博士論文

創薬への応用を志向した芳香族化合物を対象とする化学変換法の開発

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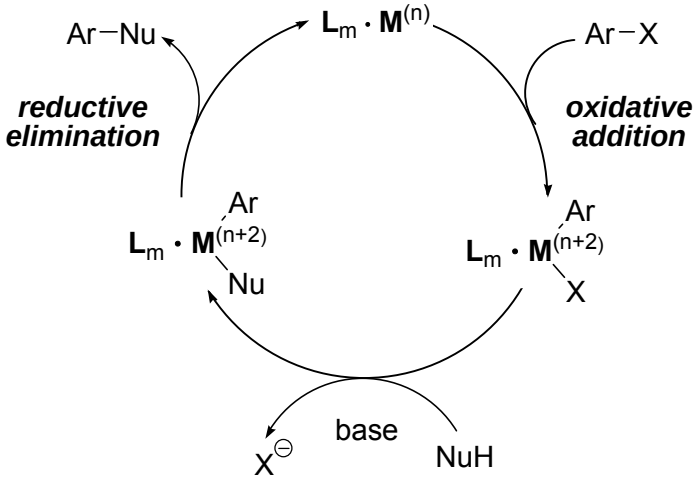
第１章　序論

第１節　はじめに

芳香族化合物は医薬品や天然物などの生物活性化合物中に遍在する重要構造であり、今後も新規医薬品創製において重要な役割を担うと考えられる。そのため、芳香族化合物を対象とした化学変換法の開発は非常に重要である。

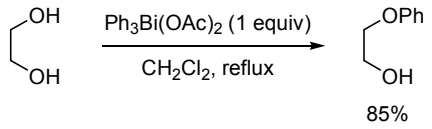
本研究において著者は、芳香族化合物を対象とする高効率反応の開発に挑戦した。ジオール類に対する選択的アリール化法、複素環式構造を含む有用分子の簡便合成法、さらに芳香族への重水素精密導入手法の確立を試みた。これら芳香族化合物合成において適当な脱離基を有するAr－Xから求核置換したAr－Nuを合成するルートを選択した。下図に示すように、遷移金属触媒（$M^{(n)}$）と配位子（L）の組み合わせを適切に選択すれば、これらの新反応を開発出来ると期待した。すなわち酸化的付加および還元的脱離を含む触媒サイクルを基盤とする新たな化学結合形成を目指して本研究を行なった。その結果、第一にアリール源としてジアリールヨードニウム塩を用いたジオール類の選択的モノアリール化反応の開発と共に、触媒的不斉反応へと展開することが出来た。また、複素環式アルデヒドに対するヘテロアリールボロン酸の付加によるアルコールの生成と連続的な酸化を経る複素環ケトンの触媒的ワンポット合成を達成した。さらに、塩素原子を脱離基とした芳香族塩化物に対する効率性と選択性に優れた重水素導入法の開発に成功した。



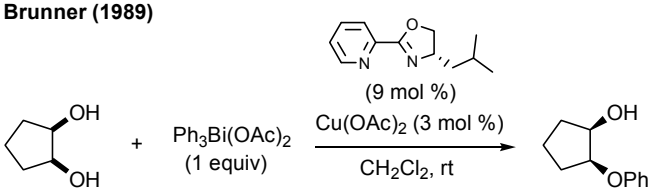
第２節　ジオール類の選択的モノアリール化反応

ジオールのモノアリール化体である β-aryloxy alcohols は有用な合成中間体であり [1]、アリール基上の置換基によっては保護基ともなり得るため、ジオール類に対する選択的モノアリール化反応の開発は有機合成化学上重要である。1981 年に David らによりフェニルビスマス試薬を用いた非触媒的なジオールのモノフェニル化反応がはじめて報告された [2]。さらに Brunner らにより銅触媒を用いたジオール類のエナンチオ選択的モノフェニル化反応が開発された [3a-c]。しかしながら、これらの反応系には触媒効率や基質一般性および化学選択性の観点から課題が残っている。

David (1981)



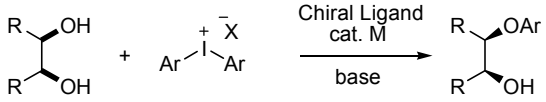
Brunner (1989)



近年、高反応性かつ低毒性であることに加えて合成も容易なジアリールヨードニウム塩が注目されており [4]、アリール源として多くの有用な反応に活用されている [5, 6]。

今回、ジアリールヨードニウム塩の高反応性を活用すると共に、遷移金属によって分子認識と反応促進を同時にはかることによりジオール類の選択的モノアリール化反応を検討した。さらに、キラル配位子を添加することにより不斉化することで触媒的不斉反応への展開も試みた 。

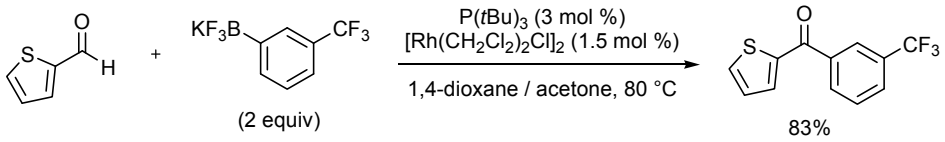
Asymmetric monoarylation of vicinal diols.



第３節　複素環ケトンの合成

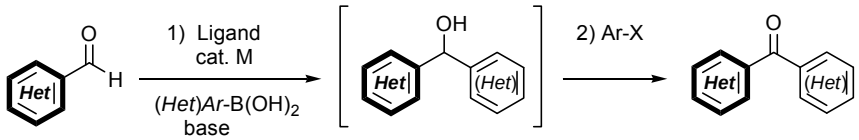
複素環ケトン類は、天然物化合物や生物活性物質のビルディングブロックとなり得るため、その効率的合成手法の確立は、有機合成化学において極めて重要性が高い [7 8]。これまでに遷移金属触媒を用いた代表的な合成法として three-component coupling 反応 [9] と cross-coupling 反応 [10]が報告されているが、いずれも触媒効率および基質適用範囲に関して発展途上にある。2004 年に Darses と Genet がアルデヒドと有機ホウ素試薬を用いたジアリールケトンの触媒的合成法を報告して以来 [11]、このようなアルデヒドのアリール化を経る合成法に対して様々な金属触媒の開発が行なわれきたが、基質耐性に課題が残っており [12]ジヘテロアリールケトンの合成は達成されていない。

Dareses and Genet (2004)



当研究室ではこれまでに *N*-ヘテロ環状カルベン配位子と遷移金属からなる錯体触媒がアルデヒドのアリール化において優れた基質耐性を示すことを見出している [13]。その知見を踏まえ、アルデヒドへの付加によるアルコールの生成と連続的な酸化を経る複素環ケトンの触媒的ワンポット合成法の開発を行った。

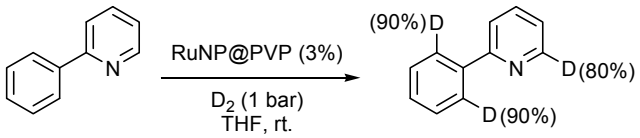
One-Pot Synthesis of Heteroaryl and Diheteroaryl Ketones.



第４節　芳香族化合物に対する重水素導入法

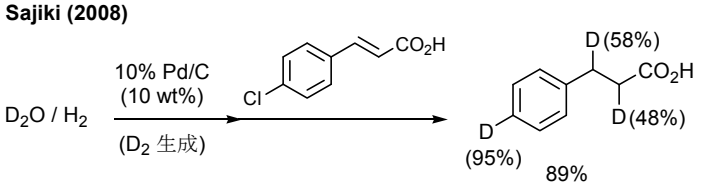
重水素化された化合物は医薬品の生物活性制御に対して高い効力を示すことが知られている[14]。そのために有機化合物に対する重水素導入法が近年、注目を集めている。芳香環は有用生物活性物質に遍在する重要な部分構造であり[15]、芳香環を対象とした様々な重水素導入反応の開発は重要である。これまでに、注目されてきた触媒的手法の代表例として H/D 交換反応が報告されているが、反応点の制御が困難であり、さらに重水素化率に関してもばらつきが生じるという欠点を持つ[16,17]。

Rousseau (2014)



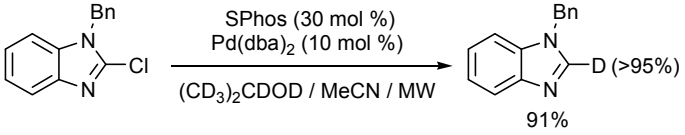
一方、安定性と多様性に優れた芳香族塩素化物を基質とする Cl/D 交換反応の開発が試みられているが、化学選択性の制御が難しいことに加えて重水素化物質を溶媒として用いることや高可燃性の重水素ガスを発生する点が課題として挙げられる[18,19]。

Sajiki (2008)



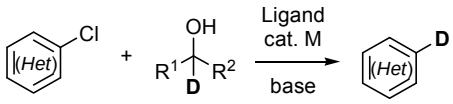
2014 年に Donald らはパラジウム触媒による Cl/D 交換反応を報告した[20]。しかしながらこの触媒系にはマイクロウェーブ照射によって反応を促進することに加えて溶媒量の重水素源が必要である。医薬品開発においては、精密に重水素を導入する必要があることから、効率性と選択性に極めて優れた実用的な重水素化法の開発が望まれる。

Donald (2014)



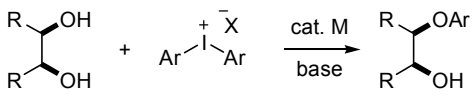
著者は安定かつ安価な芳香族塩化物を基質に用いた Cl/D 交換に着目し、副反応を回避するために反応経路を β-水素脱離経由に定めることにより、実用性と選択性に優れた重水素導入法の開発を試みた。

Deuterodechlorination of Aryl/Heteroaryl Chlorides



第２章　銅触媒を用いたジオール類に対する選択的アリール化反応の開発

Monoarylation of vicinal diols.



第１節　反応の設計

ジアリールヨードニウム塩と銅塩から形成される求電子性に優れた 3 価銅錯体 [21]を反応系に組み込むことを考えた。以下に触媒サイクルを示す (Figure 1)。1 価の銅がジアリールヨードニウム塩に酸化的付加し、3 価の銅中間体が形成される。この中間体にジオールが配位しキレート錯体が形成され、続く還元的脱離によりモノアリール化体が生成すると想定した。この高い求電子性を有する 3 価の銅錯体がジオールを認識および活性化し、さらに価数の変化を伴ってアリール化を進行させることで高効率かつ高選択的なモノアリール化が可能になると期待した。

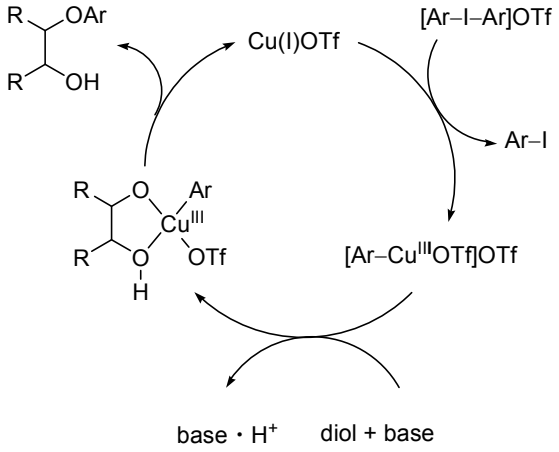
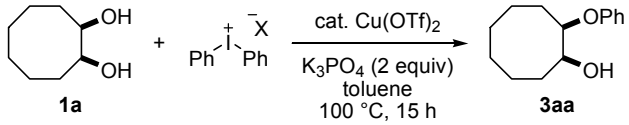


Figure 1

第２節　ジフェニルヨードニウム塩の検討

モデル基質として *cis*-1,2-cyclooctanediol (**1a**)を選択し、ジフェニルヨードニウム塩の検討を行った (Table 1)。ハロゲンイオンを有するヨードニウム塩を用いると目的生成物 **3aa** は低収率でしか得られなかった (entries 1-3)。一方、超強酸の共役塩基を持つ場合はより高い反応性を示し (entries 4-6)、$[Ph_2I]OTf$ は 72%と良好な収率で目的化合物を与えた (entries 6)。さらに、テトラフルオロホウ酸およびヘキサフルオロリン酸イオンを有するヨードニウム塩を検討したが収率は低下した (entries 7 and 8)。

Table 1. Screenig of diphenyliodonium salts.[a]

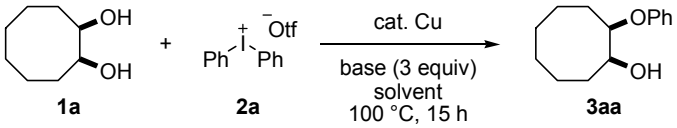


entry	X	yield (%)[b]	entry	X	yield (%)[b]
1	Cl	13	5	ClO_4	37
2	Br	21	6	OTf	72
3	I	11	7	BF_4	61
4	NO_3	20	8	PF_6	61

[a] Reaction conditions: diol **1a** (1.0 mmol), diphenyliodonium salt (1.5 mmol), $Cu(OTf)_2$ (10 mol%), K_3PO_4 (2.0 mmol), solvent (2.0 mL), 100 °C, 15 h. [b] Isolated yield.

第３節　反応条件の最適化

Table 2. Optimization of the reaction conditions[a]



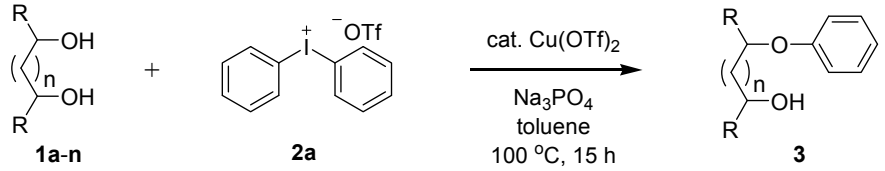
entry	Cu	base	solvent	yield (%)[b]	entry	Cu	base	solvent	yield (%)[b]
1	$Cu(OTf)_2$	K_3PO_4	toluene	76	10	$CuBr_2$	Na_3PO_4	toluene	79
2	$Cu(OTf)_2$	Na_3PO_4	toluene	89	11	CuBr	Na_3PO_4	toluene	75
3	$Cu(OTf)_2$	Li_3PO_4	toluene	73	12	$CuCl_2$	Na_3PO_4	toluene	75
4	$Cu(OTf)_2$	Cs_2CO_3	toluene	39	13	CuCl	Na_3PO_4	toluene	88
5	$Cu(OTf)_2$	K_2CO_3	toluene	0	14	$Cu(acac)_2$	Na_3PO_4	toluene	54
6	$Cu(OTf)_2$	Na_2CO_3	toluene	56	15	-	Na_3PO_4	toluene	18
7	$Cu(OTf)_2$	NaF	toluene	54	16	$Cu(OTf)_2$	Na_3PO_4	dioxane	79
8[c]	$(CuOTf)_2$·tol	Na_3PO_4	toluene	79	17	$Cu(OTf)_2$	Na_3PO_4	DMA	44
9	CuI	Na_3PO_4	toluene	81	18[d]	$Cu(OTf)_2$	Na_3PO_4	toluene	93

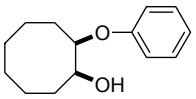
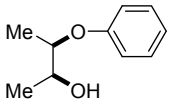
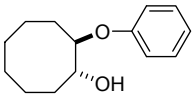
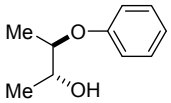
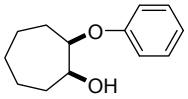
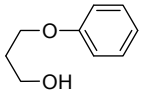
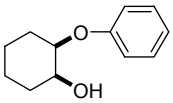
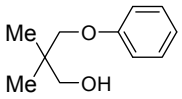
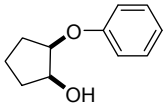
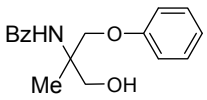
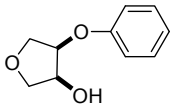
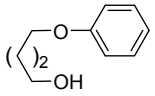
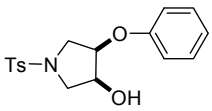
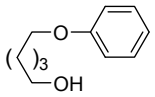
[a] Reaction conditions: diol **1a** (1.0 mmol), diphenyliodonium triflate **2a** (1.5 mmol), Cu (10 mol %), base (3.0 mmol), solvent (2.0 mL), 100 °C, 15 h. [b] Isolated yield. [c] Cu (20 mol %). [d] Toluene (1.5 mL) was used.

cis-1,2-Cyclooctanediol (**1a**) と diphenyliodonium triflate (**2a**) をモデル基質として用い、反応条件の最適化を行なった (Table 2)。塩基は Na_3PO_4 が最も良好な収率を与え (entries 1-7)、銅触媒に関しては $Cu(OTf)_2$ が最も優れた触媒活性を示した (entries 2 and 8-14)。一方、銅触媒非存在下では目的生成物はわずかしか得られなかった (entry 15)。溶媒は toluene が最も適していることが明らかとなり、さらに溶媒量を 1.5 mL に減らして溶液濃度を上げると反応効率が改善された (entries 2, 16, 17, and 18)。

第４節　ジオール類の検討

Table 3. Copper(II)-catalyzed monophenylation of diols with diphenyliodonioum triflate[a]



entry	1	product	3	yield (%)[b]	entry	1	product	3	yield (%)[b]
1	**1a**		**3aa**	93	8	**1h**		**3ha**	75
2	**1b**		**3ba**	75	9	**1i**		**3ia**	57
3	**1c**		**3ca**	94	10	**1j**		**3ja**	83
4[c]	**1d**		**3da**	70	11	**1k**		**3ka**	83
5	**1e**		**3ea**	78	12	**1l**		**3la**	62
6	**1f**		**3fa**	88	13	**1m**		**3ma**	90
7	**1g**		**3ga**	83	14	**1n**		**3na**	37

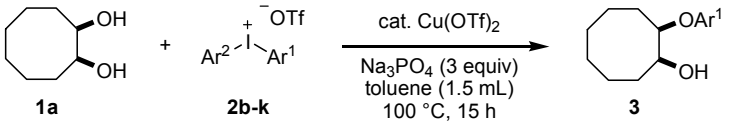
[a] Reaction conditions: Diol **1** (1.0 mmol), diphenyliodonium triflate **2a** (1.5 mmol), $Cu(OTf)_2$ (10 mol %), Na_3PO_4 (3.0 mmol), toluene (1.5 mL), 100°C, 15h. [b] Isolated yield. [c] Diphenyliodonium triflate **2a** (2.5 mmol) and toluene (2.0 mL) were used.

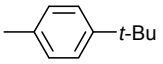
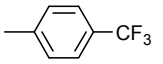
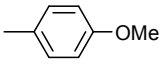
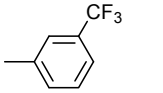
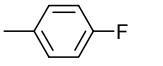
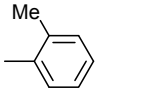
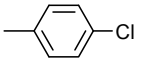
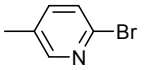
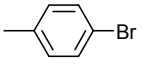
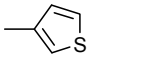
最適条件を用いて様々なジオール類の検討を行った（Table 3)。環状ジオールを用いた場合には、対応するモノアリール化体 **3aa-3ea** を高収率で与えた (entries 1-5)。さらに、複素環式ジオールにも適用可能であることを見い出した (entries 6 and 7)。続いて、鎖状ジオールの検討を行った。*meso*-2,3-butanediol からは良好な収率で目的化合物が得ることができたが、*threo*-2,3-butanediol を用いると収率は中程度にとどまった (entries 8 and 9)。さらに、1,3-ジオールである **1j-k** からは高効率的にモノアリール化体へと変換された (entries 10 and 11)。これに加えて、第二級アミドを有するジオールについてもアリー

ル化は進行し、中程度の収率で対応する化合物 **3la** を与えた (entry 13)。また 1,4-ジオールは優れた収率で速やかに目的化合物 **3ma** へと変換されたが、1,5-ジオールに関しては低収率にとどまった (entries 13 and 14)。

第５節　ジアリールヨードニウムトリフラートの検討

Table 4. Copper(II)-catalyzed monoarylation of *cis*-1,2-cyclooctanediol with diaryliodonium triflates[a]



entry	Ar^2	Ar^1	2	3	yield (%)[b]	entry	Ar^2	Ar^1	2	3	yield (%)[b]
1	(=Ar^1)		**2b**	**3ab**	93	6	(=Ar^1)		**2g**	**3ag**	99
2	(=Ar^1)		**2c**	**3ac**	92	7	(=Ar^1)		**2h**	**3ah**	94
3	(=Ar^1)		**2d**	**3ad**	94	8	(=Ar^1)		**2i**	**3ai**	94
4	(=Ar^1)		**2e**	**3ae**	96	9	(Tep[d])		**2j**	**3aj**	61
5	(=Ar^1)		**2f**	**3af**	99	10[c]	(Mes[e])		**2k**	**3ak**	70

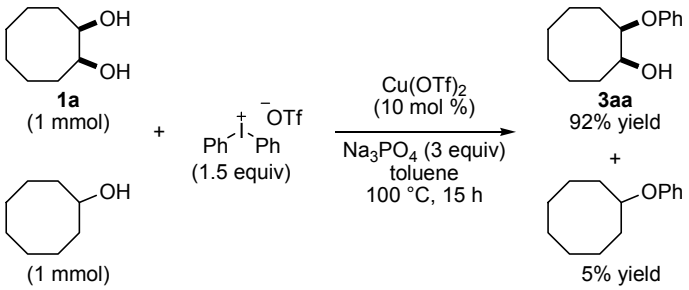
[a] Reaction conditions: diol **1** (1.0 mmol), diphenyliodonium triflate **2** (1.5 mmol), $Cu(OTf)_2$ (10 mol %), Na_3PO_4 (3.0 mmol), toluene (1.5 mL), 100° C, 15 h. [b] Isolated yield. [c] Diphenyliodonium triflate **2** was used. [d] Tep: 2,4,6-triethylphenyl. [e] Mes: 2,4,6-trimethylphenyl.

同一条件下において *cis*-1,2-cyclooctanediol (**1a**) を用い、様々な置換基を持つジアリールヨードニウムトリフラートを検討した (Table 4)。電子供与性および電子求引性置換基が存在する場合でもアリール基上の電子的な影響を受けることなく優れた収率でモノアリール化体を与えた (entries 1-7)。立体障害を持つヨードニウム塩も本反応に適用可能であり良好に反応が進行した (entry 8)。また、窒素および硫黄原子を有する芳香族性複素環の導入にも成功した (entries 9 and 10)。

第６節　化学選択性および位置選択性の検討

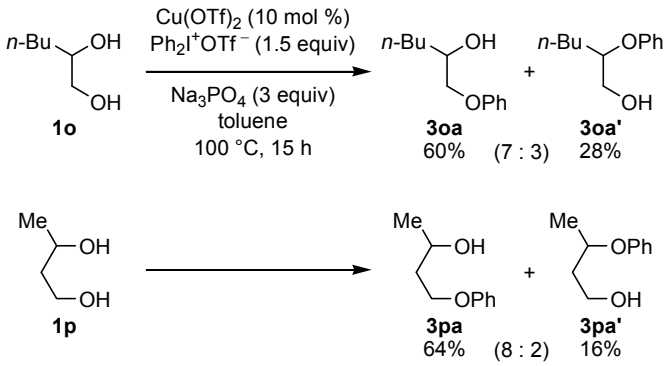
化学選択性を検討するために *cis*-1,2-cyclooctanediol (**1a**)と cyclooctanol を 1:1 のモル比で混合した状態でアリール化反応を試みた。その結果、高収率でモノアリール化体 **3aa** を得る一方、モノオールのアリール化体の生成は 5%にとどまった。反応系中にジオールおよびモノオールの両方が共存する場合にも、ジオールが優れた化学選択性でモノアリール化されることが明らかとなった。

Scheme 1. Copper(II)-catalyzed phenylation with *cis*-1,2-cyclooctanediol and cyclooctanol



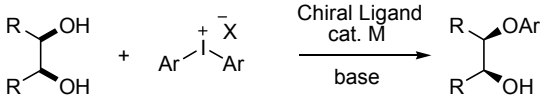
次に非対称な 1,2-ジオール **1o** と 1,3-ジオール **1p** を用いて位置選択性の検討を行った。**1o** および **1p** ともに反応は良好な収率で進行し、立体障害の小さい一級水酸基が良好な選択性でアリール化された。

Scheme 2. Copper(II)-catalyzed monophenylation of unsymmetrical diols



第３章　キラル銅触媒によるジオール類の不斉モノアリール化反応の開発

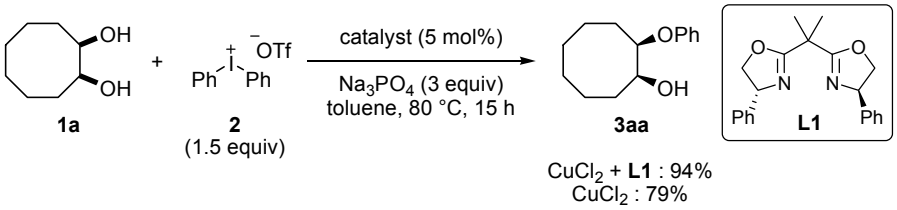
Asymmetric monoarylation of vicinal diols.



第１節　不斉配位子による反応の加速効果

最初に *cis*-1,2-cyclooctanediol (**1a**) と diphenyliodonium triflate (**2a**) をモデル基質として用いて、配位子による反応の加速効果を検討した (Scheme 3)。(*R*,*R*)-Ph-Box を用いないで反応を行なうと収率は 79%に留まった一方、(*R*,*R*)-Ph-Box を添加することで収率は 94%に向上し、加速効果が観測された。

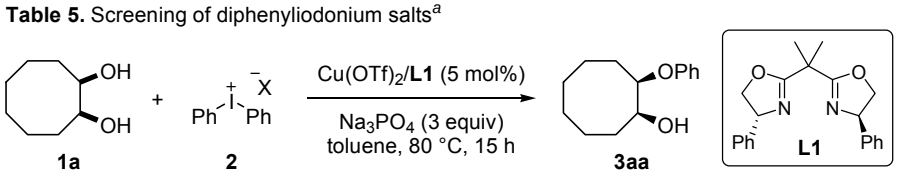
Scheme 3.



第２節　ジフェニルヨードニウム塩の検討

cis-1,2-cyclooctanediol (**1a**) を基質としてジフェニルヨードニウム塩の検討を行った (Table 5)。ハロゲンや硝酸イオンを有するヨードニウム塩を用いた場合、極めて低い収率かつ選択性で目的化合物 **3aa** が得られた（entries 1-3)。一方、[Ph_2I]OTf に関しては高い反応性を示し、良好な不斉収率で目的化合物を与えた（entry 4)。収率およびエナンチオ選択性の改善を試みてテトラフルオロホウ酸およびヘキサフルオロリン酸イオンを有するヨードニウム塩を検討したが収率と選択性は共に低下した（entries 5 and 6)。

Table 5. Screening of diphenyliodonium salts[a]



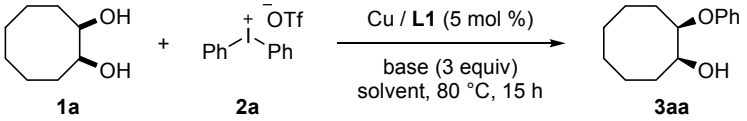
entry	X	yield (%)[b]	ee (%)[c]	entry	X	yield (%)[b]	ee (%)[c]
1	Br	4	3	4	OTf	90	59
2	I	1	2	5	BF_4	50	29
3	NO_3	15	1	6	PF_6	64	0

[a] Reaction conditions: diol **1a** (1 mmol), diphenyliodonium salt **2** (1.5 mmol), $Cu(OTf)_2$ (5 mol %), Na_3PO_4 (3 mmol), solvent (1.5 mL), 80° C, 15 h. [b] Isolated yield. [c] Determined by HPLC.

第３節　反応条件の最適化

モデル基質に *cis*-1,2-cyclooctanediol (**1a**) と diphenyliodonium triflate (**2a**) を用いて条件検討を行なった (Table 6)。無機塩基では Na_3PO_4 が最も良好な収率およびエナンチオ選択性で目的化合物 **3aa** を与えた一方、*N*,*N*-diisopropylethylamine を用いた場合、不斉収率は中程度にとどまった (entries 1-6)。また、2 価の銅錯体は 1 価の銅錯体と同等の反応性を示し、$CuCl_2$ を用いてアリール化を行なったところ、94%収率、76% ee でモノアリール化体を与えた (enrries 2 and 7-16)。溶媒は toluene を用いた場合のみ良好なエナンチ選択性で目的化合物を与えた (entries 2 and 17-20)。

Table 6. Optimization of the reaction conditions[a]



1a　　**2a**　　**3aa**

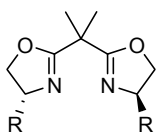
entry	Cu	base	solvent	yield (%)[b]	ee (%)[c]	entry	Cu	base	solvent	yield (%)[b]	ee (%)[c]
1	$Cu(OTf)_2$	K_3PO_4	toluene	21	3	11	$CuCl_2$	Na_3PO_4	toluene	94	76
2	$Cu(OTf)_2$	Na_3PO_4	toluene	90	59	12	CuCl	Na_3PO_4	toluene	89	43
3	$Cu(OTf)_2$	Li_3PO_4	toluene	52	9	13	CuF_2	Na_3PO_4	toluene	9	0
4	$Cu(OTf)_2$	Na_2CO_3	toluene	50	41	14	$Cu(OAc)_2$	Na_3PO_4	toluene	82	54
5	$Cu(OTf)_2$	NaF	toluene	88	9	15	CuOAc	Na_3PO_4	toluene	77	67
6	$Cu(OTf)_2$	DIPEA	toluene	95	33	16	$Cu(tfac)_2$[d]	Na_3PO_4	toluene	82	54
7	$(CuOTf)_2$·tol	Na_3PO_4	toluene	84	64	17	$Cu(OTf)_2$	Na_3PO_4	DCE[e]	93	2
8	CuI	Na_3PO_4	toluene	89	65	18	$Cu(OTf)_2$	Na_3PO_4	dioxane	74	11
9	$CuBr_2$	Na_3PO_4	toluene	93	69	19	$Cu(OTf)_2$	Na_3PO_4	DMA	55	11
10	CuBr	Na_3PO_4	toluene	42	39	20	$Cu(OTf)_2$	Na_3PO_4	*i*-PrOH	27	27

[a] Reaction conditions: diol **1a** (1 mmol), diphenyliodonium triflate **2a** (1.5 mmol), Cu (5 mol %), **L1** (5 mol %), base (3.0 mmol), solvent (1.5 mL), 80 °C, 15 h. [b] Isolated yield. [c] Determined byHPLC. [d] tfac: trifluoroacetylacetonate. [e] DCE: 1,2-dichloroethane.

