定化したものを触媒反応に利用することを試みた。検討に先立って吸着率の高い固定相を選定した結果、High Purity SWNT が最も高い吸着率を示した（Table 11, entry 4）。

Table 11. Screening of solid support

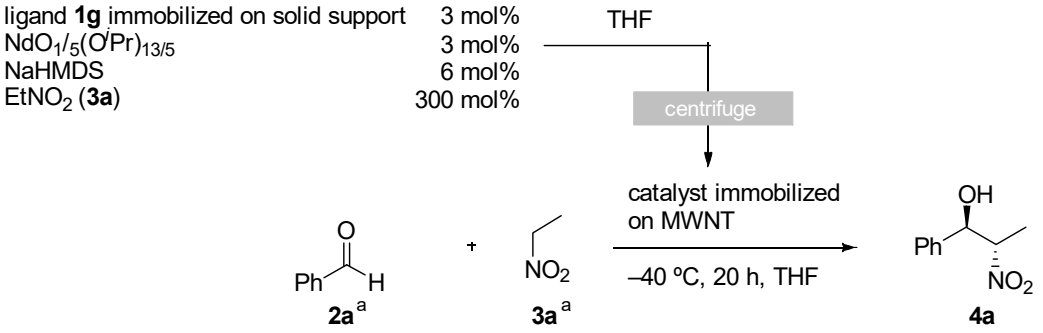
Entry	Solid support (3 WR vs. ligand)	Immobilized rate (%)	
		ligand **1g**	ligand **1a**
1	SWNT (0.7–0.9 nm diameter)	17	-
2	SWNT (0.7–1.1 nm diameter)	34	-
3	SWNT (0.7–1.3 nm diameter)	37	-
4	High Purity SWNT (<2 nm diameter)	53	7
5	MWNT C 70P (Baytube C 70P)	11	-
6	MWNT C150P	19	-
7	MWNT (6–9 nm diameter x 5 mm length)	<5	-
8	Glaphite (platelet nanofibers)	<5	-
9	Graphene monoplate	<5	-

Immobilization procedure: The mixture of solid support and THF was sonicated for 1 h and stirred for 12 h at room temperature. The filtrate was dried to afford immobilized ligand on solid support. Immobilized rate was calculated based on quantitative analysis of ligand in the mother liquid.

次に High Purity SWNT に固定化した配位子 **1g** を用いて Nd/Na 異種 2 核金属触媒の調製

を試み、ベンズアルデヒド **2a** とニトロエタン **3a** との *anti* 選択的不斉ニトロアルドール反応に適用した。その結果、反応収率は低く、反応成績体の dr および ee も中程度に留まった (Table 12, entry 1)。小川らの検討では、種々の固定相存在下にて Nd/Na 異種 2 核金属触媒を調製し、固定相担持型触媒を用いて 3,5-ジヨードベンズアルデヒドとニトロエタンとの *anti* 選択的不斉アルドール反応を検討した結果、MWNT の一種である Baytube C 70P が優れた収率および立体選択性を示す一方、SWNT を始めとした他の固定相は著しい収率および立体選択性の低下がみられた [17a]。したがって、本検討のように事前に固定相に吸着させた配位子を用いて調製した Nd/Na 異種 2 核金属触媒による *anti* 選択的不斉アルドール反応においても同様に固定相の影響によって収率および立体選択性の低下がみられたと推察された。

Table 12. *anti*-Selective nitroaldore reaction with Nd/Na bimetallic catalyst immobilized on carbon nanotube



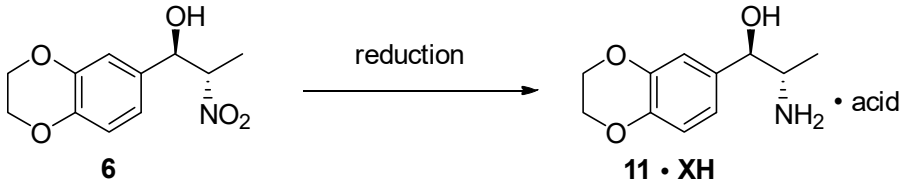
Entry	Ligand	Solid support	Ligand loading rate [%]	Yield [%] [b]	*anti*/*syn* [c]	ee [%] [d]
1	**1g**	High Purity SWNT	10	27	7.2/1	61
2	**1g**	-	-	94	>20/1	79
3	**1a**	-	-	99	>20/1	93

[a] **2a**: 0.4 mmol, **3a**: 4.0 mmol
[b] Determined by ^{1}H NMR analysis of the crude mixture with DMF as an internal standard.
[c] Determined by ^{1}H NMR analysis of the crude mixture.
[d] Ee of *anti* diastereomer. Determined by chiral stationary phase HPLC analysis.

2-7. 鍵中間体の合成

フロー反応にて得られたニトロアルコール体 **6** からアミノアルコールへの水素添加反応は添加剤がない場合、ベンジルアルコール体が主成分として生成するが、酢酸を添加することにより目的とするアミノアルコール体が酢酸塩体として収率良く得られることを見出した（Table 13, entry 3）。

Table 13. Reduction of nitro group on nitroalcohol **6**

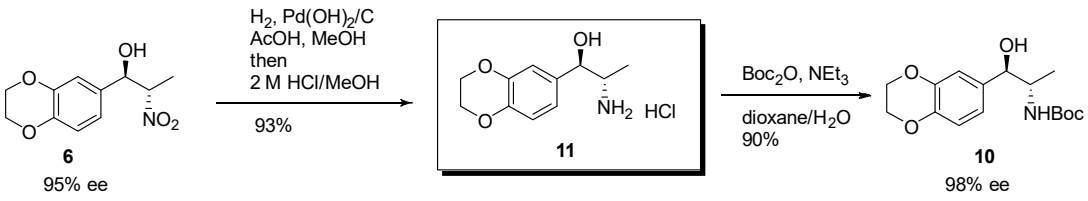


6 **11 • XH**

Entry	Condition	Additive	Time	Result
1	$Pd(OH)_2/C$ (5mol%)	-	15 h	Benzyl alcohol major
2	$Pd(OH)_2/C$ (5mol%)	HCl (1 eq.)	10 h	29% (SM was remained)
3	$Pd(OH)_2/C$ (5mol%)	AcOH (1 eq.)	10 h	>95%

上記反応条件により得られるアミノアルコール酢酸塩体は系中にて塩酸を作用させることで目的とするアミノアルコール塩酸塩体 **11** を収率良く得た（Scheme 17）。アミノアルコール塩酸塩体 **11** を Boc 体 **10** へと変換し、単結晶 XRD 解析により得られた化合物は望む絶対立体配置を有することを確認した（Figure 14）。また Boc 体 **10** の ee を確認することにより、ニトロ基還元の際に光学純度が低下していないことを確認した。主要原料費に基づき算出した鍵中間体 **11** の製造変動費概算を比較した結果、従来法は約 42 万円/kg に対し、今回報告した方法は約 29 万円/kg となり高い TON に起因したコスト面の優位性が示された [28]。

以上、Nd/Na 異種 2 核金属触媒を用いたフロー反応は高い立体選択性および TON を示し、本反応を活用することで医薬品候補化合物鍵中間体を効率よく合成できることを示した。



Scheme 17. Reduction of nitroaldol product to key intermediate **11**

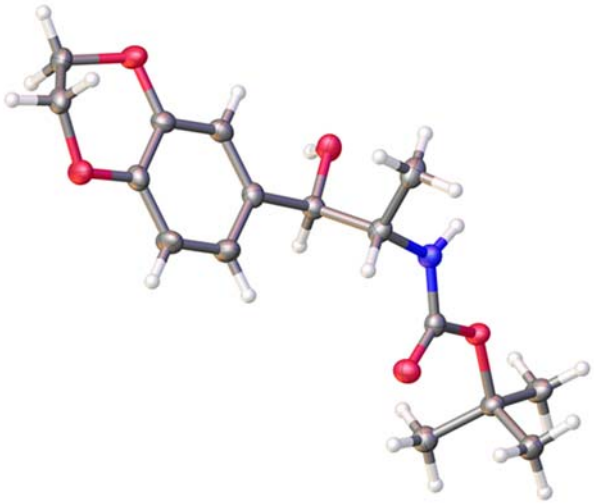


Figure 14. Absolute configuration of Boc **10** by X-ray analysis

結論

第 1 章では安価、入手容易かつ空気中で取り扱い可能な $NdCl_3 \cdot 6H_2O$ および安価で汎用性の高い NaO^tBu を用いる Nd/Na 異種 2 核金属触媒の新規調製法を開発した。原型の触媒調製法で用いられる $NdO_{1/5}(O^iPr)_{13/5}$ は高価かつ大量入手困難であり，不活性ガス雰囲気下での取り扱いを必要としたが、新たに開発した触媒調製法は価格・入手性・安定性のすべての課題を解消し、Nd 塩・Na 塩の調達コストは約 1/120 に圧縮された。また各種分析結果より本触媒は原型の触媒と同様の微細構造を有していることが示唆され、幅広い基質における *anti* 選択的不斉ニトロアルドール反応においても、原型の触媒を用いた場合と同程度の優れた収率および立体選択性が発現することを確認した。今回開発した触媒調製法は実用性および利便性を飛躍的に向上させ、特に大規模な反応スケールではそのメリットを享受できることから商用製造での活用が期待される。

第 2 章では第 1 章で開発した触媒調製法より得られた Nd/Na 異種 2 核金属触媒の触媒能を探求し、フロー反応を活用した医薬品候補化合物 AZD7594 の鍵中間体の合成を果たした。フロー反応、特に不均一系触媒を用いたフロー反応は利点が多く産業界からも注目を集めるが、炭素–炭素結合反応による触媒的不斉反応例は未だ乏しく、多くは TON の乏しさが課題として挙げられる。私は先述した方法から調製された Nd/Na 異種 2 核金属触媒を MWNT に固定化し、フロー反応条件を精査した結果、所望の *anti* 選択的不斉ニトロアルドール反応は不均一系触媒フロー反応系において TON が 1600 を超える程の高効率な触媒反応を実現した。ニトロアルドール成績体は容易にアミノアルコールへの変換することで AZD7594 鍵中間へと導くことが可能であり、合成経路の短縮化および経済的観点から、本フロー反応系の実践的有用性を実証した。生産性に改善の余地があるが、不均一系触媒の担持方法改良による反応効率の向上等を通じて生産性の改善を図ることができれば実用性が高まる。本研究がグリーンケミストリーの要求の高まりを背景に今後一層の発展が予想される不均一系触媒フロー反応の研究の一助となれば幸いである。

実験項

1. General

Unless otherwise noted, all reactions were carried out in an oven-dried glassware fitted with a 3-way glass stopcock under an argon atmosphere with magnetically stirred chips. All work-up and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Thin layer chromatography (TLC) was performed on Merck TLC plates (0.25 mm) pre-coated with silica gel 60 F254 and visualized by UV quenching and staining with bromocresol green for carboxylic acids, ninhydrin for amines, and $KMnO_4$, anisaldehyde or ceric ammonium molybdate solution for other compounds. Flash column chromatography was performed on a Teledyne CombiFlash Rf 200 or a Biotage Isolera Spektra One.

2. Instrumentation

Infrared (IR) spectra were recorded on a HORIBA FT210 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL ECS-400, a Bruker AVANCE III HD400 or a Bruker AVANCE III 500. Chemical shifts (δ) are given in ppm relative to residual solvent peaks. Data for ^1H NMR are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet), q (quartet), m (multiplet), br (broad). For ^{19}F NMR, chemical shifts were reported in the scale relative to $PhCF_3$ (δ –62.7680 ppm in $CDCl_3$) as an external reference. High performance liquid chromatography (HPLC) analysis was performed on Jasco analytical instruments with dual pumps, mixer and degasser, a variable wavelength UV detector, and an auto-sampler. The eluent was monitored simultaneously at 210 nm, 254 nm, 280 nm and 301 nm. Optical rotation was measured using a 1 mL cell with a 1.0 dm path length on a JASCO polarimeter P-1030. High-resolution mass spectra were measured on a Thermo Fisher Scientific LTQ Orbitrap XL.

3. Materials

Aldehydes were purchased from commercial suppliers (Sigma-Aldrich, TCI) and were used after usual purification procedure. Nd salts were purchased from Sigma-Alrdich ($Nd(HMDS)_3$, $Nd(OH)_3$, $Nd(OAc)_3 \cdot H_2O$, $Nd(NO_3)_3 \cdot 6H_2O$, NdF_3, $NdBr_3$), Wako Pure Chemical Co. Ltd. ($NdCl_3$, $NdCl_3 \cdot 6H_2O$). $NdO_{1/5}(O^iPr)_{13/5}$ was purchased from Kojundo Chemical Co. Ltd. (http://www.kojundo.co.jp/English/index.html, Fax: +81-49-284-1351, e-mail: sales kojundo.co.jp.) and the powder was handled in a dry box under Ar atmosphere.

2-Me-THF was purchased from TCI Co. Ltd. THF, Et_2O, DME, CPME and toluene were passed through a solvent purification system (Glass Contour). Flash column chromatography was performed using Biotage systems with Redisep column. Amide-based ligand **1a** was prepared by following the reported procedure. Nitroethane was purchased from TCI Co. Ltd. and used after pretreatment [nitroethane was distilled and subsequently suspended with dried MS3Å pellets (ca. 4 g MS3Å/20 mL nitroethane, pre-dried by microwave oven and subsequent vacuum drying [0.9 kPa, 30 min], 4 cycles) and powdered $NaHCO_3$ at room temperature for 1 h. Filtration through a syringe filter (0.2 μm) gave dried and acid-free nitroethane]. Multi-walled carbon nanotubes (Baytubes® C 70P, C-purity ≥95 wt%) were purchased from Bayer MaterialScience. YMC stainless steel empty columns (φ 10 x 30 mm) were used to prepare precolumns ($NaHCO_3$, MS3Å) and an empty column (φ 4.6 x 100 mm) was used for a catalyst column with stainless steel frits (2 μm). Substrates were transferred by 100 mL gastight syringes with Harvard syringe pump PHP-ULTRA 4400. YMC Deneb mixer (stainless steel, 30 x 30 x 1.8 mm, mixing volume 32 μL) was used to mix the each stream of aldehyde and nitroethane. These units were concatenated by stainless steel tubing (inner diameter: 0.5 mm, outer diameter 1/16 inch) and stainless steel ferrules.

4. General Procedure (Chapter 1)

4-1. Screening of Nd salts (Table 2, entry 2, 3).

To a flame dried test tube (20 mL) equipped with a magnetic stirring bar and 3-way glass stopcock was charged with Nd salts (0.012 mmol, 7.5 mg for $Nd(HMDS)_3$; 2.3 mg for $Nd(OH)_3$) and the salts were dried under vacuum at room temperature. Ar was backfilled (evacuation/backfill was repeated for several times) to the test tube, and THF (200 μL) and ligand **1a** (200 μL, 0.6 M/THF, 0.012 mmol) were added successively by well-dried syringes and needles at room temperature. After stirring the resulting solution at the same temperature for 10 min ($Nd(HMDS)_3$: solution, $Nd(OH)_3$: white suspension), NaHMDS (24 μL, 0.024 mmol, 1.0 M/THF) was added dropwise at room temperature. After stirring the resulting mixture for 1 h ($Nd(HMDS)_3$: white suspension, $Nd(OH)_3$: white suspension), nitroethane (**3a**) (86 μL, 1.2 mmol) was added ($Nd(HMDS)_3$: cloudy solution, $Nd(OH)_3$: white suspension). For $Nd(HMDS)_3$, self-assembly of the Nd/Na catalyst initiated in a few minutes after addition of nitroethane (**3a**) to give white suspension. After stirring the resulting suspension at room temperature for 2 h, the whole suspension was transferred to an Eppendorf tube with THF (1.2 mL) and the tube was centrifuged at ca. 10^4 rpm for 30 sec. The supernatant was decanted and dry THF (1.2 mL) was added to the precipitate. The tube was agitated using a vortex mixer for 30 sec and the resulting tube was centrifuged again, then the supernatant was decanted (washing process). The resulting precipitate was agitated

with dry THF (1.6 mL) and the resulting suspension was transferred to a flame-dried 20 mL test tube. After adding nitroethane (**3a**) (286 μL, 4.0 mmol), the mixture was cooled to –40 °C and benzaldehyde (**2a**) (41 μL, 0.4 mmol) was added dropwise. After stirring the reaction mixture at the same temperature for 20 h, 2 M AcOH/THF was added and the resulting mixture was extracted with EtOAc (x2). The combined organic layers were washed with sat. aq. $NaHCO_3$, H_2O, and brine, and dried over Na_2SO_4. After removal of volatiles under reduced pressure, the resulting residue was analyzed by ^1H NMR to determine chemical yield (DMF (8.03 ppm) was used as an internal standard) and diastereomeric ratio of product 4a. Enantiomeric excess was determined by HPLC analysis [DAICEL CHIRALPAK IC (φ 0.46 cm x 25 cm), 2-propanol/*n*-hexane 1/20, flow rate 1.0 mL/min, detection at 254 nm, tR 11.3 min (*anti* major-enantiomer: (1*R*,2*S*)) and 14.4 min (*anti* minor-enantiomer: (1*S*,2*R*))].

4-2. Screening of Nd salts (Table 3, entry 4−9).

To a flame dried test tube (20 mL) equipped with a magnetic stirring bar and 3-way glass stopcock was charged with Nd salts (0.012 mmol), and dried under vacuum at room temperature. Ar was backfilled (evacuation/backfill was repeated for several times) to the test tube, and THF (200 μL) and NaHMDS (36 μL, 0.036 mmol, 1.0 M/THF) were successively added at room temperature. After stirring the resulting solution at 60 °C for 12 h, ligand **1a** (200 μL, 0.6 M/THF, 0.012 mmol) was added dropwise (sparingly cloudy solution was formed for $NdCl_3$, white suspension was formed for $Nd(NO_3)_3$▪$6H_2O$, grinded $NdCl_3$▪$6H_2O$, $Nd(OAc)_3$▪H_2O, NdF_3, $NdBr_3$). Additional NaHMDS (24 μL, 0.024 mmol, 1.0 M/THF) was subsequently added at room temperature. After stirring the resulting mixture at room temperature for 1 h, nitroethane (**3a**) (86 μL, 1.2 mmol) was added and the resulting mixture was stirred for 6 h at the same temperature. The whole suspension was transferred to an Eppendorf tube and the tube was centrifuged at ca. 10^4 rpm for 30 sec. The supernatant was decanted and dry THF (1.2 mL) was added to the precipitate. The tube was agitated using a vortex mixer for 30 sec and the resulting tube was centrifuged again, then the supernatant was decanted (washing process). The resulting precipitate was agitated with dry THF (1.6 mL) and the resulting suspension was transferred to a flame-dried 20 mL test tube. After adding nitroethane (**3a**) (286 μL, 4.0 mmol), the mixture was cooled to –40 °C and benzaldehyde (**2a**) (41 μL, 0.4 mmol) was added dropwise. After stirring the reaction at the same temperature for 20 h, 0.2 M AcOH/THF was added and the resulting mixture was extracted with EtOAc (x2). The combined organic layers were washed with sat. aq. $NaHCO_3$, H_2O, and brine, and dried over Na_2SO_4. After removal of volatiles under reduced pressure, the resulting residue was analyzed by ^1H NMR to determine chemical yield (DMF (8.03 ppm) was used as an internal standard) and diastereomeric ratio of product **4a**. Enantiomeric

excess was determined by HPLC analysis [DAICEL CHIRALPAK IC (φ 0.46 cm x 25 cm), 2-propanol/*n*-hexane 1/20, flow rate 1.0 mL/min, detection at 254 nm, tR 11.3 min (*anti* major-enantiomer: (1*R*,2*S*)) and 14.4 min (*anti* minor-enantiomer: (1*S*,2*R*))].

4-3. Optimized procedure using $NdCl_3$▪$6H_2O$/NaO^tBu (Table 6, entry 1).

To a flame dried test tube (20 mL) equipped with a magnetic stirring bar and 3-way glass stopcock was charged with $NdCl_3$▪$6H_2O$ (4.3 mg, 0.012 mmol), and dried under vacuum at room temperature. Ar was backfilled (evacuation/backfill was repeated for several times) to the test tube, and THF (100 μL) and ligand **1a** (200 μL, 0.012 mmol, 0.6 M/THF were added successively by well-dried syringes and needles at room temperature. After stirring the resulting slightly cloudy solution at 60 °C for 30 min, NaO^tBu (36 μL, 0.072 mmol, 2.0 M/THF) was added dropwise at the same temperature. After stirring the resulting mixture at 60 °C for 1 h (white precipitate appeared), the mixture was cooled to room temperature and nitroethane (**3a**) (86 μL, 1.2 mmol) was added (the precipitate was partly dissolved). Self-assembly of Nd/Na catalyst initaiated in a few minutes and the resulting mixture was stirred at room temperature for 12 h to give a thick white suspension. The whole suspension was transferred to an Eppendorf tube and the tube was centrifuged at ca. 10^4 rpm for 30 sec. The supernatant was decanted and dry THF (1.2 mL) was added to the precipitate. The tube was agitated using a vortex mixer for 30 sec and the resulting tube was centrifuged again, then the supernatant was decanted (washing process). The resulting precipitate was agitated with dry THF (1.6 mL) and the resulting suspension was transferred to a flame-dried 20 mL test tube. After adding nitroethane (**3a**) (286 μL, 4.0 mmol), the mixture was cooled to –40 °C and benzaldehyde (**2a**) (41 μL, 0.4 mmol) was added dropwise. After stirring the reaction mixture at the same temperature for 20 h, 0.2 M AcOH/THF was added and the resulting mixture was extracted with EtOAc (x2). The combined organic layers were washed with sat. aq. $NaHCO_3$, H_2O, and brine, and dried over Na_2SO_4. After removal of volatiles under reduced pressure, the resulting residue was analyzed by ^1H NMR to determine diastereomeric ratio of product **4a** (*anti*/*syn* = >20/1). The crude product was purified by silica gel column chromatography (neutral SiO_2 (Kanto Chemical 60N; spherical, 50 − 60 μm), eluent: *n*-hexane/ethyl acetate 8/1) to give **4a** (70 mg, 0.38 mmol, 96%). Enantiomeric excess was determined by HPLC analysis [93% ee, DAICEL CHIRALPAK IC (φ 0.46 cm x 25 cm), 2-propanol/*n*-hexane 1/20, flow rate 1.0 mL/min, detection at 254 nm, tR 11.3 min (*anti* major-enantiomer: (1*R*,2*S*)) and 14.4 min (*anti* minor-enantiomer: (1*S*,2*R*)]. Other runs in Table 6 were operated in a similar manner. DME was used as reaction solvents (after preparation of 6 mol% of the catalyst in THF) in Table 6, entry 8−10.

4-4. Procedure for the preparation of MWNT-confined catalyst from $NdCl_3 \cdot 6H_2O$/NaO^tBu (Table 3, entry 10)

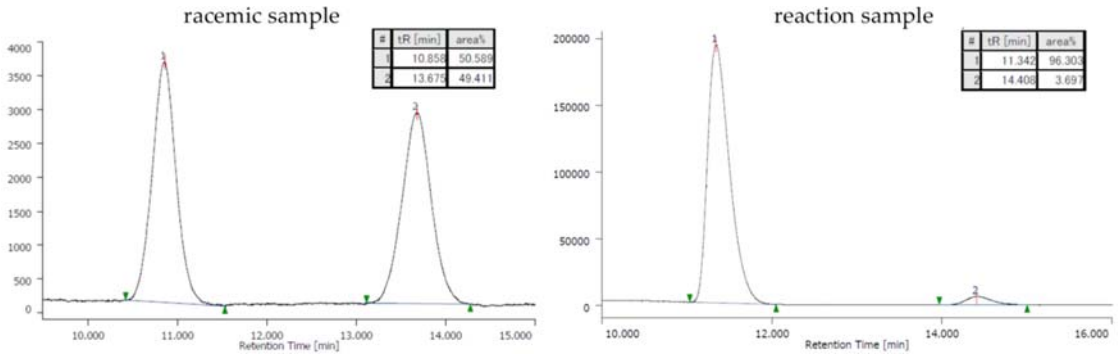
To a flame dried test tube (20 mL) equipped with a magnetic stirring bar and 3-way glass stopcock was charged with grinded $NdCl_3 \cdot 6H_2O$ (4.3 mg, 0.012 mmol), and dried under vacuum at room temperature. Ar was backfilled (evacuation/backfill was repeated for several times) to the test tube, and THF (100 μL) and ligand **1a** (200 μL, 0.012 mmol, 0.6 M/THF were added successively by well-dried syringes and needles at room temperature. After stirring the resulting cloudy solution at 60 °C for 30 min, NaO^tBu (36 μL, 0.072 mmol, 2.0 M/THF) was added dropwise at the same temperature. After stirring the resulting mixture at 60 °C for 1 h (white precipitate appeared), the mixture was cooled to room temperature, and MWNT (Baytubes® C 70P, 18 mg, 400 wt% to ligand **1a**) and nitroethane (**3a**) (86 μL, 1.2 mmol) were successively added to initiate self-assembly of the catalyst in the fibrous matrix of MWNT. After stirring at room temperature for 12 h, the black suspension (MWNT-confined catalyst), which contained small amount of insoluble white solid (likely coproduced NaCl), was transferred to an Eppendorf tube and the tube was centrifuged at ca. 10^4 rpm for 30 sec. The supernatant was decanted and dry THF (1.2 mL) was added to the precipitate. The tube was agitated using a vortex mixer for 30 sec and the resulting tube was centrifuged again, then the supernatant was decanted (washing process). The resulting precipitate was agitated with dry THF (1.6 mL) and the resulting suspension was transferred to a flame-dried 20 mL test tube. After adding nitroethane (**3a**) (286 μL, 4.0 mmol), the mixture was cooled to –40 °C and benzaldehyde (**2a**) (41 μL, 0.4 mmol) was added dropwise. After stirring the reaction mixture at the same temperature for 20 h, 0.2 M AcOH/THF and EtOAc was added and the resulting mixture filtered through a syringe filter (0.2 μm), and the resulting mixture was extracted with EtOAc (x2). The combined organic layers were washed with sat. aq. $NaHCO_3$, H_2O, and brine, and dried over Na_2SO_4. After removal of volatiles under reduced pressure, the resulting residue was analyzed by ^1H NMR to determine determine chemical yield (97%, DMF (8.03 ppm) was used as an internal standard) and diastereomeric ratio of product **4a** (*anti*/*syn* = >20/1). Enantiomeric excess was determined by HPLC analysis [93% ee, DAICEL CHIRALPAK IC (φ 0.46 cm x 25 cm), 2-propanol/*n*-hexane 1/20, flow rate 1.0 mL/min, detection at 254 nm, tR 11.3 min (*anti* major-enantiomer: (1*R*,2*S*)) and 14.4 min (*anti* minor-enantiomer: (1*S*,2*R*))].

5. Reaction with Various Aldehydes (Table 6)

All the products were reported compounds in ref 12b (in ESI or in the maintext). Spectroscopic data of these compounds matched to the reported ones. Improved HPLC conditions and HPLC traces were listed below.

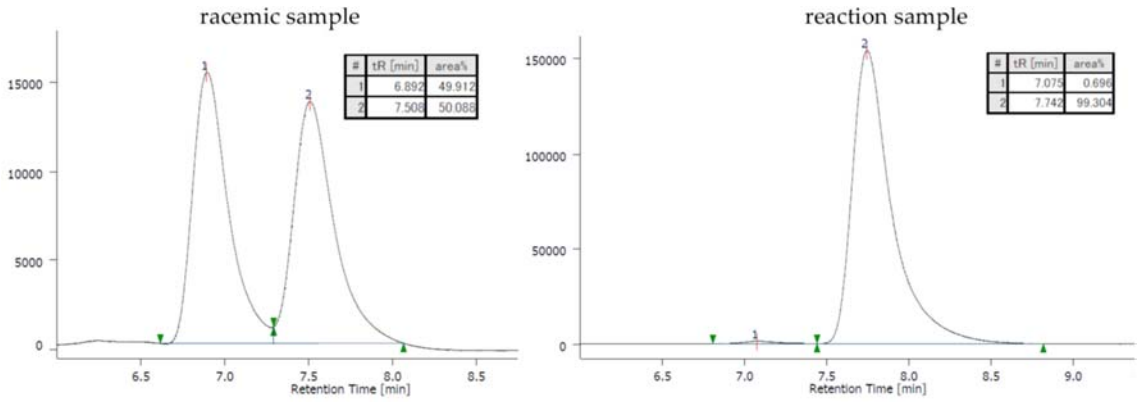
(1*R*,2*S*)-2-Nitro-1-phenylpropan-1-ol (4a)

93% ee; HPLC [DAICEL CHIRALPAK IC (φ 0.46 cm x 25 cm), 2-propanol/*n*-hexane 1/20, flow rate 1.0 mL/min, detection at 254 nm, tR 11.3 min (*anti* major-enantiomer: (1*R*,2*S*)) and 14.4 min (*anti* minor-enantiomer: (1*S*,2*R*))].



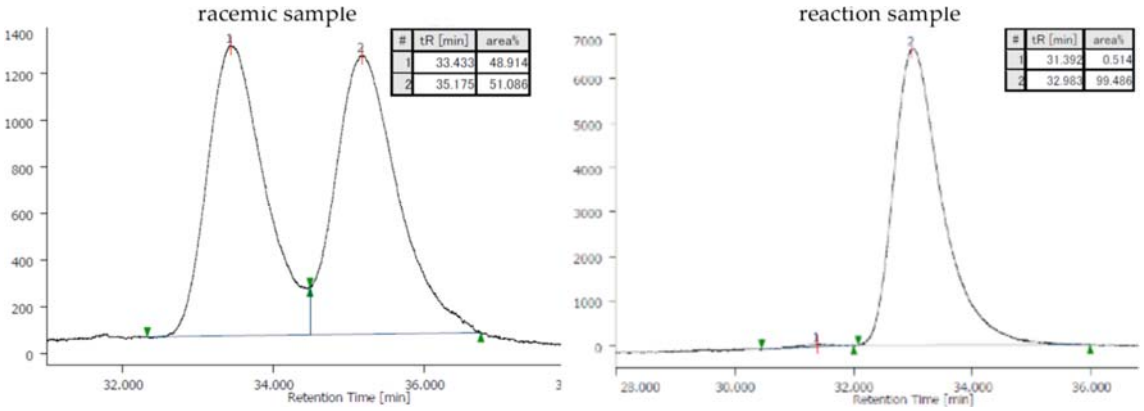
(1*R*,2*S*)-1-(2,4-Dimethylphenyl)-2-nitropropan-1-ol (4b)

99% ee sample; HPLC [DAICEL CHIRALPAK AD-H (φ 0.46 cm x 25 cm), 2-propanol/*n*-hexane 1/9, flow rate 1.0 mL/min, detection at 254 nm, tR 7.1 min (*anti* minor-enantiomer: (1*S*,2*R*)) and 7.7 min (*anti* major-enantiomer: (1*R*,2*S*))].



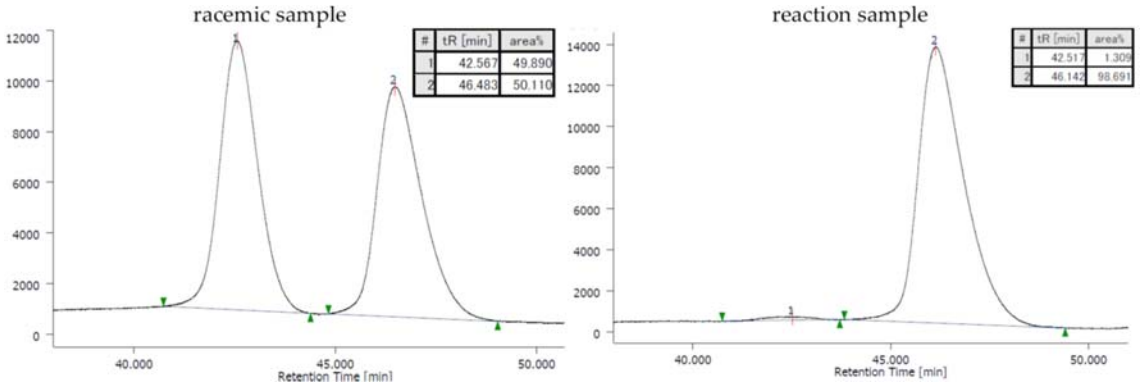
(1*R*,2*S*)-1-(4-(Benzyloxy)phenyl)-2-nitropropan-1-ol (4c)

99% ee sample; HPLC [DAICEL CHIRALPAK AD-H (φ 0.46 cm x 25 cm x 2), 2-propanol/*n*-hexane 1/9, flow rate 1.0 mL/min, detection at 254 nm, tR 31.4 min (*anti* minor-enantiomer: (1*S*,2*R*)) and 33.0 min (*anti* major-enantiomer: (1*R*,2*S*))].



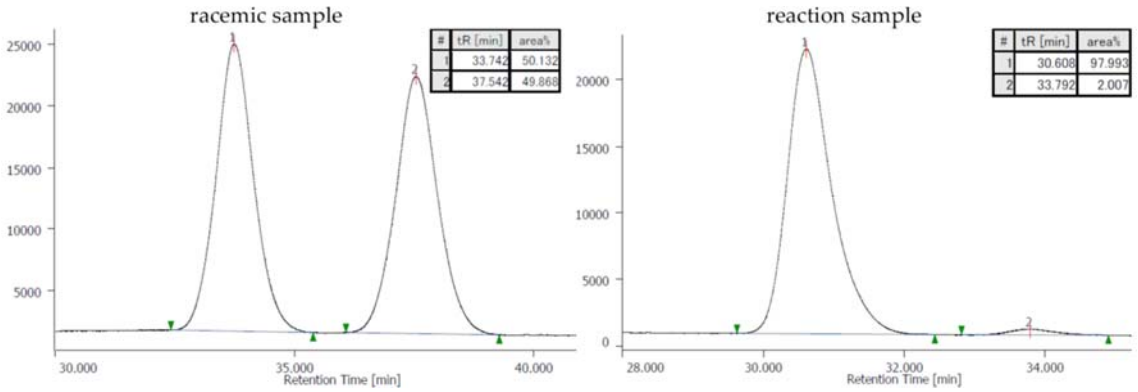
4-((1*R*,2*S*)-1-Hydroxy-2-nitropropyl)benzonitrile (4d)

97% ee sample; HPLC [DAICEL CHIRALPAK IF (φ 0.46 cm x 25 cm), 2-propanol/*n*-hexane 1/20, rate 1.0 mL/min, detection at 254 nm, tR 42.5 min (*anti* minor-enantiomer: (1*S*,2*R*)) and 46.1 min (*anti* major-enantiomer: (1*R*,2*S*))].