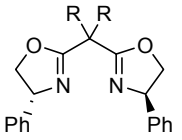
第４節　配位子の検討

cis-1,2-Cyclooctanediol (**1a**) と diphenyliodonium triflate (**2a**) を用いて光学活性なオキサゾリン骨格を有する二座および三座配位子の検討を行なった (Table 7)。キラルビスオキサゾリン配位子中の 4 位における置換基を種々検討したところ、フェニル基を置換基に持つ配位子が高収率かつ良好なエナンチオ選択的で目的化合物 **3aa** を与えた (entries 1-5)。また、メチレン架橋部がブチル基に置換された配位子はアリル基やベンジル基で置換された配位子よりも優れた反応性と選択性を示した(entries 6-8)。キラルビスオキサゾリン配位子中の 5 位が置換された配位子を用いた場合、殆ど不斉は誘起されなかった (entries 9 and 10)。さらに、他のキラルオキサゾリン配位子を用いて不斉モノアリールを試みたが、いずれも極めて低い不斉収率で **3aa** を与えた (entries 11-18)。

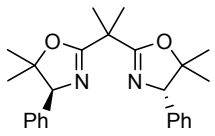
Figure 2. Chiral ligands based on optically active oxazolines



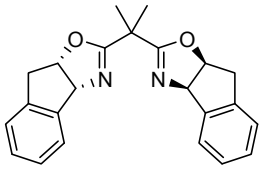
L1: R= Ph
L2: R= 4-MeOPh
L3: R= 2-naph
L4: R= 2,4,6-Me_3Ph
L5: R= Bn



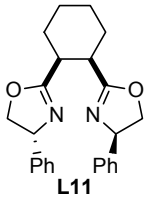
L6: R= *n*-Bu
L7: R= allyl
L8: R= Bn



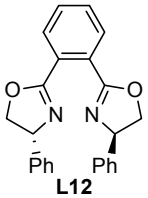
L9



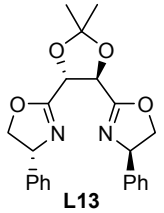
L10



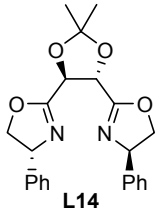
L11



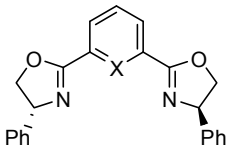
L12



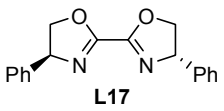
L13



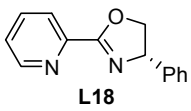
L14



L15: X= CH
L16: X= N

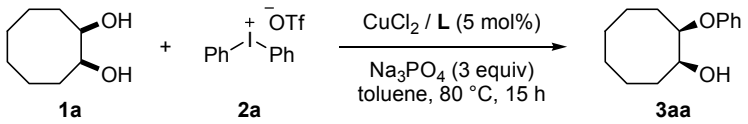


L17



L18

Table 7. Screening of chiral ligands in the copper-catalyzed asymmetric mono-phenylation of *cis*-1,2-cyclooctanediol[a]



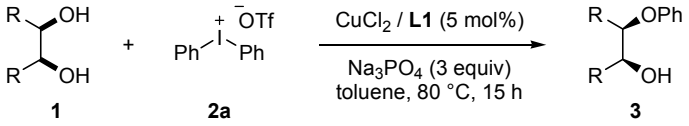
1a **2a** **3aa**

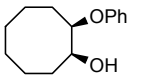
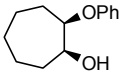
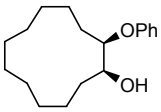
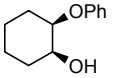
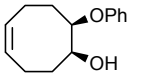
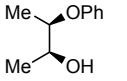
entry	L	yield (%)[b]	ee (%)[c]	entry	L	yield (%)[b]	ee (%)[c]
1	**L1**	94	76	10	**L10**	8	2
2	**L2**	96	68	11	**L11**	59	4
3	**L3**	75	53	12	**L12**	60	6
4	**L4**	51	30	13	**L13**	49	6
5	**L5**	78	40	14	**L14**	64	3
6	**L6**	87	77	15	**L15**	65	2
7	**L7**	84	74	16	**L16**	56	12
8	**L8**	71	50	17	**L17**	82	0
9	**L9**	81	0	18	**L18**	77	0

[a] Reaction conditions: diol **1a** (1 mmol), diphenyliodonium triflate **2a** (1.5 mmol), $CuCl_2$ (5 mol %), **L** (5 mol %), Na_3PO4 (3.0 mmol), toluene (1.5 mL), 80 °C, 15 h.
[b] Isolated yield. [c] Determined by HPLC.

第４節　ジオール類の検討

Table 8. The chiral copper-catalyzed asymmetric monophenylation of *meso*-1,2-diols with diphenyliodonium triflate[a]



entry	1	product	3	yield (%)[b]	ee (%)[c]	entry	1	product	3	yield (%)[b]	ee (%)[c]
1	**1a**		**3aa**	94	76	4	**1c**		**3ca**	89	59
2[d,e]	**1q**		**3qa**	84	85	5	**1d**		**3da**	47	24
3[d]	**1r**		**3ra**	70	64	6[f]	**1h**		**3ha**	54	37

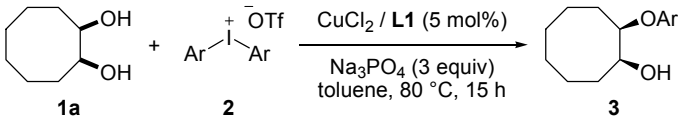
[a] Reaction conditions: diol **1** (1 mmol), diphenyliodonium triflate **2a** (1.5 mmol), $CuCl_2$ (5 mol %), **L1** (5 mol %), Na_3PO_4 (3 mmol), toluene (1.5 mL), 80°C, 15h. [b] Isolated yield. [c] Determined by HPLC. [d] **L6** was used instead of **L1**. [e] toluene (2.5 mL). [f] $Cu(OTf)_2$ was used instead of $CuCl_2$.

最適条件下、環状および鎖状ジオールを用いて不斉アリール化反応の検討を行なった。*cis*-1,2-cyclododecanediol (**1q**) を用いた時は *cis*-1,2-cyclooctanediol (**1a**) に比べて目的化合物の収率が低下した一方、不斉収率の向上が観測された (entries 1 and 2)。π 結合を有する *cis*-1,2-diol を用いて反応を行なったところ、反応収率およびエナンチオ選択性共に低下する結果となった (entry 3)。また、環状 1,2-diol に関しては小員環になるにつれて収率と不斉収率の低下が観測された (entries 1, 4, and 5)。鎖状ジオールである *meso*-2,3-butanediol からは中程度の収率かつエナンチオ選択性で目的化合物が得られた (entry 6)。

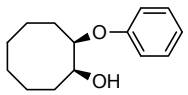
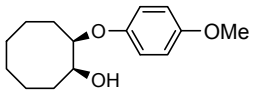
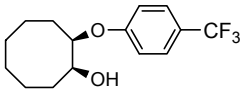
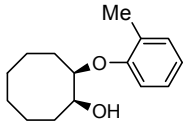
第５節　ジアリールヨードニウムトリフラートの検討

最適化した条件においてジアリールヨードニウム塩の検討を行なった。電子豊富なアリール基を持つヨードニウム塩からはラセミ生成物 **3ac** が得られた(entry 2)。アリール基上に電子求引性基が存在するジアリールヨードニウム塩を用いた場合においては良好な収率かつ中程度のエナンチオ選択性でモノアリール化体を与えた(entry 3)。立体障害を有するヨードニウム塩 **2i** を用いた場合、反応は速やかに進行した一方、不斉収率に関してはジフェニルヨードニウム塩に比べて低下した(entry 1 and 4)。ジアリールヨードニウム塩中の置換基はその性質に関わらず、反応の進行を妨げないことが明らかとなった。

Table 9. The chiral copper-catalyzed asymmetric monoarylation of *cis*-1,2-cyclooctanediol with diaryliodonium triflates

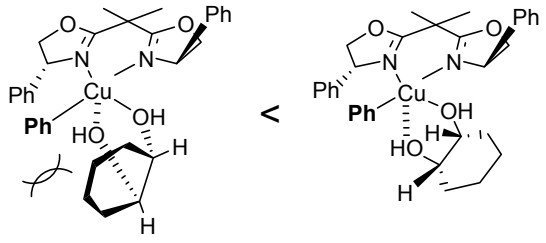


1a **2** **3**

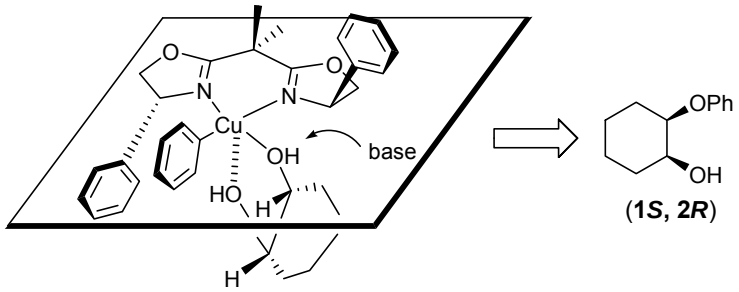
entry	product	3	yield (%)[b]	ee (%)[c]
1		**3aa**	94	76
2		**3ac**	84	0
3		**3aj**	94	54
4		**3ai**	89	63

[a] Reaction conditions: diol **1a** (1 mmol), diaryliodonium triflate **2** (1.5 mmol), $CuCl_2$ (5 mol %), **L1** (5 mol %), Na_3PO_4 (3 mmol), toluene (1.5 mL), 80 °C, 15 h. [b] Isolated yield. [c] Determined by HPLC.

第 6 節　立体選択性発現機構



A **B**



C (**1*S*, 2*R***)

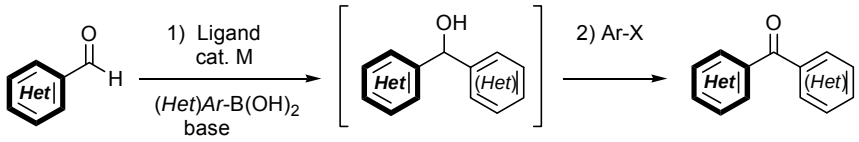
Figure 3

3ca および **3da** の旋光度を過去に報告された文献に記述されている旋光度[22]と比較することで絶対配置をいずれも(1*S*,2*R*)と決定した。この結果を基に不斉発現の機構を推定した (Figure 3)。

銅錯体のジフェニルヨードニウム塩に対する酸化的付加により形成された 3 価の銅中間体に対してジオールの水酸基の 1 つが配位子し、(*R*,*R*)-Ph-Box と共に平面四配位錯体を形成する。もう一方の水酸基は、(*R*,*R*)-Ph-Box のフェニル基との立体反発を避けるように下方向からアピカル位に配位する (**A** in Figure 3)。ジオールの環状部が紙面手前を向いて配位する場合と奥側を向いて配位する場合が考えられるが、銅に配位したフェニル基との立体反発を避けるように **B** の構造を優先して取ると考えられる (**B** in Figure 3)。この後、アピカル位よりも空いた環境にあるもう一方の水酸基が塩基により脱プロトン化を受け、続いて還元的脱離が進行すると考えることにより (1*S*,2*R*) を有する目的物を与えることを説明することができる(**C** in Figure 3)。

第３章　複素環ケトンの触媒的ワンポット合成法の開発

One-Pot Synthesis of Heteroaryl and Diheteroaryl Ketones.



第１節　配位子の検討

当研究室では副配位部としてチオエーテル部位を有する *N*-ヘテロ環状カルベン配位子とパラジウムからなる錯体触媒が、アルデヒドに対するアリールボロン酸の付加反応に対して優れた基質耐性を示すことを見いだしている [13]。そこで本触媒の特長を活用することにより、複素環ケトンの効率的なワンポット合成が可能となると期待してＣ－Ｓ型配位子の検討を行なった (Table 10)。モデル基質に 3-quinolinecarbaldehyde (**4a**) と phenylboronic acid (**5a**) を選択した。メシチル基を有する配位子 **L19-21** を用いた場合、いずれも低収率で目的化合物 **6aa** を与える結果となった (entries 1-3)。一方、嵩高い 2,6-ジイソプロピルフェニル基に置き換えた配位子を用いると収率の向上が観測された。なかでも、フェニルチオ基を有する **L23** を検討したところ、ケトン体 **6aa** を収率 82%で与え、パラジウムに対するチオエーテル部の立体的および電子的効果が重要であることが示唆された (entries 4-6)。またパラジウムと配位子の割合を種々検討したところパラジウムに対して小過剰の配位子を用いる時に最良の結果を与えることが明らかとなり (entries 5 and 7-8)、さらに Pd の触媒量を 3 mol %に増やすことで収率は 95%に向上した (entries 6 and 9-10)。配位子を添加しない場合は目的化合物を得ることは出来なかった (entry 11)。

Figure 4. Precursors of *N*-heterocyclic carbene ligands.

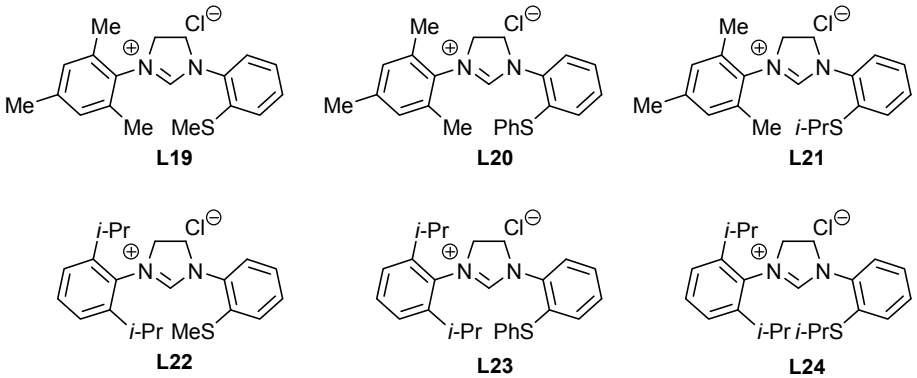
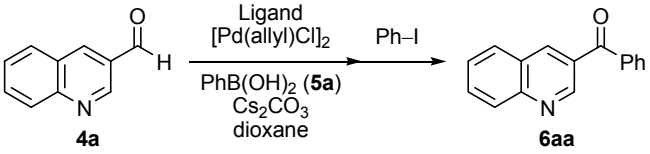


Table 10. Screening of thioether-imidazolinium chlorides[a].



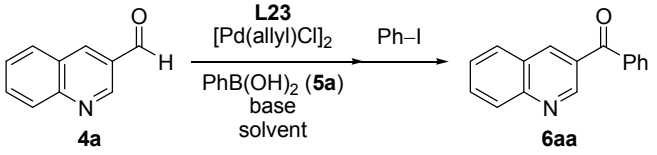
entry	L	Pd (mol %)	Pd/ligand	yield (%)[b]
1	**L19**	1.0	1:1.5	6
2	**L20**	1.0	1:1.5	7
3	**L21**	1.0	1:1.5	6
4	**L22**	1.0	1:1.5	58
5	**L23**	1.0	1:1.5	82
6	**L24**	1.0	1:1.5	65
7	**L23**	1.0	1:1	80
8	**L23**	1.0	1:2	80
9	**L23**	2.0	1:1.5	94
10	**L23**	3.0	1:1.5	95
11	**none**	1.0	-	0

[a] Reaction conditions: 3-quinolinecarbaldehyde **4a** (1 mmol), Phenylboronic acid **5a** (1.5 mmol), Cs_2CO_3 (2.5 mmol), dioxane (2 mL), 100 °C, 1 h (addition), PhI (2 mmol), 100 °C, 15 h (oxidation), [b] Isolated yield.

第２節　塩基と溶媒の検討

次に、ヘテロアリールケトン **6aa** の合成において塩基と溶媒の検討を行なった(Table 11)。塩基は Cs_2CO_3 が最も適していることが明らかとなった (entries 1-5)。溶媒は 1,4-dioxane を用いたときに最も優れた収率で目的化合物を与えた一方、高極性溶媒を用いた場合は大幅な収率の低下が見られた。(entries 1 and 6-8)。

Table 11. Screening of bases and solvents[a]



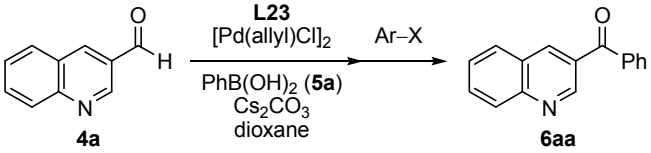
entry	base	solvent	yield (%)[b]	entry	base	solvent	yield (%)[b]
1	Cs_2CO_3	dioxane	82	5	CsF	dioxane	12
2	K_2CO_3	dioxane	10	6	Cs_2CO_3	toluene	61
3	Na_2CO_3	dioxane	2	7	Cs_2CO_3	DMF	27
4	K_3PO_4	dioxane	32	8	Cs_2CO_3	DMSO	0

[a] Reaction conditions: 3-quinolinecarbaldehyde **4a** (1 mmol), Phenylboronic acid **5a** (1.5 mmol), **L23** (1.5 mol %), Pd (1 mol %), base (2.5 mmol), 100 °C, 1h (addition), PhI (2 mmol), 100 °C, 15 h (oxidation), [b] Isolated yield.

第３節　ハロゲン化アリールの検討

酸化剤として機能するハロゲン化アリールの検討を行なった (Table 12)。臭化ベンゼンに関しては十分に反応が進行しなかった一方、より反応性が高いヨウ化ベンゼンを用いると収率は大幅に向上した (entries 1-2)。次に、アリール基上の置換基を種々検討したところ、トリフルオロメチル基を導入するとわずかながら収率の向上が観測された (entries 3-5)。さらに、立体障害を有するヨウ化アリールを反応に用いたところ明確に収率が改善され、2-MePh-I に関しては 95%収率で目的化合物 **6aa** を与えた (entries 6-9)。ヨウ化アリールのアリール基が立体障害を持つことで還元的脱離の段階が促進されていることが示唆された。また、ハロゲン化物を添加しない場合には目的化合物を殆ど得ることが出来なかった (entries 10)。

Table 12. Screening of aryl halides[a]



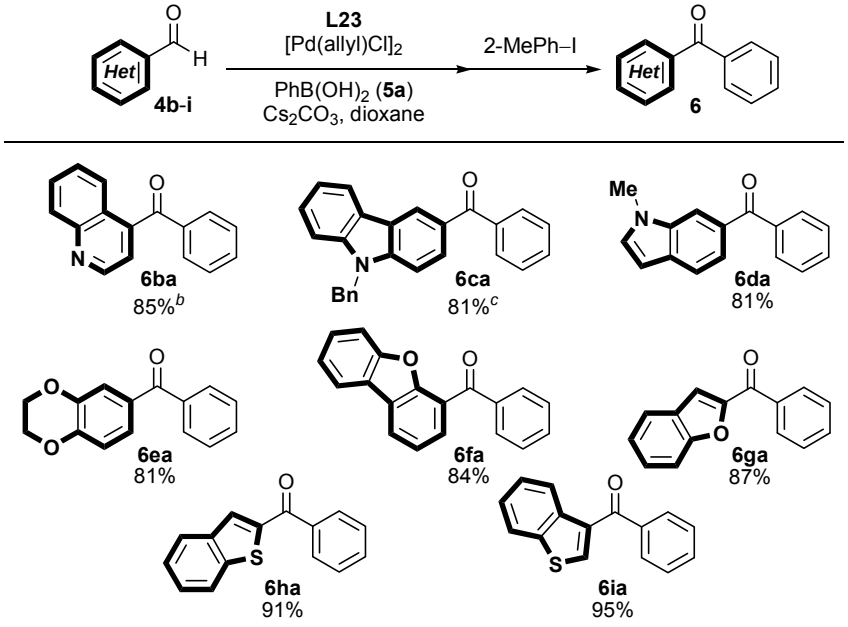
entry	Ar-X	yield (%)[b]	entry	Ar-X	yield (%)[b]
1	PhBr	21	6	3-MePhI	87
2	PhI	82	7	2-MePhI	95
3	4-CF_3PhI	86	8	2-*i*-PrPhI	93
4	4-MeOPhI	79	9	2,6-$(Me)_2$Ph-I	92
5	4-MePhI	83	10	none	5

[a] Reaction conditions: 3-quinolinecarbaldehyde **4a** (1 mmol), Phenyl boronic acid **5a** (1.5 mmol), **L23** (1.5 mol %), Pd (1 mol %),100 ^{o}C, 1 h (addition), 100 ^{o}C, 15 h (oxidation), [b] Isolated yield.

第４節　ヘテロアリールケトンおよびジヘテロアリールケトンの合成

最適化した条件で phenylboronic acid (**5a**) と様々なヘテロアリールアルデヒドを用いてヘテロアリールケトンの合成を行なった (Scheme 4)。窒素および酸素原子を持つ複素環アルデヒド **4b-4g** から対応するケトン体が高収率で得られた (**6ba-6ga**)。また、ベンゾチオフェン骨格を有する基質 **4h-4i** に関しても反応は良好に進行した (**6ha-6ia**)。

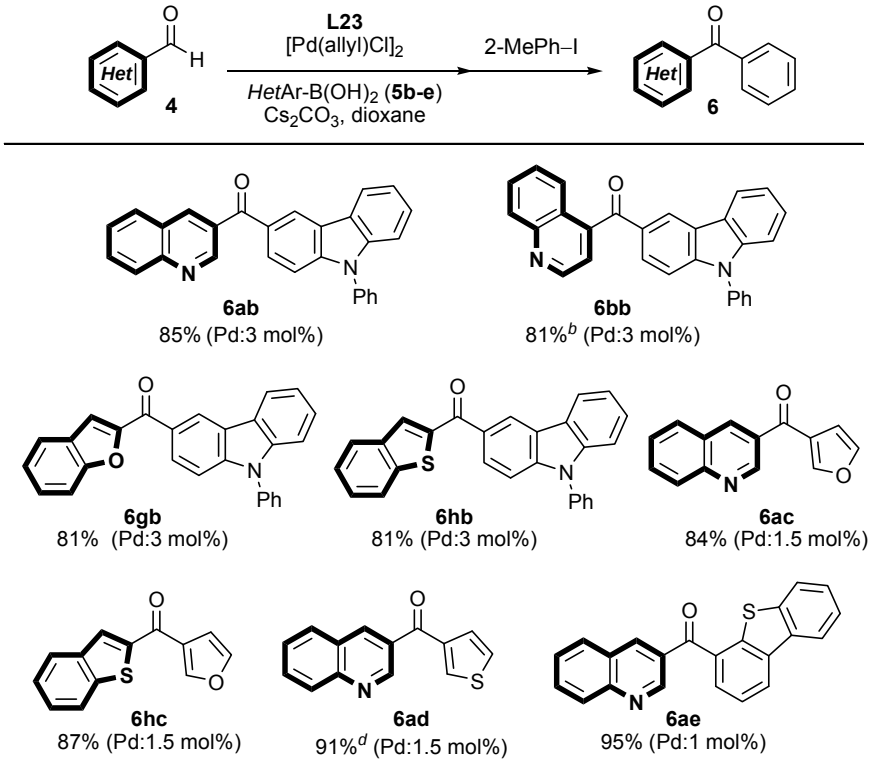
Scheme 4. One-Pot Synthesis of Heteroaryl Ketones.[a]



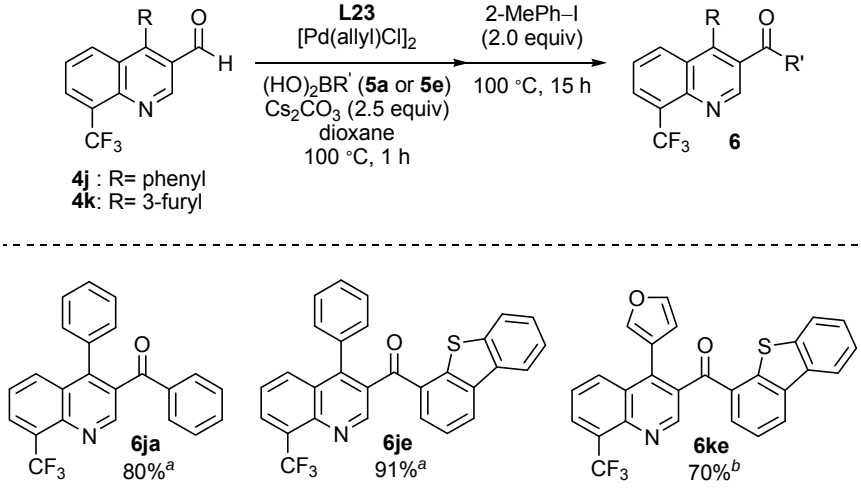
[a] Reaction conditions: aldehyde **4** (1 mmol), Pd (1 mol %), **L23** (1.5 mol %), phenylboronic acid **5a** (1.5 mmol), Cs_2CO_3 (2.5 mmol), dioxane (2 mL), 100°C, 1h (addition), 2-MePhI (2 mmol), 100 °C, 15h (oxidation). [b] 3-MePhI (2 mmol) was used. [c] The catalyst (3 mol %).

次に、複素環を有するアルデヒドおよびボロン酸を用いてジヘテロアリールケトンのワンポット合成を行なった (Scheme 5)。9-Phenylcarbazole-3-boronic acid (**5b**)を用いたとき、キノリン、ベンゾフランおよびベンゾチオフェン骨格を持つアルデヒド体から高収率でそれぞれ複素環ケトンが得られた (**6ab**, **6bb**, **6gb**, and **6hb**)。また、フランやチオフェンなどの複素環を有するボロン酸も本反応に適用可能であり、それぞれ複素環アルデヒドとの付加－酸化反応を経由して対応するジヘテロアリールケトンを 84-95%収率で与えた(**6ac**, **6hc**, **6ad**, and **6ae**)。

Scheme 5. One-Pot Synthesis of diheteroaryl Ketones.[a]



[a] Reaction conditions: aldehyde **4** (1 mmol), Pd /**L23** (1/1.5), arylboronic acid **5** (1.5 mmol), Cs_2CO_3 (2.5 mmol), dioxane (2 mL), 100°C, 1h (addition), 2-MePhI (2 mmol), 100 °C, 15 h (oxidation). [b] 3-MePhI (2 mmol) was used. [d] Cs_2CO_3 (3 mmol), 80 °C, 1 h (addition).



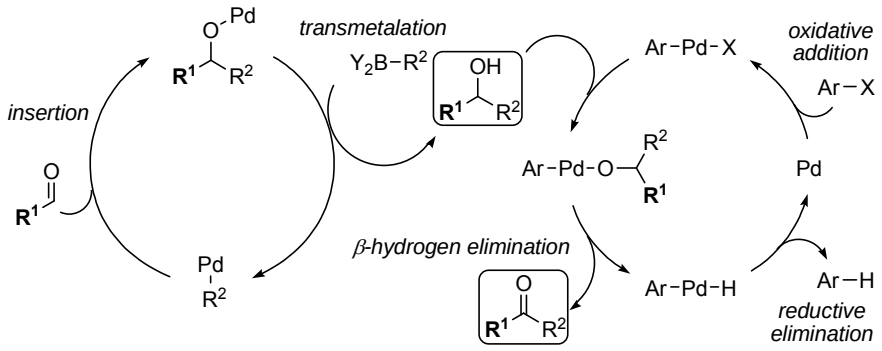
Scheme 6. Synthesis of quinoline-based lead agonist and its derivatives for liver X receptor. Reaction conditions: aldehyde **4** (1 mmol), arylboronic acid **5** (1.5 mmol).[a] **L23** (4.5 mol %), Pd (3 mol %). [b] **L23** (2.25 mol %), Pd (1.5 mol %).

さらに、本ワンポット合成によりキノリン骨格を有する肝臓 X 受容体アゴニスト [23] およびその類縁体の合成を行なった(Scheme 6)。反応点近傍が立体的に嵩高い

4-phenyl(8-trifluoromethyl)quinoline-3-carbaldehyde (**4j**)を用いたとき、フェニルボロン酸および複素環式有機ボロン酸から高収率で目的化合物 **6ja** と **6je** が得られた。また、フラン環を持つキノリン骨格のアルデヒド体からより複雑な肝臓 X 受容体アゴニスト類縁体 (**6ke**)の合成を達成した。

第５節　反応機構

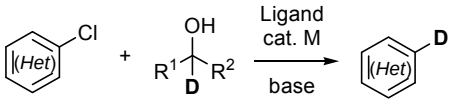
Figure 5. Proposed pathway for one-pot synthesis of ketones through palladium-catalyzed 1,2-addition and oxidation



推定される反応機構を上に示す (Figure 6)。本ワンポット合成は付加反応と酸化反応の 2 つの工程から成る。まず、付加の工程において Pd 錯体と有機ホウ酸の間でトランスメタル化が起こり、Pd-R^2 が形成される。アルデヒドへの挿入的付加が進行することでアルコール体が生成する。続く酸化の工程においては、Pd(0)のハロゲン化アリールへの酸化的付加により、Ar-Pd(II)-X が形成される。次に、付加反応において生じたアルコール体が Pd に配位し、β 水素脱離を経て目的化合物であるケトン体と Ar-Pd(II)-H が生成する。還元的脱離により Pd(II)は Pd(0)に再生する。

第５章　非対称型 NHC 配位子を用いた芳香族塩化物に対する重水素化反応の開発

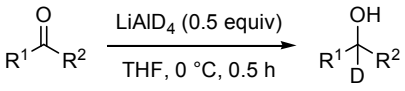
Deuterodechlorination of Aryl/Heteroaryl Chlorides

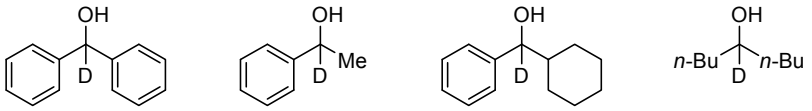


第１節　重水素化剤の合成

本反応において重水素源として用いられる α-deuterioalcohols の合成法を Scheme 7 に示す。入手容易なケトン体から lithium aluminium deuteride により定量的かつ 99%を超える重水素化率で α-deuterioalcohols (**7a-7d**)を得た。特に、**7a** は安定な固体であるため取り扱いが容易である。一方、**7b-7d** に関しては室温において液体として得られた。

Scheme 7. Synthesis of α-Deuterioalcohols





7a 96%, >99% D　　**7b** 95%, >99% D　　**7c** 99%, >99% D　　**7d** 99%, >99% D

第２節　配位子の検討

1-Chloro-3,5-dimethoxybenzene (**8a**)と重水素化剤に α-deuteriobenzhydrol (**7a**) を用いて配位子の検討を行なった (Table 13)。配位子非存在下では反応は殆ど進行しなかった (entry 1)。続いて、当研究室で開発された非対称型 NHC 配位子の検討を試みた (entries 2-6)。イミダゾール環の 4 位と 5 位にメチル基を持たない配位子前駆体 **L25** を用いた場合、中程度の収率に留まった(entry 2)。イミダゾール環の 4 位と 5 位にメチル基を導入した配位子前駆体 **L26** を検討したところ、収率は 68%に向上した(entry 3)。ベンジル部位をよりかさ高くした場合は収率の低下が観測された一方、1 位のアリール基を立体的にかさ高くすることで収率の改善が可能となることを見出し、**L29** を用いたときには 94%収率かつ 99%を超える重水素化率で目的化合物 **9a** を得た (entries 3-6)。また、Pd と配位子の割合を 1:1 で反応を行なったところ、収率は 76%に低下した (entry 7)。

次に、既知である対称な NHC 配位子を本反応に用いた (entries 8-13)。いずれも収率は中程度に留まり、立体的に極めてかさ高い対称な配位子 **L30** および **L31** については重水素化率の低下が見られた (entries 10-11)。これらの結果から非対称型 NHC 配位子におけるベンジル部位が重要な役割を果たしていることが示唆された。さらに、カップリング反応等で効果の高いホスフィン配位子についても検討を行なった (entries 14-20)。

Triphenyl phosphine では殆ど重水素化体 **9a** が得られなかったが、より電子豊富であり、立体的にかさ高いアリール基を持つ triarylphosphine を用いることにより収率および重水素化率が改善された (entries 14-17)。以上の結果を基に、よりかさ高く、電子豊富な trialkylphosphonium 塩を用いたところ、中程度の収率で目的化合物 **9a** を与えた (entries 18-19)。このとき重水素化率は 98%まで向上した。また、SPhos を適用しても収率および重水素化率ともに改善はみられなかった (entry 20)。

Figure 6. Unsymmetrical, or Symmetrical NHC Precursors, and SPhos

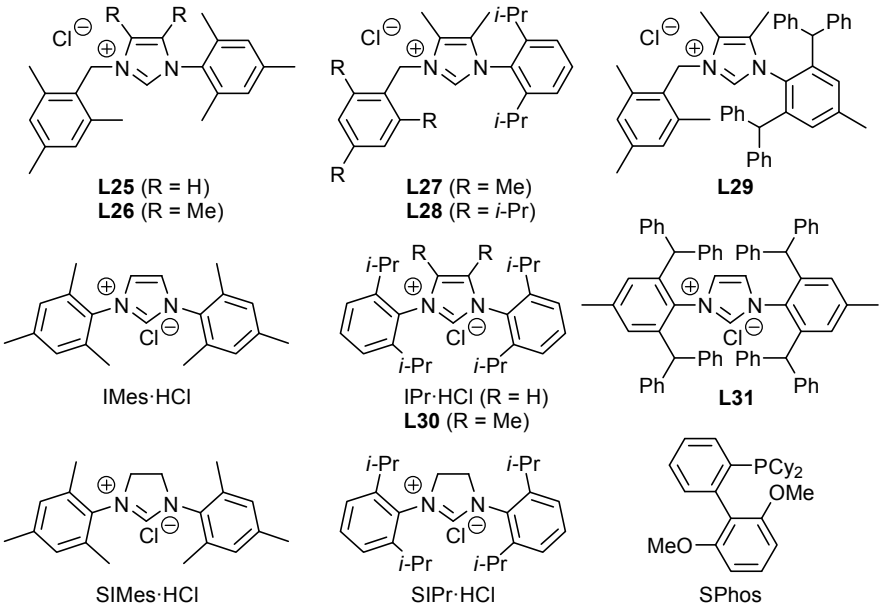
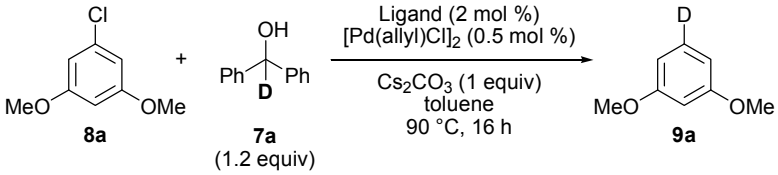


Table 13. Screening of ligands [a]



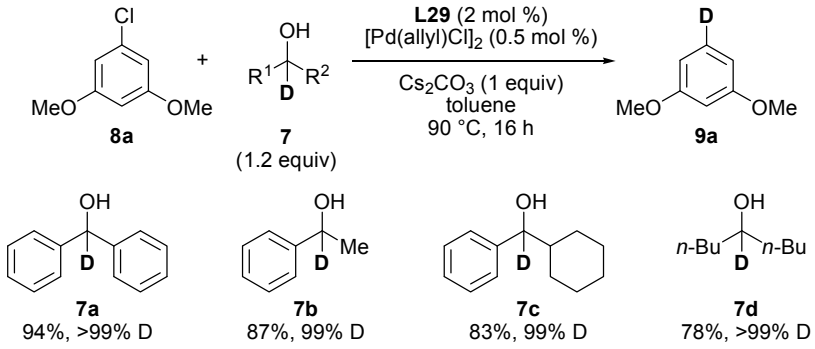
entry	L	yield (%)[b]	D content (%)[c]	entry	L	yield (%)[b]	D content (%)[c]
1	**none**	trace	ND	11	**L31**	42	93
2	**L25**	42	>99	12	SIMes·HCl	36	99
3	**L26**	68	>99	13	SIPr·HCl	31	99
4	**L27**	74	>99	14	Ph_3P	trace	ND
5	**L28**	66	>99	15	$(4\text{-}FPh)_3P$	19	33
6	**L29**	94	>99	16	$(4\text{-}MeO)_3P$	20	50
7[d]	**L29**	76	>99	17	$(2\text{-}MePh)_3P$	23	72
8	IMes·HCl	53	>99	18	$t\text{-}Bu_3P{\cdot}HBF_4$	62	98
9	IPr·HCl	63	>99	19	$Cy_3P{\cdot}HBF_4$	44	98
10	**L30**	62	96	20	SPhos	62	98

[a] Reaction conditions: **8a** (1 mmol), **7a** (1.2 mmol),ligand (2 mol%), Pd (1 mol %), Cs_2CO_3 (1 mmol), toluene (2 mL), 90 °C, 16 h. [b] Isolated yield. [c] Determined by ^1H NMR. [d] Pd/**L29** = 1/1.