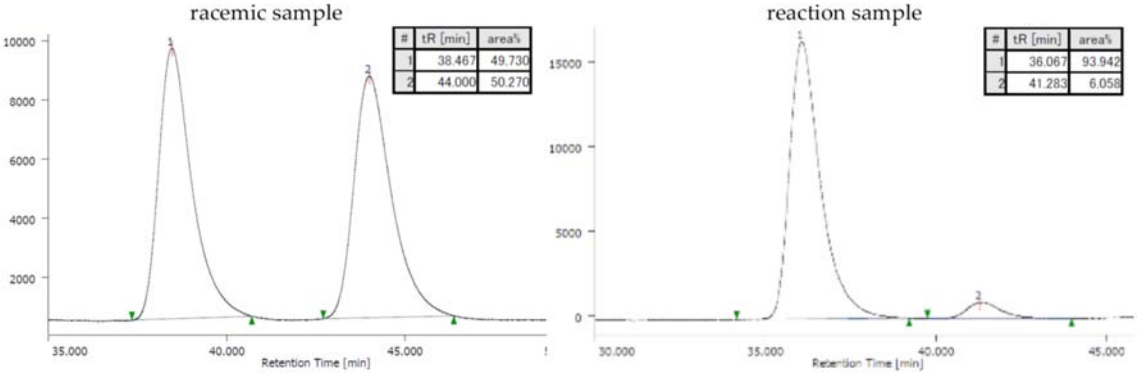
Methyl 4-((1*R*,2*S*)-1-hydroxy-2-nitropropyl)benzoate (4e)

96% ee sample; HPLC [DAICEL CHIRALPAK IC (φ 0.46 cm x 25 cm), 2-propanol/*n*-hexane 1/9, flow rate 0.5 mL/min, detection at 254 nm, tR 30.6 min (*anti* major-enantiomer: (1*R*,2*S*)) and 33.8 min (*anti* minor-enantiomer: (1*S*,2*R*))].



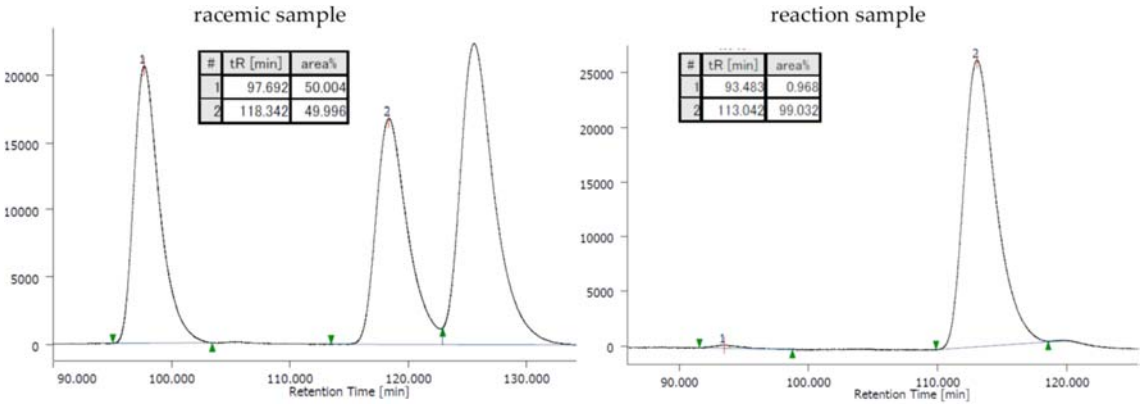
(1*R*,2*S*)-2-Nitro-1-(4-nitrophenyl) propan-1-ol (4f)

88% ee sample; HPLC [DAICEL CHIRALPAK AD-H (φ 0.46 cm x 25 cm), CHIRALCEL OD-H (φ 0.46 cm x 25 cm), 2-propanol/*n*-hexane 1/9, flow rate 1.0 mL/min, detection at 254 nm, tR 36.1 min (*anti* major-enantiomer: (1*R*,2*S*)) and 41.3 min (*anti* minor-enantiomer: (1*S*,2*R*))].



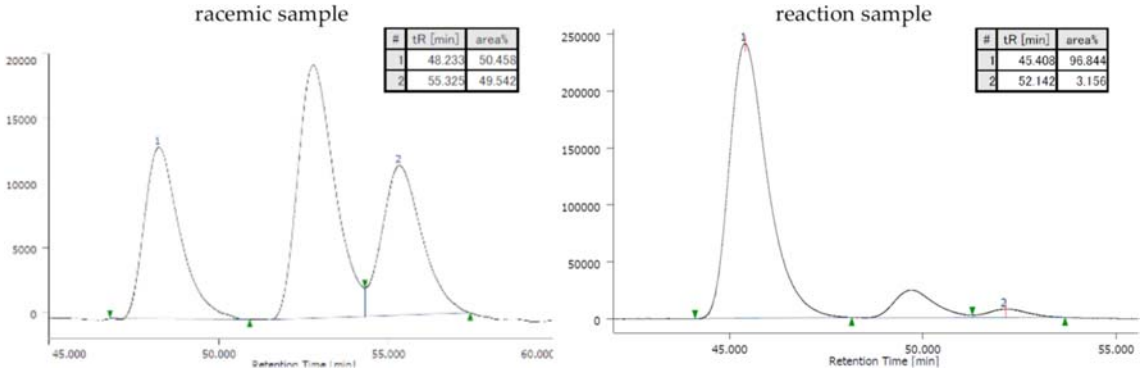
(3R,4S,E)-4-Nitro-1-phenylpent-1-en-3-ol (4g)

98% ee sample; HPLC [DAICEL CHIRALPAK AD-H (φ 0.46 cm x 25 cm x2), 2-propanol/*n*-hexane 1/9, flow rate 0.5 mL/min, detection at 254 nm, tR 93.5 min (*anti* minor-enantiomer: (1*S*,2*R*)) and 113.0 min (*anti* major-enantiomer: (1*R*,2*S*))].



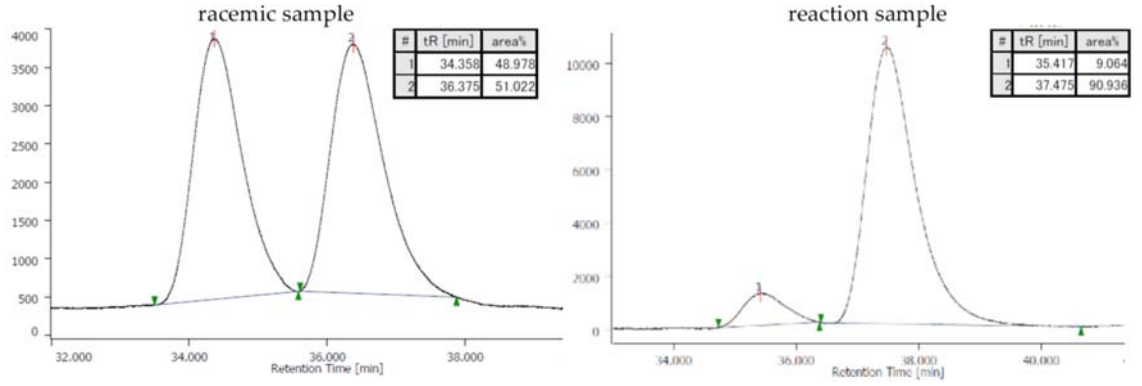
(1*R*,2*S*)-1-Cyclohexyl-2-nitropropan-1-ol (4h)

94% ee sample; HPLC [DAICEL CHIRALPAK AD-H (φ 0.46 cm x 25 cm x2), 2-propanol/*n*-hexane 1/20, flow rate 0.5 mL/min, detection at 210 nm, tR 45.4 min (*anti* major-enantiomer: (1*R*,2*S*)) and 52.1 min (*anti* minor-enantiomer: (1*S*,2*R*))].



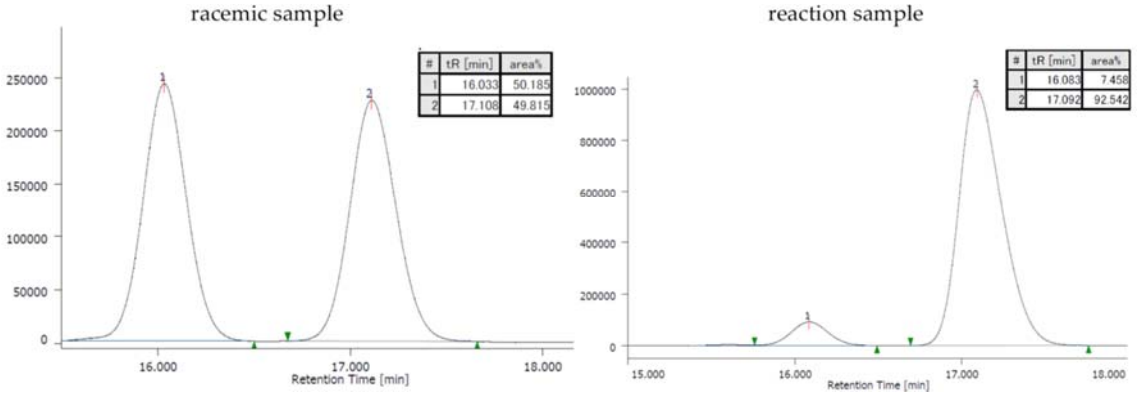
(3*R*,4*S*)-4-Nitro-1-phenylpentan-3-ol (4i)

82% ee sample; HPLC [DAICEL CHIRALPAK AD-H (φ 0.46 cm x 25 cm x2), 2-propanol/*n*-hexane 1/9, flow rate 0.5 mL/min, detection at 254 nm, tR 35.4 min (*anti* minor-enantiomer: (1*S*,2*R*)) and 37.5 min (*anti* major-enantiomer: (1*R*,2*S*))].



(2*S*,3*R*)-2-Nitroundecan-3-ol (4j)

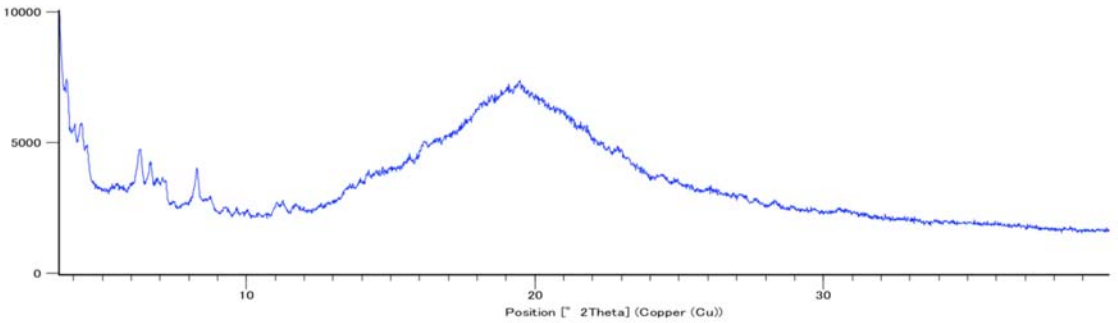
85% ee sample; HPLC [DAICEL CHIRALPAK ID (φ 0.46 cm x 25 cm x2), 2-propanol/*n*-hexane 1/20, flow rate 0.5 mL/min, detection at 210 nm, tR 16.1 min (*anti* minor-enantiomer: (1*S*,2*R*)) and 17.1 min (*anti* major-enantiomer: (1*R*,2*S*))].



6. Powder-XRD and STEM Analysis of the Catalyst

Powder XRD spectra of the Nd/Na heterobimetallic catalyst is shown in Figure 4 and Figure S1. The original catalyst ($NdO_{1/5}(O^iPr)_{13/5}$/NaHMDS) was prepared as described in the literature 17b. The new catalyst ($NdCl_3 \cdot 6H_2O$/NaO^tBu) was prepared as described above. Similar spectral pattern suggested that nearly identical heterobimetallic assembly was formed, which is in line with the similar catalytic performance of them in terms of both catalytic efficiency and stereoselectivity. A striking difference, an intence peak appeared in the spectrum of new catalyst at 2θ = 31.6978 °, was assained as a peak derived from NaCl, which was coproduced in the self-assembly of $NdCl_3 \cdot 6H_2O$/NaO^tBu/ligand **1a**. Peak at 2θ = 28.3086 ° can be also assigned to NaCl. A specimen for STEM, MWNT-confined catalyst, was prepared by following the procedure as described above. Stem images and EDS mapping analysis were shown in Figure 5. Na was not detectable because the energy of Na(Kα) is close to that of Nd(Mα). EELS image was shown in Figure 5.

(a) Nd/Na heterobimetallic catalyst prepared by the original protocol ($NdO_{1/5}(O^iPr)_{13/5}$/NaHMDS)



(b) Nd/Na heterobimetallic catalyst prepared by the new protocol ($NdCl_3$·$6H_2O$/NaO^tBu)

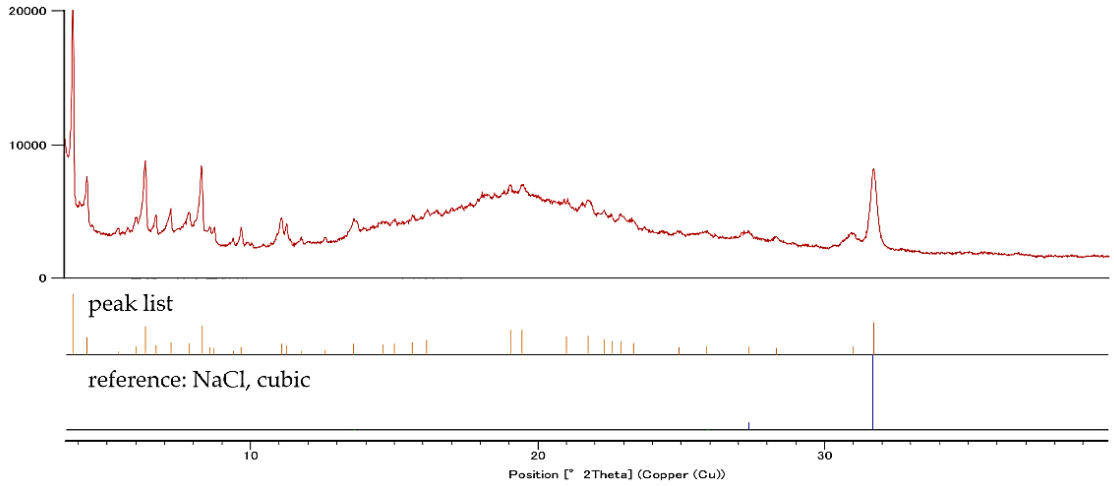


Figure S1. XRD analysis of the catalyst of (a) the original catalyst; (b) new catalyst

7. General Procedure (Chapter 2)

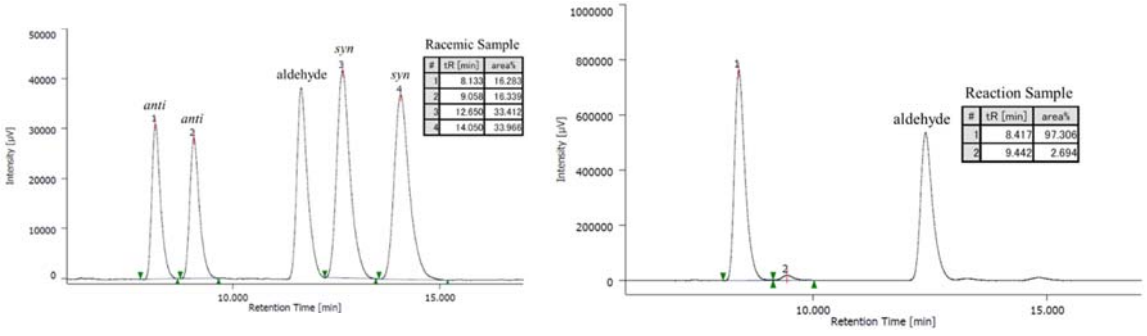
Screening of ligands and solvents

To a flame dried test tube (20 mL) equipped with a magnetic stirring bar and 3-way glass stopcock was charged with $NdCl_3$·$6H_2O$ (4.3 mg, 0.012 mmol), and dried under vacuum at room temperature. Ar was backfilled (evacuation/backfill was repeated for several times) to the test tube, and THF (100 μL) and ligand **1a** (200 μL, 0.012 mmol, 0.06 M/THF were added successively by well-dried syringes and needles at room temperature. After stirring the resulting slightly cloudy solution at 60 °C for 30 min, NaO^tBu (36 μL, 0.072 mmol, 2.0 M/THF) was added dropwise at the same temperature. After stirring the resulting mixture at 60 °C for 1 h (white precipitate appeared), the mixture was cooled to room temperature and nitroethane (**3a**) (86 μL, 1.2 mmol) was added (the precipitate was partly dissolved). Self-assembly of Nd/Na catalyst initiated and the resulting mixture was stirred at room temperature for 12 h to give a thick white suspension. The whole suspension was transferred to an Eppendorf tube and the tube was centrifuged at ca. 10^4 rpm for 30 sec. The supernatant

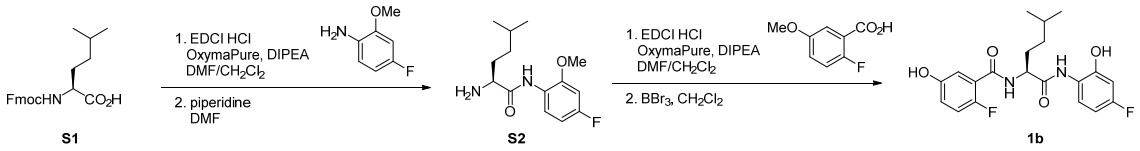
was decanted and dry 2-Me-THF or appropriate solvent (1.2 mL) was added to the precipitate. The tube was agitated using a vortex mixer for 30 sec and the resulting tube was centrifuged again, then the supernatant was decanted (washing process). The resulting precipitate was agitated with dry 2-Me-THF or appropriate solvent (1.0 mL) and the resulting suspension was transferred to a flame-dried 20 mL test tube. After adding nitroethane (**3a**) (286 μL, 4.0 mmol), the mixture was cooled to –40 °C and 3, 4-ethylenedioxybenzaldehyde (**5**) (65.7 mg, 0.4 mmol) was added. After stirring the reaction mixture at the same temperature for 20 h, 0.2 M AcOH/THF (300 μL) was added and the resulting mixture was extracted with EtOAc (x2). The combined organic layers were washed with sat. aq. $NaHCO_3$, H_2O, and brine, and dried over Na_2SO_4. After removal of volatiles under reduced pressure, the resulting residue was analyzed by ^1H NMR to determine chemical yield (DMF (8.03 ppm) was used as an internal standard) and diastereomeric ratio of product **6**. Enantiomeric excess was determined by HPLC analysis.