第３節　重水素化剤の検討

本触媒系において重水素化剤として機能する α-deuterioalcohol の検討を試みた (Scheme 8)。α 位に 2 つのフェニル基が置換された **7a** を用いた時に、最も効率的に重水素を導入することに成功した。ベンゼン環をアルキル鎖に置き換えたアルコール体に関しては収率の低下が観測された (**7b-7d**)。

Scheme 8. Screening of α-Deuterioalcohols



第４節　反応の経時変化

配位子 **L29**、 IPr·HCl また SPhos を用いて本反応の経時変化を追跡した (Figure 7)。**L29** を用いた場合の反応速度は誘導期を経た後に急速に上昇し、3 時間以内に 90%を超える収率で重水素化体を与えた。一方、IPr·HCl と SPhos の反応速度は時間の経過と共に低下し、収率 60%に到達するのに 12 時間以上必要であることが明らかとなった。

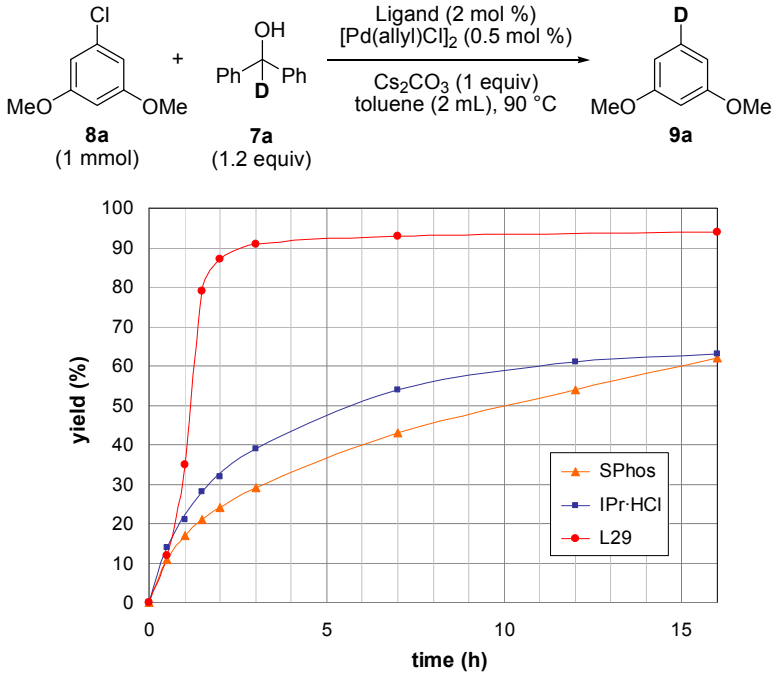
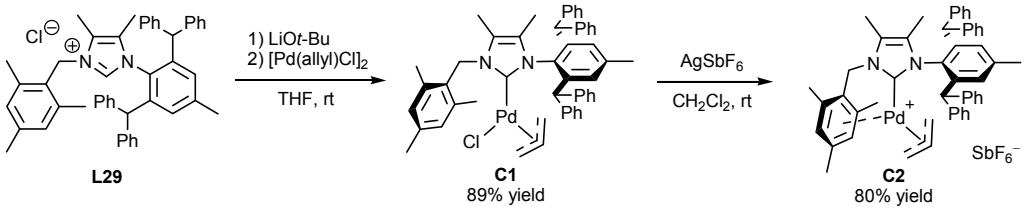


Figure 7. Time courses for the conversion of **8a** to **9a** in the palladium-catalyzed deuterodechlorination with **L29**, IPr·HCl, and SPhos. Isolated yields were usded for the plotting.

第 5 節　Pd-NHC 錯体の合成と X 線結晶構造解析

触媒系に関するより詳細な知見を得るために、Pd-NHC 錯体の合成を試みた (Scheme 8)。配位子前駆体 **L29** と lithium *tert*-butoxide, および [Pd(allyl)Cl]$_2$ から錯体 **C1** を 89% 収率で合成し、この中性錯体 **C1** を $AgSbF_6$ で処理することでカチオン錯体 **C2** に変換した。X 線結晶構造解析により **C1** および **C2** の錯体構造を決定した (Figure 9)。カチオン錯体 **C2** に関しては Pd とベンジル基の芳香環との間に Pd-arene 相互作用が観測された。本相互作用は触媒系の安定化や、活性および寿命の向上に寄与することが報告されている [24]。

Scheme 9. Synthesis of Pd-NHC Complexes.



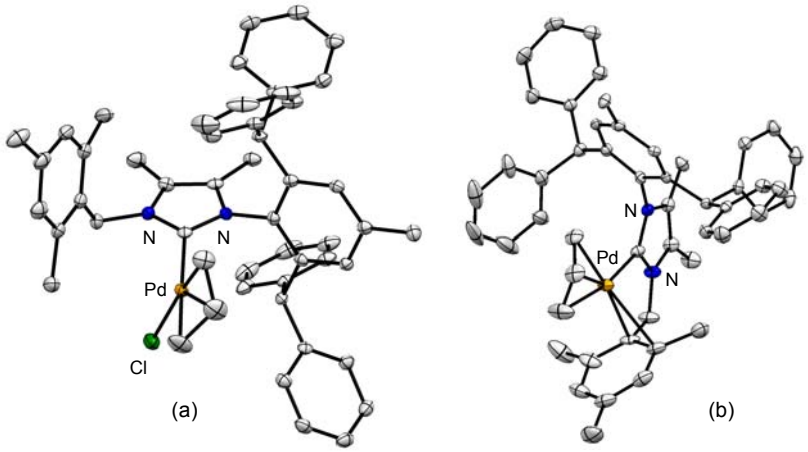
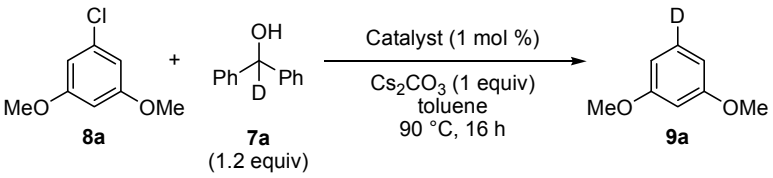


Figure 8. (a) The crystal structure of neutral complex **C1**. Hydrogen atoms were omitted for clarity. (b) The crystal structure of cationic complex **C2**. Hydrogen atoms, a hexafluoroantimonate anion, and a residual dichloromethane molecule were omitted for clarity.

錯体 **C1** および **C2** をモデル反応に適用するとそれぞれ 75%および 76%収率で **9a** が得られた。これは、系中においてパラジウムと配位子前駆体 **L29** の割合を 1:1 で錯体調製して反応を行なった Table 16 の entry 7 と対応する結果となった (Table 17, entries 1 and 3)。次に、錯体 **C1** あるいは **C2** と **L29** を用い、系中で錯体調製をした後に重水素化反応を試みたところ、いずれの場合に関してもパラジウムと配位子前駆体 **L29** の割合を 1:2 で錯体調製して反応を行なった Table 16 の entry 6 の結果と一致した (Table 17, entries 2 and 4)。以上の検討結果から、優れた触媒性能を達成するにはパラジウム 1 分子に対

して 1 分子の配位子前駆体が必須であり、2 分子目の配位子前駆体は安定な触媒前駆体を形成するために必要であると考えられる。

Table 17. Palladium-Catalyzed Deuterodechlorination with Pd-NHC Complexes.[a]



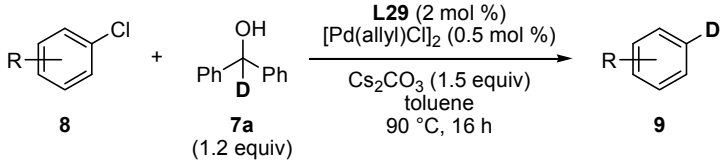
entry	**catalyst**	yield (%)[b]	D content (%)[c]
1	**C1** (Pd/**L29** = 1/1)	75	>99
2[d]	**C1**+ **L29** (Pd/**L29** = 1/2)	94	>99
3	**C2** (Pd/**L29** = 1/1)	76	>99
4[d]	**C2**+ **L29** (Pd/**L29** = 1/2)	94	>99

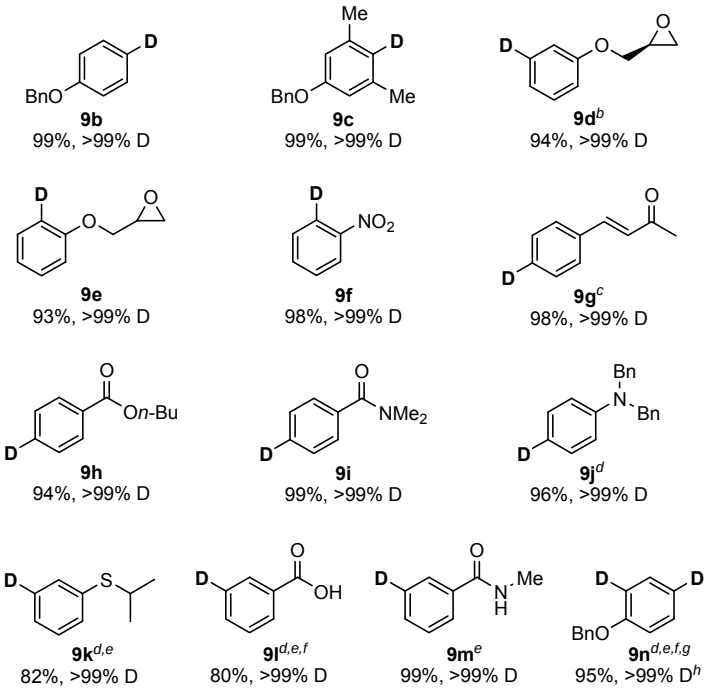
[a] Reaction conditions: **8a** (1 mmol), **7a** (1.2 mmol),ligand (2 mol %), **C** (1 mol %), Cs_2CO_3 (1 mmol), toluene (2 mL), 90 °C, 16 h. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] The catalyst was formed from **C** (1 mol %) and **L29** (1mol %) *in situ*.

第 6 節　基質適用範囲の検討

最適条件下において様々な官能基を有する芳香族塩化物に対して重水素導入を試みた (Scheme 9)。電子豊富であり、また反応点近傍に立体障害を持つ塩化アリールからは極めて高い収率で重水素化体が得られた (**9b, c**)。エポキシ部位を含む基質は開裂することなく本反応条件に耐えうることが明らかとなり、キラルなエポキシ型基質についても光学純度を維持したまま変換が可能であった (**9d, e**)。還元を受けうるニトロあるいはエノン部位を有する電子不足な基質についても、本手法により極めて優れた選択性で重水素化することに成功した (**9f, g**)。また、エステルやアミド部位を持つ基質においてはエステル交換等の副反応は起こらず、高収率かつ高い重水素化率で目的化合物を与えた (**9h, i**)。本触媒系は、チオエーテルならびにアミン部位を含む芳香環塩化物に関しても反応阻害を受けることなく良好に適用可能であった (**9j, k**)。さらに、カルボン酸および 2 級アミド部位存在下においても重水素化率は低下することなく高効率的に重水素化体を与えた (**9l, m**)。複数の塩素を一挙に重水素と交換した際にも十分な触媒活性が保たれることが明らかとなった (**9n**)。

Scheme 9. Scope of Aryl Chlorides in Palladium-Catalyzed Deuterodechlorination[a]



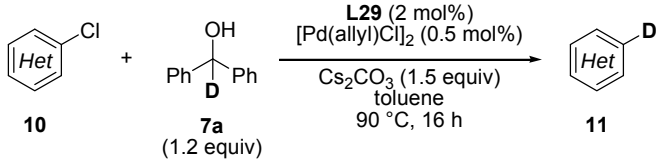


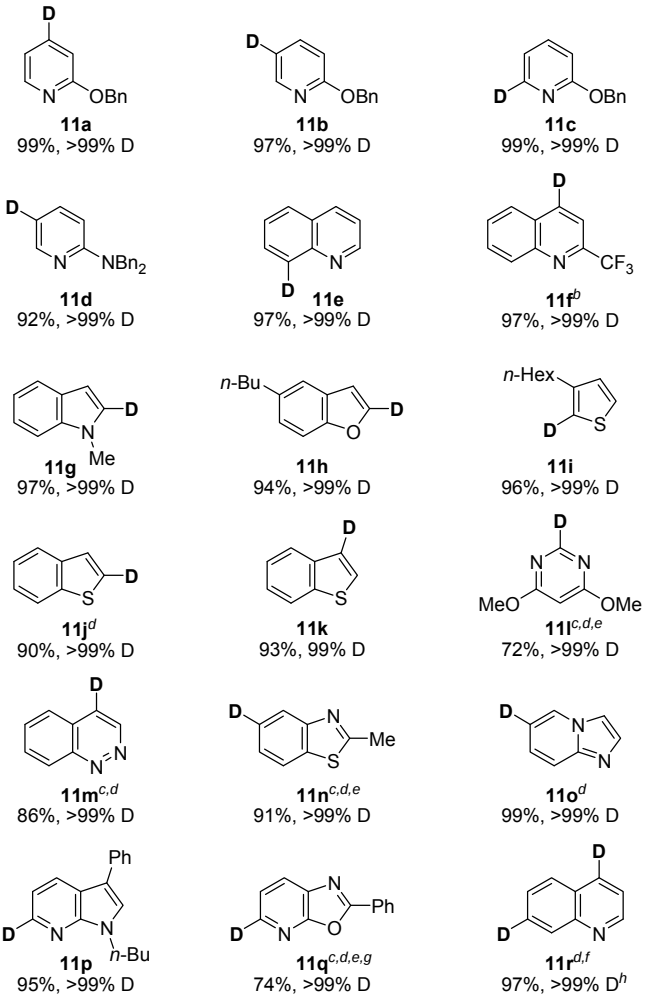
[a] Reaction conditions: **8** (1mmol), **7a** (1.2 mmol), **L29** (2 mol %), Pd (1 mol %), Cs_2CO_3 (1.5 mmol), toluene (2 mL), 90 °C, 16 h.[b] The substrate **8f** (91% ee) was converted to **3f** with 91% ee. [c] IPr·HCl and SPhos led to 54% (>99% D) and 0% yields, respectively. [d] The catalyst. (3 mol %). [e] 100 °C. [f] Cs_2CO_3 (3 equiv). [g] **7a** (2.4 equiv). [h] Both reactive sites gave >99% D.

次に、複素環式芳香族塩化物に対して重水素導入を行なった (Scheme 10)。反応点が種々異なる電子不足なピリジン型基質からも極めて優れた収率かつ重水素化率で重水素化体が得られ、金属原子へ強く配位しうるアミノ基を有するピリジン型基質に対しても問題なく適用可能であった（**11a-d**)。キノリン骨格を持つ基質を用いた場合においても反応は円滑に進行した（**11e, f**)。このとき **10f** に関しては触媒量を 0.5 mol %および 0.1 mol %に減らして反応を行なっても重水素化率は低下することなく、それぞれ 85%および 46%収率で重水素化体が得られた。一方、電子豊富なインドールおよびベンゾフラン誘導体も本反応に適用可能であり、ベンゾチオフェンや立体障害を有するチオフェン基質に対しても高効率的な重水素導入に成功した（**11g, k**)。さらに、複数のヘテロ原子を有する複素環式芳香族塩化物の検討を行なった。ピリミジン、シンノリンまたベンゾチアゾールが骨格である芳香族塩化物を用いて重水素化を行なったところ効率的に反応は進行し、いずれも 99%を超える重水素化率で目的化合物を得た（**11l-n**)。さらに、ア

ザインドール、イミダゾピリジンまたオキサゾロピリジンを基本骨格とする基質に関しても適用可能であった**(11o, 11p)**。複素環式芳香族塩化物に対しても一挙に 2 つの重水素を導入することに成功した **(11r)**。いずれの複素環基質に対しても定量的に重水素を導入することに成功しており、優れた触媒効率と基質耐性が示された。

Scheme 10. Scope of Heteroaryl Chlorides in Palladium-Catalyzed Deuterodechlorination[a]



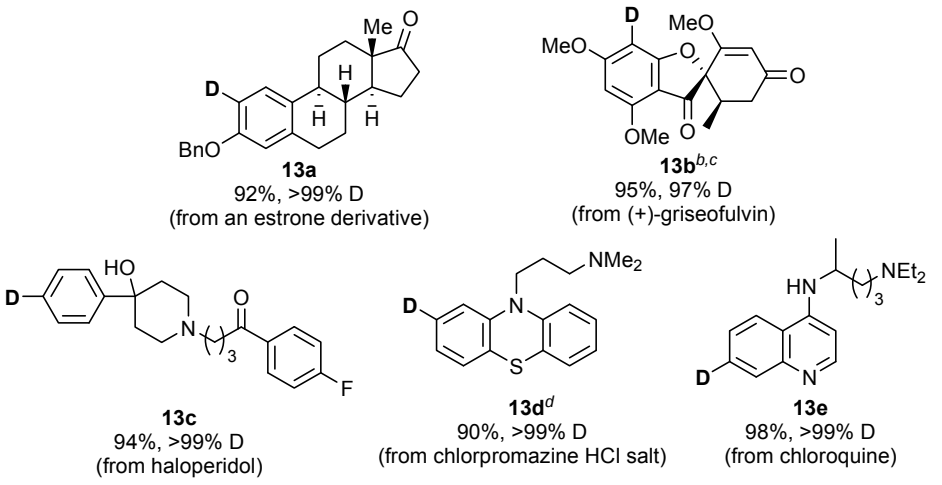


[a] Reaction conditions: **10** (1 mmol), **7a** (1.2 mmol), **L29** (2 mol %), Pd (1 mol %), Cs_2CO_3 (1.5 mmol), toluene (2 mL), 90 °C, 16 h.[b] The catalyst (0.5 and 0.1 mol %) led to 85% (>99% D) and 46% (>99% D), respectively. [c] The catalyst (3 mol %). [d] 100 °C. [e] Cs_2CO_3 (2 equiv). [f] Cs_2CO_3 (3 equiv), **7a** (2.4 equiv). [g] 32 h. [h] Both reactive sites gave >99% D.

本触媒系のさらなる有用性を示すために複数の官能基が共存する生物活性化合物に対して重水素導入を行なった (Scheme 11)。エストロン誘導体についてはベンジル部位

およびケトン部位は還元されることなく高収率かつ 99%を超える重水素化率で目的化合物へ変換された (**13a**)。高度に官能基化されたスピロ環型化合物である (+)-guriseofulvin (**12b**)に関しては 95%収率、97%の重水素化率で重水素化体を与える結果となった (**13b**)。さらに、環状アミンおよび水酸基が共存する haloperidol (**12c**) に加え、フェノキサジンおよびキノリン環を基本骨格としてアミン部位を持つ場合も本触媒系に適用可能であった (**13c-e**)。

Scheme 11. Catalytic Deuterodechlorination of Bioactive Compounds and their Derivatives[a]

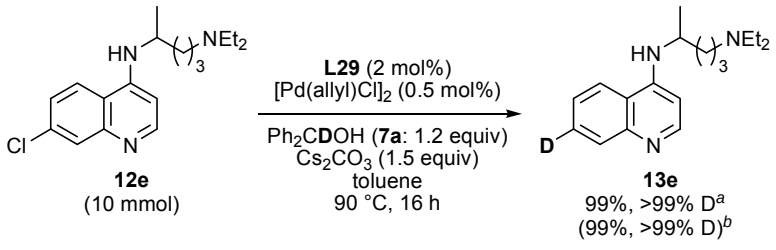


[a] Reaction conditions: **12** (1 mmol), **1a** (1.2 mmol), **L29** (2 mol %), $[Pd(allyl)Cl]_2$ (0.5 mol %), Cs_2CO_3 (1.5 equiv), toluene (2 mL), 90 °C, 16 h.[b] Cat. (3 mol %). [c] **7a** (1.5 equiv). [d] Cs_2CO_3 (2.5 equiv).

第 7 節　グラムスケールにおける重水素化反応

Chloroquine (**12e**) を用いてグラムスケールにおける重水素導入を試みたところ 99%収率、99%を超える重水素化率で目的化合物を得ることに成功した (Scheme 12)。この重水素化体 **13e** は逆抽出を行なうだけでも精製可能である。さらに、本反応により生じた benzophenone を定量的に回収して lithium aluminium deuteride により α-deuterioalcohols (**7a**) を合成した。この重水素化剤と Chloroquine (**12e**) を用いて反応を行なった場合にも収率および重水素化率は低下することなく **13e** が得られた。

Scheme 12. Gram-Scale Deuterodechlorination with Chloroquine as a substrate[a]

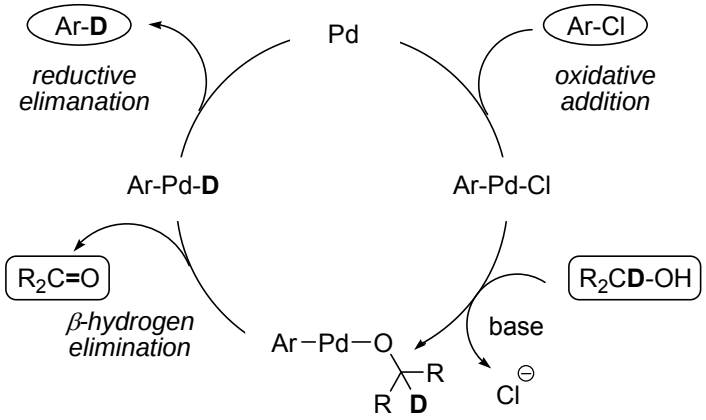


[a] Reaction conditions: **12e** (10 mmol), **7a** (12 mmol), **L29** (2 mol %), Pd (1 mol %), Cs_2CO_3 (15 mmol), toluene (20 mL), 90 °C, 16 h [b] Benzophenone was recovered in 99%. [c] 1 mmol scale synthesis with **7a** prepared from recovered benzophenone.

第 7 節　反応機構

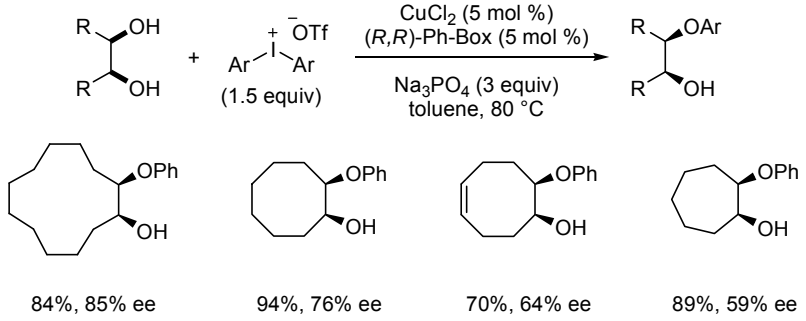
推定される反応機構を Figure 10 に示す。0 価のパラジウムが芳香族塩化物に対して酸化的付加し、Ar-Pd(II)-Cl が形成される。次に重水素化剤である α-deuterioalcohol がパラジウムに配位し、β-水素脱離を経由して中間体 Ar-Pd(II)-D とケトン体が生じる。続く還元的脱離によって重水素化体を与え、パラジウムは 0 価に再生される。

Figure 10. Proposed Pathway for Palladium-Catalyzed Deuterodechlorination

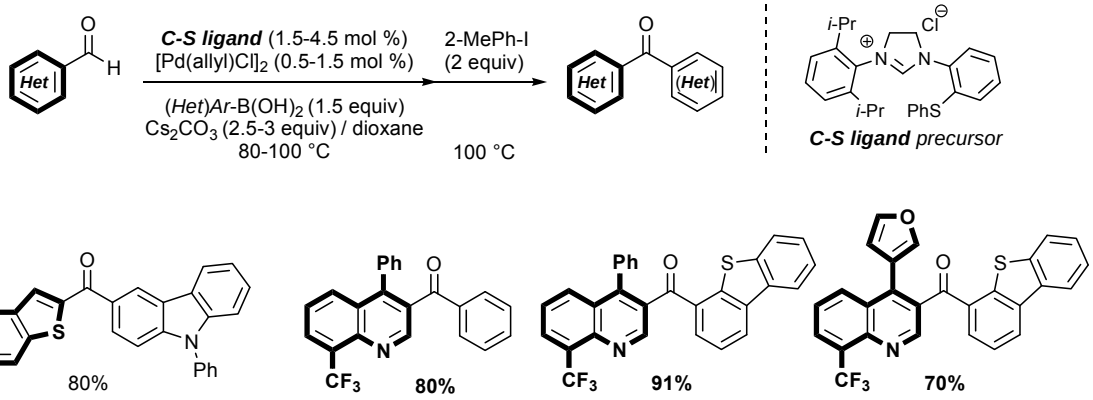


第 6 章　結論

著者は、銅触媒とジアリールヨードニウム塩を用いることでジオール類の選択的モノアリール化反応の開発に成功した[25]。本反応系は、反応性と選択性の同時制御を可能とすると共に広い基質適用範囲を示し、さらに、キラルビスオキサゾリン配位子により銅錯体を不斉化することでジオール類の不斉モノアリール化を達成した[26]。

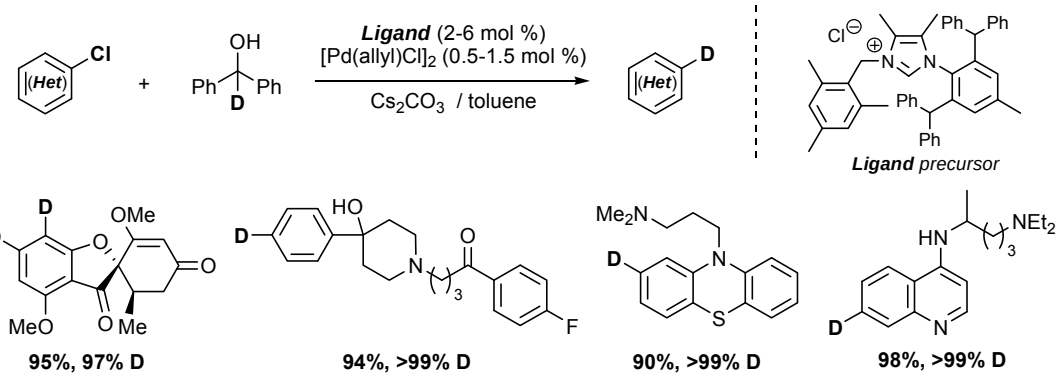


またＣ－Ｓ型配位子－パラジウム錯体を用いてアルデヒドを基質としたワンポット複素環ケトン合成法の開発を行なった。酸化剤としてハロゲン化アリールを選択することにより、副反応で複素環類を損なうことなく、多様な複素環ケトン類の合成を達成すると共に生物活性化合物の基本骨格合成にも成功した[27]。



Liver X receptor agonist and its derivatives

さらに、著者はパラジウム触媒存在下において進行するβ-水素脱離を経由した還元を利用することにより、非対称型 NHC 配位子と安定な重水素化源を用いた芳香族塩化物の触媒的重水素導入法の開発に成功した。この新規配位子のメシチレン部位はパラジウムーアレーン相互作用により触媒系に対して有効な効果を与えていることが明らかとなった。本反応系は、優れた効率性と選択性を兼ね備え、極めて広い基質適用範囲を示し、複数の官能基が共存している生物活性化合物に対しても適用が可能である。


Cl
(Het)
+
OH
Ph
Ph
D
Ligand (2-6 mol %)
[Pd(allyl)Cl]2 (0.5-1.5 mol %)
Cs2CO3 / toluene
(Het)
D
Cl
Ph
Ph
N
N
Ph
Ph
Ligand precursor
D
OMe
MeO
O
O
MeO
O
Me
HO
D
N
O
3
F
Me2N
D
N
S
HN
NEt2
3
D
N
95%, 97% D
94%, >99% D
90%, >99% D
98%, >99% D

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Experimental Section

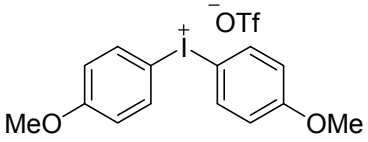
Chapter 2

General. All melting points are not corrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were taken at 400, 100, and 376 MHz, respectively. Chemical shift values of ^{1}H NMR are given in ppm relative to internal or external TMS. In ^{19}F NMR, they were expressed in ppm relative to fluorobenzene (-113.6 ppm in $CDCl_3$, -112.6 ppm in DMSO-d_6, and -113.7 ppm in CD_3OD). Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded using electron ionization (EI) or fast atom bombardment (FAB) mass spectrometry. The products were isolated by silica gel column chromatography.

The diols **1a**-**b**, **1d**-**f**, **1h**-**k**, **1m**-**n**, iodonium triflates **2a**-**b**, all of copper sources, sodium phosphate tribasic, lithium phosphate tribasic, cesium carbonate, potassium carbonate, sodium carbonate, and sodium fluoride were used as received. Potassium phosphate tribasic was ground to a fine powder prior to use. Toluene and dioxane were distilled from sodium benzophenone ketyl under argon atmosphere. DMA was distilled from calcium hydride under argon atmosphere. The diols **1c** [1], **1g** [2], **1l** [3], iodonium triflates **2d**-**f** [4], and **2k** [5] were prepared as previously reported.

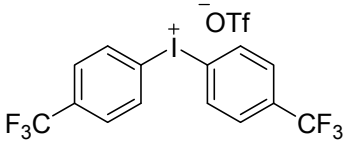
Synthesis of Organoiodonium Triflates. The iodonium triflates **2c** and **2g-i** were prepared based on the previous report by Olofsson.[6] On the other hand, the iodonium triflate **2j** was synthesized according to the reported synthetic procedure by MacMillan.[5]

Di(4-methoxyphenyl)iodonium triflate (2c).



Under argon atmosphere, MCPBA (9.0 mmol, 77% active oxidant) was charged in a reaction flask and dissolved in CH_2Cl_2 (31.2 mL). To the solution was added 1-iodo-4-methoxybenzene (8.1 mmol) and the reaction mixture was stirred at 80 °C. After 10 min, the reaction flask was cooled to -78 °C, and then the mixture of $BF_3 \cdot OEt_2$ (20.25 mmol) and 4-methoxyphenylboronic acid (9.0 mmol) in CH_2Cl_2 (31.2 mL) was transferred to the reaction flask at 0 °C. The resulting dark solution was stirred for 30 min at -78 °C. Then, triflic acid (9.0 mmol) was added at room temperature and the reaction mixture was stirred for 15 min. The crude was applied on a silica plug (24.9 g) and eluted with CH_2Cl_2 (300 mL) and CH_2Cl_2/MeOH (20:1, 900 mL). The latter fraction eluted with CH_2Cl_2/MeOH was concentrated and Et_2O (31.2 mL) was added to the residue to induce a precipitation of **2c**. The solution was stirred for 15 min, and then the ether phase was decanted. The solids were washed twice more with Et_2O (31.2 mL×2) and dried in vacuo to give **2c** as white solids of mp 114-115 °C in 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (s, 6H), 6.96-6.95 (m, 4H), 7.86-7.90 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.5 (CH_3), 102.3 (C), 117.7 (CH), 120.2 (C) (q, J = 318.6 Hz, $CF_3SO_3^-$), 136.9 (CH), 162.6 (C). ^{19}F NMR (376 MHz, $CDCl_3$): δ -78.7. IR (ATR): 1220, 1490 cm^{-1}. HRMS (FAB) *m/z* Calcd for $C_{14}H_{14}IO_2$ ($[M\text{-}TfO^-]^+$): 341.0038. Found: 341.0031.

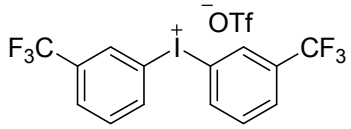
Di(4-trifluoromethylphenyl)iodonium triflate (2g).



Under argon atmosphere, MCPBA (4.95 mmol, 77% active oxidant) was charged in a flask and dissolved in CH_2Cl_2 (17.3 mL). To the solution was added 1-iodo-4-(trifluoromethyl)benzene (4.50 mmol) followed by $BF_3 \cdot OEt_2$ (11.25 mmol) at room temperature. The resulting yellow solution was stirred for 60 min. Then, 4-(trifluoromethyl)phenylboronic acid (4.95 mmol) was added at 0 °C and the mixture was stirred at room temperature. After 30 min, triflic acid (4.95 mmol) was added and the mixture was stirred at room temperature for 15 min. The crude was

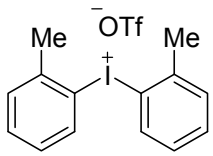
applied on a silica plug (13.8 g) and eluted with CH_2Cl_2 (170 mL) and CH_2Cl_2/MeOH (20:1, 517 mL). The latter fraction eluted with CH_2Cl_2/MeOH was concentrated, and Et_2O (17.3 mL) was added to the residue to induce a precipitation of **2g**. The solution was stirred for 15 min, and then the ether phase was decanted. The solids were washed twice more with Et_2O (17.3 mL×2) and then dried in vacuo to give **2g** as white solids of mp 209-210 °C in 56% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.95 (d, J = 8.3 Hz, 4H), 8.51 (d, J = 8.3 Hz, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 120.8 (C) (q, J = 320.0 Hz, $CF_3SO_3^-$), 121.0 (C), 123.4 (C) (q, J = 271.7 Hz), 128.5 (CH) (d, J = 3.3 Hz), 132.3 (C) (q, J = 32.5 Hz), 136.4 (CH). ^{19}F NMR (376 MHz, DMSO-d_6): δ -61.6 (6F), -77.3 (3F). IR (ATR): 1160, 1220, 1240, 1600 cm^{-1}. HRMS (FAB) *m/z* Calcd for $C_{14}H_8F_6I$ ([M-TfO$^-$]$^+$): 416.9575. Found: 416.9587.

Di(3-trifluoromethylphenyl)iodonium triflate (2h).



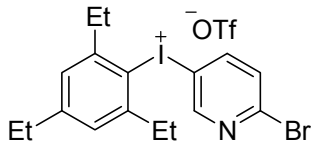
After preparation in the same manner as **2g**, the purification through column chromatography (AcOEt) gave **2h** as white solids of mp 90-91 °C in 42% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80 (t, J = 7.8 Hz, 2H), 8.08 (d, J = 7.8 Hz, 2H), 8.61 (d, J = 7.8 Hz, 2H), 8.82 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 117.3 (C), 120.8 (C) (q, J = 320.3 Hz, $CF_3SO_3^-$), 123.0 (C) (q, J = 271.7 Hz), 129.1 (CH), (d, J = 2.5 Hz), 131.7 (C) (q, J = 32.9 Hz), 132.2 (CH) (d, J = 2.5 Hz), 132.9 (CH), 139.5 (CH). ^{19}F NMR (376 MHz, DMSO-d_6): δ -60.8 (6F), -77.3 (3F). IR (ATR): 1130, 1170, 1190, 1220, 1240, 1600 cm^{-1}. HRMS (FAB) *m/z* Calcd for $C_{14}H_8F_6I$ ([M-TfO$^-$]$^+$): 416.9575. Found: 416.9580.

Di(2-methylphenyl)iodonium triflate (2i).



Preparation of **2i** was conducted in the same manner as **2g** with the exception that the half reaction time was adopted, giving **2i** as white solids of mp 170-171 °C in 71% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.61 (s, 6H), 7.28-7.32 (m, 2H), 7.55-7.60 (m, 4H), 8.30-8.32 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.0 (CH_3), 119.2 (C) (q, J = 320.0 Hz, $CF_3SO_3^-$), 120.6 (C), 129.3 (CH), 131.6 (CH), 132.7 (CH), 137.2 (CH), 140.7 (C). ^{19}F NMR (376 MHz, DMSO-d_6): δ -77.31. IR (ATR): 750, 1020, 1160, 1240 cm^{-1}. HRMS (FAB) *m/z* Calcd for $C_{14}H_{14}I$ ([M-TfO$^-$]$^+$): 309.0140. Found: 309.0150.

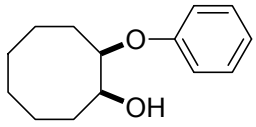
(6-Bromo-3-pyridyl)(2,4,6-triethylphenyl)iodonium triflate (2j).



The mixture of MCPBA (19.4 mmol, 77% active oxidant) and 2-bromo-5-iodopyridine (17.6 mmol) in CH_2Cl_2 (78.5 mL) were heated to 80 ºC for 2 h. Then, 1,3,5-triethylbenzene (19.4 mmol) and triflic acid (58.1 mmol) were added at 0 ºC and the mixture was slowly warmed to room temperature over 6 h. The solvent was removed in vacuo, and then Et_2O was added. The heterogeneous mixture was cooled to -20 ºC for at 60 min. The solids were collected via filtration, washed with Et_2O, and dried under vacuum. Then, **2j** was obtained as white solids of mp 169-170 °C in 31% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 1.23-1.32 (m, 9H), 2.73 (q, *J* = 7.6 Hz, 2H), 3.01 (q, *J* = 7.6 Hz, 4H), 7.33 (s, 2H), 7.73 (d, *J* = 8.8 Hz, 1H), 8.06 (dd, *J* = 2.4, 8.8 Hz, 1H), 8.74 (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD): δ 15.5 (CH_3), 15.6 (CH_3), 29.4 (CH_2), 34.6 (CH_2), 112.4 (C), 121.6 (C) (q, *J* = 317.0 Hz, $CF_3SO_3^-$), 121.7 (C), 129.4 (CH), 133.0 (CH), 144.4 (CH), 146.4 (C), 149.0 (C), 152.7 (C), 153.8 (CH). ^{19}F NMR (376 MHz, CD_3OD): δ -78.37. IR (ATR): 1020, 1080, 1220 cm^{-1}. HRMS (FAB) *m/z* Calcd for $C_{17}H_{20}{}^{79}BrIN$ ($[M\text{-}TfO^-]^+$): 443.9824. Found: 443.9834.

Typical procedure for copper(II)-catalyzed monoarylation of diols with diaryliodonium salts. Under argon atmosphere, a reaction tube was charged with $Cu(OTf)_2$ (36.2 mg, 0.1 mmol) and sodium phosphate tribasic (492 mg, 3.0 mmol), and then toluene (1.5 ml) was added. The mixture was stirred for 10 min at room temperature. Then, *cis*-1,2-cyclooctanediol **1a** (144 mg, 1.0 mmol) and diphenyliodonium triflate **2a** (645 mg, 1.5 mmol) were added and the reaction mixture was stirred at 100 °C for 15 h. The mixture was cooled to room temperature and water and saturated NH_4Cl were added. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. Concentration and purification through silica gel column chromatography gave the desired product **3aa**.

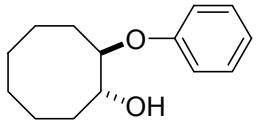
***cis*-2-Phenoxycyclooctanol[7] (3aa).**



Silica gel column chromatography (hexane/AcOEt = 10/1) gave 205 mg (0.93 mmol, 93% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.45-1.86 (m, 10H), 1.89-1.99 (m, 1H), 2.09-2.18 (m, 1H), 2.52 (brs, 1H), 4.06-4.10 (m, 1H), 4.45-4.49 (m, 1H), 6.88-6.91 (m, 2H), 6.93-6.98 (m, 1H) 7.26-7.32 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.7

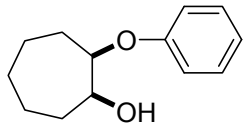
(CH_2), 25.1 (CH_2), 25.3 (CH_2), 26.1 (CH_2), 26.9 (CH_2), 29.2 (CH_2), 71.6 (CH), 79.5 (CH), 115.9 (CH), 120.9 (CH), 129.5 (CH), 157.2 (C). IR (ATR): 690, 730, 750, 840, 890, 1240, 1270, 1490, 1590, 1600, 3580 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{14}H_{20}O_2$ (M^+): 220.1463. Found: 220.1471.

***trans*-2-Phenoxycyclooctanol (3ba).**



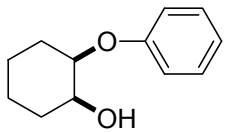
Silica gel column chromatography (hexane/AcOEt = 10/1, benzene/Et_2O = 20/1) gave 165 mg (0.75 mmol, 75% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.43-2.02 (m, 12H), 2.70 (s, 1H), 3.90-3.95 (m, 1H), 4.23-4.27 (m, 1H), 6.91 (d, *J* = 8.1 Hz, 2H), 6.96 (t, *J* = 8.1 Hz, 1H), 7.29 (t, *J* = 8.1 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.0 (CH_2), 24.7 (CH_2), 25.3 (CH_2), 26.4 (CH_2), 27.9 (CH_2), 29.6 (CH_2), 74.5 (CH), 82.9 (CH), 116.2 (CH), 121.1 (CH), 129.5 (CH), 157.4 (C). IR (ATR): 690, 730, 750, 850, 880, 1230, 1490, 1590, 1600, 3570 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{14}H_{20}O_2$ (M^+): 220.1463. Found: 220.1447.

***cis*-2-Phenoxycycloheptanol[7] (3ca).**



Silica gel column chromatography (hexane/AcOEt = 5/1) gave 194 mg (0.94 mmol, 94% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.38-1.50 (m, 2H), 1.54-1.92 (m, 7H), 1.98-2.08 (m, 1H), 2.40 (s, 1H), 4.07-4.12 (m, 1H), 4.36-4.40 (m, 1H), 6.89-6.97 (m, 3H), 7.23-7.31 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.4 (CH_2), 22.5 (CH_2), 26.2 (CH_2), 27.6 (CH_2), 31.7 (CH_2), 72.0 (CH), 80.6 (CH), 116.0 (CH), 121.0 (CH), 129.5 (CH), 157.4 (C). IR (ATR): 690, 750, 860, 1200, 1240, 1490, 1590, 1600, 3420 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{13}H_{18}O_2$ (M^+): 206.1307. Found: 206.1312.

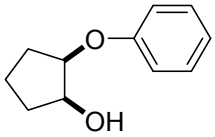
***cis*-2-Phenoxycyclohexanol[8] (3da).**



Silica gel column chromatography (hexane/AcOEt = 5/1, benzene/Et_2O = 20/1) gave 134 mg (0.70 mmol, 70% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.29-1.42 (m, 2H), 1.60-1.76 (m, 4H), 1.86-2.02 (m, 2H), 2.18 (d, *J* = 5.6 Hz, 1H), 3.93-3.97 (m, 1H), 4.37-4.40 (m, 1H), 6.93-6.98 (m, 3H), 7.26-7.31 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.4 (CH_2), 21.7 (CH_2), 26.4 (CH_2), 30.4 (CH_2), 69.2 (CH), 77.3 (CH), 116.4 (CH), 121.2 (CH),

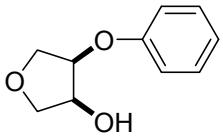
129.5 (CH), 157.3 (C). IR (ATR): 690, 750, 890, 1230, 1490, 1590, 1600, 3420 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{12}H_{16}O_2$ (M^+): 192.1150. Found: 192.1125.

***cis*-2-Phenoxycyclopentanol**[8] **(3ea).**



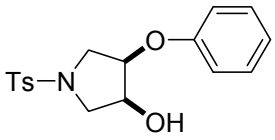
Silica gel column chromatography (hexane/AcOEt = 5/1, benzene/Et_2O = 20/1) gave 139 mg (0.78 mmol, 78% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.55-1.64 (m, 1H), 1.78-1.97 (m, 4H), 1.99-2.09 (m, 1H), 2.40 (d, *J* = 5.4 Hz, 1H), 4.23-4.28 (m, 1H), 4.53-4.57 (m, 1H), 6.92-6.99 (m, 3H), 7.26-7.32 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 19.6 (CH_2), 28.2 (CH_2), 31.1 (CH_2), 73.2 (CH), 79.6 (CH), 115.6 (CH), 121.1 (CH), 129.5 (CH), 157.5 (C). IR (ATR): 690, 750, 800, 820, 870, 890, 1240, 1490, 1590, 1600, 3460 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{11}H_{14}O_2$ (M^+): 178.0994. Found: 178.0988.

***cis*-4-Phenoxy-3-tetrahydrofuranol (3fa).**



Silica gel column chromatography (hexane/AcOEt = 2/1) gave 158 mg (0.88 mmol, 88% yield) of the product as white solids of mp 68-69 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.62 (d, *J* = 6.3 Hz, 1H), 3.83 (dd, *J* = 4.9, 9.5 Hz, 1H), 3.93 (dd, *J* = 4.4, 10.0 Hz, 1H), 4.04 (dd, *J* = 5.6, 9.5 Hz, 1H), 4.14 (dd, *J* = 5.6, 10.0 Hz, 1H), 4.47-4.52 (m, 1H), 4.74-4.78 (m, 1H), 6.91-6.94 (m, 2H), 7.01-7.05 (m, 1H), 7.29-7.34 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 70.2 (CH_2), 70.7 (CH_2), 72.6 (CH), 76.7 (CH), 115.4 (CH), 121.7 (CH), 129.5 (CH), 157.0 (C). IR (ATR): 690, 750, 810, 880, 910, 1070, 1240, 1490, 1580, 1600, 3350 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{10}H_{12}O_3$ (M^+): 180.0786. Found: 180.0776.

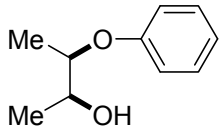
***cis*-4-Phenoxy-1-(4-toluenesulfonyl)-3-pyrrolidinol (3ga).**



Silica gel column chromatography (hexane/AcOEt = 2/1) gave 278 mg (0.83 mmol, 83% yield) of the product as white solids of mp 99-100 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.37 (d, *J* = 6.8 Hz, 1H), 2.43 (s, 3H), 3.24 (dd, *J* = 5.8, 10.3 Hz, 1H), 3.37 (dd, *J* = 4.4, 11.0 Hz, 1H), 3.69-3.74 (m, 2H), 4.35-4.41 (m, 1H), 4.64 (m, 1H), 6.71-6.73 (m, 2H), 6.99-7.03 (m, 1H), 7.24-7.29 (m, 4H), 7.67 (d, *J* = 8.0 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.4 (CH_3), 49.6 (CH_2), 51.8

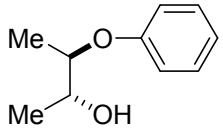
(CH_2), 70.2 (CH), 75.9 (CH), 115.5 (CH), 122.0 (CH), 127.3 (CH), 129.5 (CH), 129.6 (CH), 133.2 (C), 143.6 (C), 156.2 (C). IR (ATR): 750, 810, 1150, 1160, 1210, 1230, 1340, 1490, 3370 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{17}H_{19}NO_4S$ (M^+): 333.1035. Found: 333.1038.

***erythro*-3-Phenoxy-2-butanol**[7] **(3ha).**



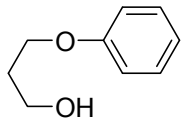
Silica gel column chromatography (hexane/AcOEt = 5/1) gave 124 mg (0.75 mmol, 75% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.24 (d, *J* = 6.6 Hz, 3H), 1.27 (d, *J* = 6.1 Hz, 3H), 2.05 (brs, 1H), 4.00-4.06 (m, 1H), 4.31-4.36 (m, 1H), 6.90-6.97 (m, 3H), 7.26-7.31 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.4 (CH_3), 17.8 (CH_3), 69.4 (CH), 77.2 (CH), 116.0 (CH), 121.0 (CH), 129.5 (CH), 157.5 (C). IR (ATR): 690, 750, 800, 900, 1230, 1490, 1590, 1600, 3400 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{10}H_{14}O_2$ (M^+): 166.0994. Found: 166.0965.

***threo*-3-Phenoxy-2-butanol (3ia).**



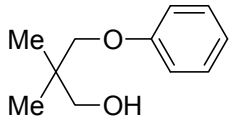
Silica gel column chromatography (hexane/AcOEt = 7/1) gave 94 mg (0.57 mmol, 57% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.253 (d, *J* = 6.1 Hz, 3H), 1.255 (d, *J* = 5.9 Hz, 3H), 2.53 (brs, 1H), 3.81-3.87 (m, 1H), 4.12-4.18 (m, 1H), 6.92-6.99 (m, 3H), 7.26-7.31 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 15.5 (CH_3), 18.4 (CH_3), 70.8 (CH), 78.8 (CH), 116.1 (CH), 121.1 (CH), 129.5 (CH), 157.6 (C). IR (ATR): 690, 750, 900, 1240, 1490, 1590, 1600, 3420 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{10}H_{14}O_2$ (M^+): 166.0994. Found: 166.0974.

3-Phenoxy-1-propanol[8] **(3ja).**



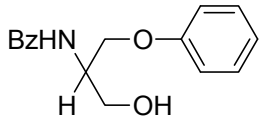
Silica gel column chromatography (hexane/AcOEt = 3/1) gave 127 mg (0.83 mmol, 83% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.79 (brs, 1H), 2.05 (quintet, *J* = 5.9 Hz, 2H), 3.88 (t, *J* = 5.9 Hz, 2H), 4.13 (t, *J* = 5.9 Hz, 2H), 6.90-6.97 (m, 3H), 7.29 (t, *J* = 8.3 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 31.8 (CH_2), 59.9 (CH_2), 65.2 (CH_2), 114.3 (CH), 120.7 (CH), 129.3 (CH), 158.6 (C). IR (ATR): 690, 750, 880, 1240, 1500, 1600, 3350 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_9H_{12}O_2$ (M^+): 152.0837. Found: 152.0826.

2,2-Dimethyl-3-phenoxy-1-propanol (3ka).



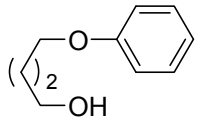
Silica gel column chromatography (hexane/AcOEt = 5/1) gave 149 mg (0.83 mmol, 83% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.04 (s, 6H), 1.91 (brs, 1H), 3.57 (s, 2H), 3.78 (s, 2H), 6.89-6.97 (m, 3H), 7.26-7.30 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.5 (CH_3), 36.2 (C), 69.4 (CH_2), 74.4 (CH_2), 114.4 (CH), 120.6 (CH), 129.3 (CH), 159.0 (C). IR (ATR): 690, 750, 1240, 1500, 1600, 3400 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{11}H_{16}O_2$ (M^+): 180.1150. Found: 180.1146.

2-Benzoylamino-3-phenoxy-1-propanol (3la).



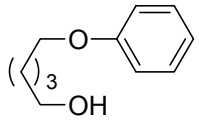
Silicagel chromatography (hexane/AcOEt = 3/2) gave 167 mg (0.62 mmol, 62% yield) of the product as yellow solids of mp 81-82 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.58 (brs, 1H), 3.92 (dd, *J* = 4.2, 11.2 Hz, 1H), 4.08 (dd, *J* = 4.2, 11.2 Hz, 1H), 4.24 (dd, *J* = 4.6, 9.5 Hz, 1H), 4.28 (dd, *J* = 4.6, 9.5 Hz, 1H), 4.52 (quintet, *J* = 3.7 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 2H), 7.00 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.80 (d, *J* = 7.3 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 50.8 (CH), 62.7 (CH_2), 67.1 (CH_2), 114.5 (CH), 121.4 (CH), 127.0 (CH), 128.6 (CH), 129.6 (CH), 131.8 (CH), 134.0 (C), 158.2 (C), 167.9 (C). IR (ATR): 1240, 1490, 1600, 1640, 3320 cm^{-1} HRMS (EI) *m/z* Calcd for $C_{16}H_{17}NO_3$ (M^+): 271.1208. Found: 271.1211.

4-Phenoxy-1-butanol[8] **(3ma).**



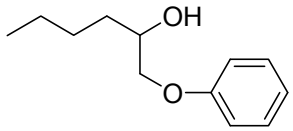
Silica gel column chromatography (hexane/AcOEt = 3/1) gave 150 mg (0.90 mmol, 90% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.62 (brs, 1H), 1.73-1.80 (m, 2H), 1.86-1.92 (m, 2H), 3.73 (t, *J* = 6.3 Hz, 2H), 4.01 (t, *J* = 6.3 Hz, 2H), 6.89-6.96 (m, 3H), 7.25-7.31 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.7 (CH_2), 29.4 (CH_2), 62.4 (CH_2), 67.5 (CH_2), 114.4 (CH), 120.6 (CH), 129.3 (CH), 158.8 (C) . IR (ATR): 690, 750, 810, 880, 1240, 1500, 1590, 1600, 3320 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{10}H_{14}O_2$ (M^+): 166.0994. Found: 166.0965.

5-Phenoxy-1-pentanol[8] **(3na).**



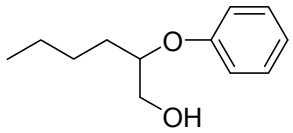
Silica gel column chromatography (hexane/AcOEt = 2/1) gave 66 mg (0.37 mmol, 37% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz,$CDCl_3$): δ 1.51-1.68 (m, 5H), 1.78-1.85 (m, 2H), 3.67 (t, *J* = 6.6 Hz, 2H), 4.00 (t, *J* = 6.6 Hz, 2H), 6.87-6.95 (m, 3H), 7.25-7.30 (m, 2H) ^{13}C-NMR (100 MHz, $CDCl_3$): δ 22.3 (CH_2), 29.0 (CH_2), 32.4 (CH_2), 62.8 (CH_2), 67.6 (CH_2), 114.4 (CH), 120.5 (CH), 129.4 (CH), 159.0 (C). IR (ATR): 690, 750, 810, 880, 1240, 1500, 1590, 1600, 3350 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{11}H_{16}O_2$ (M^+): 180.1150. Found: 180.1147.

1-Phenoxy-2-hexanol[9] **(3oa).**



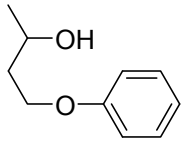
Silica gel column chromatography (hexane/AcOEt = 7/1) gave 116 mg (0.60 mmol, 60% yield) of the product as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.1 Hz, 3H), 1.32-1.63 (m, 6H), 2.30 (brs, 1H), 3.81-3.85 (m, 1H), 3.97-4.04 (m, 2H), 6.90-6.99 (m, 3H), 7.25-7.33 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 22.6 (CH_2), 27.6 (CH_2), 32.7 (CH_2), 70.0 (CH), 72.1 (CH_2), 114.5 (CH), 121.0 (CH), 129.4 (CH), 158.5 (C). IR (ATR): 690, 750, 1500, 3400 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{12}H_{18}O_2$ (M^+): 194.1307. Found: 194.1298.

2-Phenoxy-1-hexanol (3oa').



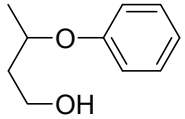
Silica gel column chromatography (hexane/AcOEt = 7/1) gave 54 mg (0.28 mmol, 28% yield) of the product as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.1 Hz, 3H), 1.29-1.42 (m, 4H), 1.60-1.77 (m, 2H), 1.89 (brs, 1H), 3.73 (dd, *J* = 6.1, 11.7 Hz, 1H), 3.81-3.83 (m, 1H), 4.32-4.38 (m, 1H), 6.93-6.98 (m, 3H), 7.26-7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 22.7 (CH_2), 27.4 (CH_2), 30.2 (CH_2), 64.4 (CH_2), 78.9 (CH), 116.1 (CH), 121.1 (CH), 129.5 (CH), 158.2 (C). IR (ATR): 690, 750, 880, 1490, 3390 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{12}H_{18}O_2$ (M^+): 194.1307. Found: 194.1303.

4-phenoxy-2-butanol[10] **(3pa).**



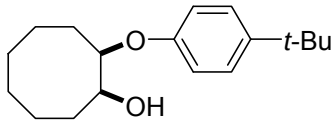
Silica gel column chromatography (hexane/AcOEt = 5/1) gave 106 mg (0.64 mmol, 64% yield) of the product as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 6.4 Hz, 3H), 1.90-1.95 (m, 2H), 2.12 (brs, 1H), 4.07-4.20 (m, 3H), 6.91 (d, *J* = 7.6 Hz, 2H), 6.96 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5 (CH_3), 38.0 (CH_2), 65.5 (CH_2), 66.0 (CH), 114.4 (CH), 120.8 (CH), 129.4 (CH), 158.6 (C). IR (ATR): 690, 750, 1500, 1600, 3370 cm^{-1}. HRMS (EI) Calcd for $C_{10}H_{14}O_2$ (M^+): 166.0994. Found: 166.0971.

3-phenoxy-1-butanol[10] **(3pa').**



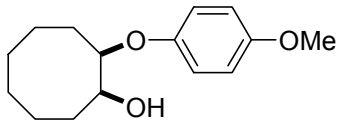
Silica gel column chromatography (hexane/AcOEt = 5/1) gave 27 mg (0.16 mmol, 16% yield) of the product as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, *J* = 6.1 Hz, 3H), 1.79 (brs, 1H), 1.85-2.03 (m, 2H), 3.78-3.89 (m, 2H), 4.58-4.66 (m, 1H), 6.92 (d, *J* = 7.8 Hz, 2H), 6.95 (t, *J* = 7.8 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7 (CH_3), 39.0 (CH_2), 60.1 (CH_2), 72.3 (CH), 116.1 (CH), 121.0 (CH), 129.5 (CH), 157.6 (C). IR (ATR): 690, 750, 1490, 1600, 3360 cm^{-1}. HRMS (EI) Calcd for $C_{10}H_{14}O_2$ (M^+): 166.0994. Found: 166.0971.

***cis*-2-(4-*tert*-Butylphenoxy)cyclooctanol (3ab).**



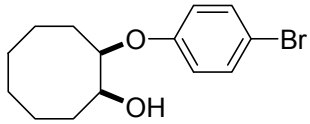
Silica gel column chromatography (hexane/AcOEt = 10/1) gave 256 mg (0.93 mmol, 93% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 9H), 1.45-1.85 (m, 10H), 1.88-1.98 (m, 1H), 2.05-2.17 (m, 1H), 2.52 (d, *J* = 3.4 Hz, 1H), 4.05-4.07 (m, 1H), 4.41-4.45 (m, 1H), 6.81-6.84 (m, 2H), 7.28-7.32 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.8 (CH_2), 25.1 (CH_2), 25.4 (CH_2), 26.2 (CH_2), 26.9 (CH_2), 29.2 (CH_2), 31.5 (CH_3), 34.1 (C), 71.7 (CH), 79.6 (CH), 115.4 (CH), 126.3 (CH), 143.7 (C), 155.0 (C). IR (ATR): 810, 830, 890, 1240, 1270, 1510, 1610, 3400 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{18}H_{28}O_2$ (M^+): 276.2089. Found: 276.2076.

***cis*-2-(4-Methoxyphenoxy)cyclooctanol (3ac).**



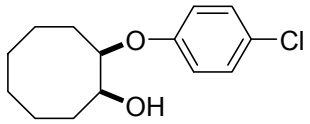
Silica gel column chromatography (hexane/AcOEt = 5/1) gave 231 mg (0.92 mmol, 92% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.49-1.84 (m, 10H), 1.88-1.98 (m, 1H), 2.04-2.13 (m, 1H), 2.57 (s, 1H), 3.77 (s, 3H), 4.04-4.07 (m, 1H), 4.32-4.36 (m, 1H), 6.83-6.86 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.9 (CH_2), 25.2 (CH_2), 25.3 (CH_2), 26.1 (CH_2), 26.8 (CH_2), 29.3 (CH_2), 55.7 (CH_3), 71.6 (CH), 80.8 (CH), 114.7 (CH_2), 117.5 (CH_2), 151.3 (C), 154.1 (C). IR (ATR): 820, 1040, 1220, 1500, 3480 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{15}H_{22}O_3$ (M^+): 250.1569. Found: 250.1553.

cis-2-(4-Bromophenoxy)cyclooctanol (3ad).



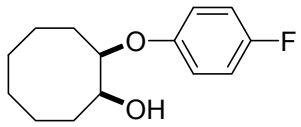
Silica gel column chromatography (hexane/AcOEt = 5/1) gave 297 mg (0.99 mmol, 99% yield) of the product as yellow solids of mp 45-46 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.50-1.85 (m, 10H), 1.88-1.98 (m, 1H), 2.08-2.17 (m, 1H), 2.41 (s, 1H), 4.04-4.08 (m, 1H), 4.40-4.43 (m, 1H), 6.75-6.79 (m, 2H), 7.36-7.40 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.7 (CH_2), 25.1 (CH_2), 25.2 (CH_2), 25.9 (CH_2), 26.8 (CH_2), 29.3 (CH_2), 71.6 (CH), 80.1 (CH), 113.1 (C), 117.8 (CH), 132.4 (CH), 156.4 (C). IR (ATR): 800, 820, 1070, 1240, 1490, 1590, 3420 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{14}H_{19}{}^{79}BrO_2$ (M^+): 298.0568. Found: 298.0547.

cis-2-(4-Chlorophenoxy)cyclooctanol (3ae).