(1*R*,2*S*)-1-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-nitropropan-1-ol (6)

Colorless oil; $[\alpha]_D^{26}$ 2.5 (c 0.61, CHCl3 95% ee sample); ^1H NMR (400 MHz, $CDCl_3$) d 6.89−6.80 (m, 3H), 5.24 (d, *J* = 3.9 Hz, 1H), 4.64 (qd, *J* = 6.6, 3.9 Hz, 1H), 4.24 (s, 4H), 2.64 (brs, 1H), 1.50 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) d 143.7 (2C), 131.7, 118.9, 117.5, 115.0, 87.4, 73.5, 64.3 (2C), 12.3; IR (neat) *ν* 3019, 1550, 1508, 1288, 1216, 756, 669 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{13}NO_5Na$ m/z 262.0686 $[M+Na]^+$, found 262.0686; HPLC analysis [DAICEL CHIRALPAK IC (φ 0.46 cm x 25 cm), 2-propanol/*n*-hexane 1/4, flow rate 1.0 mL/min, detection at 230 nm, tR 8.4 min (*anti* major-enantiomer: (1*R*,2*S*)) and 9.4 min (*anti* minor-enantiomer: (1*S*,2*R*))]. Small amount of aldehyde **5** was detected due to retro-nitroaldol reaction during PTLC purification of the reaction sample.



8. Preparation and Chracterization of New Amide Ligands 1b-1m



(*S*)-2-Amino-*N*-(4-fluoro-2-methoxyphenyl)-5-methylhexanamide (S2)

To a solution of EDCI·HCl (573.2 mg, 2.99 mmol) in DMF (7 mL) and CH_2Cl_2 (7 mL) were successively added OxymaPure® (425.0 mg, 2.99 mmol) and **S1** (1.00 g, 2.72 mmol) at room temperature. After stirring the reaction mixture for 5 min, 4-fluoro-2-methoxyaniline (470.6 mg, 2.99 mmol) dissolved in DMF (1 mL) and DIPEA (590 μL, 4.08 mmol) were added, the reaction mixture was stirred at the same temperature for 11 h. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and 1 N HCl aq. was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with aqueous saturated $NaHCO_3$ twice, H_2O, brine and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and dried in vacuo to give crude amide as brown solid. To the amide in DMF (9 mL) was added piperidine (240 μL, 4.08 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate and H_2O was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with H_2O, brine, dried over Na_2SO_4. Filtrate was concentrated and the resulting residue was purified by silica gel chromatography (ethyl acetate/*n*-hexane = 12/88 to 100/0) to give **S2** (464.9 mg, 1.73 mmol, 64% over 2 steps) as a pale brown oil.

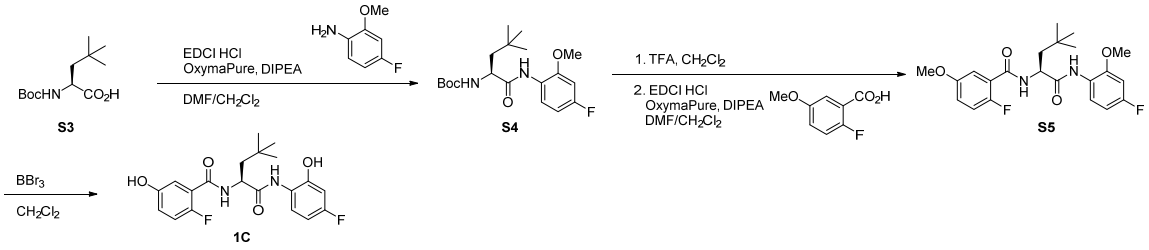
Pale brown oil; $[\alpha]_D^{27}$ −6.1 (*c* 0.44, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (dd, *J* = 8.8 , 6.2 Hz, 1H), 6.84 (dd, *J* = 10.5, 2.7 Hz, 1H), 6.66 (ddd, *J* = 8.8, 8.6, 2.7 Hz, 1H), 3.89 (s, 3H), 3.46 (dd, *J* = 7.3, 5.6 Hz, 1H), 1.86−1.77 (m, 1H), 1.66−1.53 (m, 2H), 1.35−1.29 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 176.3, 161.4 (d, *J* = 240.6 Hz), 152.7 (d, *J* = 10.2 Hz), 124.3 (d, *J* = 3.6 Hz), 123.4 (d, *J* = 9.5 Hz), 107.1 (d, *J* = 21.9 Hz), 100.2 (d, *J* = 27.0 Hz), 56.9, 56.6, 35.8, 34.2, 29.2, 23.0, 22.9; ^{19}F NMR (376 MHz, CD_3OD) δ –117.4; IR (neat) *ν* 3019, 2959, 1673, 1611, 1531, 1465, 1415, 1216, 757, 669 cm^{-1}; HRMS (ESI) calcd. for $C_{14}H_{22}N_2O_2F$ *m*/*z* 269.1660 $[M+H]^+$, found 269.1651.

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

To a solution of EDCI·HCl (264.5 mg, 1.38 mmol) in DMF (3.5 mL) and CH_2Cl_2 (3.5 mL) were successively added OxymaPure® (196.1 mg, 1.28 mmol) and 2-fluoro-5-methoxybenzoic acid (234.9 mg, 1.38 mmol) at room temperature. After the mixture was stirred for 5 min, **S2** (370.5 mg, 1.38 mmol) and DIPEA (299 μL, 2.07 mmol) were added, the reaction mixture was stirred for 10 h. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and 1 N HCl aq. was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with aqueous saturated $NaHCO_3$ twice, H_2O, brine and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure, dried in vacuo to give crude diamide as a brown oil. To the diamide in CH_2Cl_2 (6.9 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 6.9 mL, 6.9 mmol) over 5 min at 0 °C. After

stirring for 24 h, the reaction was quenched with *i*-PrOH at the same temperature, and then water was added. The resulting mixture was extracted with $CHCl_3$ twice and the combined organic layers were washed with aqueous saturated $NaHCO_3$, H_2O, brine, and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (acetone/*n*-hexane = 8/92 to 66/34) to give **1b** (275.4 mg, 701.8 μmol, 51% over 2 steps) as a white amorphous.

White amorphous; $[\alpha]_D^{27}$ −5.8 (*c* 0.16, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 7.73 (dd, *J* = 8.8 , 6.2 Hz, 1H), 7.15 (dd, *J* = 5.7, 3.1 Hz, 1H), 7.05 (dd, *J* = 10.4, 8.9 Hz, 1H), 6.92 (ddd, *J* = 8.9, 4.0, 3.1 Hz, 1H), 6.60 (dd, *J* = 10.0, 2.9 Hz, 1H), 6.55 (ddd, *J* = 8.8, 8.4, 2.9 Hz, 1H), 4.69 (dd, *J* = 8.0, 5.5 Hz, 1H), 2.07−1.98 (m, 1H), 1.90−1.80 (m, 1H), 1.67−1.57 (m, 1H), 1.44−1.33 (m, 2H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.6, 166.7 (d, *J* = 2.2 Hz), 161.7 (d, *J* = 240.6 Hz), 155.1 (d, *J* = 1.5 Hz), 155.0 (d, *J* = 238.4 Hz), 151.3 (d, *J* = 10.9 Hz), 124.8 (d, *J* = 10.2 Hz), 123.8 (d, *J* = 15.3 Hz), 123.0 (d, *J* = 2.9 Hz), 120.7 (d, *J* = 8.0 Hz), 117.9 (d, *J* = 24.8 Hz), 117.0 (d, *J* = 1.5 Hz), 106.5 (d, *J* = 22.6 Hz), 103.8 (d, *J* = 25.5 Hz), 56.1, 35.9, 31.1, 29.0, 23.0, 22.8; ^{19}F NMR (376 MHz, CD_3OD) δ –118.1, −128.2; IR (KBr) *ν* 3247, 2962, 1649, 1618, 1538, 1501, 1452, 1317, 1228, 1143 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{22}N_2O_4F_2Na$ *m*/*z* 415.1440 $[M+Na]^+$, found 415.1421.



(*S*)-*tert*-Butyl (1-((4-fluoro-2-methoxyphenyl)amino)-4,4-dimethyl-1-oxopentan-2 yl)carbamate (S4)

To a solution of EDCI·HCl (858.8 mg, 4.48 mmol) in DMF (10 mL) and CH_2Cl_2 (10 mL) were successively added OxymaPure® (637.0 mg, 4.48 mmol) and **S3** (999.3 mg, 4.07 mmol) at room temperature. After stirring the reaction mixture for 5 min, 4-fluoro-2-methoxyaniline (704.2 mg, 4.48 mmol) in DMF (1 mL) and DIPEA (882 μL, 6.11 mmol) were added, and the resulting mixture was stirred for 10 h at the same temperature. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and 1 N HCl aq. was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with aqueous saturated $NaHCO_3$ twice, H_2O, brine and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (ethyl acetate/*n*-hexane = 8/92 to 66/34) to give **S4** (1.41 g, 3.83 mmol, 94%) as a white solid.

White solid; m.p. 120−122 °C; $[\alpha]_D^{25}$ −45.4 (*c* 0.32, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ 8.02 (dd, *J* = 8.8, 6.4 Hz, 1H), 6.84 (dd, *J* = 10.5, 2.7 Hz, 1H), 6.66 (ddd, *J* = 8.8, 8.6, 2.7 Hz, 1H), 4.23 (dd, *J* = 9.3, 4.2 Hz, 1H), 3.89 (s, 3H), 1.88 (dd, *J* = 14.4, 2.3 Hz, 1H), 1.56 (dd, *J* = 14.4, 9.5 Hz, 1H), 1.48 (s, 9H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 159.2 (d, *J* = 241.3 Hz), 156.6,

155.5, 149.2 (d, J = 10.2 Hz), 120.5 (d, J = 9.5 Hz), 106.6 (d, J = 21.1 Hz), 98.7 (d, J = 27.0 Hz), 80.2, 55.9, 53.1, 45.5, 30.4, 29.6 (3C), 28.3 (3C); ^{19}F NMR (376 MHz, CD_3OD) δ –117.3; IR (neat) ν 3019, 2361, 1685, 1510, 1216, 759, 669 cm^{-1}; HRMS (ESI) calcd. for $C_{19}H_{30}N_2O_4F$ m/z 369.2184 $[M+H]^+$, found 369.2168.

(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-methoxyphenyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-5-methoxybenzamide (S5)

To a solution of **S4** (1.22 g, 3.31 mmol) in CH_2Cl_2 (12 mL) was added TFA (6 mL). The reaction mixture was stirred at room temperature for 2 h and concentrated. Toluene was added to the residue and the volatiles were removed under reduced pressure, which was repeated twice. The resulting residue was dried in vacuo to give crude amine·TFA salt as a white solid. To a solution of EDCI·HCl (634.5 mg, 3.31 mmol) in DMF (8.3 mL) and CH_2Cl_2 (8.3 mL) were successively added OxymaPure® (470.4 mg, 3.31 mmol) and 2-fluoro-5-methoxybenzoic acid (563.2 mg, 3.31 mmol) at room temperature. After stirring for 5 min, the crude amine·TFA salt and DIPEA (717 μL, 4.97 mmol) were added, and then the resulting mixture was stirred for 9 h at the same temperature. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and 1 N HCl aq. was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with aqueous saturated $NaHCO_3$ twice, H_2O, brine and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (ethyl acetate/*n*-hexane = 8/92 to 66/34) to give **S5** (1.16 g, 2.76 mmol, 84% over 2 steps) as a colorless amorphous.

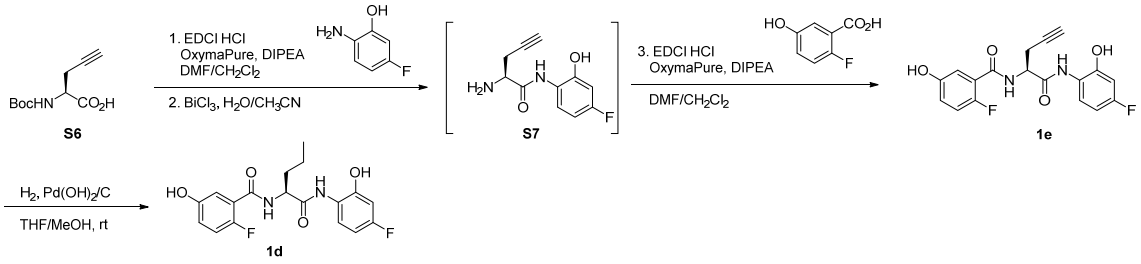
Colorless amorphous; $[\alpha]_D^{26}$ −38.3 (c 1.12, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (dd, J = 8.8, 6.1 Hz, 1H), 7.24 (dd, J = 5.6, 3.2 Hz, 1H), 7.17 (dd, J = 10.0, 9.0 Hz, 1H), 7.10 (ddd, J = 9.0, 3.9, 3.2 Hz, 1H), 6.84 (dd, J = 10.5, 2.7 Hz, 1H), 6.66(ddd, J = 8.6, 8.6, 2.7 Hz, 1H), 4.81 (dd, J = 9.1, 3.4 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.00 (dd, J = 14.4, 3.4 Hz, 1H), 1.76 (dd, J = 14.4, 9.1 Hz, 1H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.9, 166.5 (d, J = 1.5 Hz), 161.5 (d, J = 241.3 Hz), 157.4 (d, J = 2.2 Hz), 155.6 (d, J = 240.6 Hz), 152.7 (d, J = 10.2 Hz), 124.2 (d, J = 1.5 Hz), 124.1 (d, J = 10.9 Hz), 123.7 (d, J = 9.5 Hz), 119.7 (d, J = 8.8 Hz), 118.1 (d, J = 25.5 Hz), 115.4 (d, J = 2.9 Hz), 107.1 (d, J = 21.9 Hz), 100.3 (d, J = 27.0 Hz), 56.7, 56.4, 53.7, 46.0, 31.5, 30.1 (3C); ^{19}F NMR (376 MHz, CD_3OD) δ –116.9, –126.5; IR (neat) ν 3019, 1686, 1656, 1531, 1492, 1216, 1216, 1036, 757, 689 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{26}N_2O_4F_2Na$ m/z 443.1753 $[M+Na]^+$, found 443.1744.

(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-hydroxyphenyl)amino)-4,4-dimethyl-1-oxopentan-2-yl)-5-hydroxybenzamide (1c)

To a solution of **S5** (1.05 g, 2.50 mmol) in CH_2Cl_2 (25 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 12.5 mL, 12.5 mmol) over 10 min at 0 °C. After the reaction mixture was stirred for 24.5 h, additional BBr_3 (1.0 M in CH_2Cl_2, 5 mL, 5 mmol) was added and the reaction mixture was stirred for 18 h at the same temperature, then warmed to room temperature and stirred for 17 h. The reaction mixture was quenched with *i*-PrOH at 0 °C then water was added. The resulting mixture was extracted with $CHCl_3$ twice and the combined organic layers were washed with aqueous saturated $NaHCO_3$, H_2O, brine, and dried over Na_2SO_4. After filtration,

the residue was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (acetone/*n*-hexane = 8/92 to 66/34) to give **1c** (791.2 mg, 2.02 mmol 81%) as a white amorphous.

White amorphous; $[\alpha]_D^{26}$ −30.0 (*c* 0.33, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 7.78 (dd, *J* = 8.8, 6.1 Hz, 1H), 7.13 (dd, *J* = 5.6, 3.2 Hz, 1H), 7.04 (dd, *J* = 10.3, 9.0 Hz, 1H), 6.91 (ddd, *J* = 9.0, 3.9, 3.2 Hz, 1H), 6.60 (dd, *J* = 10.0, 2.9 Hz, 1H), 6.54 (ddd, *J* = 8.8, 8.6, 2.9 Hz, 1H), 4.80 (dd, *J* = 9.1, 3.2 Hz, 1H), 1.99 (dd, *J* = 14.4, 3.4 Hz, 1H), 1.77 (dd, *J* = 14.4, 9.0 Hz, 1H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.2, 166.8 (d, *J* = 1.5 Hz), 161.6 (d, *J* = 240.6 Hz), 155.1 (d, *J* = 2.2 Hz), 154.9 (d, *J* = 238.4 Hz), 150.9 (d, *J* = 10.9 Hz), 124.1 (d, *J* = 9.5 Hz), 124.0 (d, *J* = 15.3 Hz), 123.3 (d, *J* = 3.7 Hz), 120.6 (d, *J* = 8.0 Hz), 117.9 (d, *J* = 24.8 Hz), 116.9 (d, *J* = 2.2 Hz), 106.5 (d, *J* = 21.9 Hz), 103.7 (d, *J* = 25.5 Hz), 53.7, 46.1, 31.5, 30.1 (3C); ^{19}F NMR (376 MHz, CD_3OD) δ –118.2, –128.2; IR (KBr) *ν* 3198, 1646, 1533, 1496, 1444, 1317, 1246, 1226, 1187, 1142, 976, 761 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{23}N_2O_4F_2$ *m*/*z* 393.1620 $[M+H]^+$, found 393.1602.