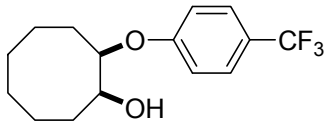
Silica gel column chromatography (hexane/AcOEt = 10/1) gave 244 mg (0.96 mmol, 96% yield) of the product as white solids of mp 44-45°C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.50-1.84 (m, 10H), 1.89-1.98 (m, 1H), 2.08-2.17 (m, 1H), 2.43 (s, 1H), 4.05-4.08 (m, 1H), 4.40-4.42 (m, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.7 (CH_2), 25.1 (CH_2), 25.2 (CH_2), 26.0 (CH_2), 26.8 (CH_2), 29.3 (CH_2), 71.6 (CH), 80.3 (CH), 117.3 (CH), 125.8 (C), 129.4 (CH), 155.9 (C). IR (ATR): 800, 820, 1090, 1240, 1490, 1590, 3410 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{14}H_{19}{}^{35}ClO_2$ (M^+): 254.1074. Found: 254.1066.

cis-2-(4-Fluorophenoxy)cyclooctanol (3af).



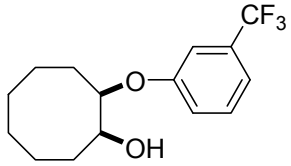
Silica gel column chromatography (hexane/AcOEt = 10/1) gave 224 mg (0.94 mmol, 94% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.45-1.85 (m, 10H), 1.89-1.99 (m, 1H), 2.05-2.16 (m, 1H), 2.46 (d, *J* = 3.7 Hz, 1H), 4.04-4.08 (m, 1H), 4.36-4.39 (m, 1H), 6.81-6.86 (m, 2H), 6.94-7.00 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.8 (CH_2), 25.07 (CH_2), 25.12 (CH_2), 26.0 (CH_2), 26.7 (CH_2), 29.3 (CH_2), 71.5 (CH), 80.7 (CH), 115.8 (CH) (d, *J* = 23.1 Hz), 117.2 (CH) (d, *J* = 8.2 Hz) 153.3 (C) (d, *J* = 2.5 Hz), 157.3 (C) (d, *J* = 239.2 Hz). IR (ATR): 800, 830, 900, 1100, 1130, 1200, 1240, 1500, 3410 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{14}H_{19}FO_2$ (M^+): 238.1369. Found: 238.1358.

***cis*-2-(4-Trifluoromethylphenoxy)cyclooctanol (3ag).**



Silica gel column chromatography (hexane/AcOEt = 5/1) gave 286 mg (0.99 mmol, 99% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.48-1.84 (m, 10H), 1.90-2.00 (m, 1H), 2.10-2.22 (m, 1H), 2.37 (d, *J* = 2.4 Hz, 1H), 4.09-4.11 (m, 1H), 4.52-4.54 (m, 1H), 6.95 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.6 (CH_2), 25.1 (CH_2), 25.2 (CH_2), 26.0 (CH_2), 26.8 (CH_2), 29.3 (CH_2), 71.6 (CH), 80.0 (CH), 115.6 (CH), 123.0 (C) (q, *J* = 33.0 Hz), 124.3 (C) (q, *J* = 270.0 Hz), 127.0 (CH) (q, *J* = 3.3 Hz), 159.8 (C). IR (ATR): 740, 840, 1250, 1520, 1590, 1610, 3430 cm^{-1} HRMS (EI) *m/z* Calcd for $C_{15}H_{19}F_3O_2$ (M^+): 288.1337. Found: 288.1327.

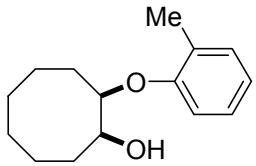
***cis*-2-(3-Trifluoromethylphenoxy)cyclooctanol (3ah).**



Silica gel column chromatography (hexane/AcOEt = 5/1) gave 272 mg (0.94 mmol, 94% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.47-1.87 (m, 10H), 1.91-2.01 (m, 1H), 2.10-2.23 (m, 1H), 2.39 (d, *J* = 3.6 Hz, 1H), 4.08-4.11 (m, 1H), 4.50 (dt, *J* = 2.4, 6.6 Hz, 1H), 7.04-7.07 (m, 1H), 7.12 (s, 1H), 7.21 (d, *J* = 8.1 Hz, 1H), 7.40 (t, *J* = 8.1 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.7 (CH_2), 25.0 (CH_2), 25.1 (CH_2), 26.0 (CH_2), 26.8 (CH_2), 29.4 (CH_2), 71.6 (CH), 80.2 (CH), 112.9 (CH) (q, *J* = 4.1 Hz), 117.6 (CH) (q, *J* = 4.1 Hz), 119.0 (CH), 123.8 (C) (q, *J* = 272.3 Hz), 130.1 (CH), 131.9 (C) (q, *J* = 32.1 Hz), 157.4 (C). IR (ATR):

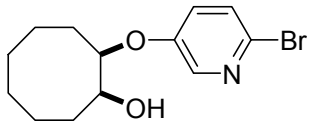
700, 740, 750, 780, 860, 880, 900, 1230, 1490, 1590, 1610, 3430 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{15}H_{19}F_3O_2$ (M^+): 288.1337. Found: 288.1337.

***cis*-2-(2-Methylphenoxy)cyclooctanol (3ai).**



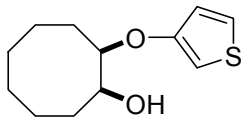
Silica gel column chromatography (hexane/AcOEt = 10/1) gave 221 mg (0.94 mmol, 94% yield) of the product as colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.44-1.87 (m, 10H), 1.93-2.02 (m, 1H), 2.09-2.19 (m, 1H), 2.23 (s, 3H), 2.54 (s, 1H), 4.08-4.11 (m, 1H), 4.47-4.50 (m, 1H), 6.82 (d, *J* = 7.3 Hz, 1H), 6.87 (t, *J* = 7.3 Hz, 1H), 7.13-7.17 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 16.5 (CH_3), 21.9 (CH_2), 25.2 (CH_2), 26.3 (CH_2), 26.7 (CH_2), 29.3 (CH_2), 72.0 (CH), 79.6 (CH), 112.8 (CH), 120.6 (CH), 126.7 (CH), 127.6 (C), 131.0 (CH), 155.2 (C). IR (ATR): 710, 750, 800, 830, 840, 870, 1240, 1490, 1600, 3590 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{15}H_{22}O_2$ (M^+): 234.1620. Found: 234.1604.

***cis*-2-(6-bromo-3-pyridyloxy)cyclooctanol (3aj).**



Silica gel column chromatography (hexane/AcOEt = 5/1) gave 183 mg (0.61 mmol, 61% yield) of the product as yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.44-1.82 (m, 10H), 1.85-2.00 (m, 1H), 2.12-2.21 (m, 1H), 2.28 (brs, 1H), 4.08-4.11 (m, 1H), 4.44-4.46 (m, 1H), 7.10 (dd, *J* = 3.2, 8.6 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 8.06 (d, *J* = 2.9 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.6 (CH_2), 24.9 (CH_2), 25.2 (CH_2), 25.9 (CH_2), 26.7 (CH_2), 29.5 (CH_2), 71.6 (CH), 81.1 (CH), 126.2 (CH), 128.3 (CH), 132.3 (C), 138.9 (CH), 153.4 (C). IR (ATR): 1230, 3390 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{13}H_{18}{}^{79}BrNO_2$ (M^+): 299.0521. Found: 299.0520.

***cis*-2-(3-thienyloxy)cyclooctanol (3ak).**



Silica gel column chromatography (hexane/AcOEt = 10/1) gave 158 mg (0.70 mmol, 70% yield) of the product as green oil. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.44-1.96 (m, 11H), 2.05-2.24 (m, 1H), 2.40 (brs, 1H), 4.08-4.13 (m, 1H), 4.31-4.33 (m, 1H), 6.25-6.26 (m, 1H), 6.74-6.76 (m, 1H), 7.19 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.5 (CH_2), 25.0 (CH_2), 25.5 (CH_2), 26.0

(CH_2), 26.8 (CH_2), 29.2 (CH_2), 71.3 (CH), 82.1 (CH), 99.0 (CH) 120.0 (CH), 124.6 (CH), 155.8 (C). IR (ATR): 750, 1230, 3440 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{12}H_{18}O_2S$ (M^+): 226.1028. Found: 226.1006.

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Chapter 3

General. All melting points are not corrected. IR spectra were expressed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were taken at 400 and 100 MHz, respectively. Chemical shift values of ^{1}H NMR are given in ppm relative to internal or external TMS. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded using electron ionization (EI) mass spectrometry. The products were isolated by silica gel column chromatography. The absolute configuration of several desired products was determined by reference to the previous report by Zhou,[1] and that of the others was shown in the tables as expected configuration (1*S*,2*R*) based on an empirical enantioinduction mechanism with chiral bis(oxazoline) ligands bearing (*R*,*R*) configuration.

Cis-1,2-cyclooctanediol **1a**, *cis*-1,2-cyclohexanediol **1e**, *meso*-2,3-butanediol **1f**, diphenyliodonium triflate **2a**, all of copper sources, chiral ligands **L1**, **L5**, **L16,** sodium phosphate tribasic, lithium phosphate tribasic, sodium carbonate, sodium fluoride, *N*,*N*-diisopropylethylamine, anhydrous 1,2-dichloroethane, anhydrous DMA, and anhydrous *i*-PrOH were used as received. Potassium phosphate tribasic was ground to a fine powder prior to use. Toluene and dioxane were distilled from sodium benzophenone ketyl under argon atmosphere. *Cis*-1,2-cyclododecanediol **1b**[2], *cis*-cyclooct5-ene-1,2-diol **1c**[3], *cis*-1,2-cyclo-heptanediol **1d**[4], di(2-methylphenyl)iodonium triflate **2b**[5], di(4-methoxyphenyl)iodonium triflate **2c**[5], di(4-trifluoromethylphenyl)iodonium triflate **2d**[5], and chiral ligands **L2**[6], **L3**[7,] **L4**[8], **L7-8**[9], **L9**[10], **L10**[11], **L11**[12], **L12**[13], **L13-14**[14], **L15**[15], **L17**[16], **L18**[17] were prepared as previously reported.

Synthesis of (*R*,*R*)-2,2'-(nonane-5,5-diyl)bis(4-phenyl-2-oxazoline) (L6)

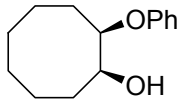
Chiral ligand **L6** was prepared on the basis of the previous report by Wong[18]. To the solution of 2,2'-methylene-bis[(4*R*)-4-phenyl-2-oxazoline] (172 mg, 0.56 mmol), TMEDA (130 mg, 1.12 mmol) and diisopropylamine (57 mg, 0.56 mmol) in THF (10 mL) was added *n*-BuLi (1.6 M in hexane, 1.12 mmol) at −65 °C. The solution was stirred at −25 °C for 20 min, then cooled to −65 °C and 1-iodobutane (206 mg, 1.12 mmol) was added dropwise. The mixture was warmed to room temperature and stirred for 12 h. The reaction was quenched with saturated NH_4Cl and diluted with Et_2O. The layers were separated, and organic layer was concentrated. Silica gel column chromatography (hexane/AcOEt = 3/1) gave 212 mg (0.51 mmol, 90% yield) of the product as colorless oil. $[\alpha]^{27}_{D}$ +69.1 (*c* 0.64, CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.2 Hz, 6H) 1.27-1.40 (m, 8H), 2.04-2.18 (m, 4H), 4.12 (t, *J* = 8.4 Hz, 2H), 4.66 (t, *J* = 8.4 Hz, 2H), 5.25 (t, *J* = 8.4 Hz, 2H), 7.26-7.35 (m, 10H), ^{13}C-NMR (100 MHz, $CDCl_3$): δ

13.9, 22.8, 26.1, 32.2, 46.1, 69.5, 74.9, 126.7, 127.5, 128.6, 142.4, 169.2. IR (ATR): 700, 1450, 1650, 2960 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{27}H_{34}N_2O_2$ (M^+): 418.2620. Found: 418.2637.

Typical procedure of chiral copper-catalyzed asymmetric monoarylation of vicinal diols with diaryliodonium triflates

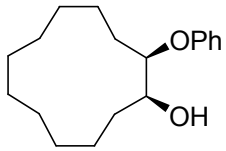
Under argon atmosphere, a reaction tube was charged with $CuCl_2$ (6.7 mg, 0.05 mmol), (*R*,*R*)-Ph-BOX **L1** (16.7 mg, 0.05 mmol), and sodium phosphate tribasic (492 mg, 3.0 mmol). After toluene (1.5 mL) was added, the mixture was stirred at 80 °C for 15 min and cooled to room temperature. Then, *cis*-1,2-cyclooctanediol (**1a**) (144 mg, 1.0 mmol) and diphenyliodonium triflate (**2a**) (645 mg, 1.5 mmol) were added and the reaction mixture was stirred at 80 °C for 15 h. The mixture was cooled to room temperature, and water and saturated NH_4Cl were added. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. Concentration and purification through silica gel column chromatography gave the desired product **3aa**.

(−)-2-Phenoxycyclooctanol (3aa).



Silica gel column chromatography (hexane/AcOEt = 10/1) gave 207 mg (0.94 mmol, 94% yield) of the product as colorless oil. $[\alpha]^{25}_D$ −3.1 (*c* 1.0, $CHCl_3$). 76% *ee* (HPLC, Daicel Chiralcel OD-H, hexane/*i*-PrOH = 200/1, 1.0 mL/min, 254 nm, major 23.5 min and minor 20.2 min). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.51-1.86 (m, 10H), 1.89-1.99 (m, 1H), 2.09-2.18 (m, 1H), 2.51 (d, *J* = 3.6 Hz, 1H), 4.06-4.10 (m, 1H), 4.46-4.49 (m, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.96 (t, *J* = 7.6 Hz, 1H), 7.26-7.31 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.6, 25.0, 25.2, 26.0, 26.8, 29.2, 71.6, 79.5, 116.0, 121.0, 129.6, 157.3. IR (ATR): 750, 1110, 1240, 1490, 1610, 2920, 3440 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{14}H_{20}O_2$ (M^+): 220.1463. Found: 220.1465.

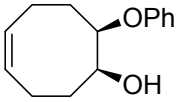
(−)-2-Phenoxycyclododecanol (3ba).



Silica gel column chromatography (benzene/Et_2O = 20/1) gave 233 mg (0.84 mmol, 84% yield) of the product as white solids of mp 72-73 °C. $[\alpha]^{27}_D$ −7.4 (*c* 1.0, $CHCl_3$). 85% *ee* (HPLC, Daicel Chiralcel OD-H, hexane/*i*-PrOH = 200/1, 1.0 mL/min, 254 nm, major 22.4 min and minor 28.6 min). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.36-1.59 (m, 17H), 1.70-1.85 (m, 3H), 1.91 (d,

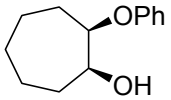
J = 6.0 Hz, 1H), 3.95-4.00 (m, 1H), 4.44-4.80 (m, 1H), 6.91-6.98 (m, 3H), 7.26-7.31 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.4, 21.6, 21.68, 21.74, 23.9, 24.0, 24.2, 24.3, 24.8, 28.4, 70.2, 79.6, 116.2, 121.1, 130.0, 158.2. IR (ATR): 690, 750, 1230, 1490, 1600, 2930, 3500 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{18}H_{28}O_2$ (M^+): 276.2089. Found: 276.2082.

(+)-8-Phenoxycyclooct-4-enol (3ca).



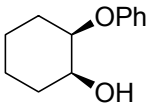
Silica gel column chromatography (benzene/Et_2O = 100/1) gave 153 mg (0.70 mmol, 70% yield) of the product as colorless oil. $[\alpha]^{26}_D$ +15.9 (*c* 0.84, $CHCl_3$). 64% *ee* (HPLC, Daicel Chiralcel OD-H, hexane/*i*-PrOH = 50/1, 1.0 mL/min, 254 nm, major 20.1 min and minor 17.2 min). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.80-1.89 (m, 2H), 1.97-2.18 (m, 5H), 2.60-2.72 (m, 2H), 4.17-4.20 (m, 1H), 4.61 (dd, *J* = 3.9, 9.2 Hz, 1H), 5.67-5.79 (m, 2H), 6.89-6.95 (m, 3H), 7.25-7.30 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 22.0, 22.5, 28.5, 32.6, 73.7, 80.6, 116.1, 120.9, 129.4, 129.6, 130.7, 157.9. IR (ATR): 790, 1000, 1020, 1240, 1260, 1490, 1600, 2930, 3410 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{14}H_{18}O_2$ (M^+): 218.1307. Found: 218.1305.

(1*S*,2*R*)-(−)-2-Phenoxycycloheptanol[1] (3da).



Silica gel column chromatography (benzene/ Et_2O = 50/1) gave 183 mg (0.89 mmol, 89% yield) of the product as colorless oil. $[\alpha]^{26}_D$ −8.3 (*c* 1.0, $CHCl_3$). 59% *ee* (HPLC, Daicel Chiralcel OD-H, hexane/*i*-PrOH = 200/1, 1.0 mL/min, 254 nm, major 47.3 min and minor 30.2 min).^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.38-1.50 (m, 2H), 1.56-1.91 (m, 7H), 1.99-2.07 (m, 1H), 2.38 (d, *J* = 4.8 Hz, 1H), 4.09-4.11 (m, 1H), 4.37-4.40 (m, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.96 (t, *J* = 7.2 Hz, 1H), 7.26-7.31 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.4, 22.5, 26.2, 27.6, 31.6, 72.1, 80.7, 116.1, 121.1, 129.6, 157.5. IR (ATR): 750, 1010, 1030, 1230, 1490, 1590, 1600, 2930, 3420 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{13}H_{18}O_2$ (M^+): 206.1307. Found: 206.1312.

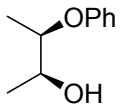
(1*S*,2*R*)-(−)-2-Phenoxycyclohexanol[1] (3ea).



Silica gel column chromatography (benzene/Et_2O = 20/1) gave 90 mg (0.47 mmol, 47% yield) of the product as colorless oil. $[\alpha]^{25}_D$ −9.6 (*c* 0.75, $CHCl_3$). 24% *ee* (HPLC, Daicel Chiralcel

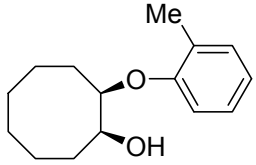
OD-H, hexane/*i*-PrOH = 50/1, 1.0 mL/min, 254 nm, major 17.5 min and minor 13.2 min). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.30-1.44 (m, 2H), 1.62-1.76 (m, 4H), 1.86-2.00 (m, 2H), 2.18 (d, *J* = 5.2 Hz, 1H), 3.94-3.95 (m, 1H), 4.37-4.40 (m, 1H), 6.94-6.98 (m, 3H), 7.26-7.31 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.3, 21.6, 26.4, 30.3, 69.2, 77.3, 116.4, 121.3, 129.6, 157.5. IR (ATR): 690, 750, 980, 1050, 1070, 1220, 1490, 1600, 2940, 3430 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{12}H_{16}O_2$ (M^+): 192.1150. Found: 192.1143.

(2*S*,3*R*)-(−)-3-Phenoxybutan-2-ol[1](3fa)



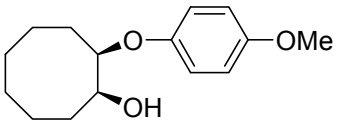
. Silica gel column chromatography (hexane/AcOEt = 8/1) gave 90 mg (0.54 mmol, 54% yield) of the product as colorless oil. $[\alpha]^{27}_{D}$ −11.2 (*c* 1.23, $CHCl_3$). 37% *ee* (HPLC, Daicel Chiralcel OD-H, hexane/*i*-PrOH = 30/1, 1.0 mL/min, 254 nm, major 27.5 min and minor 14.4 min).^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.24 (d, *J* = 6.5 Hz, 3H), 1.27 (d, *J* = 6.5 Hz, 3H), 2.02 (brs, 1H), 4.01-4.06 (m, 1H), 4.31-4.37 (m, 1H), 6.90-6.98 (m, 3H), 7.26-7.31 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.4, 17.8, 69.3, 77.3, 116.1, 121.1, 130.0, 157.6. IR (ATR): 690, 750, 1050, 1080, 1230, 1490, 1590, 1600, 2980, 3370 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{10}H_{14}O_2$ (M^+): 166.0994. Found: 166.0989.

(−)-2-(2-Methylphenoxy)cyclooctanol (3ab).



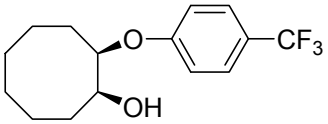
Silica gel column chromatography (hexane/ AcOEt = 12/1) gave 209 mg (0.89 mmol, 89% yield) of the product as colorless oil. $[\alpha]^{26}_{D}$ −5.7 (*c* 1.0, $CHCl_3$). 63% *ee* (HPLC, Daicel Chiralcel OD-H, hexane/*i*-PrOH = 200/1, 1.0 mL/min, 254 nm, major 15.9 min and minor 24.8 min). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.52-1.86 (m, 10H), 1.93-2.02 (m, 1H), 2.07-2.17 (m, 1H), 2.23 (s, 3H), 2.53 (d, *J* = 4.0 Hz, 1H), 4.08-4.11 (m, 1H), 4.48-4.50 (m, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 7.13-7.17 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 16.4, 21.9, 25.2, 26.3, 26.7, 29.2, 72.1, 79.7, 112.9, 120.7, 126.8, 127.7, 131.1, 155.4. IR (ATR): 750, 1030, 1050, 1240, 1450, 1460, 1490, 2920, 3420 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{15}H_{22}O_2$ (M^+): 234.1620. Found: 234.1620.

(±)-2-(4-Methoxyphenoxy)cyclooctanol (3ac).



Silica gel column chromatography (hexane/ AcOEt = 5/1) gave 210 mg (0.84 mmol, 84% yield) of the product as colorless oil. 0% *ee* (HPLC, Daicel Chiralcel OD-H, hexane/*i*-PrOH = 100/1, 1.0 mL/min, 254 nm, 19.2 min and 25.5 min). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.49-1.84 (m, 10H), 1.88-1.98 (m, 1H), 2.04-2.13 (m, 1H), 2.57 (s, 1H), 3.77 (s, 3H), 4.04-4.07 (m, 1H), 4.32-4.36 (m, 1H), 6.83-6.86 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.9, 25.2, 25.3, 26.1, 26.8, 29.3, 55.7, 71.6, 80.8, 114.7, 117.5, 151.3, 154.1. IR (ATR): 820, 1040, 1220, 1500, 3480 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{15}H_{22}O_3$ (M^+): 250.1569. Found: 250.1553.

(+)-2-[4-(Trifluoromethyl)phenoxy]cyclooctanol (3ad).



Silica gel column chromatography (hexane/AcOEt = 9/1) gave 271 mg (0.94 mmol, 94% yield) of the product as colorless oil. $[\alpha]^{27}_{D}$ +3.1 (*c* 2.40, AcOEt). 54% *ee* (HPLC, Daicel Chiralcel AS, hexane/EtOH = 400/1, 1.0 mL/min, 254 nm, major 17.5 min and minor 13.4). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.48-1.84 (m, 10H), 1.90-2.00 (m, 1H), 2.10-2.22 (m, 1H), 2.37 (d, *J* = 3.4 Hz, 1H), 4.08-4.11 (m, 1H), 4.52-4.54 (m, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.5, 25.0, 25.1, 25.9, 26.8, 29.3, 71.7, 80.0, 115.7, 123.1 (q, *J* = 33.0 Hz), 124.4 (q, *J* = 270.0 Hz), 127.1 (q, *J* = 3.3 Hz), 159.9. IR (ATR): 830, 1070, 1110, 1160, 1250, 1320, 1520, 1610, 2920, 3420 cm^{-1} HRMS (EI) *m/z* Calcd for $C_{15}H_{19}F_3O_2$ (M^+): 288.1337. Found: 288.1339.

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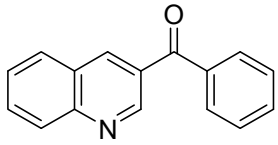
Chapter 4

Genaral. All melting points are not corrected. ^{1}H and ^{13}C NMR spectra were taken at 400 and 100 MHz, respectively. Chemical shift values are expressed in ppm relative to internal or external TMS. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Aldehydes, organoboronic acids, iodoarenes, and palladium sources were used as received. Toluene and dioxane were distilled from sodium benzophenone ketyl under an argon atmosphere. DMF and DMSO were distilled from calcium hydride under an argon atmosphere. Cesium carbonate, potassium carbonate, sodium carbonate, and cesium fluoride were used as received. Potassium phosphate tribasic was ground to a fine powder prior to use.

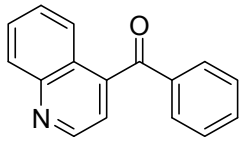
Typical procedure for the one-pot synthesis of heteroaryl and diheteroaryl ketones via palladium-catalyzed 1,2-addition and oxidation. Under an argon atmosphere, a reaction tube was charged with $[Pd(allyl)Cl]_2$ (1.83 mg, 0.005 mmol), imidazolinium chloride **L23** (6.77 mg, 0.015 mmol), and cesium carbonate (815 mg, 2.5 mmol), and then dioxane (2.0 mL) was added. The mixture was stirred at 80 °C for 15 min and cooled to room temperature. Then, 3-quinolinecarbaldehyde (**4a**) (157 mg, 1.0 mmol) and phenylboronic acid (**5a**) (183 mg, 1.5 mmol) were added. After the reaction mixture was stirred at 100 °C for 1 h and cooled to room temperature, 2-iodotoluene (436 mg, 2.0 mmol) was added. The reaction mixture was stirred at 100 °C for 15 h and cooled to room temperature. Water and saturated NH_4Cl were added, and then the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. Concentration and purification through silica gel column chromatography gave the product **6aa**.

Phenyl(3-quinolinyl)methanone[1] (**6aa**).



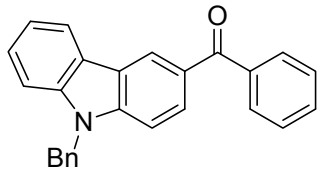
Silica gel column chromatography (hexane/AcOEt = 3/1) gave 222 mg (0.95 mmol, 95% yield) of the product as pale yellow solids of mp 67-68 °C. ^{1}H NMR ($CDCl_3$): δ 7.55 (t, *J* = 8.0 Hz, 2H), 7.62-7.69 (m, 2H), 7.85-7.89 (m, 3H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.57 (d, *J* = 2.0 Hz, 1H), 9.33 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 126.6, 127.5, 128.6, 129.1, 129.5, 130.0, 131.8, 133.0, 137.0, 138.8, 149.4, 150.3, 194.8. IR (ATR): 1650 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{16}H_{11}NO$ (M^+): 233.0841. Found: 233.0839.

Phenyl(4-quinolinyl)methanone (**6ba**).



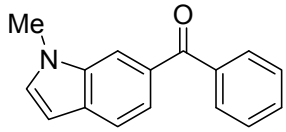
Silica gel chromatography (hexane/AcOEt = 2/1) gave 197 mg (0.85 mmol, 85% yield) of the product as pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.41 (d, *J* = 4.2 Hz, 1H), 7.47-7.57 (m, 3H), 7.63-7.67 (m, 1H), 7.76-7.80 (m, 1H), 7.85-7.88 (m, 3H), 8.21 (d, *J* = 8.6 Hz, 1H), 9.04 (d, *J* = 4.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 119.6, 124.9, 125.4, 127.6, 128.8, 130.0, 130.3, 134.2, 136.6, 144.4, 148.6, 149.5, 196.1. IR (ATR): 1660 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{16}H_{11}NO$ (M^+): 233.0841. Found 233.0839.

9-Benzylcarbazol-3-yl(phenyl)methanone (**6ca**).



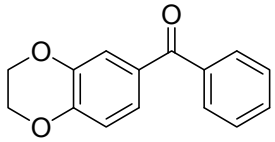
Silica gel chromatography (hexane/AcOEt = 10/1) gave 291 mg (0.81 mmol, 81% yield) of the product as white solids of mp 132-133 °C. ^{1}H NMR ($CDCl_3$): δ 5.56 (s, 2H), 7.14-7.16 (m, 2H), 7.25-7.31 (m, 4H), 7.40-7.53 (m, 5H), 7.58-7.61 (m, 1H), 7.83-7.85 (m, 2H), 7.98 (dd, *J* = 1.7, 8.5 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 8.64 (d, *J* = 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 46.7, 108.4, 109.4, 120.3, 120.7, 122.6, 123.1, 123.9, 126.3, 126.6, 127.7, 128.1, 128.6, 128.8, 128.9, 129.8, 131.6, 136.4, 138.9, 141.3, 143.2, 196.5. IR (ATR): 1590 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{26}H_{19}NO$ (M^+): 361.1467. Found: 361.1458.

1-Methylindol-6-yl(phenyl)methanone (**6da**).



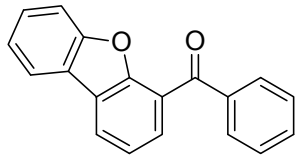
The starting material, 1-methylindole-6-carbaldehyde (**4d**), was prepared according to the reported method[2]. Silica gel chromatography (hexane/AcOEt = 5/1) gave 191 mg (0.81 mmol, 81% yield) of the product as pale brown solids of mp 94-95 °C. ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 3H), 6.56 (dd, *J* = 1.0, 3.2 Hz, 1H), 7.25 (d, *J* = 3.2 Hz, 1H), 7.47-7.51 (m, 2H), 7.57-7.61 (m, 2H), 7.66 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.82-7.84 (m, 2H), 7.92 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 32.9, 101.3, 112.3, 120.1, 121.7, 128.0, 129.8, 130.7, 131.6, 131.9, 132.4, 135.9, 138.8, 197.1. IR (ATR): 1640 cm^{-1}. HRMS (EI) Calcd for $C_{16}H_{13}NO$ (M^+): 235.0997. Found: 235.0985.

2,3-Dihydro-1,4-benzodioxin-6-yl(phenyl)methanone (**6ea**).



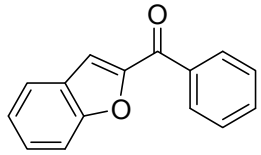
Silica gel chromatography (hexane/AcOEt = 7/1) gave 195 mg (0.81 mmol, 81% yield) of the product as pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 4.29-4.35 (m, 4H), 6.93 (d, *J* = 8.3 Hz, 1H), 7.36-7.41 (m, 2H), 7.45-7.49 (m, 2H), 7.54-7.59 (m, 1H), 7.75-7.77 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 64.1, 64.6, 117.0, 120.0, 124.4, 128.1, 129.7, 130.9, 131.9, 138.0, 143.1, 147.7, 195.3. IR (ATR): 890, 1650 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{15}H_{12}O_3$ (M^+): 240.0786. Found: 240.0770.

4-Dibenzofuranyl(phenyl)methanone (**6fa**).



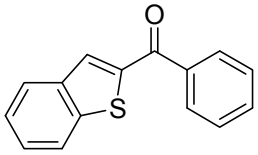
Silica gel chromatography (hexane/AcOEt = 10/1) gave 228 mg (0.84 mmol, 84% yield) of the product as white solids of mp 64-65 °C. ^{1}H NMR ($CDCl_3$): δ 7.38 (t, *J* = 7.5 Hz, 1H), 7.43-7.56 (m, 5H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 2H), 8.00 (d, *J* = 7.5 Hz, 1H), 8.16 (d, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 112.1, 120.6, 122.4, 123.1, 123.2, 124.1, 125.5, 127.7, 128.3, 128.6, 130.2, 133.1, 137.7, 153.8, 156.3, 193.9. IR (ATR): 1650 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{19}H_{12}O_2$ (M^+): 272.0837. Found: 272.0818.

2-Benzofuranyl(phenyl)methanone[3] (**6ga**).



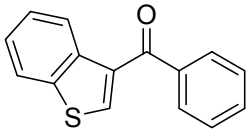
Silica gel chromatography (hexane/AcOEt = 5/1) gave 193 mg (0.87 mmol, 87% yield) of the product as pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.32-7.36 (m, 1H), 7.49-7.56 (m, 4H), 7.63-7.66 (m, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 8.04-8.06 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 112.4, 116.5, 123.2, 123.9, 126.9, 128.3, 128.4, 129.3, 132.8, 137.1, 152.1, 155.9, 184.3. IR (ATR): 1630 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{15}H_{10}O_2$ (M^+): 222.0681. Found: 222.0662.

2-Benzothienyl(phenyl)methanone (**6ha**).



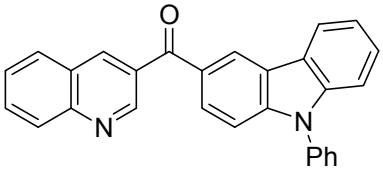
Silica gel chromatography (hexane/AcOEt = 10/1) gave 217 mg (0.91 mmol, 91% yield) of the product as yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.42 (t, *J* = 7.6 Hz, 1H), 7.47-7.56 (m, 3H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.86-7.93 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 122.9, 125.0, 126.0, 127.4, 128.5, 129.2, 132.2, 132.5, 137.8, 139.0, 142.7, 143.1, 189.6. IR (ATR): 1630 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{15}H_{10}OS$ (M^+): 238.0452. Found: 238.0441.

3-Benzothienyl(phenyl)methanone[4] (**6ia**).



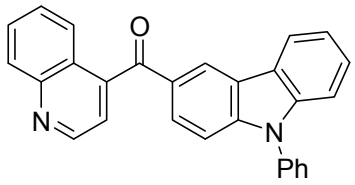
Silica gel chromatography (hexane/AcOEt = 15/1) gave 226 mg (0.95 mmol, 95% yield) of the product as yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.42-7.53 (m, 4H), 7.57-7.62 (m, 1H), 7.85-7.91 (m, 3H), 7.99 (s, 1H), 8.56-8.58 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 122.3, 125.1, 125.6, 125.7, 128.4, 129.5, 132.3, 134.8, 137.4, 138.3, 139.2, 140.0, 191.0. IR (ATR): 1640 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{15}H_{10}OS$ (M^+): 238.0452. Found: 238.0441.

9-Phenylcarbazol-3-yl(3-quinolinyl)methanone (**6ab**).



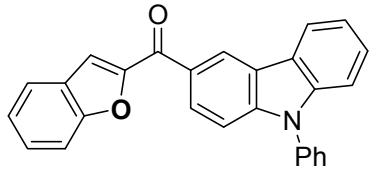
Silica gel column chromatography (hexane/AcOEt = 3/1) gave 357 mg (0.90 mmol, 90% yield) of the product as pale yellow solids of mp 97-98 °C. ^{1}H NMR ($CDCl_3$): δ 7.33-7.37 (m, 1H), 7.42-7.69 (m, 9H), 7.86-7.90 (m, 1H), 7.96 (dd, *J* = 1.2, 8.4 Hz, 1H), 8.02 (dd, *J* = 1.6, 8.4 Hz, 1H), 8.15-8.18 (m, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.64 (d, *J* = 1.2 Hz, 1H), 8.71-8.72 (m, 1H), 9.39 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 109.6, 110.2, 120.6, 120.9, 123.1, 123.7, 126.6, 126.8, 126.9, 127.3, 128.1, 128.3, 128.9, 129.3, 130.0, 131.25, 131.30, 136.6, 138.2, 141.7, 143.5, 149.1, 150.4, 194.2. IR (ATR): 1600 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{28}H_{18}N_2O$ (M^+): 398.1419. Found: 398.1410.

9-Phenylcarbazol-3-yl(4-quinolinyl)methanone (**6bb**).



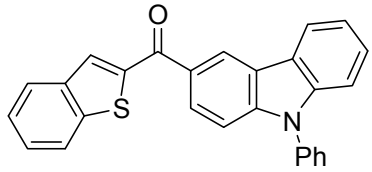
Silica gel column chromatography (hexane/AcOEt = 2/1) gave 330 mg (0.83 mmol, 83% yield) of the product as pale yellow solids of mp 88-89 °C. ^{1}H NMR ($CDCl_3$): δ 7.31-7.35 (m, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.44-7.56 (m, 6H), 7.63-7.66 (m, 2H), 7.76-7.80 (m, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.95-7.98 (m, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.63 (s, 1H), 9.08 (d, *J* = 4.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 109.8, 110.3, 119.3, 120.7, 121.2, 123.2, 123.3, 124.1, 125.3, 125.6, 127.0, 127.4, 128.3, 128.4, 128.9, 129.90, 129.91, 130.1, 136.5, 141.8, 144.1, 145.6, 148.6, 149.6, 195.3. IR (ATR): 1590 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{28}H_{18}N_2O$ (M^+): 398.1419. Found: 398.1409.

2-Benzofuranyl(9-phenylcarbazol-3-yl)methanone (**6gb**).



Silica gel column chromatography (hexane/AcOEt = 8/1) gave 355 mg (0.92 mmol, 92% yield) of the product as pale yellow solids of mp 64-65 °C. ^{1}H NMR ($CDCl_3$): δ 7.34-7.40 (m, 2H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.47-7.61 (m, 7H), 7.65-7.71 (m, 3H), 7.77 (d, *J* = 8.1 Hz, 1H), 8.21 (dd, *J* = 1.7, 8.8 Hz, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 8.96 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 109.2, 110.0, 112.1, 115.4, 120.4, 120.7, 122.90, 122.93 123.1, 123.6, 126.6, 126.7, 126.9, 127.6, 127.7, 127.8, 128.9, 129.8, 136.5, 141.4, 143.2, 143.2, 152.7, 155.5, 183.3. IR (ATR): 1590 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{27}H_{17}NO_2$ (M^+): 387.1259. Found: 387.1271.

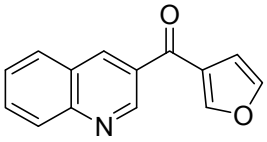
2-Benzothienyl(9-phenylcarbazol-3-yl)methanone (**6hb**).



Silica gel column chromatography (hexane/AcOEt = 10/1) gave 324 mg (0.80 mmol, 80% yield) of the product as pale yellow solids of mp 76-77 °C. ^{1}H NMR ($CDCl_3$): δ 7.35-7.38 (m, 1H), 7.42-7.56 (m, 6H), 7.59-7.61 (m, 2H), 7.65-7.68 (m, 2H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.94-7.96 (m, 2H), 8.07 (dd, *J* = 1.7, 8.6 Hz, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 8.81 (d, *J* = 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 109.4, 110.1, 120.5, 120.8, 122.6, 122.7, 123.0, 123.1 124.7, 125.7, 126.7, 126.8, 126.9, 127.7, 127.9, 129.6, 129.9, 131.2, 136.6, 138.9, 141.5, 142.1, 143.2, 143.6,

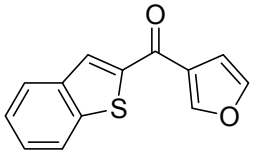
188.7. IR (ATR): 1590 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{27}H_{17}NOS$ (M^+): 403.1031. Found: 403.1010.

3-Furanyl(3-quinolinyl)methanone (**6ac**).



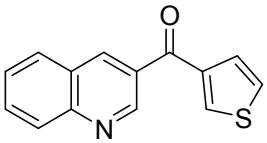
Silica gel column chromatography (hexane/AcOEt = 3/1) gave 168 mg (0.75 mmol, 75% yield) of the product as pale yellow solids of mp 117-118 °C. ^{1}H NMR ($CDCl_3$): δ 6.97-6.98 (m, 1H), 7.58-7.59 (m, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.85-7.89 (m, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 8.02-8.03 (m, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.65 (d, *J* = 2.0 Hz, 1H), 9.35 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 109.9, 126.4, 126.6, 127.6, 129.0, 129.4, 131.1, 131.7 137.3, 144.4, 148.6, 149.3, 149.5, 187.3. IR (ATR): 750, 1650 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{14}H_9NO_2$ (M^+): 223.0633. Found: 223.0610.

2-Benzothienyl(3-furanyl)methanone (**6hc**).



Silica gel column chromatography (hexane/AcOEt = 10/1) gave 185 mg (0.81 mmol, 81% yield) of the product as pale yellow solids of mp 96-97 °C. ^{1}H NMR ($CDCl_3$): δ 6.97-6.98 (m, 1H), 7.41-7.51 (m, 2H), 7.55 (dd, *J* = 1.6, 3.2 Hz, 1H), 7.91 (dd, *J* = 1.6, 7.8 Hz, 2H), 8.03 (s, 1H), 8.19 (d, *J* = 1.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 110.0, 122.8, 125.1, 125.9, 126.3, 127.3, 129.6, 138.9 142.2, 143.4, 144.1, 147.3, 181.6. IR (ATR): 740, 1610 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{13}H_8O_2S$ (M^+): 228.0245. Found: 228.0232.

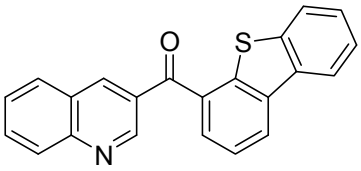
3-Quinolinyl(3-thienyl)methanone (**6ad**).



Silica gel column chromatography (hexane/AcOEt = 3/1) gave 167 mg (0.70 mmol, 70% yield) of the product as pale yellow solids of mp 103-104 °C. ^{1}H NMR ($CDCl_3$) : δ 7.47 (dd, *J* = 2.8, 5.2 Hz, 1H), 7.64-7.68 (m, 2H), 7.85-7.89 (m, 1H), 7.96 (dd, *J* = 1.2, 8.2 Hz, 1H), 8.03 (dd, *J* = 1.2, 2.8 Hz, 1H), 8.21 (dd, *J* = 0.8, 8.2 Hz, 1H), 8.64 (d, *J* = 1.6 Hz, 1H), 9.36 (d, *J* = 2.4 Hz,

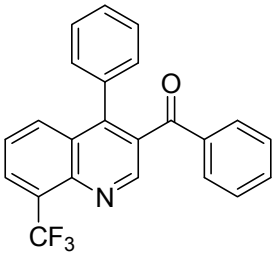
1H). ^{13}C NMR ($CDCl_3$): δ 126.5, 126.7, 127.4, 128.2, 128.9, 129.3, 130.9, 131.6 134.2, 137.7, 140.8, 149.3, 149.7, 187.8. IR (ATR): 790, 1630 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{14}H_9NOS$ (M^+): 239.0405. Found: 239.0403.

4-Dibenzothienyl(3-quinolinyl)methanone (**6ae**).



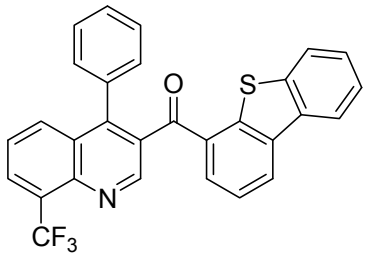
Silica gel column chromatography (hexane/AcOEt = 3/1) gave 308 mg (0.91 mmol, 91% yield) of the product as white solids of mp 164-165 °C. ^1H NMR ($CDCl_3$) δ 7.52-7.59 (m, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.66-7.70 (m, 1H), 7.86-7.91 (m, 1H), 7.96-8.01 (m, 3H), 8.23 (d, *J* = 8.6 Hz, 1H), 8.26-8.28 (m, 1H), 8.49 (dd, *J* = 1.2, 7.8 Hz, 1H), 8.60 (d, *J* = 2.0 Hz, 1H), 9.35 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 121.4, 122.7, 123.9, 124.6, 126.2, 126.5, 127.3, 127.5, 128.9, 129.4, 129.8, 130.6, 131.4, 131.6, 133.7, 137.5, 138.1, 140.8, 141.6, 149.1, 149.9, 193.6. IR (ATR): 1640 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{22}H_{13}NOS$ (M^+): 339.0718. Found: 339.0716.

Phenyl[4-phenyl(8-trifluoromethyl)quinolin-3-yl]methanone (6ja).



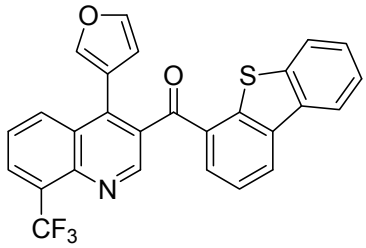
The starting material, 4-phenyl(8-trifluoromethyl)quinoline-3-carbaldehyde (4j), was prepared on the basis of previous reports.[5,6] Purification through silica gel column chromatography (hexane/AcOEt = 3/1) gave 308 mg (0.91 mmol, 91% yield) of the product as white solids of mp 164-165 °C. ^1H NMR ($CDCl_3$) δ 7.52-7.59 (m, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.66-7.70 (m, 1H), 7.86-7.91 (m, 1H), 7.96-8.01 (m, 3H), 8.23 (d, *J* = 8.6 Hz, 1H), 8.26-8.28 (m, 1H), 8.49 (dd, *J* = 1.2, 7.8 Hz, 1H), 8.60 (d, *J* = 2.0 Hz, 1H), 9.35 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 121.4, 122.7, 123.9, 124.6, 126.2, 126.5, 127.3, 127.5, 128.9, 129.4, 129.8, 130.6, 131.4, 131.6, 133.7, 137.5, 138.1, 140.8, 141.6, 149.1, 149.9, 193.6. IR (ATR): 1640 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{22}H_{13}NOS$ (M^+): 339.0718. Found: 339.0716.

4-Dibenzothienyl[4-phenyl(8-trifluoromethyl)quinolin-3-yl]methanone (6je).



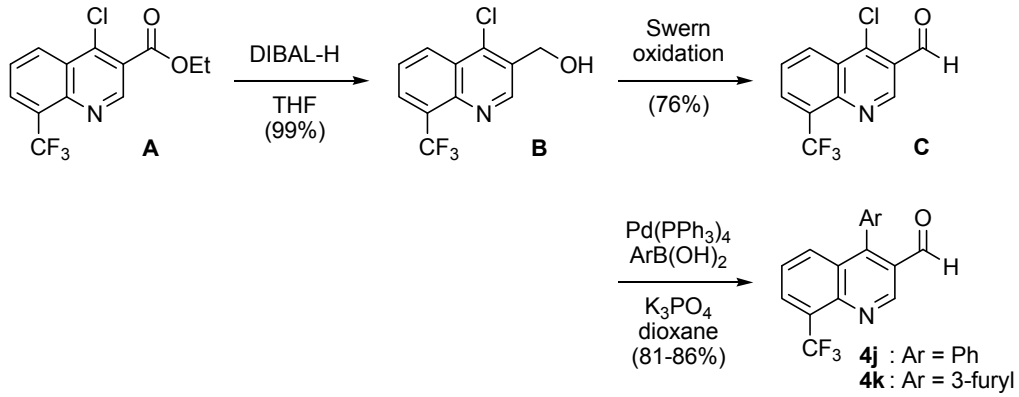
Purification through silica gel column chromatography (hexane/AcOEt = 3/1) gave 308 mg (0.91 mmol, 91% yield) of the product as white solids of mp 164-165 °C. ^{1}H NMR ($CDCl_3$) δ 7.52-7.59 (m, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.66-7.70 (m, 1H), 7.86-7.91 (m, 1H), 7.96-8.01 (m, 3H), 8.23 (d, *J* = 8.6 Hz, 1H), 8.26-8.28 (m, 1H), 8.49 (dd, *J* = 1.2, 7.8 Hz, 1H), 8.60 (d, *J* = 2.0 Hz, 1H), 9.35 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 121.4, 122.7, 123.9, 124.6, 126.2, 126.5, 127.3, 127.5, 128.9, 129.4, 129.8, 130.6, 131.4, 131.6, 133.7, 137.5, 138.1, 140.8, 141.6, 149.1, 149.9, 193.6. IR (ATR): 1640 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{22}H_{13}NOS$ (M^+): 339.0718. Found: 339.0716.

4-Dibenzothienyl{[4-(3-furanyl)](8-trifluoromethyl)quinolin-3-yl}methanone (6ke).

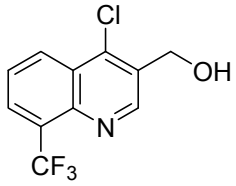


The starting material, [4-(3-furanyl)](8-trifluoromethyl)quinoline-3-carbaldehyde (**4k**), was prepared on the basis of previous reports.[5,6] Purification through silica gel column chromatography (hexane/AcOEt = 3/1) gave 308 mg (0.91 mmol, 91% yield) of the product as white solids of mp 164-165 °C. ^{1}H NMR ($CDCl_3$) δ 7.52-7.59 (m, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.66-7.70 (m, 1H), 7.86-7.91 (m, 1H), 7.96-8.01 (m, 3H), 8.23 (d, *J* = 8.6 Hz, 1H), 8.26-8.28 (m, 1H), 8.49 (dd, *J* = 1.2, 7.8 Hz, 1H), 8.60 (d, *J* = 2.0 Hz, 1H), 9.35 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 121.4, 122.7, 123.9, 124.6, 126.2, 126.5, 127.3, 127.5, 128.9, 129.4, 129.8, 130.6, 131.4, 131.6, 133.7, 137.5, 138.1, 140.8, 141.6, 149.1, 149.9, 193.6. IR (ATR): 1640 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{22}H_{13}NOS$ (M^+): 339.0718. Found: 339.0716.

Preparation of aldehydes (**4j** and **4k**)

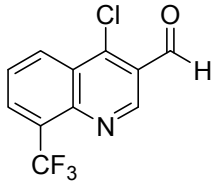


(4-Chloro-8-(trifluoromethyl)quinolin-3-yl)methanol[7] (**B**).



To ethyl 4-chloro-8-(trifluoromethyl)quinoline-3-carboxylate[8] (**A**) (9.7 g, 32 mmol) in dry THF (300 mL) was added DIBAL-H (17% solution in toluene) (201 mL, 201 mmol) at −78 °C over 30 min. The reaction mixture was stirred for 1 h with rising temperature from −78 °C to room temperature. Then, saturated NH_4Cl (100 mL) was added after the resulting mixture was cooled to 0 °C. The precipitate was removed by filtration and washed with ethyl acetate. The filtrate was washed with water (300 mL x3). The organic layer was separated and dried over Na_2SO_4. Concentration and purification through silica gel column chromatography (hexane/AcOEt = 2/1) gave 8.32 g (32 mmol, 99% yield) of the product as white solids of mp 128-129 °C. ^{1}H NMR ($CDCl_3$): δ 2.09 (brs, 1H), 5.07 (d, *J* = 6.0 Hz, 2H), 7.72 (t, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 8.50 (d, *J* = 8.0 Hz, 1H), 9.17 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 60.8, 123.8 (q, *J* = 272.5 Hz), 126.4, 126.5, 128.0 (q, *J* = 30.5 Hz), 128.4, 128.5 (q, *J* = 5.7 Hz), 131.7, 140.6, 144.8, 150.9. IR (ATR): 1120, 3340 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{11}H_7{}^{35}ClF_3NO$ (M^+): 261.0168, Found: 261.0161.

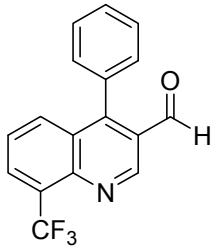
4-Chloro-8-(trifluoromethyl)quinoline-3-carbaldehyde[9] (**C**).



DMSO (3.2 mL, 45 mmol) was added to oxalyl chloride (1.95 mL, 22.7 mmol) in CH_2Cl_2 (22.5

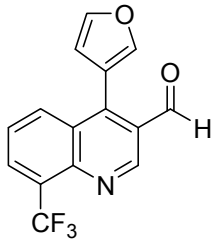
mL) at −78 °C. After 15 min, compound **B** (7.5 mmol, 1.96 g) in CH_2Cl_2 (5.8 mL) and triethylamine (90 mmol, 12.6 mL) were added. The reaction mixture was allowed to warm to room temperature and stirred for 3h. The resulting mixture was washed with saturated sodium bicarbonate (20 mL) and dried over Na_2SO_4. Concentration and purification through silica gel column chromatography (hexane/AcOEt = 8/1) gave 1.48 g (5.7 mmol, 76% yield) of the product as pale yellow solids of mp 120-121 °C. ^{1}H NMR ($CDCl_3$): δ 7.83 (t, *J* = 7.8 Hz, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 8.65 (d, *J* = 7.8 Hz, 1H), 9.41 (s, 1H), 10.7 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 123.4 (q, *J* = 272.5 Hz), 124.7, 126.2, 127.4, 128.7 (q, *J* = 30.4 Hz), 129.3, 131.3 (q, *J* = 5.8 Hz), 147.2, 147.9, 149.3, 188.3. IR (ATR): 1130, 1680 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{11}H_5{}^{35}ClF_3NO$ (M^+): 259.0012, Found: 258.9995.

4-Phenyl-8-(trifluoromethyl)quinoline-3-carbaldehyde[10] (**4j**).



A solution of compound **C** (260 mg, 1.0 mmol), phenylboronic acid (146 mg, 1.2 mmol), K_3PO_4 (828 mg, 3.9 mmol), and $Pd(PPh_3)_4$ (95.9 mg, 0.083 mmol) in dioxane (8.3 mL) was stirred under reflux. After 20 h, the reaction mixture was cooled to room temperature and water was added. The resulting mixture was extracted with ethyl acetate and the organic layer was dried over Na_2SO_4. Concentration and purification through silica gel column chromatography (hexane/AcOEt = 10/1) gave 259 mg (0.86 mmol, 86% yield) of the product as white solids of mp 111-112 °C. ^{1}H NMR ($CDCl_3$): δ 7.41-7.44 (m, 2H), 7.59-7.63 (m, 4H), 7.92 (d, *J* = 8.6 Hz, 1H), 8.21 (d, *J* = 7.3 Hz, 1H), 9.57 (s, 1H), 9.97 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 123.8 (q, *J* = 272.5 Hz), 125.6, 126.3, 127.3, 128.4 (q, *J* = 30.5 Hz), 128.8, 129.6, 130.2, 130.3 (q, *J* = 5.8 Hz), 131.7, 131.8, 146.6, 148.9, 153.1, 191.0. IR (ATR): 1120, 1690 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{17}H_{10}F_3NO$ (M^+): 301.0714, Found: 301.0706.

4-(3-Furanyl)-8-(trifluoromethyl)quinoline-3-carbaldehyde (**4k**).



Compound **4k** was prepared with the same procedure as that for **4j**. Concentration and purification through silica gel column chromatography (hexane/AcOEt = 6/1) gave desired product **4k** as pale yellow solids of mp 139-140 °C in 81% yield. ^{1}H NMR ($CDCl_3$): δ 6.70-6.71 (m, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.71-7.72 (m, 1H), 7.76 (t, *J* = 1.7 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 2H), 9.54 (s, 1H), 10.23 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 113.1, 116.3, 123.7, (q, *J* = 272.5 Hz), 126.4, 126.5, 127.5, 128.6 (q, *J* = 30.4 Hz), 130.4 (q, *J* = 5.8 Hz), 131.2, 143.2, 144.3, 144.4, 146.7, 149.0, 190.9. IR (ATR): 1130, 1680 cm^{-1}. HRMS (EI) *m/z* Calcd for $C_{15}H_8F_3NO_2$ (M^+): 291.0507, Found: 291.0510.

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4) Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem*. **1998**, *63*, 4726-4731.

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6) a) Thomas, K. D.; Adhikari, A. V.; Telkar, S.; Chowdhury, I. H.; Mahmood, R.; Pal, N. K.; Row, G.; Sumesh, E. *Eur. J. Med. Chem.* **2011**, *46*, 5283-5292. b) Hu, B.; Bernotas, R.; Unwalla, R.; Collini, M.; Quinet, E.; I.; Feingold, I.; Goss-Nilsson, A.; Wilhelmsson, A.; Nambi, P.; Evans, M.; Wrobel, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 689-693. c) Baruah, A.; De, D.; Khanna, I. K.; Pillarisetti, S.; Maitra, S.; Alexander, C. W.; Sreenu, J.; Dager, I. U.S. Pat. Appl. Publ. (**2007**), US 2007015758. d) Dyck, B.; Grigoriadis, D. E.; Gross, R. S.; Guo, Z.; Haddach, M.; Marinkovic, D.; McCarthy, J. R.; Moorjani, M.; Regan, C. F.; Saunders, J.; Schwaebe, M. K.; Szabo, T.; Williams, J. P.; Zhang, X.; Bozigian, H.; Chen, T. K. *J. Med. Chem*. **2005**, *48*, 4100-4110.

7) The reaction conditions were decided on the basis of the following report: Baruah, A.; De, D.; Khanna, I. K.; Pillarisetti, S.; Maitra, S.; Alexander, C. W.; Sreenu, J.; Dager, I. U.S. Pat. Appl. Publ. (**2007**), US 2007015758.

8) Compound **A** was prepared according to the following reports: a) Thomas, K. D.; Adhikari, A. V.; Telkar, S.; Chowdhury, I. H.; Mahmood, R.; Pal, N. K.; Row, G.; Sumesh, E. *Eur. J. Med. Chem.* **2011**, *46*, 5283-5292; b) Hu, B.; Bernotas, R.; Unwalla, R.; Collini, M.; Quinet, E.; Feingold, I.; Goss-Nilsson, A.; Wilhelmsson, A.; Nambi, P.; Evans, M.; Wrobel, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 689-693.

9) The reaction conditions were decided on the basis of the following report: Dyck, B.; Grigoriadis, D. E.; Gross, R. S.; Guo, Z.; Haddach, M.; Marinkovic, D.; McCarthy, J. R.; Moorjani, M.; Regan, C. F.; Saunders, J.; Schwaebe, K. M.; Szabo, T.; Williams, J. P.; Zhang, X.; Bozigian, H.; Chen, T. K. *J. Med. Chem.* **2005**, *48*, 4100-4110

10) The reaction conditions were decided on the basis of the following report: Hu, B.; Collini, M.; Unwalla, R.; Miller, C.; Singhaus, R.; Quinet, E.; Savio, D.; Halpern, A.; Basso, M.; Keith, J.; Clerin, V.; Chen, L.; Resmini, C.; Liu, Q.-Y.; Feingold, I.; Huselton, C.; Azam, F.; Farnegardh, M.; Enroth, C.; Bonn, T.; Goos-Nilsson, A.; Wilhelmsson, A.; Nambi, P.; Wrobel, J. *J. Med. Chem.* **2006**, *49*, 6151-6154.

Chapter 5

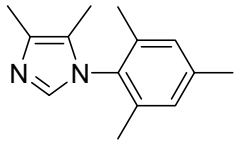
1. General. All melting points are not corrected. IR spectra were expressed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were taken at 500 and 100 MHz respectively. Chemical shift values are expressed in ppm relative to internal or external TMS. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded using electron ionization (EI) mass spectrometry or fast atom bombardment (FAB) mass spectrometry. The products were isolated by silica gel column chromatography. The degree of deuterium incorporation was determined by ^{1}H-NMR (500 MHz). All reactions were performed under argon atmosphere unless otherwise specified. Toluene was distilled from sodium benzophenone ketyl under argon. Ary chlorides **8b-e**, **8h**, **8j-k**, **8m-n**, **10c-d**, **10h**, **10k**, and **12b** were synthesized as new compounds. On the other hand, **10a**[1], **10b**[2], **10g**[3], **10j**[3], **10m**[4], **10o**[5], **10p**[6], and **10q**[7] were prepared as previously reported. Chloroquine **6f** was obtained from purchased chloroquine diphosphate salt by treatment with aqueous 10% NaOH solution. All other chemicals were purchased and used as received.

2. Synthetic procedures and physical data of compounds.

2.1. Synthesis of unsymmetrical NHC ligand precursors.

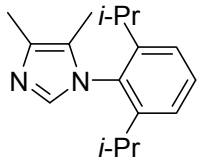
2.1.1. General synthetic procedure of 1-arylimidazoles. This modified procedure for synthesis of 1-arylimidazoles was optimized on the basis of Orru's method.[8] Exceptionally, 1-(2,4,6-trimethylphenyl)-1*H*-imidazole was prepared according to Waymouth's report.[9] To a aniline derivative (12 mmol) in dry $CHCl_3$ (20 mL), diacetyl (861 mg, 10 mmol), acetic acid (3.0 g, 50 mmol), NH_4OAc (925 mg, 12 mmol), paraformaldehyde (480 mg, 10 mmol), and H_2O (0.5 mL) were added and the mixture was refluxed for 48 h. After removal of the solvent, the dark residue was dissolved in Et_2O and basified to pH 14 in an ice bath with aqueous 40% KOH solution. The resulting mixture was extracted with Et_2O and the combined organic layers were washed with H_2O and dried over Na_2SO_4. Concentration and purification through silica gel column chromatography gave a 1-arylimidazole.

1-Mesityl-4,5-dimethyl-1*H*-imidazole (Im-1).



Silica gel chromatography (hexane/AcOEt = 3/1) gave 1.46 g of the product (6.8 mmol, 68% yield) as pale brown solids of mp 130-131 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.84 (s, 3H), 1.93 (s, 6H), 2.24 (s, 3H), 2.34 (s, 3H), 6.97 (s, 2H), 7.25 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 8.0 (CH_3), 12.8 (CH_3), 17.2 (CH_3), 20.9 (CH_3), 122.5 (C), 128.9 (CH), 132.4 (C), 133.8 (C), 134.4 (CH), 136.0 (C), 138.6 (C). IR (ATR): 770, 1490 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{14}H_{18}N_2$: 214.1470; Found: 214.1461.

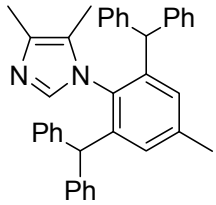
1-(2,6-Diisopropylphenyl)-4,5-dimethyl-1*H*-imidazole (Im-2).



Silica gel chromatography (hexane/AcOEt = 1/2) gave 1.59 g of the product (6.2 mmol, 62% yield) as brown oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.09 (d, *J* = 7.1 Hz, 6H), 1.14 (d, *J* = 7.1 Hz, 6H), 1.85 (s, 3H), 2.26 (s, 3H), 2.32-2.40 (m, 2H), 7.24 (s, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 8.1 (CH_3), 12.6 (CH_3), 22.8 (CH_3), 24.8 (CH_3), 27.6 (CH), 123.3 (C), 123.5 (CH), 129.5 (CH), 131.5 (C), 133.4 (C), 135.3 (CH), 146.7 (C). IR

(ATR): 770, 1490 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{17}H_{24}N_2$: 256.1939; Found: 256.1933.

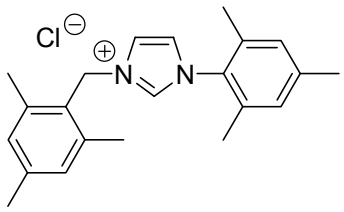
1-(2,6-Dibenzhydryl-4-methylphenyl)-4,5-dimethyl-1*H*-imidazole (Im-3).



This 1-arylimidazole was prepared with 2.5 mmol of diacetyl. Silica gel chromatography (hexane/AcOEt = 2/1) gave 585 mg of the product (1.13 mmol, 45% yield) as pale yellow solids of mp 87-88 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.30 (s, 3H), 2.15 (s, 3H), 2.26 (s, 3H), 4.99 (s, 2H), 6.61 (s, 1H), 6.86 (s, 2H), 6.89 (d, *J* = 7.2 Hz 4H), 6.95 (d, *J* = 7.2 Hz, 4H), 7.15-7.25 (m, 12H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 7.6 (CH_3), 12.8 (CH_3), 21.7 (CH_3), 51.3 (CH), 123.3 (C), 126.5 (CH), 128.3 (CH), 128.4 (CH), 129.2 (CH), 129.5 (CH), 129.6 (CH), 132.3 (C), 133.8 (C), 135.6 (CH), 138.8 (C), 142.4 (C), 142.78 (C), 142.85 (C). IR (ATR): 700, 1490 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{38}H_{34}N_2$: 518.2722; Found: 518.2719.