(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-hydroxyphenyl)amino)-1-oxopent-4-yn-2-yl)-5 hydroxybenzamide (1e)

To a solution of EDCI·HCl (240.0 mg, 1.25 mmol) in DMF (3.1 mL) and CH_2Cl_2 (3.1 mL) were successively added OxymaPure® (177.6 mg, 1.25 mmol) and **S6** (266.7 mg, 1.25 mmol) at 0 °C. After stirring the reaction mixture for 5 min, 2-amino-5-fluorophenol (159.0 mg, 1.25 mmol) and DIPEA (238 μL, 1.63 mmol) were added, and the resulting mixture was stirred for 10 min at the same temperature. The reaction mixture was warmed to room temperature and stirred for 8 h. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and 1 N HCl aq. was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with aqueous saturated $NaHCO_3$ twice, H_2O, brine and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and dried in vacuo to give crude amide as brown oil. To the amide in CH_3CN (6 mL) and H_2O (120 μL) was added $BiCl_3$ (788.0 mg, 2.50 mmol). After the reaction mixture was stirred for 2 h at 55 °C, $NaHCO_3$ powder (1.05 g) was added and filtrate was concentrated under reduced pressure to give crude **S7** as brown oil. To a solution of EDCI·HCl (216.0 mg, 1.13 mmol) in DMF (3 mL) and CH_2Cl_2 (3 mL) were successively added OxymaPure® (160.0 mg, 1.13 mmol) and 2-fluoro-5-hydroxybonzoic acid (176.0 mg, 1.13 mmol) at room temperature. After stirring the reaction mixture for 5 min, crude **S7** in DMF (1 mL) and DIPEA (244 μL, 1.69 mmol) were added, and the resulting mixture was stirred for 12 h at room temperature. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and 1 N HCl aq. was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were

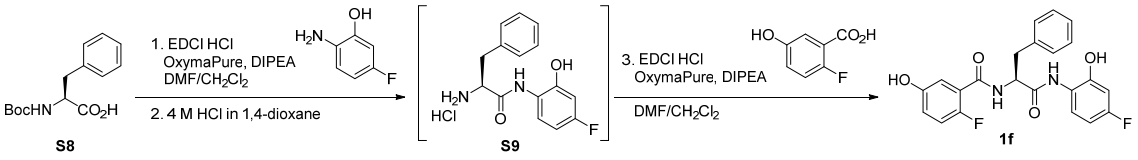
washed with aqueous saturated $NaHCO_3$ twice, H_2O, brine, then dried over Na_2SO_4. Filtrate was concentrated and the resulting residue was purified by silica gel chromatography (acetone/*n*-hexane = 12/88 to 100/0) to give **1e** (173.2 mg, 480.7 μmol, 38% over 3 steps) as a white amorphous.

White amorphous; $[\alpha]_D^{27}$ −5.2 (*c* 0.38, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 7.80 (dd, *J* = 8.8, 6.1 Hz, 1H), 7.22 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.06 (dd, *J* = 10.6, 8.9 Hz, 1H), 6.94 (ddd, *J* = 8.9, 4.2, 3.2 Hz, 1H), 6.60 (dd, *J* = 10.0, 2.7 Hz, 1H), 6.55 (ddd, *J* = 8.8, 8.6, 2.7 Hz, 1H), 4.91 (dd, *J* = 7.1, 6.0 Hz, 1H), 2.91 (ddd, *J* = 16.9, 6.0, 2.7 Hz, 1H), 2.84 (ddd, *J* = 16.9, 7.1, 2.7 Hz, 1H), 2.44 (t, *J* = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 170.4, 166.4 (d, *J* = 2.8 Hz), 161.7 (d, *J* = 240.6 Hz), 155.3 (d, *J* = 238.4 Hz), 155.1 (d, *J* = 2.2 Hz), 151.0 (d, *J* = 10.9 Hz), 124.5 (d, *J* = 10.2 Hz), 123.2, 123.0 (d, *J* = 2.2 Hz), 121.0 (d, *J* = 8.8 Hz), 118.0 (d, *J* = 25.5 Hz), 117.2 (d, *J* = 2.2 Hz), 106.5 (d, *J* = 21.9 Hz), 103.7 (d, *J* = 24.8 Hz), 79.9, 72.7, 54.4, 22.7; ^{19}F NMR (376 MHz, CD_3OD) δ –118.1, −127.6; IR (KBr) *ν* 3305, 1639, 1601, 1528, 1510, 1455, 1259, 1243 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{14}N_2O_4F_2Na$ *m*/*z* 383.0814 $[M+Na]^+$, found 383.0801.

(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-hydroxyphenyl)amino)-1-oxopentan-2-yl)-5-hydroxybenzamide (1d)

To a solution of **1e** (105.7 mg, 293.4 μmol) in THF (1 mL) and MeOH (1 mL) was $Pd(OH)_2/C$ (10.5 mg [20 wt%Pd, 50% wet]) and the resulting mixture was stirred at room temperature under H_2 atmosphere for 18 h. After filtration, the filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (acetone/*n*-hexane = 8/92 to 66/34) to give **1d** (99.4 mg, 272.9 μmol, 93%) as a white amorphous.

White amorphous; $[\alpha]_D^{26}$ −12.0 (*c* 0.17, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 7.73 (dd, *J* = 8.8, 6.1 Hz, 1H), 7.15 (dd, *J* = 5.7, 3.0 Hz, 1H), 7.04 (dd, *J* = 9.8, 9.8 Hz, 1H), 6.92 (ddd, *J* = 9.8, 3.7, 3.0 Hz, 1H), 6.61 (dd, *J* = 10.0, 2.7 Hz, 1H), 6.55 (ddd, *J* = 8.8, 8.6, 2.7 Hz, 1H), 4.73 (dd, *J* = 8.8, 5.4 Hz, 1H), 2.01−1.92 (m, 1H), 1.88−1.79 (m, 1H), 1.60−1.44 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.7, 166.8 (d, *J* = 2.2 Hz), 161.7 (d, *J* = 240.6 Hz), 155.1 (d, *J* = 2.2 Hz), 155.0 (d, *J* = 238.4 Hz), 151.2 (d, *J* = 10.9 Hz), 124.7 (d, *J* = 9.5 Hz), 123.8 (d, *J* = 15.3 Hz), 123.1 (d, *J* = 2.9 Hz), 120.7 (d, *J* = 8.0 Hz), 117.9 (d, *J* = 25.5 Hz), 117.0 (d, *J* = 1.5 Hz), 106.5 (d, *J* = 21.9 Hz), 103.8 (d, *J* = 25.5 Hz), 55.8 35.2, 20.1, 14.0; ^{19}F NMR (376 MHz, CD_3OD) δ –118.1, –128.2; IR (KBr) *ν* 3239, 1652, 1618, 1532, 1499, 1451, 1320, 1247, 1228, 1146, 971 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{18}N_2O_4F_2Na$ *m*/*z* 387.1127 $[M+Na]^+$, found 387.1111.

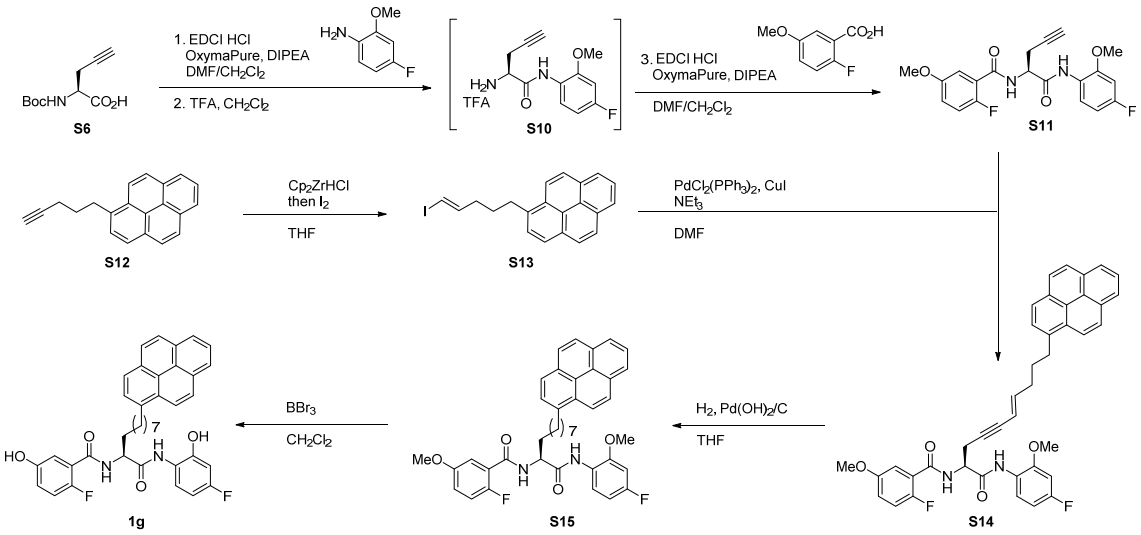


(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-hydroxyphenyl)amino)-1-oxo-3-phenylpropan-2-yl)-5-hydroxybenzamide (1f)

To a solution of EDCI·HCl (360.0 mg, 1.88 mmol) in DMF (4.7 mL) and CH_2Cl_2 (4.7 mL) were successively added OxymaPure® (267.0 mg, 1.88 mmol) and Boc-Phe-OH (**S8**) (500.0 mg, 1.88 mmol) at room temperature. After stirring the reaction mixture for 5 min, 2-amino-5-fluorophenol (240.0 mg, 1.88 mmol) and DIPEA (353 μL, 2.44 mmol) were added, and the

reaction mixture was stirred for 8 h at the same temperature. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and 1 N HCl aq. was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with aqueous saturated $NaHCO_3$ twice, H_2O, brine and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and dried in vacuo to give crude amide as brown oil. The resulting residue was treated with 4 N HCl in 1,4-dioxane (5.64 mL, 22.6 mmol) and stirred at room temperature for 2 h. The resulting precipitates were filtered, and washed with 1,4-dioxane, and the precipitates were dried in vacuo at 40 °C to give crude **S9** as a pale purple solid. To a solution of EDCI·HCl(253.0 mg, 1.32 mmol) in DMF (3.3 mL) and CH_2Cl_2 (3.3 mL) was successively added OxymaPure® (188.0 mg, 1.32 mmol) and 2-fluoro-5-hydroxybonzoic acid (206.0 mg, 1.32 mmol) at room temperature. After stirring the reaction mixture for 5 min, the crude **S9** obtained above and DIPEA (286 μL, 1.98 mmol) were added, the reaction mixture was 12 h at the same temperature. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and 1 N HCl aq. was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with aqueous saturated $NaHCO_3$ twice, H_2O, brine, then dried over Na_2SO_4. Filtrate was concentrated and the resulting residue was purified by silica gel chromatography (acetone/*n*-hexane = 12/88 to 100/0) to give **1f** (514.3 mg, 1.25 mmol, 68% over 3 steps) as a white amorphous.

White amorphous; $[\alpha]_D^{27}$ −6.7 (*c* 0.16, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 7.62 (dd, *J* = 8.8 , 6.1 Hz, 1H), 7.28−7.16 (m, 5H), 7.06 (dd, *J* = 5.7, 3.1 Hz, 1H), 6.96 (dd, *J* = 10.5, 9.0 Hz, 1H), 6.86 (ddd, *J* = 9.0, 3.7, 3.1 Hz, 1H), 6.55 (dd, *J* = 10.0, 2.7 Hz, 1H), 6.50 (ddd, *J* = 8.8, 8.6, 2.7 Hz, 1H), 4.97 (dd, *J* = 7.0, 7.0 Hz, 1H), 3.31−3.27 (m, 1H), 3.10 (dd, *J* = 13.9, 8.3 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 171.7, 166.3 (d, *J* = 2.2 Hz), 161.8 (d, *J* = 240.6 Hz), 155.1 (d, *J* = 238.4 Hz), 155.0 (d, *J* = 2.2 Hz), 151.3 (d, *J* = 11.7 Hz), 138.0, 130.4 (2C), 129.5 (2C), 127.9, 124.8 (d, *J* = 10.2 Hz), 123.3 (d, *J* = 14.6 Hz), 122.9 (d, *J* = 11.6 Hz), 120.8 (d, *J* = 8.8 Hz), 117.9 (d, *J* = 25.5 Hz), 117.1 (d, *J* = 1.5 Hz), 106.5 (d, *J* = 21.9 Hz), 103.8 (d, *J* = 24.8 Hz), 57.2, 39.0; ^{19}F NMR (376 MHz, CD_3OD) δ −118.0, −127.6; IR (KBr) *ν* 3314, 1644, 1609, 1574, 1546, 1498, 1312, 1267, 1200 cm^{-1}; HRMS (ESI) calcd. for $C_{22}H_{18}N_2O_4F_2Na$ *m*/*z* 435.1127 $[M+Na]^+$, found 435.1107.



(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-methoxyphenyl)amino)-1-oxopent-4-yn-2-yl)-5-methoxybenzamide (S11)

To a solution of EDCI·HCl (1.08 g, 5.63 mmol) in DMF (14 mL) and CH_2Cl_2 (14 mL) were successively added OxymaPure (800.1 mg, 5.63 mmol) and **S6** (1.20 g, 5.63 mmol) at room temperature. After stirring the reaction mixture for 5 min, 4-fluoro-2-methoxyaniline (884.6 mg, 5.63 mmol) and DIPEA (1.06 mL, 7.32 mmol) were added, and the reaction mixture was stirred for 5 h at the same temperature. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and 1 N HCl aq. was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with aqueous saturated $NaHCO_3$ twice, H_2O, brine and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and dried in vacuo to give crude amide as a brown oil.

To the crude amide in CH_2Cl_2 (20 mL) was added TFA (10 mL). The reaction mixture was stirred at room temperature for 5 h and concentrated. Toluene was added to the residue and the volatiles were removed under reduced pressure, which was repeated twice. The resulting residue was dried in vacuo to give crude amine **S10** as a brown oil. To a solution of EDCI·HCl (1.08 g, 5.63 mmol) in DMF (14 mL) and CH_2Cl_2 (14 mL) were successively added OxymaPure (800.0 mg, 5.63 mmol) and 2-fluoro-5-methoxybenzoic acid (958.0 mg, 5.63 mmol) at room temperature. After stirring the reaction mixture for 5 min, the crude amine **S10** in DMF (1 mL) and DIPEA (1.22 mL, 8.45 mmol) were added, and the resulting mixture was stirred for 12 h at the same temperature. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and 1 N HCl aq. was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with aqueous saturated $NaHCO_3$ twice, H_2O, brine, and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (ethyl acetate/*n*-hexane = 8/92 to 66/34) to give **S11** (1.36 g, 3.57 mmol, 62% over 3 steps) as a white solid.

White solid; m.p. 130−132 °C; $[\alpha]_D^{26}$ −17.6 (*c* 1.66, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD) δ 7.97

(dd, *J* = 8.8, 6.1 Hz, 1H), 7.34 (dd, *J* = 5.6, 3.2 Hz, 1H), 7.18 (dd, *J* = 10.3, 9.0 Hz, 1H), 7.11 (ddd, *J* = 9.0, 4.0, 3.2 Hz, 1H), 6.84 (dd, *J* = 10.5, 2.7 Hz, 1H), 6.67 (ddd, *J* = 8.8, 8.4, 2.7 Hz, 1H), 4.93 (dd, *J* = 7.1, 6.1 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 2.91 (ddd, *J* = 16.9, 6.1, 2.7 Hz, 1H), 2.83 (ddd, *J* = 16.9, 7.1, 2.7 Hz, 1H), 2.45 (t, *J* = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 163.3 (d, *J* = 3.7 Hz), 159.5 (d, *J* = 242.1 Hz), 156.0 (d, *J* = 1.5 Hz), 155.3 (d, *J* = 239.9 Hz), 149.4 (d, *J* = 10.2 Hz), 123.2 (d, *J* = 3.7 Hz), 120.9 (d, *J* = 9.5 Hz), 120.4 (d, *J* = 8.8 Hz), 120.3 (d, *J* = 13.1 Hz), 117.1 (d, *J* = 27.0 Hz), 114.6 (d, *J* = 2.2 Hz), 106.7 (d, *J* = 21.9 Hz), 98.8 (d, *J* = 27.0 Hz), 79.0, 72.1, 56.0, 55.9, 52.9, 22.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.6, −123.1; IR (KBr) *ν* 3413, 3307, 3019, 1658, 1493, 1216, 758, 668 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{18}N_2O_4F_2Na$ *m*/*z* 411.1127 $[M+Na]^+$, found 411.1123.

(*E*)-1-(5-Iodopent-4-en-1-yl)pyrene (S13)

To a solution of **S12** (2.08 g, 7.76 mmol) in THF (78 mL) was added Cp_2ZrHCl (3.00 g, 11.6 mmol) and the reaction mixture was stirred for 2 h 45 min at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. Iodine (3.06 g, 11.6 mmol) was added to the reaction mixture at 0 °C, the reaction mixture was warmed to room temperature. After stirring for 10 h 30 min. the reaction mixture was diluted with ethyl acetate and aqueous saturated $Na_2S_2O_3$ was added. The resulting mixture was extracted with ethyl acetate twice. The combined organic layers were washed with H_2O, brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (ethyl acetate/*n*-hexane = 1/99) to give **S13** (1.76 g, 4.44 mmol, 57%) as a white solid.

White solid; m.p. 107−109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.2 Hz, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 8.17 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 9.2 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 8.00 (t, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 6.61 (dt, *J* = 14.5, 7.3 Hz, 1H), 6.06 (d, *J* = 14.5 Hz, 1H), 3.33 (t, *J* = 7.6 Hz, 2H), 2.20 (q, *J* = 7.6 Hz, 2H), 1.96 (quin, *J* = 7.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.0, 136.0, 131.1, 130.8, 129.8, 128.6, 127.5, 127.3, 127.2, 126.6, 125.8, 125.1, 125.0, 124.9, 124.7, 124.7, 123.2, 75.1, 35.8, 32.6, 30.2; IR (KBr) *ν* 3019, 1216, 908, 759, 669 cm^{-1}; HRMS (ESI) calcd. for $C_{21}H_{18}I$ *m*/*z* 397.0448 $[M+H]^+$, found 397.0445.