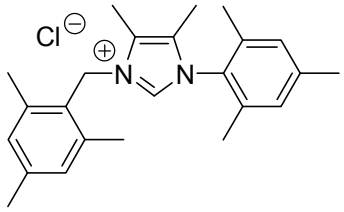
2.1.2. Benzylation of 1-arylimidazoles. Arylmethyl chloride (2.0 mmol) was added to a 1-arylimidazole (2.0 mmol) in dry THF (2 mL). The mixture was refluxed for 15 h and then evaporated. The resulting solids were filtered and washed with THF to give a desired imidazolium chloride.

3-Mesityl-1-(2,4,6-trimethylbenzyl)imidazolium chloride (L25).



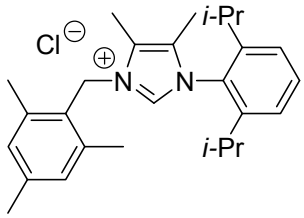
The desired product was obtained in 59% yield (414 mg, 1.17 mmol) as white solids of mp 286-287 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.08 (s, 6H), 2.30 (s, 3H), 2.349 (s, 3H), 2.354 (s, 6H), 6.05 (s, 2H), 6.94 (s, 2H), 7.01 (s, 2H), 7.03 (t, *J* = 1.8 Hz, 1H), 7.11 (t, *J* = 1.8 Hz, 1H), 11.01 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 17.2 (CH_3), 19.5 (CH_3), 20.70 (CH_3), 20.72 (CH_3), 48.0 (CH_2), 121.3 (CH), 123.6 (CH), 125.7 (C), 129.6 (CH), 129.7 (CH), 130.6 (C), 133.9 (C), 137.9 (C), 138.1 (CH), 139.5 (C), 141.0 (C). IR (ATR): 760, 1190, 1540 cm^{-1}. HRMS (FAB) *m/z*: $[M–Cl]^+$ Calcd for $C_{22}H_{27}N_2$: 319.2174; Found: 319.2157.

3-Mesityl-4,5-dimethyl-1-(2,4,6-trimethylbenzyl)imidazolium chloride (L26).



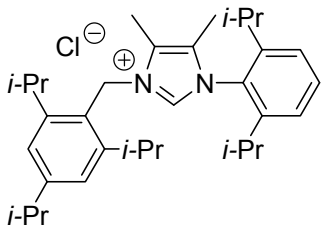
The desired product was obtained in 70% yield (535 mg, 1.40 mmol) as white solids of mp 285-286 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.91 (s, 3H), 2.01 (s, 6H), 2.13 (s, 3H), 2.28 (s, 3H), 2.34 (s, 6H), 2.35 (s, 3H), 5.99 (s, 2H), 6.89 (s, 2H), 7.02 (s, 2H), 9.92 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 7.8 (CH_3), 8.8 (CH_3), 17.1 (CH_3), 19.6 (CH_3), 20.5 (CH_3), 20.6 (CH_3), 47.1 (CH_2), 125.4 (C), 127.5 (C), 128.1 (C), 128.6 (C), 129.6 (CH), 129.7 (CH), 134.3 (C), 135.1 (CH), 137.3 (C), 138.9 (C), 141.0 (C). IR (ATR): 850, 1550 cm^{-1}. HRMS (FAB) *m/z*: $[M–Cl]^+$ Calcd for $C_{24}H_{31}N_2$: 347.2487; Found: 347.2488.

3-(2,6-Diisopropylphenyl)-4,5-dimethyl-1-(2,4,6-trimethylbenzyl)imidazolium chloride (L27).



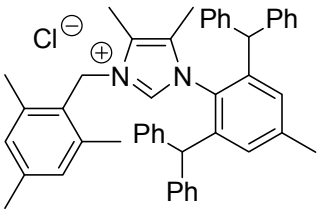
The desired product was obtained in 48% yield (403 mg, 0.95 mmol) as white solids of mp 267-268 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.17 (d, *J* = 6.9 Hz, 6H), 1.19 (d, *J* = 6.9 Hz, 6H), 1.92 (s, 3H), 2.21 (septet, *J* = 6.9 Hz, 2H), 2.23 (s, 3H), 2.27 (s, 3H), 2.34 (s, 6H), 6.04 (s, 2H), 6.89 (s, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.53 (t, *J* = 8.0 Hz, 1H), 9.71 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 8.2 (CH_3), 9.2 (CH_3), 19.6 (CH_3), 20.7 (CH_3), 22.7 (CH_3), 24.8 (CH_3), 28.4 (CH), 47.3 (CH_2), 124.7 (CH), 125.3 (C), 128.0 (C), 128.5 (C), 128.6 (C), 129.9 (CH), 131.8 (CH), 134.8 (CH), 137.7 (C), 139.4 (C), 145.5 (C). IR (ATR): 810, 1460 cm^{-1}. HRMS (FAB) *m/z*: $[M–Cl]^+$ Calcd for $C_{22}H_{27}N_2O$: 389.2957; Found: 389.2955.

1-(2,4,6-Triisopropylbenzyl)-3-(2,6-diisopropylphenyl)-4,5-dimethylimidazolium chloride (L28).



The desired product was obtained in 51% yield (515 mg, 1.01 mmol) as white solids of mp 208-209 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.07 (d, *J* = 6.8 Hz, 6H), 1.18 (d, *J* = 6.8 Hz, 6H), 1.22-1.25 (m, 18H), 2.02 (s, 3H), 2.24 (septet, *J* = 6.8 Hz, 2H), 2.69 (s, 3H), 2.88 (septet, *J* = 6.8 Hz, 1H), 3.16 (septet, *J* = 6.8 Hz, 2H), 5.79 (s, 2H), 7.08 (s, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.51 (t, *J* = 7.8 Hz, 1H), 8.00 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 8.5 (CH_3), 9.8 (CH_3), 23.1 (CH_3), 23.5 (CH_3), 24.1 (CH_3), 24.7 (CH_3), 28.2 (CH), 29.6 (CH), 34.0 (CH), 45.0 (CH_2), 121.5 (C), 122.1 (CH), 124.8 (CH), 127.9 (C), 129.4 (C), 129.7 (C), 131.9 (CH), 132.1 (CH), 145.6 (C), 148.7 (C), 151.4 (C). IR (ATR): 760, 1540 cm^{-1}. HRMS (FAB) *m/z*: $[M–Cl]^+$ Calcd for $C_{33}H_{49}N_2$: 473.3896; Found: 473.3901.

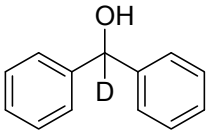
3-(2,6-Dibenzhydryl-4-methylphenyl)-4,5-dimethyl-1-(2,4,6-trimethylbenzyl)imidazolium chloride (L29).



The desired product was obtained in 69% yield (941 mg, 1.37 mmol) as white solids of mp 214-215 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.26 (s, 3H), 2.15 (s, 6H), 2.23 (s, 6H), 2.28 (s, 3H), 4.99 (s, 2H), 5.66 (s, 2H), 6.80 (s, 2H), 6.83 (s, 2H), 6.92-6.95 (m, 8H), 7.20-7.28 (m, 12H), 8.63 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 7.6 (CH_3), 9.1 (CH_3), 19.8 (CH_3), 20.7 (CH_3), 21.5 (CH_3), 47.0 (CH_2), 51.4 (CH), 125.2 (C), 127.0 (CH), 127.1 (CH), 128.2 (C), 128.5 (CH), 128.6 (CH), 128.7 (CH), 129.2 (CH), 129.7 (CH), 130.4 (CH), 134.7 (CH), 137.4 (C), 139.2 (C), 140.7 (C), 141.1 (C), 141.4 (C). IR (ATR): 700, 1490 cm^{-1}. HRMS (FAB) *m/z*: $[M–Cl]^+$ Calcd for $C_{48}H_{47}N_2$: 651.3739; Found: 651.3743. Anal. Calcd for $C_{48}H_{47}N_2Cl$: C, 83.87; H, 6.89; N, 4.08. Found: C, 83.77; H, 7.04; N, 4.01.

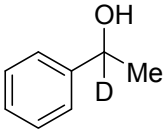
2.2. General synthetic procedure of α-deuterioalcohols. Under argon atmosphere, benzophenone (546 mg, 3 mmol) in THF (5 mL) was added to the suspension of lithium aluminum deuteride (63 mg, 1.5 mmol) in THF (4.2 mL) at 0 °C. After the reaction mixture was stirred for 30 min at 0 °C, water was added. The resulting mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. Concentration and purification through silica gel chromatography gave α-deuteriobenzhydrol (**7a**).

α-Deuteriobenzhydrol[10] (7a).



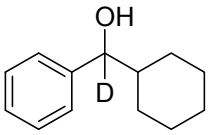
Silica gel chromatography (hexane/AcOEt = 5/1) gave 531 mg of the product (2.87 mmol, 96% yield) as white solids of mp 64-65 °C. >99% D (D content was judged with the peak at 5.80 ppm (a deuterated site) compared to the peak at 7.32-7.40 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.20 (s, 1H), 7.25-7.28 (m, 2H), 7.32-7.35 (m, 4H), 7.37-7.40 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 75.4 (t, *J* = 22.4 Hz, C), 126.5 (CH), 127.3 (CH), 128.3 (CH), 143.7 (C). IR (ATR): 730, 1040, 1190, 1490, 1600, 3260 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{13}H_{11}DO$: 185.0951; Found: 185.0958.

α-Deuterio-α-phenylethanol (7b).



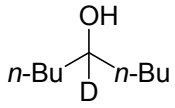
This compound was prepared from acetophenone (4 mmol). Silica gel chromatography (hexane/ AcOEt = 7/1) gave 468 mg of the product (3.80 mmol, 95% yield) as colorless oil. >99% D (D content was judged with the peak at 4.90 ppm (a deuterated site) compared to the peak at 7.34-7.39 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.50 (s, 3H), 1.76 (s, 1H), 7.26-7.29 (m, 1H), 7.34-7.39 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 24.8 (CH_3), 69.6 (t, *J* = 21.5 Hz, C), 125.3 (CH), 127.3 (CH), 128.3 (CH), 145.8 (C). IR (ATR): 700, 750, 1130, 1450, 2970, 3330 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for C_8H_9DO: 123.0794; Found: 123.0796.

α-Deuterio-α-cyclohexylbenzenemethanol (7c).



This compound was prepared from cyclohexyl(phenyl)methanone (8 mmol). Silica gel chromatography (hexane/AcOEt = 8/1) gave 1.52 g of the product (7.94 mmol, 99% yield) as colorless oil. >99% D (D content was judged with the peak at 4.37 ppm (a deuterated site) compared to the peak at 1.97-2.01 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.89-0.97 (m, 1H), 1.01-1.27 (m, 4H), 1.36-1.40 (m, 1H), 1.59-1.68 (m, 3H), 1.75-1.79 (m, 2H), 1.97-2.01 (m, 1H), 7.25-7.36 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.8 (CH_2), 25.9 (CH_2), 26.2 (CH_2), 28.6 (CH_2), 29.0 (CH_2), 44.6. (CH), 78.6 (t, *J* = 21.5 Hz, C), 126.6 (CH), 127.2 (CH), 128.0 (CH), 143.6 (C). IR (ATR): 700, 760, 1450, 2850, 2920, 3370 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{13}H_{17}DO$: 191.1420; Found: .191.1420.

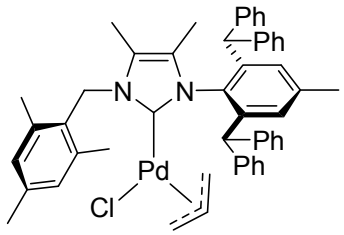
5-Deuterio-5-nonanol (7d).



This compound was prepared from nonan-5-one (8 mmol). Silica gel chromatography (hexane/ AcOEt = 10/1) gave 1.15 g of the product (7.92 mmol, 99% yield) as colorless oil. >99% D (D content was judged with the peak at 3.59 ppm (a deuterated site) compared to the peak at 0.91 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.1 Hz, 6H), 1.25 (s, 1H), 1.27-1.50 (m, 12H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.7 (CH_3), 22.5 (CH_2), 27.6 (CH_2), 36.8 (CH_2), 71.0 (t, *J* = 21.5 Hz, C). IR (ATR): 2860, 2870, 2930, 2960, 2970, 3340 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_9H_{19}DO$: 145.1577; Found: 145.1571.

2.3. Synthesis of Pd-NHC complexes.

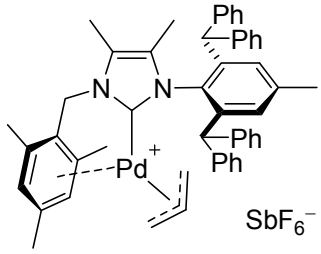
Allylchloro{4,5-dimethyl-3-[2,6-bis(diphenylmethyl)-4-methylphenyl]-1-(2,4,6-trimethylbenzyl)imidazol-2-ylidene}palladium(II) (C1).



Under argon atmosphere, a reaction flask was charged with ligand precursor **L29** (289 mg, 0.42 mmol) and LiO*t*-Bu (39 mg, 0.49 mmol). After dry THF (28 mL) was added. The reaction mixture was stirred for 4 h at room temperature. Then, $[Pd(allyl)Cl]_2$ (77 mg, 0.21 mmol) was added. After the mixture was stirred for 3 h at room temperature, the resulting mixture was filtered through celite. Concentration and purification through silica gel chromatography (hexane/AcOEt = 4/1) gave 311 mg of the product (0.37 mmol, 89% yield) as pale yellow solids of mp 205-206 °C, which were recrystallized from CH_2Cl_2/hexane. ^{1}H-NMR (500 MHz, $CDCl_3$): δ –0.07 (s, 3H), 1.56-1.57 (m, 1H), 1.61 (s, 3H), 2.28 (s, 3H), 2.29 (s, 3H), 2.44 (s, 6H), 2.66 (d, *J* = 6.7 Hz, 1H), 3.06 (d, *J* = 13.5 Hz, 1H), 4.18 (dd, *J* = 1.5, 7.5 Hz, 1H), 4.75-4.83 (m, 1H), 5.75 (d, *J* = 15.7 Hz, 1H), 5.77 (s, 2H), 5.86 (d, *J* = 15.7 Hz, 1H), 6.85 (s, 2H), 6.96-7.25 (m, 22H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 7.21, 8.93, 20.8, 21.1, 21.7, 49.6, 50.0, 50.7, 50.9, 71.9, 114.4, 125.8, 126.2, 126.3, 128.03, 128.05, 128.08, 129.4, 129.56, 129.63, 129.7, 129.8, 129.9, 130.0, 130.7, 135.2, 137.3, 137.5, 138.0, 142.1, 142.3, 142.4, 142.5, 143.1, 143.4, 181.3. IR (ATR): 700, 1450, 1490 cm^{-1}. HRMS (FAB) *m/z*: $[M–Cl]^+$ Calcd for $C_{51}H_{51}N_2{}^{106}Pd$:

797.3082; Found: 797.3095. Anal. Calcd for $C_{51}H_{51}ClN_2Pd$: C, 73.46; H, 6.16; N, 3.36. Found: C, 73.36; H, 5.83; N, 3.26.

Allyl{4,5-dimethyl-3-[2,6-bis(diphenylmethyl)-4-methylphenyl]-1-(2,4,6-trimethylbenzyl)imidazol-2-ylidene}palladium(II) hexafluoroantimonate (C2).



Complex **C1** (50 mg, 0.06 mmol) in dry CH_2Cl_2 (16 mL) was treated with $AgSbF_6$ (21 mg, 0.06 mmol) for 1 h at room temperature. The resulting mixture was filtered through celite. Concentration and purification through silica gel chromatography (hexane/AcOEt = 1/1.5) gave 50 mg of the product (0.048 mmol, 80% yield) as pale yellow solids of mp 147-148 °C, which were recrystallized from CH_2Cl_2/pentane. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.02 (s, 3H), 1.20 (d, *J* = 11.7 Hz, 1H), 1.77-1.78 (m, 1H), 2.32 (s, 3H), 2.34 (s, 3H), 2.32-2.34 (m, 1H), 2.41 (s, 3H), 2.51 (s, 3H), 2.69 (s, 3H), 2.90 (d, *J* = 13.7, Hz, 1H), 4.67-4.77 (m, 1H), 4.93-5.04 (m, 4H), 6.90 (t, *J* = 7.3 Hz, 4H), 6.97 (d, *J* = 7.8 Hz, 2H), 7.04 (s, 1H), 7.09-7.12 (m, 3H), 7.20-7.28 (m, 13H), 7.39 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 8.19, 9.10, 20.77, 20.84, 21.8, 46.4, 51.6, 51.7, 52.1, 90.2, 112.8, 118.1, 126.1, 126.9, 127.0, 127.16, 127.19, 128.49, 128.55, 128.6, 128.82, 128.83, 129.0, 129.1, 129.5, 129.6, 129.7, 140.0, 141.50, 141.53, 141.58, 141.61, 141.65, 141.70, 142.1, 174.2. IR (ATR): 700, 1450, 1490 cm^{-1}. HRMS (FAB) *m/z*: $[M–SbF_6]^+$ Calcd for $C_{51}H_{51}N_2{}^{106}Pd$: 797.3082; Found: 797.3090. Anal. Calcd for $C_{51}H_{51}F_6N_2PdSb$: C, 59.23; H, 4.97; N, 2.71. Found: C, 59.36; H, 4.82; N, 2.74.

2.4. Crystal data of Pd-NHC complexes.

Allylchloro{4,5-dimethyl-3-[2,6-bis(diphenylmethyl)-4-methylphenyl]-1-(2,4,6-trimethyl-benzyl)imidazol-2-ylidene}palladium(II) (C1)

#1606a

$C_{51}H_{51}ClN_2Pd$ (M_r = 833.83)

orthorhombic

a = 10.5786(10) Å

b = 17.4231(17) Å

c = 22.099(2) Å

$\alpha = \beta = \gamma = 90$ °

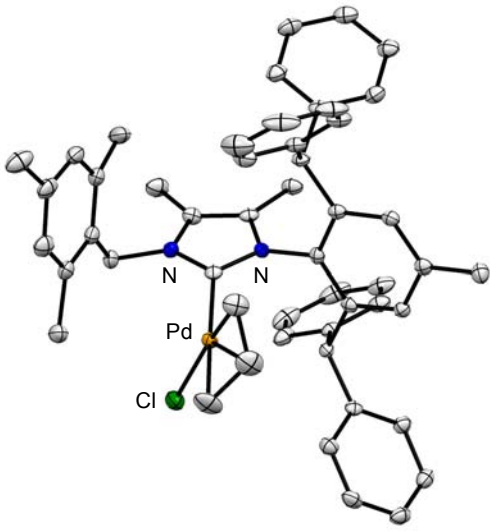
V = 4073.1(7) $Å^3$

Space Group: $P2_12_12_1$ (#19)

Z value = 4

D_{calc} = 1.360 g/cm^3

R = 0.0271



(Hydrogen atoms were omitted for clarity.)

Allyl{4,5-dimethyl-3-[2,6-bis(diphenylmethyl)-4-methylphenyl]-1-(2,4,6-trimethylbenzyl)-imidazol-2-ylidene}palladium(II) hexafluoroantimonate (C2)

#1619b

$C_{52}H_{46}Cl_2F_6N_2PdSb$ (M_r = 1112.00)

monoclinic

a = 14.091(2) Å

b = 12.527(2) Å

c = 27.256(4) Å

$\alpha = \gamma = 90$ °, $\beta = 92.128(3)$ °

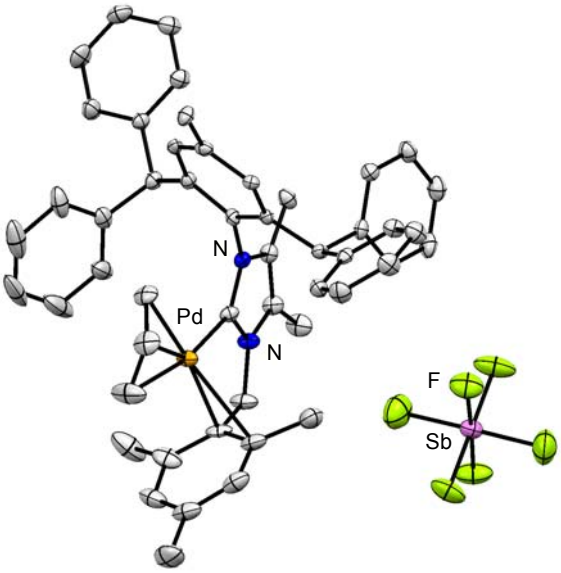
V = 4807.9(12) $Å^3$

Space Group: $P2_1/c$ (#14)

Z value = 4

D_{calc} = 1.536 g/cm^3

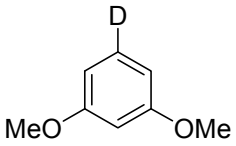
R = 0.0638



(Hydrogen atoms and a residual dichloromethane molecule were omitted for clarity. The central carbon of allyl group was disordered and refined over two positions with occupancies of 0.75 and 0.25.)

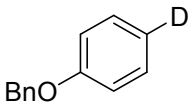
2.5. General procedure for palladium-catalyzed deuterodechlorination of aryl/heteroaryl chlorides. Under argon atmosphere, a reaction tube was charged with ligand precursor **L29** (13.7 mg, 0.02 mmol), $[Pd(allyl)Cl]_2$ (1.83 mg, 0.005 mmol), and Cs_2CO_3 (489 mg, 1.5 mmol). After toluene (2.0 mL) was added, the mixture was stirred for 15 min at 80 °C and cooled to room temperature. Then, aryl chloride **8b** (219 mg, 1.0 mmol) and α-deuterioalcohol **7a** (222 mg, 1.2 mmol) were added. The reaction mixture was stirred for 16 h at 90 °C and cooled to room temperature. Water was added, and then the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. Concentration and purification through silica gel column chromatography gave desired product **9b**.

1-Deuterio-3,5-dimethoxybenzene (9a).



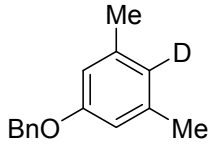
Silica gel chromatography (hexane/ether = 100/1) gave 137 mg of the product (0.99 mmol, 99% yield) as colorless oil. >99% D (D content was judged with the peak at 7.19 ppm (a deuterated site) compared to the peak at 6.47 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.80 (s, 6H), 6.47 (t, J = 2.4 Hz, 1H), 6.51-6.52 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 55.2 (CH_3), 100.5 (CH), 106.1 (CH), 129.6 (t, $J_{C\text{-}D}$ = 24.0 Hz, C), 160.9 (C). IR (ATR): 1200, 1430, 1600 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_8H_9DO_2$: 139.0744; Found: 139.0756.

1-Benzyloxy-4-deuteriobenzene (9b).



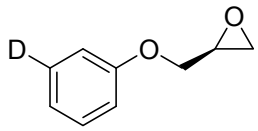
Silica gel chromatography (hexane/ether = 100/1) gave 184 mg of the product (0.99 mmol, 99% yield) as white solids of mp 38-39 °C. >99% D (D content was judged with the peak at 6.97-7.00 ppm (a deuterated site) compared to the peak at 5.07 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.07 (s, 2H), 6.97-7.00 (m, 2H), 7.28-7.34 (m, 3H), 7.37-7.40 (m, 2H), 7.44 (d, J = 7.6 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 69.8 (CH_2), 114.8 (CH), 120.7 (t, $J_{C\text{-}D}$ = 24.0 Hz, C), 127.5 (CH), 127.9 (CH), 128.6 (CH), 129.4 (CH), 137.1 (C), 158.9 (C). IR (ATR): 1010, 1240, 1590 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{13}H_{11}DO$: 185.0951; Found: 185.0938.

1-Benzyloxy-4-deuterio-3,5-dimethylbenzene (9c).



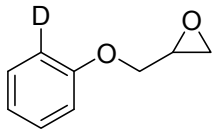
Silica gel chromatography (hexane/ether = 100/1) gave 211 mg of the product (0.99 mmol, 99% yield) as colorless oil. >99% D (D content was judged with the peak at 6.62 ppm (a deuterated site) compared to the peak at 7.30-7.44 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.29 (s, 6H), 5.03 (s, 2H), 6.62 (s, 2H), 7.32 (t, *J* = 7.2 Hz, 1H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.43 (d, *J* = 7.2 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.3 (CH_3), 69.7 (CH_2), 112.6 (CH), 122.4 (t, $J_{C\text{-}D}$ = 23.2 Hz, C), 127.5 (CH), 127.8 (CH), 128.5 (CH), 137.3 (C), 139.1 (C), 159.0 (C). IR (ATR): 850, 1060, 1590 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{15}H_{15}DO$: 213.1264; Found: 213.1262.

(*S*)-(+)-2-[(3-Deuteriophenoxy)methyl]oxirane (9d).



Silica gel column chromatography (hexane/benzene = 1/1) gave 142 mg (0.94 mmol, 94% yield) of the product as colorless oil. >99% D (D content was judged with the peak at 7.28-7.31 ppm (a deuterated site) compared to the peak at 4.31 ppm by ^{1}H-NMR). $[\alpha]^{21}_D$ +11.8 (*c* 1.58, EtOH). 91% *ee* (HPLC: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 9/1, 0.8 mL/min, 220 nm, (*s*)-isomer 14.3 min and (*R*)-isomer 9.0 min). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.71 (dd, *J* = 2.7, 5.1 Hz, 1H), 2.84 (dd, *J* = 4.3, 5.1 Hz, 1H), 3.31-3.34 (m, 1H), 3.82 (dd, *J* = 6.5, 11.4 Hz, 1H), 4.31 (dd, *J* = 2.7, 11.4 Hz, 1H), 6.94-6.97 (m, 3H), 7.28-7.31 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 44.3 (CH_2), 49.9 (CH), 68.5 (CH_2), 114.4 (CH), 114.5 (CH), 121.0 (CH), 129.1 (t, $J_{C\text{-}D}$ = 24.0 Hz, C), 129.4 (CH), 158.4 (C). IR (ATR): 790, 840, 1050, 1220, 1590 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_9H_9DO_2$: 151.0744; Found: 151.0737.

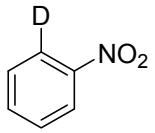
2-[(2-Deuteriophenoxy)methyl]oxirane (9e).



Silica gel chromatography (hexane/benzene = 1/1) gave 140 mg of the product (0.93 mmol, 93% yield) as colorless oil. >99% D (D content was judged with the peak at 6.93-6.97 ppm (a deuterated site) compared to the peak at 4.31 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.71 (dd, *J* = 2.7, 5.1 Hz, 1H), 2.84 (t, *J* = 5.1 Hz, 1H), 3.31-3.37 (m, 1H), 3.82 (dd, $J_{C\text{-}D}$ = 6.3, 11.2 Hz, 1H), 4.31 (dd, *J* = 2.7, 11.2 Hz, 1H), 6.93-6.97 (m, 2H), 7.28-7.31 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 44.4 (CH_2), 49.9 (CH), 68.5 (CH_2), 114.2 (t, *J* = 24.2 Hz,

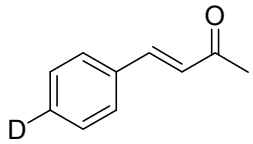
C), 114.5 (CH), 121.1 (CH), 129.3 (CH), 129.4 (CH), 158.4 (C). IR (ATR): 760, 840, 1050, 1230, 1590 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_9H_9DO_2$: 151.0744; Found: 151.0746.

1-Deuterio-2-nitrobenzene (9f).



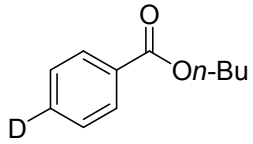
Silica gel chromatography (hexane/benzene = 3/1) gave 121 mg of the product (0.98 mmol, 98% yield) as pale yellow oil. >99% D (D content was judged with the peak at 8.23-8.25 ppm (a deuterated site) compared to the peak at 7.54-7.57 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.54-7.57 (m, 2H), 7.71 (dt, *J* = 1.0, 7.5 Hz, 1H), 8.23-8.25 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 123.2 (t, $J_{C\text{-}D}$ = 25.7 Hz, C), 123.5 (CH), 129.2 (CH), 129.3 (CH), 134.6 (CH), 148.2 (C). IR (ATR): 1340, 1520 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_6H_4DNO_2$: 124.0383; Found: 124.0362.

(*E*)-4-(4-Deuteriophenyl)but-3-en-2-one (9g).



Silica gel chromatography (hexane/AcOEt = 10/1) gave 144 mg of the product (0.98 mmol, 98% yield) as pale yellow solids of mp 39-40 °C. >99% D (D content was judged with the peak at 7.40 ppm (a deuterated site) compared to the peak at 6.73 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.39 (s, 3H), 6.73 (d, *J* = 16.4 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.52 (d, *J* = 16.4 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 27.4 (CH_3), 127.2 (CH), 128.3 (CH), 128.9 (CH), 130.2 (t, $J_{C\text{-}D}$ = 24.0 Hz, C), 134.5 (C), 143.5 (CH), 198.5 (C). IR (ATR): 990, 1190, 1680 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{10}H_9DO$: 147.0794; Found: 147.0771.

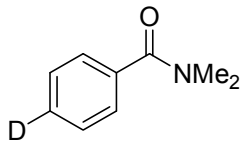
Butyl 4-deuteriobenzoate (9h).



Silica gel chromatography (hexane/Benzene = 5/1) gave 168 mg of the product (0.94 mmol, 94% yield) as colorless oil. >99% D (D content was judged with the peak at 7.55 ppm (a deuterated site) compared to the peak at 7.45 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ

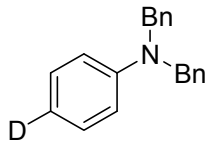
0.99 (t, J = 7.5 Hz, 3H), 1.45-1.52 (m, 2H), 1.73-1.79 (m, 2H), 4.33 (t, J = 6.5 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 8.05 (d, J = 8.0 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 19.1 (CH_2), 30.6 (CH_2), 64.7 (CH_2), 128.1 (CH), 129.5 (CH), 130.5 (C), 132.4 (t, $J_{C\text{-}D}$ = 24.8 Hz, C), 166.6 (C). IR (ATR): 1100, 1270, 1720, 2960 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{11}H_{13}DO_2$: 179.1057; Found: 179.1056.

4-Deuterio-*N*,*N*-dimethylbenzamide (9i).



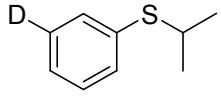
Silica gel chromatography (benzene/AcOEt = 2/1) gave 149 mg of the product (0.99 mmol, 99% yield) as colorless oil. >99% D (D content was judged with the peak at 7.04 ppm (a deuterated site) compared to the peak at 7.32 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, benzene-d_6): δ 2.29 (brs, 3H), 2.76 (brs, 3H), 7.04 (d, J = 7.8 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 34.9 (CH_3), 39.2 (CH_3), 126.8 (CH), 128.0 (CH), 128.9 (t, $J_{C\text{-}D}$ = 24.8 Hz, C), 136.2 (C), 171.4 (C). IR (ATR): 860, 1080, 1620 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_9H_{10}DNO$: 150.0903; Found: 150.0906.

4-Deuterio-*N*,*N*-dibenzylbenzeneamine (9j).



Silica gel chromatography (hexane/ benzene = 10/1) gave 263 mg of the product (0.96 mmol, 96% yield) as colorless oil. >99% D (D content was judged with the peak at 6.73-6.75 ppm (a deuterated site) compared to the peak at 4.65 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.65 (s, 4H), 6.73-6.75 (m, 2H), 7.16 (d, J = 8.8 Hz, 2H), 7.23-7.26 (m, 6H), 7.31-7.34 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 54.1 (CH_2), 112.4 (CH), 116.5 (t, $J_{C\text{-}D}$ = 24.8 Hz, C), 126.6 (CH), 126.9 (CH), 128.6 (CH), 129.1 (CH), 138.6 (C), 149.2 (C). IR (ATR): 730, 1350, 1590 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{20}H_{18}DN$: 274.1580; Found: 274.1576.