(*S*,*E*)-2-Fluoro-*N*-(1-((4-fluoro-2-methoxyphenyl)amino)-1-oxo-10-(pyren-1-yl)dec-6-en-4-yn-2-yl)-5-methoxybenzamide (S14)

To a solution of **S11** (457.5 mg, 1.18 mmol) and **S13** (459.7 mg, 1.18 mmol) in DMF (5.9 mL) were successively added $PdCl_2(PPh_3)_2$ (41.4 mg, 0.059 mmol), CuI (22.5 mg, 0.12 mmol) and triethylamine (492 μL, 3.54 mmol) at room temperature. After stirring the reaction mixture for 16 h, the resulting mixture was diluted with ethyl acetate and 1 N HCl aq. was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with H_2O, brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (ethyl acetate/*n*-hexane = 12/88 to 100/0) to give **S14** (315.5 mg, 480.4 μmol, 41%) as a brown solid.

Brown solid; m.p. 156−158 °C; $[\alpha]_D^{27}$ −8.6 (*c* 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.33 (dd, *J* = 8.8, 6.1 Hz, 1H), 8.23 (d, *J* = 9.2 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 2H), 8.10 (d, *J*

= 7.8 Hz, 1H), 8.09 (d, *J* = 9.2 Hz, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 8.00 (d, *J* = 9.0 Hz, 1H), 7.98 (t, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.76–7.71 (m, 1H), 7.59 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.04 (dd, *J* = 11.0, 9.0 Hz, 1H), 6.97 (ddd, *J* = 9.0, 4.2, 3.2 Hz, 1H), 6.66 (ddd, *J* = 8.8, 8.6, 2.6 Hz, 1H), 6.55 (dd, *J* = 10.0, 2.6 Hz, 1H), 6.19 (ddd, *J* = 15.9, 7.1 Hz, 1H), 5.52 (dd, *J* = 15.9, 1.7 Hz, 1H), 4.98–4.92 (m, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.33 (t, *J* = 7.3 Hz, 2H), 3.16 (ddd, *J* = 17.1, 4.9, 1.7 Hz, 1H), 2.88 (ddd, *J* = 17.1, 7.3, 1.7 Hz, 1H), 2.25 (q, *J* = 7.3 Hz, 2H), 1.95 (quin, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 163.2 (d, *J* = 3.6 Hz), 159.4 (d, *J* = 241.3 Hz), 156.0 (d, *J* = 2.2 Hz), 155.3 (d, *J* = 240.0 Hz), 149.3 (d, *J* = 9.5 Hz), 144.3, 136.2, 131.4, 130.8, 129.8, 128.6, 127.4, 127.3, 127.2, 126.6, 125.8, 125.1, 125.0, 124.9, 124.7, 124.7, 123.3, 123.2, 120.8 (d, *J* = 8.8 Hz), 120.5 (d, *J* = 13.1 Hz), 120.3 (d, *J* = 8.7 Hz), 117.1 (d, *J* = 26.3 Hz), 114.6 (d, *J* = 1.5 Hz), 109.8, 106.7 (d, *J* = 21.9 Hz), 98.8 (d, *J* = 27.0 Hz), 82.9, 82.8, 56.0, 55.9, 53.4, 32.8, 32.8, 30.6, 23.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.7, −123.1; IR (KBr) *ν* 3019, 1513, 1425, 1216, 758, 673 cm^{-1}; HRMS (ESI) calcd. for $C_{41}H_{34}N_2O_4F_2Na$ *m*/*z* 679.2379 $[M+Na]^+$, found 679.2374.

(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-methoxyphenyl)amino)-1-oxo-10-(pyren-1-yl)decan-2-yl)-5-methoxybenzamide (S15)

To a solution of **S14** (315.5 mg, 480.4 μmol) in THF (6.3 mL) was added $Pd(OH)_2/C$ (10.5 mg [20 wt%Pd, 50% wet]) and the reaction mixture was stirred at room temperature under H_2 atmosphere for 5 h. After filtration, the filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (ethyl acetate/*n*-hexane = 8/92 to 66/34) to give **S15** (235.1 mg, 354.7 μmol, 74%) as a white amorphous.

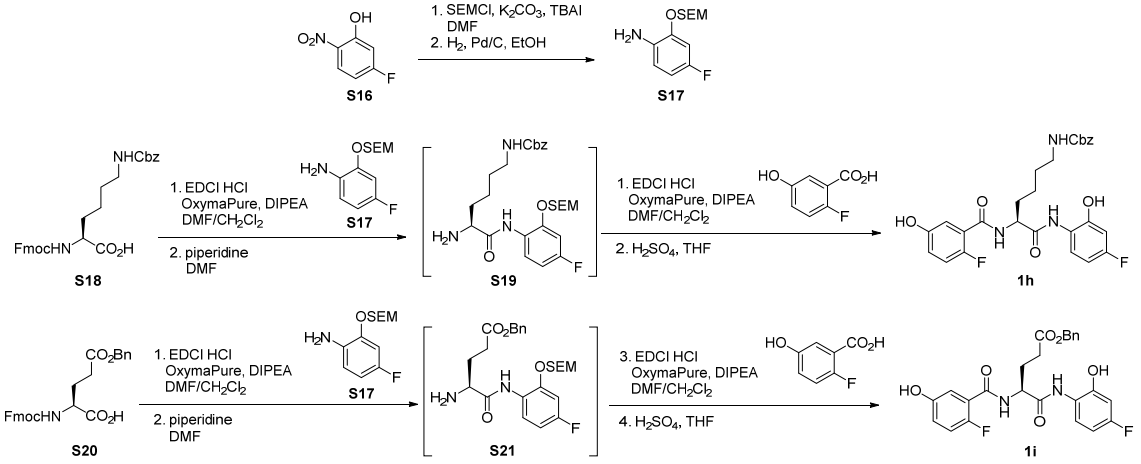
White amorphous; $[\alpha]_D^{25}$ –8.2 (*c* 0.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.8 , 6.1 Hz, 1H), 8.27 (d, *J* = 9.3 Hz, 1H), 8.22 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 8.09 (d, *J* = 9.3 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.98 (t, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.57 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.35–7.30 (m, 1H), 7.04 (dd, *J* = 11.0, 8.9 Hz, 1H), 6.97 (ddd, *J* = 8.9, 4.2, 3.2 Hz, 1H), 6.66 (ddd, *J* = 8.8, 8.6, 2.7 Hz, 1H), 6.58 (dd, *J* = 10.0, 2.7 Hz, 1H), 4.82–4.77 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.31 (t, *J* = 7.8 Hz, 2H), 2.11–2.02 (m, 1H), 1.87–1.79 (m, 3H), 1.50–1.31 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 163.2 (d, *J* = 3.6 Hz), 159.4 (d, *J* = 241.3 Hz), 156.0 (d, *J* = 1.5 Hz), 155.1 (d, *J* = 239.2 Hz), 149.3 (d, *J* = 9.5 Hz), 137.2, 131.4, 130.9, 129.6, 128.5, 127.5, 127.2, 127.0, 126.4, 125.7, 125.0, 125.0, 124.7, 124.6, 123.5, 123.3, 123.2, 120.8 (d, *J* = 9.5 Hz), 120.7 (d, *J* = 13.1 Hz), 120.1 (d, *J* = 8.8 Hz), 117.0 (d, *J* = 27.0 Hz), 114.6 (d, *J* = 1.5 Hz), 106.7 (d, *J* = 21.9 Hz), 98.7 (d, *J* = 27.0 Hz), 55.9, 55.9, 54.7, 33.5, 32.3, 31.8, 29.7, 29.4, 29.3, 29.2, 25.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ –115.9, −123.3; IR (KBr) *ν* 3019, 1518,1492, 1216, 757, 669 cm^{-1}; HRMS (ESI) calcd. for $C_{41}H_{40}N_2O_4F_2Na$ *m*/*z* 685.2848 $[M+Na]^+$, found 685.2841.

(*S*)-2-Fluoro-*N*-(1-((4-fluoro-2-hydroxyphenyl)amino)-1-oxo-10-(pyren-1-yl)decan-2-yl)-5-hydroxybenzamide (1g)

To a solution of **S15** (235.1 mg, 354.7 μmol) in CH_2Cl_2 (5.3 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 1.8 mL, 1.8 mmol) at 0 °C, the reaction mixture was warmed to room temperature. After stirring for 9 h, the reaction was quenched with *i*-PrOH at 0 °C, and then water was added. The resulting mixture was extracted with $CHCl_3$ twice and the combined organic layers were washed with aqueous saturated $NaHCO_3$, H_2O, brine, and dried over Na_2SO_4.

After filtration, the residue was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (acetone/*n*-hexane = 12/88 to 100/0) to give **1g** (167.1 mg, 263.3 μmol, 74%) as a white solid.

White solid; m.p. 163−164 °C; $[\alpha]_D^{26}$ 1.59 (*c* 1.54, $(CH_3)_2CO$); ^1H NMR (400 MHz, $(CD_3)_2CO$) δ 9.44 (brs, 1H), 9.31 (s, 1H), 8.67 (brs, 1H), 8.34 (d, *J* = 9.3 Hz, 1H), 8.21 (d, *J* = 7.8 Hz, 2H), 8.16 (d, *J* = 7.8 Hz, 1H), 8.16 (d, *J* = 9.3 Hz, 1H), 8.09 (d, *J* = 8.9 Hz, 1H), 8.06 (d, *J* = 8.9 Hz, 1H), 8.01 (t, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.80−7.76 (m, 1H), 7.70 (dd, *J* = 8.8 , 6.1 Hz, 1H), 7.36 (dd, *J* = 6.1, 3.2 Hz, 1H), 7.07 (dd, *J* = 10.8, 9.0 Hz, 1H), 6.98 (ddd, *J* = 9.0, 4.2, 3.2 Hz, 1H), 6.69 (dd, *J* = 10.0, 2.9 Hz, 1H), 6.61 (ddd, *J* = 8.8, 8.4, 2.9 Hz, 1H), 4.89−4.84 (m, 1H), 3.32 (t, *J* = 7.8 Hz, 2H), 2.09−2.01 (m, 1H), 1.95−1.87 (m, 1H), 1.81 (quin, *J* = 7.8 Hz, 2H), 1.56−1.27 (m, 10H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 172.3, 164.4 (d, *J* = 2.9 Hz), 161.3 (d, *J* = 239.9 Hz), 155.0 (d, *J* = 237.7 Hz), 154.7 (d, *J* = 1.5 Hz), 150.6 (d, *J* = 11.7 Hz), 138.4, 132.5, 132.0, 130.8, 129.6, 128.5, 128.5, 128.1, 127.5, 127.0, 126.0, 125.9, 125.9, 125.8, 125.7, 124.6, 124.1 (d, *J* = 9.5 Hz), 123.9 (d, *J* = 2.9 Hz), 123.6 (d, *J* = 14.6 Hz), 120.6 (d, *J* = 8.8 Hz), 117.9 (d, *J* = 25.5 Hz), 117.6 (d, *J* = 2.2 Hz), 106.9 (d, *J* = 22.6 Hz), 104.9 (d, *J* = 25.5 Hz), 55.4, 34.1, 33.0, 32.9, 30.7, 30.5, 30.2, 30.0, 26.5; ^{19}F NMR (376 MHz, $(CD_3)_2CO$) δ −118.1, −126.7; IR (KBr) *ν* 3390, 3259, 2925, 2851, 1654, 1509, 843 cm^{-1}; HRMS (ESI) calcd. for $C_{39}H_{36}N_2O_4F_2Na$ *m*/*z* 657.2535 $[M+Na]^+$, found 657.2565.



4-Fluoro-2-((2-(trimethylsilyl)ethoxy)methoxy)aniline (S17)

To a solution of **S16** (3.90 g, 22.6 mmol) in DMF (110 mL) were added K_2CO_3 (7.08 g, 25.9 mmol), TBAI (383.0 mg, 45.2 mmol) and SEMCl (4.33 g, 25.9 mmol), then the resulting mixture was stirred at 70 °C for 2.5 h. The reaction mixture was quenched with H_2O and the mixture was extracted with ethyl acetate twice. The combined organic layers were washed with aqueous saturated NH_4Cl, H_2O, brine and dried over Na_2SO_4. Filtrate was concentrated under reduced pressure and dried in vacuo. To the resulting residue in EtOH (75 mL) was added Pd/C (343.0 mg [10 wt%Pd, 50% wet]) and the reaction mixture was stirred at room temperature under H_2 atmosphere for 8.5 h. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (ethyl acetate/*n*-hexane = 6/94 to 50/50) to give **S17** (5.72 g, 22.2 mmol, 98% over 2 steps) as a pale brown oil.

Pale brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (dd, *J* = 10.3, 2.7 Hz, 1H), 6.65 (dd, *J* = 8.6, 5.6 Hz, 1H), 5.22 (s, 2H), 6.55 (ddd, *J* = 8.6, 8.6, 2.7 Hz, 1H), 3.77 (t, *J* = 8.3 Hz, 2H), 3.79–3.75 (brs, 2H), 0.98 (t, *J* = 8.3 Hz, 2H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2 (d, *J* = 234.8 Hz), 145.5 (d, *J* = 10.2 Hz), 132.2 (d, *J* = 2.2 Hz), 115.3 (d, *J* = 8.8 Hz), 107.9 (d, *J* = 21.9 Hz), 103.0 (d, *J* = 26.3 Hz), 93.6, 66.4, 18.0, −1.5 (3C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –124.0; IR (neat) *ν* 3019, 2960, 1509, 1216, 1002, 940, 859, 838, 756, 669 cm^{-1}; HRMS (ESI) calcd. for $C_{12}H_{21}NO_2FSi$ *m*/*z* 258.1320 $[M+H]^+$, found 258.1309.

(*S*)-Benzyl 5-((4-fluoro-2-hydroxyphenyl)amino)-4-(2-fluoro-5-hydroxybenzamido)-5-oxopentanoate (1h)

To a solution of EDCI･HCl (260.7 mg, 1.36 mmol) in DMF (3.5 mL) and CH_2Cl_2 (3.5 mL) were successively added OxymaPure® (193.3 mg, 1.36 mmol) and **S18** (625.0 mg, 1.36 mmol) at room temperature. After stirring the reaction mixture for 5 min, **S17** (350.0 mg, 1.36 mmol) and DIPEA (295 μL, 2.04 mmol) were added. The reaction mixture was stirred at the same temperature for 10 h. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and 1 N HCl aq. was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with aqueous saturated $NaHCO_3$ twice, H_2O, brine and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and dried in vacuo to give crude amide as a white solid. To the amide in DMF (4.5 mL) was added piperidine (120 μL, 2.04 mmol), and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate and H_2O was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with H_2O, brine, dried over Na_2SO_4. Filtrate was concentrated and dried in vacuo to give crude **S19** as a yellow solid.

To a solution of EDCI･HCl (233.9 mg, 1.22 mmol) in DMF (3 mL) and CH_2Cl_2 (3 mL) were successively added OxymaPure® (170.9 mg, 1.22 mmol) and 2-fluoro-5-hydroxybenzoic acid (190.5 mg, 1.22 mmol) at room temperature. After stirring for 5 min, **S19** and DIPEA (264 μL, 1.83 mmol) were added, the reaction mixture was stirred for 12 h. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and 1 N HCl aq. wasadded. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with aqueous saturated $NaHCO_3$ twice, H_2O, brine and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure to give crude diamide as a yellow oil. To the crude diamide in THF (6.1 mL) was added H_2SO_4 (260 μL, 4.88 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate and aqueous saturated $NaHCO_3$ was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with H_2O, brine, then dried over Na_2SO_4. Filtrate was concentrated and the resulting residue was purified by silica gel chromatography (acetone/*n*-hexane = 12/88 to 100/0) to give **1h** (184.2 mg, 380.2 μmol, 28% over 4 steps) as a white amorphous.

White amorphous; $[\alpha]_D^{26}$ −8.1 (*c* 0.12, CH_3OH); ^{1}H NMR (400 MHz, CD_3CN) δ 8.66 (s, 1H), 7.80 (brs, 1H), 7.53, (t, *J* = 7.5 Hz, 1H), 7.46 (dd, *J* = 8.8, 6.2 Hz, 1H), 7.36−7.31 (m, 5H), 7.26 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.06 (dd, *J* = 10.9, 8.8 Hz, 1H), 6.95 (ddd, *J* = 8.8, 4.0, 3.2 Hz, 1H), 6.68 (dd, *J* = 10.1, 2.9 Hz, 1H), 6.60 (ddd, *J* = 8.8, 8.4, 2.9 Hz, 1H), 5.08 (s, 2H), 4.76−4.71 (m, 1H), 2.55 (t,

J = 7.6 Hz, 2H), 2.36–2.28 (m, 1H), 2.18–2.09 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 174.3, 171.8, 166.8 (d, *J* = 2.2 Hz), 161.7 (d, *J* = 240.6 Hz), 155.1 (d, *J* = 2.2 Hz), 155.1 (d, *J* = 239.2 Hz), 151.3 (d, *J* = 10.9 Hz), 137.5, 129.5 (2C), 129.2 (3C), 124.8 (d, *J* = 9.5 Hz), 123.6 (d, *J* = 15.3 Hz), 123.0 (d, *J* = 2.9 Hz), 120.8 (d, *J* = 8.0 Hz), 118.0 (d, *J* = 25.5 Hz), 117.1 (d, *J* = 1.5 Hz), 106.5 (d, *J* = 22.1 Hz), 103.7 (d, *J* = 24.8 Hz), 67.5, 55.1, 31.4, 28.2; ^{19}F NMR (376 MHz, CD_3OD) δ –118.0, −127.9; IR (KBr) *ν* 3304, 1731, 1688, 1638, 1595, 1531, 1499, 1452, 1434, 1251, 1193 cm^{-1}; HRMS (ESI) calcd. for $C_{25}H_{23}N_2O_6F_2$ *m*/*z* 485.1519 $[M+H]^+$, found 485.1495.

(*S*)-Benzyl (5-amino-6-((4-fluoro-2-((2-(trimethylsilyl)ethoxy)methoxy)phenyl)amino)-6-oxohexyl)carbamate (S21)

To a solution of EDCI·HCl (485.0 mg, 2.53 mmol) in DMF (6.3 mL) and CH_2Cl_2 (6.3 mL) were successively added OxymaPure® (360.0 mg, 2.53 mmol) and **S20** (1.27 g, 2.53 mmol) at 0 °C. After stirring the reaction mixture for 5 min, **S17** (651.1 mg, 2.53 mmol) in DMF (1 mL) and DIPEA (440 μL, 2.53 mmol) were added, the reaction mixture was stirred for 10 min at the same temperature, then warmed to room temperature and stirred for 3 h. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and 1 N HCl aq. was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with aqueous saturated $NaHCO_3$ twice, brine and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and dried in vacuo to give crude amide as a brown oil. The crude amide was dissolved in DMF (12 mL) and piperidine (223 μL, 3.80 mmol) was added, the reaction mixture was stirred for 2 h at room temperature, then diluted with ethyl acetate and H_2O was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with H_2O, brine, then dried over Na_2SO_4. Filtrate was concentrated and the resulting residue was purified by silica gel chromatography (ethyl acetate/*n*-hexane = 16/84 to 100/0) to give **S21** (1.10 g, 2.12 mmol, 84% over 2 steps) as a colorless oil.

Colorless oil; $[\alpha]_D^{26}$ −8.1 (*c* 0.27, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (dd, *J* = 9.0 , 6.1 Hz, 1H), 7.34–7.26 (m, 5H), 6.98 (dd, *J* = 10.5, 2.7 Hz, 1H), 6.70 (ddd, *J* = 9.0, 8.6, 2.7 Hz, 1H), 5.31 (s, 2H), 5.04 (s, 2H), 3.81 (t, *J* = 8.0 Hz, 2H), 3.48 (dd, *J* = 7.2, 5.2 Hz, 1H), 3.14 (t, *J* = 6.6 Hz, 2H), 1.86–1.79 (m, 1H), 1.65–1.46 (m, 5H), 0.95 (t, *J* = 8.0 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 158.8 (d, *J* = 241.3 Hz), 156.4, 147.2 (d, *J* = 10.2 Hz), 136.6, 128.4 (3C), 128.0 (2C), 124.1 (d, *J* = 2.9 Hz), 120.2 (d, *J* = 8.8 Hz), 107.8 (d, *J* = 21.1 Hz), 102.3 (d, *J* = 26.3 Hz), 93.7, 66.7, 66.5, 55.7, 40.6, 34.5, 29.7, 22.8, 17.9, −1.5 (3C); ^{19}F NMR (376 MHz, $CDCl_3$) δ –116.7; IR (neat) *ν* 3019, 1715, 1683, 1525, 1216, 997, 769, 670 cm^{-1}; HRMS (ESI) calcd. for $C_{26}H_{39}N_3O_5FSi$ *m*/*z* 520.2638 $[M+H]^+$, found 520.2616.

(*S*)-Benzyl (6-((4-fluoro-2-hydroxyphenyl)amino)-5-(2-fluoro-5-hydroxybenzamido)-6-oxohexyl)carbamate (1i)

To a solution of EDCI·HCl (404.0 mg, 2.11 mmol) in DMF (5.5 mL) and CH_2Cl_2 (5.5 mL) were successively added OxymaPure® (300.0 mg, 2.11 mmol) and 2-fluoro-5-hydroxybonzoic acid (330.0 mg, 2.11 mmol) at 0 °C. After stirring the reaction mixture for 5 min, **S21** (1.10 g, 2.11 mmol) and DIPEA (400 μL, 2.74 mmol) were added, and the resulting mixture was stirred for 1 h at the same temperature. The reaction mixture was warmed to room temperature and

stirred for 13.5 h. The volatiles were removed under reduced pressure. The residue was diluted with ethyl acetate and 1 N HCl aq. was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with aqueous saturated $NaHCO_3$ twice, H_2O, brine and dried over Na_2SO_4. After filtration, the residue was concentrated under reduced pressure and dried in vacuo to give crude diamide (1.43 g) as a pale brown amorphous. The crude diamide (724 mg) was dissolved in MeOH (3.7 mL) and H_2SO_4 (235 μL, 4.40 mmol) was added. The reaction mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with ethyl acetate and aqueous saturated $NaHCO_3$ was added. The resulting mixture was extracted with ethyl acetate twice, the combined organic layers were washed with H_2O, brine, then dried over Na_2SO_4. Filtrate was concentrated and the resulting residue was purified by silica gel chromatography (acetone/*n*-hexane = 12/88 to 100/0) to give **1i** (540.1 mg, 1.02 mmol, 93% over 2 steps) as a white amorphous.

White amorphous; $[\alpha]_D^{26}$ −7.1 (*c* 0.48, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 7.73 (dd, *J* = 8.8, 6.1 Hz, 1H), 7.32−7.25 (m, 5H), 7.16 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.03 (dd, *J* = 10.5, 8.8 Hz, 1H), 6.91 (ddd, *J* = 8.8, 4.0, 3.2 Hz, 1H), 6.75 (dd, *J* = 10.0, 2.9 Hz, 1H), 6.54 (ddd, *J* = 8.8, 8.6, 2.9 Hz, 1H), 5.02 (s, 2H), 4.72 (dd, *J* = 8.7, 5.3 Hz, 1H), 3.15 (t, *J* = 6.6 Hz, 2H), 2.06−1.96 (m, 1H), 1.92−1.82 (m, 1H), 1.62−1.47 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.5, 166.8 (d, *J* = 2.2 Hz), 161.7 (d, *J* = 240.6 Hz), 159.0, 155.1 (d, *J* = 1.5 Hz), 155.0 (d, *J* = 238.4 Hz), 151.2 (d, *J* = 11.7 Hz), 138.4, 129.4 (2C), 128.9, 128.7 (2C), 124.8 (d, *J* = 9.5 Hz), 123.8 (d, *J* = 14.6 Hz), 123.1 (d, *J* = 2.9 Hz), 120.7 (d, *J* = 8.0 Hz), 117.9 (d, *J* = 24.8 Hz), 117.0 (d, *J* = 2.2 Hz), 106.5 (d, *J* = 22.6 Hz), 103.8 (d, *J* = 25.5 Hz), 67.3, 55.8, 41.4, 32.7, 30.5, 24.0; ^{19}F NMR (376 MHz, CD_3OD) δ –118.2, −128.1; IR (KBr) *ν* 3300, 2937, 1660, 1527, 1454, 1433, 1276, 1190, 1141, 1098, 973, 760, 686 cm^{-1}; HRMS (ESI) calcd. for $C_{27}H_{28}N_3O_6F_2$ *m*/*z* 528.1941 $[M+H]^+$, found 528.1916.

(*S*)-2-fluoro-N-(1-((4-fluoro-2-hydroxyphenyl)amino)-4-methyl-1-oxopentan-2-yl)-5-hydroxy-4-methylbenzamide (1j)

White amorphous; $[\alpha]_D^{25}$ −10.7 (*c* 1.67, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ7.73 (dd, *J* = 8.9, 6.2 Hz, 1H), 7.13 (d, *J* = 6.4 Hz, 1H), 6.95 (d, *J* = 11.5 Hz, 1H), 6.59 (dd, *J* = 10.0, 2.7 Hz, 1H), 6.54 (ddd, *J* = 8.9, 8.7, 2.7 Hz, 1H), 4.79 (t, *J* = 7.0 Hz, 1H), 2.22 (s, 3H), 1.85−1.76 (m, 3H), 1.01 (t, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.1, 166.9 (d, *J* = 2.2 Hz), 161.7 (d, *J* = 240.6 Hz), 154.8 (d, *J* = 238.4 Hz), 153.1 (d, *J* = 2.2 Hz), 151.2 (d, *J* = 11.7 Hz), 132.3 (d, *J* = 8.0 Hz), 124.6 (d, *J* = 10.2 Hz), 123.1 (d, *J* = 2.9 Hz), 120.5 (d, *J* = 13.9 Hz), 118.8 (d, *J* = 24.8 Hz), 115.9 (d, *J* = 2.2 Hz), 106.5 (d, *J* = 22.6 Hz), 103.8 (d, *J* = 25.5 Hz), 54.5, 41.9, 26.1, 23.5, 22.0, 16.3; ^{19}F NMR (376 MHz, CD_3OD) δ –118.1, –127.7; IR (KBr) *ν* 3285, 2960, 1647, 1531, 1434, 1189 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{22}N_2O_4F_2Na$ *m*/*z* 415.1424 $[M+Na]^+$, found 415.1437.

(*S*)-6-fluoro-N-(1-((4-fluoro-2-hydroxyphenyl)amino)-4-methyl-1-oxopentan-2-yl)-3-hydroxy-2-methylbenzamide (1k)

White amorphous; $[\alpha]_D^{26}$ −38.1 (*c* 1.86, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 7.82 (dd, *J* = 8.8, 6.1 Hz, 1H), 6.82 (dd, *J* = 9.3, 8.8 Hz, 1H), 6.78 (dd, *J* = 8.8, 4.9 Hz, 1H), 6.61 (dd, *J* = 10.0, 2.9 Hz, 1H), 6.56 (ddd, *J* = 8.8, 8.6, 2.7 Hz, 1H), 4.78 (dd, *J* = 9.2, 6.2 Hz, 1H), 2.19 (s, 3H), 1.88−1.72 (m, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD)

δ 172.8, 168.9, 161.5 (d, *J* = 240.6 Hz), 153.7 (d, *J* = 234.8 Hz), 152.9 (d, *J* = 2.2 Hz), 150.8 (d, *J* = 10.9 Hz), 126.9 (d, *J* = 19.0 Hz), 124.8 (d, *J* = 2.9 Hz), 124.0 (d, *J* = 9.5 Hz), 123.3 (d, *J* = 3.7 Hz), 117.0 (d, *J* = 8.0 Hz), 113.8 (d, *J* = 23.3 Hz), 106.5 (d, *J* = 21.9 Hz), 103.7 (d, *J* = 24.8 Hz), 54.2, 41.4, 25.9, 23.6, 21.6, 13.0 (d, *J* = 1.5 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ –118.3, –130.3; IR (KBr) *ν* 3274, 3112, 2961, 1666, 1549, 1524 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{22}N_2O_4F_2Na$ *m*/*z* 415.1424 [M+Na]$^+$, found 415.1436.

(*S*)-2-fluoro-N-(1-((4-fluoro-2-hydroxy-6-methylphenyl)amino)-4-methyl-1-oxopentan-2-yl)-5-hydroxybenzamide (1l)

White amorphous; $[\alpha]_D^{26}$ −38.5 (*c* 0.62, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.14 (dd, *J* = 5.9 , 2.9 Hz, 1H), 7.04 (dd, *J* = 10.4, 8.9 Hz, 1H), 6.91 (ddd, *J* = 8.9, 4.0, 2.9 Hz, 1H), 6.48 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.45 (dd, *J* = 9.5, 2.9 Hz, 1H), 4.81 (t, *J* = 7.6 Hz, 1H), 2.18 (s, 3H), 1.91−1.80 (m, 3H), 1.04 (t, *J* = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 172.2, 166.8 (d, *J* = 2.2 Hz), 163.2 (d, *J* = 241.3 Hz), 155.6 (d, *J* = 12.4 Hz), 155.0 (d, *J* = 238.4 Hz), 155.0 (d, *J* = 2.2 Hz), 138.3 (d, *J* = 10.9 Hz), 123.7 (d, *J* = 15.3 Hz), 120.7 (d, *J* = 8.0 Hz), 120.0 (d, *J* = 2.9 Hz), 117.9 (d, *J* = 24.8 Hz), 117.0 (d, *J* = 2.2 Hz), 108.3 (d, *J* = 21.9 Hz), 101.7 (d, *J* = 24.8 Hz), 54.1, 42.1, 26.0, 23.4, 22.2, 18.4 (d, *J* = 1.5 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ –116.1, –128.1; IR (KBr) *ν* 3447, 3385, 3241, 1654, 1541, 1496 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{22}N_2O_4F_2Na$ *m*/*z* 415.1424 [M+Na]$^+$, found 415.1440.

(*S*)-2-fluoro-N-(1-((4-fluoro-2-hydroxy-5-methylphenyl)amino)-4-methyl-1-oxopentan-2-yl)-5-hydroxybenzamide (1m)

White amorphous; $[\alpha]_D^{26}$ −18.6 (*c* 1.73, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.59 (d, *J* = 8.3 Hz, 1H), 7.13 (dd, *J* = 5.9, 3.2 Hz, 1H), 7.04 (d, *J* = 10.0, 8.8 Hz, 1H), 6.91 (ddd, *J* = 8.8, 4.0, 3.2 Hz, 1H), 6.55 (d, *J* = 10.8 Hz, 1H), 4.78 (t, *J* = 7.1 Hz, 1H), 2.14 (d, *J* = 1.7 Hz, 3H), 1.83−1.77 (m, 3H), 1.01 (t, *J* = 5.6 Hz, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 173.0, 167.0 (d, *J* = 2.2 Hz), 159.6 (d, *J* = 240.0 Hz), 155.0 (d, *J* = 2.2 Hz), 154.9 (d, *J* = 238.4 Hz), 148.9 (d, *J* = 10.9 Hz), 125.8 (d, *J* = 6.6 Hz), 124.0 (d, *J* = 15.3 Hz), 122.6 (d, *J* = 2.9 Hz), 120.6 (d, *J* = 8.8 Hz), 117.9 (d, *J* = 24.8 Hz), 116.9 (d, *J* = 2.2 Hz), 115.8 (d, *J* = 18.2 Hz), 103.6 (d, *J* = 26.2 Hz), 54.5, 41.8, 26.1, 23.5, 22.0, 13.8 (d, *J* = 2.9 Hz); ^{19}F NMR (376 MHz, CD_3OD) δ –121.8, –128.3; IR (KBr) *ν* 3403, 3291, 1647, 1527, 1499 cm^{-1}; HRMS (ESI) calcd. for $C_{20}H_{22}N_2O_4F_2Na$ *m*/*z* 415.1424 [M+Na]$^+$, found 415.1434.

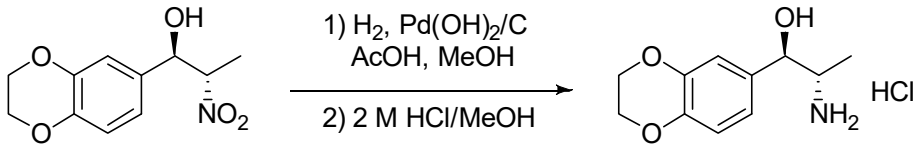
9. Procedure for nitroaldol reaction in flow

To a flame dried test tube (20 mL) equipped with a magnetic stirring bar and 3-way glass stopcock was charged with $NdCl_3 \cdot 6H_2O$ (8.6 mg, 0.024 mmol), and dried under vacuum at room temperature. Ar was backfilled (evacuation/backfill was repeated for several times) to the flask, and THF (400 μL) and ligand **1a** (400 μL, 0.024 mmol, 0.06 M/THF were added successively by well-dried syringes and needles at room temperature. After stirring the resulting cloudy solution at 60 °C for 30 min, NaO^{t}Bu (72 μL, 0.144 mmol, 2.0 M/THF) was added dropwise at the same temperature. After stirring the resulting mixture at 60 °C for 1 h (white precipitate appeared), the mixture was cooled to room temperature, and MWNT (Baytubes® C 70P, 36 mg, 400 wt% to ligand **1a**) and nitroethane (**3a**) (172 μL, 2.4 mmol) were added to initiate self-assembly of the catalyst in the fibrous matrix of MWNT. After stirring

at room temperature for 12 h, dried Celite (350 mg [pretreatment: Celite (50 g) was suspended in dry THF (250 mL) then filtered, which was subsequently washed by dry THF (250 mL). The washed Celite was dried under vacuum (ca. 0.6 kPa) at room temperature]) was added to the MWNT-catalyst. The resulting mottled black/white suspension was transferred by a glass pippet to a YMC stainless-steel empty column (φ 4.6 x 100 mm) fitted with an end-capping bearing a 2 μm stainless steel frit at the bottom under mostly Ar atmosphere (operated under the Ar flow with an inverted funnel). The elution of THF was accelerated by suction from the bottom side using a syringe. All the solid material was transferred by rinsing with minimum amount of dry THF, then the top of the column was sealed with an end-cap bearing a 2 μm stainless steel frit. Dry THF was passed through the column at 200 μL/min for 2 h to wash away soluble incomplete complexes. The catalyst column, pretreatment columns (MS3Å column: φ 10 x 30 mm, MS3Å powder (dried by 3 cycles of heating (microwave oven)/vacuum drying) was packed in full; $NaHCO_3$ column: φ 10 x 30 mm, $NaHCO_3$ powder was packed in full), a mixer (YMC Deneb mixer), a precooling coil (stainless-steel, inner diameter: 0.5 mm, outer diameter 1/16 inch), and syringe pumps (Harvard PHP-ULTRA 4400) were concatenated with stainless-steel tubing (inner diameter: 0.5 mm, outer diameter 1/16 inch) as shown in Scheme 16. THF solutions of 3, 4-ethylenedioxybenzaldehyde (**5**) (0.2 M) and nitroethane (**3a**) (2.0 M) were passed through the flow system by two syringe pumps at 1.5 mL/h at room temperature for 1 h. The precooling coil and the catalyst column were immersed into a cryogenic reactor operated at –40 °C (with ^{i}PrOH as a medium) and these substrates were passed through the flow system by two syringe pumps at 0.6 mL/h at –40 °C for 3 h. Nd^{3+} content in the initial THF wash-out and substrates wash-out was determined to be 1.6 μmol (6.5% of Nd^{3+} used for catalyst preparation was eluted without complexation) by MP-AES (microwave plasma atomic emission spectrometry) analysis, and 93.5% of Nd^{3+} (22.4 μmol) was charged in the catalyst column. The nitroaldol reaction was occasionally monitored. Diastereomeric ratio and enantiomeric excess were determined using small aliquot of the eluted sample using the same procedures described above. After 398 h, the collected eluents were concentrated and purified by silica gel column chromatography, eluent: *n*-hexane/ethyl acetate 85/15 to 34/66) to give **6** (8.89 g, 37.2 mmol, 81%, *anti*/*syn* = >20/1, 95% ee (*anti*)). TON was calculated as 1661.

10. Preparation and Characterization of 10, 11

(1*R*,2*S*)-2-amino-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)propan-1-ol (11)



6 **11**

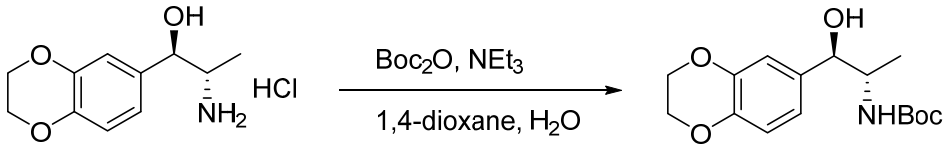
To a solution of **6** (4.68 g, 19.6 mmol, 95% ee, obtained from the flow reaction) in MeOH (47 mL) were added AcOH (1.17 mL, 20.54 mmol) and $Pd(OH)_2/C$ (468.0 mg [20 wt%Pd, 50% wet]) and the resulting mixture was stirred at room temperature under H_2 atmosphere for 9 h. After filtration through a pad of Celite, 2 M HCl/MeOH (97.8 mmol, 49 mL) was added to

the filtrate and the mixture was stirred at room temperature for 2 h. The volatile was removed under reduced pressure, diethyl ether (23 mL) was added to the residue. The slurry was stirred at room temperature for 2 h, the collected precipitates were dried in vacuo at 40 °C to give **11** (4.47 g, 18.2 mmol, 93%) as a white solid of HCl salt. **11** is a known compound (CAS: 1028459-57-5).

White solid; m.p. 218−220 °C; $[\alpha]_D^{26}$ −32.4 (*c* 1.80, CH_3OH); ^1H NMR (400 MHz, CD_3OD) δ 6.89−6.81 (m, 3H), 4.79 (d, *J* = 3.7 Hz, 1H), 4.26−4.21 (m, 4H), 3.43 (qd, *J* = 6.8, 3.7 Hz, 1H), 1.10 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 145.1, 144.8, 134.4, 120.0, 118.2, 116.1, 73.0, 65.6, 65.6, 53.7, 12.5; IR (KBr): *ν* 33307, 3073, 2979, 2209, 1593, 1509, 1490, 1314, 1286, 1064, 1045 cm^{-1}; HRMS (ESI) calcd. for $C_{11}H_{16}NO_3$ *m*/*z* 210.1125 $[M+H]^+$, found 210.1124.

Enantiopurity of amino alcohol **11** was determined after converting to **10** by the following procedure.

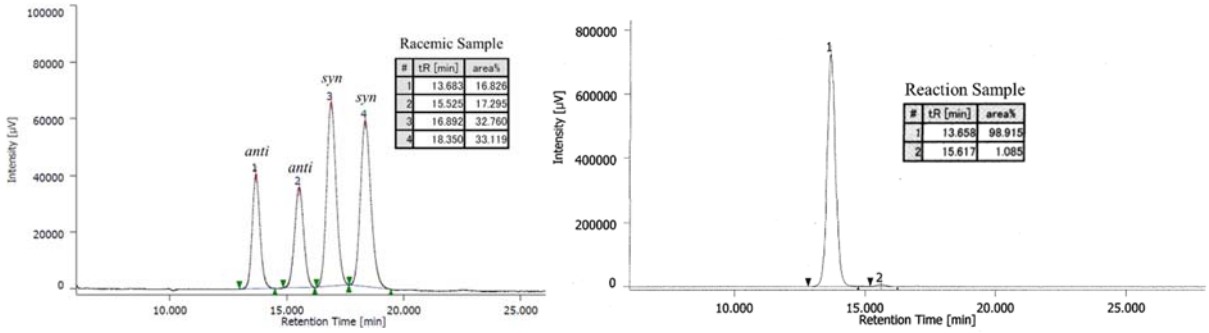
***tert*-Butyl ((1*R*,2*S*)-1-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-1-hydroxypropan-2-yl)carbamate (10)**



11 **10**

To a solution of **11** (700.0 mg, 2.85 mmol) in 1.4-dioxane (3.5 mL) and H_2O (3.5 mL) were added Boc_2O (1.24 g, 5.70 mmol) and NEt_3 (1.19 mL, 8.55 mmol), then the resulting mixture was stirred at room temperature for 3 h. An aqueous saturated NH_4Cl was added and the mixture was extracted with ethyl acetate twice. The combined organic layers were washed with H_2O, brine and dried over Na_2SO_4. Filtrate was concentrated and the resulting residue was purified by silica gel chromatography (ethyl acetate/*n*-hexane = 12/88 to 100/0) to give **10** (794.3 mg, 2.57 mmol, 90%) as a white solid. **10** is a known compound (CAS: 1028459-58-6).

White solid; m.p. 165−166 °C; $[\alpha]_D^{26}$ −60.9 (*c* 0.37, $CHCl_3$ 98% ee sample); ^1H NMR (400 MHz, $CDCl_3$) δ 6.86−6.78 (m, 3H), 4.75 (d, *J* = 3.0 Hz, 1H), 4.60 (brs, 1H), 4.25 (s, 4H), 3.95 (brs, 1H), 1.46 (s, 9H), 0.99 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 143.2, 142.8, 134.2, 119.3, 116.8, 115.3, 79.7, 76.3, 64.3 (2C), 51.9, 28.6 (C3), 14.9; IR (neat) *ν* 3019, 2960, 1509, 1216, 1002, 940, 859, 838, 756, 669 cm^{-1}; HRMS (ESI) calcd. for $C_{16}H_{23}NO_5Na$ *m*/*z* 332.1468 $[M+Na]^+$, found 332.1459. HPLC analysis [CHIRALPAK IF (*φ* 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 1/9, flow rate 1.0 mL/min, detection 215 nm, t_R = 13.5 min (major), 15.4 min (minor)]



11. Determination of Absolute Configuration of 10

The absolute configuration of nitroaldol product **6** was determined by X-ray crystallographic analysis of **10**. Single crystals of **10** were obtained from a solution of EtOAc/*n*-hexane. A suitable crystal was selected and the sample was measured on a Rigaku R-AXIS RAPID diffractometer using graphite monochromated Cu-Ka radiation. The data were collected at 93 K. Refined structure and crystallographic parameters are summarized in Figure S1 and Table S1. The ORTEP diagram was drawn by OLEX[2]. CCDC 1518441 contains the supplementary crystallographic data for **10**.

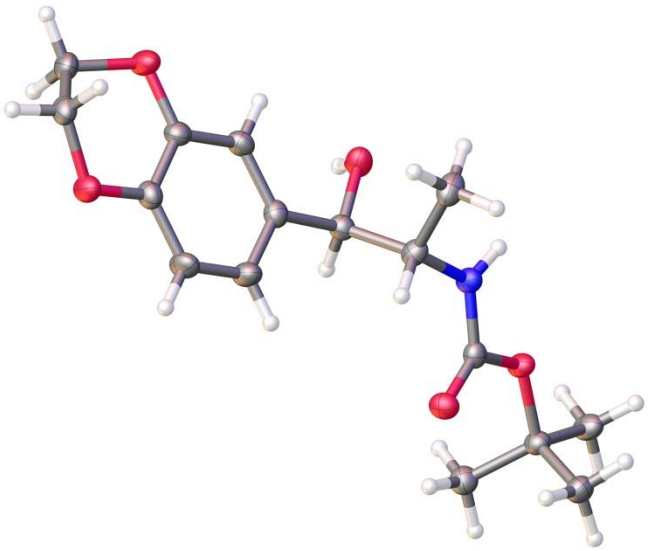


Table S1. Selected crystal data of **10**

Empirical Formula	$C_{16}H_{23}NO_5$
Formula Weight	309.36
Crystal Color, Habit	colorless, platelet
Crystal Dimensions	0.300 x 0.200 x 0.050 mm
Crystal System	orthorhombic
Lattice Parameters	
a	5.87790(11) Å
b	9.68673(19) Å
c	27.8302(5) Å
V	1615.83(11) Å^3
Space Group	$P2_12_12_1$
Z value	4

D_{calc}	1.297 g/cm^3
R1	0.0315
Flack parameter [1]	–0.09(4)
F_{000}	664.00

Figure S2. ORTEP diagram of **10**. Ellipsoids are set at 50% probability.

12. **Price List of Nd and Na salts**.

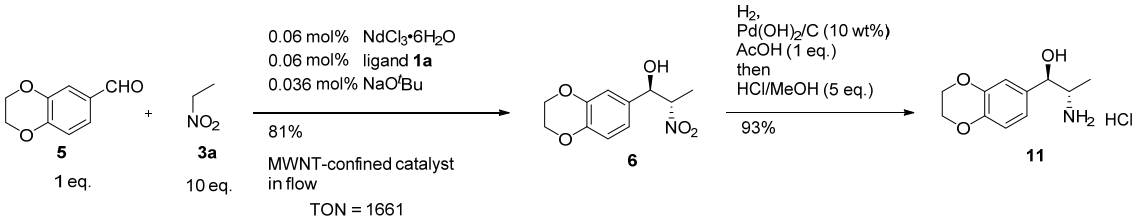
Nd source	MW	Weight [g]	Eur [	Eur/g-Nd	Supplier
$Nd_5O(O^iPr)_{13}$	1505.34	1	114.28	238.5	Kojundo Chem. Lab.Co.
$Nd(HMDS)_3$	625.40	5	224	194.2	ABCR GmbH & Co.
$Nd(OH)_3$	195.26	10	123	16.7	Sigma-Aldrich
$Nd(NO_3)_3 \cdot 6H_2O$	438.35	100	107.5	3.3	Sigma-Aldrich
$Nd(OAc) \cdot H_2O$	339.39	250	190	1.8	ABCR GmbH & Co.
NdF_3	201.24	250	177.7	1.0	ABCR GmbH & Co.
$NdCl_3$	250.60	50	308	10.7	ABCR GmbH & Co.
$NdBr_3$	383.95	25	374	39.8	ABCR GmbH & Co.
$NdCl_3 \cdot 6H_2O$	358.69	25	71.7	7.1	Sigma-Aldrich
$NdCl_3 \cdot 6H_2O$	358.69	250	156	1.6	ABCR GmbH & Co.

Na source	MW	Weight [g]	Eur	Eur/g-Na	Supplier
NaHMDS	183.37	100	444.5	35.5	Sigma-Aldrich
NaO^tBu	96.10	2500	335	0.6	Alfa Aesar
NaOEt	68.05	500	451.9	0.2	Sigma-Aldrich
NaO^tAm	110.13	500	278	2.7	Sigma-Aldrich

13. Cost Evaluation

Comparison of variable cost of **11** between new synthetic approach (Table S1) and original synthetic approach (Table S2). The variable costs were calculated based on main reagents (except for solvent and work-up cost).

Table S1. Cost evaluation of **11** by new synthetic approach

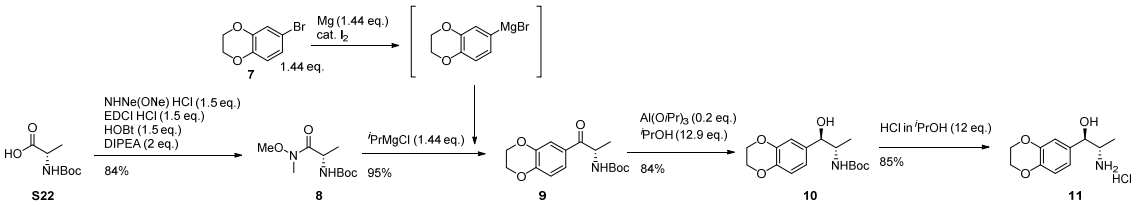


Compound	MW	Unit	Price	Variable cost per 1 kg of **11** [a]	Supplier
Aldehyde **5**	164.16	5 kg	$6,565	¥123,583	AURUM Pharmatech, LLC
Nitroethane (3a)	75.07	2.5 kg	€148	¥31,270	ABCR GmbH & Co.
Lingand **1a** [b]	378.38	1 kg	¥843,964	¥1,002	-
$NdCl_3$ $6H_2O$	358.69	0.25 kg	€156.00	¥95	ABCR GmbH & Co.
NaO^tBu	96.1	2.5 kg	€335.00	¥33	Alfa Aesar
$Pd(OH)_2$	140.43	1 kg	$4,587	¥83,587	StruChem Co., Ltd.
AcOH	60.05	18 kg	$155	¥240	Oakwood Chemical
3.3 M HCl in MeOH	36.46	18 L	$795	¥51,070	Oakwood Chemical
total				¥290,880	

[a] $1 = ¥110, €1 = ¥135

[b] Unit price was calculated as described in Table S3

Table S2. Cost evaluation of **11** by original synthetic approach

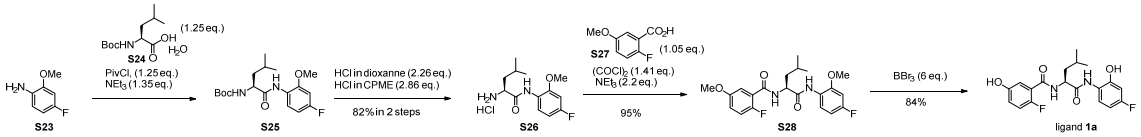


Compound	MW	Unit	Price	Variable cost per 1 kg of **11** [a]	Supplier
S22	189.21	25 kg	$1,767	¥10,031	1Click Chemistry, Inc.
NHMe(OMe) HCl	97.54	25 kg	$3,680	¥16,153	Chem-Impex International Product List Scifinder
EDCI HCl	191.7	10 kg	$2,350	¥50,683	Chem-Impex International Product List Scifinder
HOBt	135.13	25 kg	$1,620	¥9,851	Beta Pharma Scientific, Inc
DIPEA	129.25	2.5 kg	$230	¥17,844	1Click Chemistry Stock Products
7	187.17	5 kg	$5,702	¥202,876	AURUM Pharmatech, LLC

Mg turning	24.31	2.5 kg	$230	¥2,126	Alf Aesar
2 M ^{i}PrMgCl in THF	102.85	0.8 L	$120	¥71,284	Oakwood Chemical Product List
Al(O^{i}Pr)$_3$	204.25	10 kg	$512	¥1,311	Carbosynth Product List
^{i}PrOH	60.1	25 kg	$561	¥10,909	Carbosynth Product List
6 M HCl in ^{i}PrOH	36.46	18 L	$525	¥30,725	Oakwood Chemical Product List
total				¥423,792	

[a] $1 = ¥110, €1 = ¥135

Table S3. Cost evaluation of ligand **1a** by reported synthetic route[12b, 29]



Compound	MW	Unit	Price	Variable cost per 1 kg of ligand **1a** [a]	Supplier
S23	141.15	1 kg	$1,639	¥102,751	1Click Chemistry, Inc.
S24	235.28	1 kg	$200	¥26,132	Hangzhou MolCore BioPharmatech Co., Ltd.
PivCl	120.58	18 kg	$1,250	¥4,650	Oakwood Products, Inc.
NEt$_3$	101.19	25 kg	$750	¥1,821	Carbosynth Limited
4 M HCl in dioxane	36.46	15 L	$825	¥14,289	Oakwood Chemical
3 M HCl in CPME	36.46	3 L	$1,050	¥128,226	Oakwood Chemical
S27	170.14	5 kg	$3,628	¥47,223	1Click Chemistry, Inc.
(COCl)$_2$	120.58	1000 kg	$46,000	¥2,849	Chem-Impex International, Inc.
NEt$_3$	101.19	25 kg	$750	¥2,433	Carbosynth Limited
BBr$_3$	250.52	0.5 kg	$54,300	¥513,589	Sigma-Aldrich
total				¥843,964	

[a] $1 = ¥110, €1 = ¥135

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研究業績

学術論文

Preparation of Nd/Na heterogeneous catalyst from bench-stable and inexpensive Nd salt for an *anti*-selective catalytic asymmetric nitroaldol reaction

Nonoyama, A.; Hashimoto, K.; Saito, A.; Kumagai, N.; Shibasaki, M. *Tetrahedron Lett.* **2016**, *57*, 1815.

Asymmetric flow catalysis: Mix-and-go solid-phase Nd/Na catalyst for expeditious enantioselective access to a key intermediate of AZD7594

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

Synfacts **2017**, *13*, 462.

Synfacts **2017**, *13*, 559.

特許

「触媒、及びその製造方法、並びに光学活性アンチ-1,2-ニトロアルカノール化合物の製造方法」

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