Isopropyl 3-deuteriophenyl sulfide (9k).

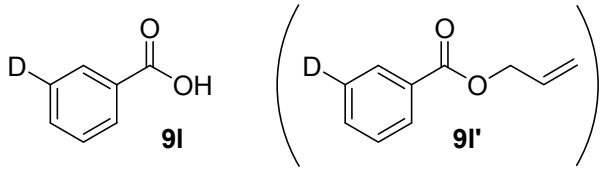


Silica gel chromatography (hexane/*i*-Pr_2O = 200/1) gave 126 mg of the product (0.82 mmol,

82% yield) as colorless oil. >99% D (D content was judged with the peak at 7.30-7.33 ppm (a deuterated site) compared to the peak at 3.43 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, CD_3CN): δ 1.26 (d, *J* = 6.5 Hz, 6H), 3.43 (septet, *J* = 6.5 Hz, 1H), 7.24 (dt, *J* = 1.0, 7.5 Hz, 1H), 7.30-7.33 (m, 1H), 7.38-7.40 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 23.0 (CH_3), 38.1 (CH), 126.6 (CH), 128.5 (t, $J_{C\text{-}D}$ = 24.0 Hz, C), 128.8 (CH), 131.8 (CH), 131.9 (CH), 135.5 (C). IR (ATR): 660, 1580, 2960 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_9H_{11}DS$: 153.0722; Found: 153.0726.

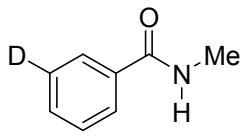
3-Deuteriobenzoic acid (9l).

Deuterated product **9l** was directly converted into allyl 3-deuteriobenzoate (**9l'**) for purification.



The allylation of 3-deuteriobenzoic acid (**9l**) was carried out according to the reported procedure.[11] To the reaction mixture was added water, and the mixture was acidified with 10% HCl. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated to give the crude product. The solution of crude product in THF (1 mL) was added to the mixture of *n*-Bu_4NHSO_4 (20 mg, 0.05 mnol) and KF (290 mg, 5.0 mmol) in THF (1 mL). Subsequently, allyl bromide (133 mg, 1.1 mmol) was added, and then the reaction mixture was stirred at room temperature for 3 h. After water was added, the resulting mixture was extracted with *i*-Pr_2O. The combined organic layers were dried over Na_2SO_4. Concentration and purification through silica gel column chromatography (hexane/benzene = 5/1) gave 131 mg of allyl 3-deuteriobenzoate (**9l'**) (0.80 mmol, 80% yield) as a colorless oil. >99% D (D content was judged with the peak at 7.43-7.46 ppm (a deuterated site) compared to the peak at 4.83 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.83 (dt, *J* = 1.0, 5.6 Hz, 2H), 5.29 (dd, *J* = 1.0, 10.5 Hz, 1H), 5.42 (dd, *J* = 1.5, 17.3 Hz, 1H), 6.01-6.09 (m, 1H), 7.43-7.46 (m, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 8.06-8.08 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 65.4 (CH_2), 118.2 (CH_2), 128.1 (t, $J_{C\text{-}D}$ = 24.8 Hz, C), 128.4 (CH), 129.5 (CH), 129.6 (CH), 130.2 (C), 132.3 (CH), 132.9 (CH), 166.3 (C). IR (ATR): 640, 1090, 1110, 1250, 1430, 1720, 3080 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{10}H_9DO_2$: 163.0744; Found: 163.0747.

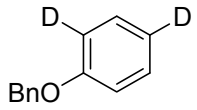
3-Deuterio-*N*-methylbenzamide (9m).



Silica gel chromatography (Benzene/AcOEt = 3/1) gave 135 mg of the product (0.99 mmol,

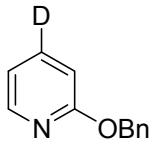
99% yield) as white solids of mp 74-75 °C. >99% D (D content was judged with the peak at 7.42-7.50 ppm (a deuterated site) compared to the peak at 7.75-7.77 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.03 (d, *J* = 4.8 Hz, 3H), 7.43 (dd, *J* = 7.5, 8.2 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.75-7.77 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 26.5 (CH_3), 126.8 (CH), 126.9 (CH), 128.0 (t, $J_{C\text{-}D}$ = 24.8 Hz, C), 128.2 (CH), 131.0 (CH), 134.4 (C), 168.5 (C). IR (ATR): 690, 1550, 1630, 2930, 3320 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for C_8H_8DNO: 136.0747; Found: 136.0749.

1-Benzyloxy-2,4-dideuteriobenzene (9n).



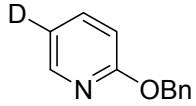
Silica gel chromatography (hexane/benzene = 50/1) gave 177 mg of the product (0.95 mmol, 95% yield) as colorless solids of mp 33-34 °C. >99% D (D content was judged with the peak at 6.98 ppm (deuterated sites) compared to the peak at 5.07 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.07 (s, 2H), 6.98 (d, *J* = 8.5 Hz, 1H), 7.29-7.34 (m, 3H), 7.37-7.40 (m, 2H), 7.43-7.45 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 69.8 (CH_2), 114.5 (t, *J* = 24.8 Hz, C), 114.9 (CH), 120.7 (t, $J_{C\text{-}D}$ = 24.8 Hz, C), 127.5 (CH), 127.9 (CH), 128.6 (CH), 129.3 (CH), 129.4 (CH), 137.1 (C), 158.8 (C). IR (ATR): 1010, 1050, 1230, 1580 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{13}H_{10}D_2O$: 186.1014; Found: 186.1016.

2-Benzyloxy-4-deuteriopyridine (11a).



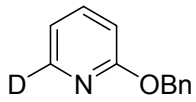
Silica gel chromatography (hexane/benzene = 1/1.5) gave 185 mg of the product (0.99 mmol, 99% yield) as colorless oil. >99% D (D content was judged with the peak at 7.62 ppm (a deuterated site) compared to the peak at 8.18 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.38 (s, 2H), 6.81 (s, 1H), 6.88 (d, *J* = 5.1 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.46-7.48 (m, 2H), 8.18 (d, *J* = 5.1 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 67.3 (CH_2), 111.0 (CH), 116.6 (CH), 127.7 (CH), 127.8 (CH), 128.3 (CH), 137.3 (C), 138.2 (t, $J_{C\text{-}D}$ = 24.8 Hz, C), 146.8 (CH), 163.5 (C). IR (ATR): 700, 990, 1220, 1560 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{12}H_{10}DNO$: 186.0903; Found: 186.0902.

2-Benzyloxy-5-deuteriopyridine (11b).



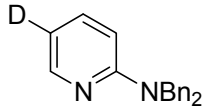
Silica gel chromatography (hexane/benzene = 1/1) gave 181 mg of the product (0.97 mmol, 97% yield) as colorless oil. >99% D (D content was judged with the peak at 6.88 ppm (a deuterated site) compared to the peak at 8.18 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.38 (s, 2H), 6.81 (dd, *J* = 1.5, 8.4 Hz, 1H), 7.30-7.33 (m, 1H), 7.36-7.39 (m, 2H), 7.46-7.48 (m, 2H), 7.58 (dd, *J* = 1.5, 8.4 Hz, 1H), 8.18 (d, *J* = 1.5 Hz 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 67.3 (CH_2), 111.2 (CH), 116.5 (t, $J_{C\text{-}D}$ = 24.8 Hz, C), 127.7 (CH), 127.9 (CH), 128.3 (CH), 137.3 (C), 138.4 (CH), 146.7 (CH), 163.6 (C). IR (ATR): 740, 990, 1590 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{12}H_{10}DNO$: 186.0903; Found: 186.0899.

2-Benzyloxy-6-deuteriopyridine (11c).



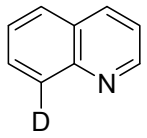
Silica gel chromatography (hexane/benzene = 1.5/1) gave 185 mg of the product (0.99 mmol, 99% yield) as colorless oil. >99% D (D content was judged with the peak at 8.18 ppm (a deuterated site) compared to the peak at 6.88 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.38 (s, 2H), 6.81 (dd, *J* = 1.0, 8.3 Hz, 1H), 6.88 (d, *J* = 7.1 Hz, 1H), 7.30-7.33 (m, 1H), 7.36-7.39 (m, 2H), 7.46-7.48 (m, 2H), 7.58 (dd, $J_{C\text{-}D}$ = 7.1, 8.3 Hz 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 67.3 (CH_2), 111.2 (CH), 116.7 (CH), 127.7 (CH), 127.9 (CH), 128.4 (CH), 137.4 (C), 138.5 (CH), 146.5 (t, *J* = 27.3 Hz, C), 163.6 (C). IR (ATR): 1250, 1590 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{12}H_{10}DNO$: 186.0903; Found: 186.0907.

2-(Dibenzylamino)-5-deuteriopyridine (11d).



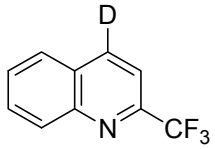
Silica gel chromatography (hexane/benzene = 1.5/1) gave 254 mg of the product (0.92 mmol, 92% yield) as colorless oil. >99% D (D content was judged with the peak at 6.58 ppm (a deuterated site) compared to the peak at 7.38 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.80 (s, 4H), 6.46 (dd, $J_{C\text{-}D}$ = 0.8, 8.5 Hz, 1H), 7.23-7.26 (m, 6H), 7.29-7.32 (m, 4H), 7.38 (dd, *J* = 2.0, 8.5 Hz, 1H), 8.20-8.21 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 50.8 (CH_2), 105.7 (CH), 111.9 (t, *J* = 25.7 Hz, C), 126.9 (CH), 127.0 (CH), 128.5 (CH), 137.3 (CH), 138.4 (C), 148.0 (CH), 158.6 (C). IR (ATR): 1240, 1490, 1580 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{19}H_{17}DN_2$: 275.1533; Found: 275.1530.

8-Deuterioquinoline (11e).



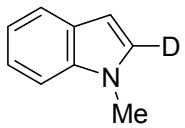
Silica gel chromatography (benzene/AcOEt = 10/1) gave 126 mg of the product (0.97 mmol, 97% yield) as colorless oil. >99% D (D content was judged with the peak at 8.12 ppm (a deuterated site) compared to the peak at 7.73 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 4.2, 8.3 Hz, 1H), 7.56 (dd, *J* = 7.0, 8.1 Hz, 1H), 7.73 (d, *J* = 7.0 Hz, 1H), 7.83 (dd, *J* = 1.7, 8.1 Hz, 1H), 8.17 (dd, *J* = 1.7, 8.3 Hz, 1H), 8.93 (dd, *J* = 1.7, 4.2 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 120.8 (CH), 126.2 (CH), 127.5 (CH), 128.0 (C), 128.9 (t, $J_{C\text{-}D}$ = 24.8 Hz, C), 129.0 (CH), 135.7 (CH), 148.0 (C), 150.1 (CH). IR (ATR): 790, 1490 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for C_9H_6DN: 130.0641; Found: 130.0645.

4-Deuterio-2-(trifluoromethyl)quinoline (11f).



Silica gel chromatography (hexane/benzene = 3/1) gave 192 mg of the product (0.97 mmol, 97% yield) as colorless solids of mp 53-54 °C. >99% D (D content was judged with the peak at 8.37 ppm (a deuterated site) compared to the peak at 7.92 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.67-7.70 (m, 1H), 7.75 (s, 1H), 7.82-7.85 (m, 1H), 7.92 (dd, *J* = 1.0, 8.5 Hz, 1H), 8.24 (d, *J* = 8.5 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 116.5 (q, *J* = 2.5 Hz, CH), 121.6 (q, *J* = 275.6 Hz, C), 127.6 (CH), 128.5 (CH), 128.7 (C), 130.0 (CH), 130.8 (CH), 137.7 (t, $J_{C\text{-}D}$ = 24.8 Hz, C), 147.1 (C), 147.9 (q, *J* = 34.8 Hz, C). IR (ATR): 770, 1120, 1200 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{10}H_5DF_3N$: 198.0515; Found: 198.0505.

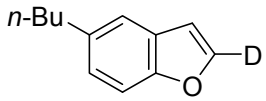
2-Deuterio-1-methyl-1*H*-indole (11g).



Silica gel chromatography (hexane/benzene = 10/1) gave 128 mg of the product (0.97 mmol, 97% yield) as colorless oil. >99% D (D content was judged with the peak at 7.31 ppm (a deuterated site) compared to the peak at 7.53 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 3.78 (s, 3H), 6.40 (d, *J* = 0.7 Hz, 1H), 7.00-7.03 (m, 1H), 7.12-7.15 (m, 1H). 7.42 (dd, *J* = 0.7, 8.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 32.4 (CH_3), 100.6 (CH), 109.1 (CH), 119.2 (CH), 120.8 (CH), 121.4 (CH), 128.4 (C), 128.5 (t, $J_{C\text{-}D}$ = 27.3

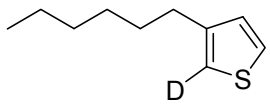
Hz, C), 136.6 (C). IR (ATR): 730, 1230, 1470 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for C_9H_8DN: 132.0798; Found: 132.0801.

5-Butyl-2-deuteriobenzofuran (11h).



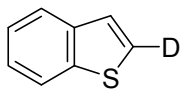
Silica gel chromatography (hexane/*i*-Pr_2O = 400/1) gave 164 mg of the product (0.94 mmol, 94% yield) as colorless oil. >99% D (D content was judged with the peak at 7.58 ppm (a deuterated site) compared to the peak at 7.39-7.41 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.5 Hz, 3H), 1.33-1.41 (m, 2H), 1.60-1.66 (m, 2H), 2.70 (t, *J* = 7.5 Hz, 2H), 6.70 (d, *J* = 0.8 Hz, 1H), 7.11 (dd, *J* = 1.5, 8.3 Hz, 1H), 7.39 (s, 1H), 7.40 (d, *J* = 8.3 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 22.2 (CH_2), 34.2 (CH_2), 35.5 (CH_2), 106.2 (CH), 110.9 (CH), 120.4 (CH), 125.0 (CH), 127.5 (C), 137.3 (C), 144.7 (t, $J_{C\text{-}D}$ = 30.6 Hz, C), 153.5 (C). IR (ATR): 810, 1030, 1450 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{12}H_{13}DO$: 175.1107; Found: 175.1107.

2-Deuterio-3-*n*-hexylthiophene (5i).



Silica gel chromatography (hexane/*i*-Pr_2O = 200/1) gave 163 mg of the product (0.96 mmol, 96% yield) as colorless oil. >99% D (D content was judged with the peak at 6.93 ppm (a deuterated site) compared to the peak at 0.88 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.5 Hz, 3H), 1.30-1.35 (m, 6H), 1.62 (quintet, *J* = 7.5 Hz, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 6.93 (d, *J* = 4.8 Hz, 1H), 7.23 (d, *J* = 4.8 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.5 (CH_2), 29.0 (CH_2), 30.2 (CH_2), 30.5 (CH_2), 31.6 (CH_2), 119.6 (t, $J_{C\text{-}D}$ = 27.3 Hz, C), 124.9 (CH), 128.3 (CH), 143.1 (C). IR (ATR): 720, 830, 1460 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{10}H_{15}DS$: 169.1035; Found: 169.1039.

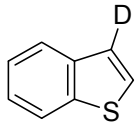
2-Deuteriobenzothiophene (11j).



This reaction was conducted at 100 °C. Silica gel chromatography (hexane/benzene = 400/1) gave 122 mg of the product (0.90 mmol, 90% yield) as colorless oil. >99% D (D content was judged with the peak at 7.44 ppm (a deuterated site) compared to the peak at 7.82-7.90 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.32-7.38 (m, 3H), 7.83 (dd, *J* = 1.8, 7.0 Hz, 1H),

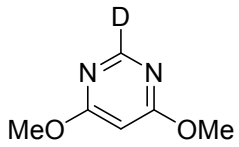
7.88-7.90 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): 122.5 (CH), 123.6 (CH), 123.7 (CH), 124.17 (CH), 124.21 (CH), 126.1 (t, $J_{C\text{-}D}$ = 28.1 Hz, C), 139.6 (C), 139.7 (C). IR (ATR): cm^{-1} 730, 840, 1450, 2920. HRMS (EI) *m/z*: (M^+) Calcd for C_8H_5DS: 135.0253; Found: 135.0254.

3-Deuteriobenzothiophene (11k).



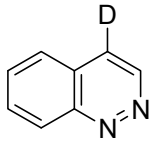
Silica gel chromatography (hexane/benzene = 400/1) gave 125 mg of the product (0.93 mmol, 93% yield) as colorless oil. 99% D (D content was judged with the peak at 6.96 ppm (a deuterated site) compared to the peak at 7.55-7.59 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, benzene-d_6): 6.91 (s, 1H), 7.04-7.07 (m, 1H), 7.12-7.15 (m, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): 122.5 (CH), 123.58 (CH), 123.62 (t, $J_{C\text{-}D}$ = 25.7 Hz, C), 124.1 (CH), 124.2 (CH), 126.2 (CH), 139.5 (C), 139.7 (C). IR (ATR): cm^{-1} 720, 860, 1460, 2920. HRMS (EI) *m/z*: (M^+) Calcd for C_8H_5DS: 135.0253; Found: 135.0252.

2-Deuterio-4,6-dimethoxypyrimidine (11l).



Silica gel chromatography (hexane/AcOEt = 15/1) gave 101 mg of the product (0.72 mmol, 72% yield) as colorless oil. >99% D (D content was judged with the peak at 8.46 ppm (a deuterated site) compared to the peak at 6.06 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.95 (s, 6H), 6.06 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 53.9 (CH_3), 90.3 (CH), 157.2 (t, $J_{C\text{-}D}$ = 31.0 Hz, C), 171.3. (C). IR (ATR): 700, 1190, 1260, 1590 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_6H_7DN_2O_2$: 141.0649; Found: 141.0645.

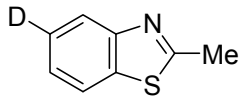
4-Deuteriocinnoline (11m).



Silica gel chromatography (benzene/AcOEt = 4/1) gave 113 mg of the product (0.86 mmol, 86% yield) as pale yellpw oil. >99% D (D content was judged with the peak at 8.24 ppm (a deuterated site) compared to the peak at 9.40 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.88-7.91 (m, 1H), 7.96-8.00 (m, 1H), 8.10 (dd, *J* = 0.7, 8.5 Hz, 1H), 8.48 (dd, *J* =

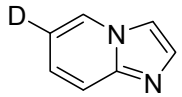
0.7, 8.5 Hz, 1H), 9.40 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 122.0, (t, $J_{C\text{-}D}$ = 25.7 Hz, C), 125.6 (C), 126.4 (CH), 129.5 (CH), 130.4 (CH), 130.9 (CH), 144.8 (CH), 150.6 (C). IR (ATR): 770, 1140, 1570 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_8H_5DN_2$: 131.0594; Found: 131.0597.

5-Deuterio-2-methylbenzo[*d*]thiazole (11n).



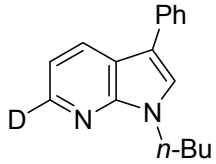
This reaction was conducted with the catalyst (3 mol%) at 100 °C in the presence of Cs_2CO_3 (2 equiv). Silica gel chromatography (benzene/*i*-Pr_2O = 20/1) gave 137 mg of the product (0.91 mmol, 91% yield) as colorless oil. >99% D (D content was judged with the peak at 7.48 ppm (a deuterated site) compared to the peak at 7.39 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 2.80 (s, 3H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.91 (s, 1H), 8.03 (dd, *J* = 0.5, 8.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 19.8 (CH_3), 121.2 (CH), 122.1 (CH), 124.4 (CH), 125.5 (t, $J_{C\text{-}D}$ = 24.8 Hz, C), 135.5 (C), 153.2 (C), 166.8 (C). IR (ATR): 1170, 1520 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for C_8H_6DNS: 150.0362; Found: 150.0365.

6-Deuterioimidazo[1,2-*a*]pyridine (11o).



Silica gel chromatography (AcOEt and AcOEt/MeOH = 10/1) gave 118 mg of the product (0.99 mmol, 99% yield) as pale yellow oil. >99% D (D content was judged with the peak at 6.78 ppm (a deuterated site) compared to the peak at 8.14 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): 7.17 (d, *J* = 9.1 Hz, 1H), 7.58-7.60 (m, 1H), 7.62-7.64 (m, 2H), 8.14 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): 111.6 (t, $J_{C\text{-}D}$ = 25.7 Hz, C), 112.0 (CH), 117.3 (CH), 123.9 (CH), 125.4 (CH), 133.0 (CH), 145.0 (C). IR (ATR): 710, 1130, 1500, 1630 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_7H_5DN_2$: 119.0594; Found: 119.0594

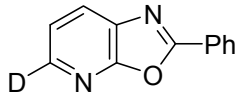
1-Butyl-6-deuterio-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (11p).



Silica gel chromatography (hexane/benzene = 1/1) gave 238 mg of the product (0.95 mmol, 95% yield) as pale yellow oil. >99% D (D content was judged with the peak at 8.37 ppm (a deuterated site) compared to the peak at 8.22 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ

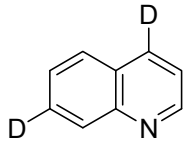
0.96 (t, J = 7.4 Hz, 3H), 1.37-1.44 (m, 2H), 1.88-1.94 (m, 2H), 4.35 (t, J = 7.4 Hz, 2H), 7.12 (d, J = 7.9 Hz, 1H), 7.27-7.30 (m, 1H), 7.43-7.46 (m, 3H), 7.64 (dd, J = 1.2, 8.3 Hz, 2H), 8.22 (d, J = 7.9 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 20.0 (CH_2), 32.3 (CH_2), 44.2 (CH_2), 114.8 (C), 115.8 (CH), 118.6 (C), 125.1 (CH), 126.0 (CH), 126.9 (CH), 128.0 (CH), 128.9 (CH), 135.1 (C), 142.7 (t, $J_{C\text{-}D}$ = 27.3 Hz, C), 148.0 (C). IR (ATR): 750, 760, 1430, 1540, 1600 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{17}H_{17}DN_2$: 251.1533; Found: 251.1532.

5-Deuterio-2-phenyloxazolo[5,4-*b*]pyridine (11q).



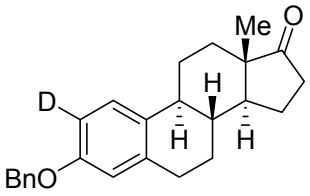
Silica gel chromatography (hexane/Et_2O = 5/1) gave 146 mg of the product (0.74 mmol, 74% yield) as white solids of mp 97-98 °C. >99% D (D content was judged with the peak at 8.36 ppm (a deuterated site) compared to the peak at 8.08 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.36 (d, J = 7.8 Hz 1H), 7.54-7.61 (m, 3H), 8.08 (d, J = 7.8 Hz, 1H), 8.29-8.32 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 120.7 (CH), 126.4 (C), 127.7 (CH), 128.1 (CH), 128.9 (CH), 132.1 (CH), 133.8 (C), 144.2 (t, $J_{C\text{-}D}$ = 28.1 Hz, C), 159.7 (C), 163.0 (C). IR (ATR): 680, 1540, 1600, 1610 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{12}H_7DN_2O$: 197.0699; Found: 197.0701.

4,7-Dideuterioquinoline (11r).



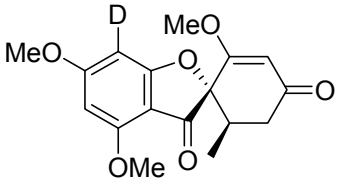
Silica gel chromatography (benzene/AcOEt = 10/1) gave 127 mg of the product (0.97 mmol, 97% yield) as colorless oil. >99% D (D content was judged with the peaks at 7.73 and 8.17 ppm (deuterated sites) compared to the peak at 8.12 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.41 (d, J = 4.2 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.84 (d, J = 8.2 Hz, 1H), 8.12 (s, 1H), 8.93 (d, J = 4.2 Hz 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 120.8 (CH), 126.3 (CH), 127.6 (CH), 128.1 (C), 129.0 (t, $J_{C\text{-}D}$ = 24.8 Hz, C), 129.2 (CH), 135.6 (t, J = 24.8 Hz, C), 148.2 (C), 150.3 (CH). IR (ATR): 710, 1490, 1560 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_9H_5D_2N$: 131.0704; Found: 131.0707.

(8*R*,9*S*,13*S*,14*S*)-3-Benzyloxy-2-deuterio-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-deca hydro-6*H*-cyclopenta[*a*]phenanthren (13a).



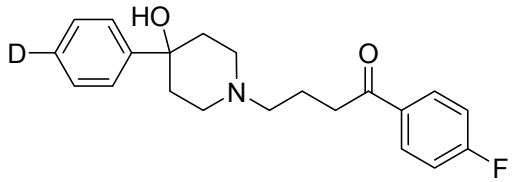
This reaction was conducted in 0.5 mmol scale. Silica gel chromatography (hexane/*i*-Pr_2O = 3/1) gave 167 mg of the product (0.46 mmol, 92% yield) as white solids of mp 126-127 °C. >99% D (D content was judged with the peak at 6.79 ppm (a deuterated site) compared to the peak at 6.74 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.91 (s, 3H), 1.40-1.67 (m, 6H), 1.94-2.08 (m, 3H), 2.11-2.18 (m, 1H), 2.23-2.28 (m, 1H), 2.38-2.42 (m, 1H), 2.48-2.53 (m, 1H), 2.88-2.92 (m, 2H), 5.04 (s, 2H), 6.74 (s, 1H), 7.20 (s, 1H), 7.30-7.33 (m, 1H), 7.37-7.44 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.7 (CH_3), 21.4 (CH_2), 25.8 (CH_2), 26.4 (CH_2), 29.5 (CH_2), 31.4 (CH_2), 35.7 (CH_2), 38.2 (CH), 43.8 (CH), 47.9 (C), 50.3 (CH), 69.8 (CH_2), 112.0 (t, $J_{C\text{-}D}$ = 24.0 Hz, C), 114.9 (CH), 126.2 (CH), 127.4 (CH), 127.8 (CH), 128.5 (CH), 132.3 (C), 137.2 (C),137.8 (C), 156.8 (C), 220.9 (C). IR (ATR): 700, 1020, 1220, 1490, 1730 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{25}H_{27}DO_2$: 361.2152; Found: 361.2157.

(2*S*,6'*R*)-7-Deuterio-2',4,6-trimethoxy-6'-methyl-3*H*-spiro[1-benzofuran-2,1'-cyclohexan]-2'-ene-3,4'-dione (13b).



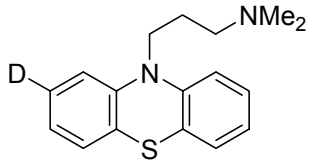
Silica gel chromatography (hexane/AcoEt = 1/1) gave 304 mg of the product (0.95 mmol, 95% yield) as white solids of mp 180-181 °C. $[\alpha]^{17}_D$ +358.2 (*c* 1.00, acetone). 97% D (D content was judged with the peak at 6.23 ppm (a deuterated site) compared to the peak at 5.54 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.98 (d, *J* = 6.7 Hz, 3H), 2.42 (dd, *J* = 4.8, 16.8 Hz, 1H), 2.73-2.80 (m, 1H), 3.08 (dd, *J* = 13.5, 16.8 Hz, 1H), 3.64 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 5.55 (s, 1H), 6.06 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3), 36.3 (CH), 39.8 (CH_2), 55.88 (CH_3), 55.90 (CH_3), 56.4 (CH_3), 88.2 (t, $J_{C\text{-}D}$ = 25.7 Hz, C), 89.7 (C), 93.2 (CH), 104.1 (C), 104.5 (CH), 159.0 (C), 170.3 (C), 171.3 (C), 175.9 (C), 192.4 (C), 197.2 (C). IR (ATR): 810, 1210, 1610 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{17}H_{17}DO_6$: 319.1166; Found: 319.1161.

4-[4-(4-Deuteriophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone (13c).



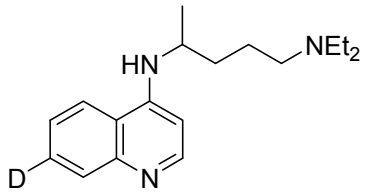
Silica gel chromatography (CH_2Cl_2/MeOH= 10/1) gave 322 mg of the product (0.94 mmol, 94% yield) as white solids of mp 136-137 °C. >99% D (D content was judged with the peak at 7.21-7.25 ppm (a deuterated site) compared to the peak at 7.30-7.39 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, CD_3CN): δ 1.50-1.55 (m, 2H), 1.79 (dt, *J* = 4.5, 12.6 Hz, 2H), 1.88-1.94 (m, 3H), 2.34 (dt, *J* = 2.6, 12.6 Hz, 2H), 2.40 (t, *J* = 6.8 Hz, 2H), 2.64 (m, 2H), 2.97 (t, *J* = 6.8 Hz, 2H), 7.21-7.25 (m, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.37-7.39 (m, 2H), 8.05-8.09 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 21.8 (CH_2), 36.2 (CH_2), 38.3 (CH_2), 49.3 (CH_2), 57.8 (CH_2), 71.1 (C), 115.6 (d, $J_{C\text{-}F}$ = 21.5 Hz, CH), 124.5 (CH), 126.6 (t, $J_{C\text{-}D}$ = 24.0 Hz, C), 128.1 (CH), 130.7 (d, $J_{C\text{-}F}$ = 9.1 Hz, CH), 133.7 (d, $J_{C\text{-}F}$ = 3.3 Hz, C), 148.5 (C), 165.6 (d, $J_{C\text{-}F}$ = 254.1 Hz, C), 198.5 (C). IR (ATR): 830, 1200, 1600, 1680, 3180 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{21}H_{23}DFNO_2$: 342.1854; Found: 342.1843.

2-Deuterio-10-[3-(dimethylamino)-1-propyl]phenothiazine (13d).



This reaction was conducted with chlorpromazine hydrochloride as a substrate. Silica gel chromatography (AcOEt/Et_3N = 60/1) gave 258 mg of the product (0.90 mmol, 90% yield) as brown oil. >99% D (D content was judged with the peak at 7.14-7.22 ppm (a deuterated site) compared to the peak at 3.90 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, DMSO-d_6): δ 1.79 (quintet, *J* = 6.9 Hz, 2H), 2.08 (s, 6H), 2.30 (t, *J* = 6.9 Hz, 2H), 3.90 (t, *J* = 6.9 Hz, 2H), 6.92-6.95 (m, 2H), 7.02-7.03 (m, 2H), 7.15 (d, *J* = 7.6 Hz, 2H), 7.18-7.22 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 25.0 (CH_2), 45.1 (CH_2), 45.4 (CH_3), 56.9 (CH_2), 115.3 (CH), 115.4 (CH), 122.1 (CH), 122.2 (CH), 124.9 (C), 126.8 (t, $J_{C\text{-}D}$ = 24.0 Hz, C), 127.1 (CH), 127.3 (CH), 145.1 (C). IR (ATR): 740, 1220, 1240, 1450 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{17}H_{19}DN_2S$: 285.1410; Found: 285.1417.

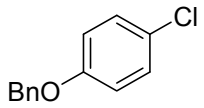
7-Deuterio-4-[4-(diethylamino)-1-methylbutylamino]quinoline (13e).



Silica gel chromatography (CH_2Cl_2/MeOH= 9/1 and CH_2Cl_2/MeOH/Et_3N= 10/1/0.1) gave 281 mg of the product (0.98 mmol, 98% yield) as pale yellow solids of mp 69-70 °C. >99% D (D content was judged with the peak at 7.61 ppm (a deuterated site) compared to the peak at 7.41 ppm by ^{1}H-NMR). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.01 (t, *J* = 7.0 Hz, 6H), 1.33 (d, *J* = 6.5 Hz, 3H), 1.58-1.78 (m, 4H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.53 (q, *J* = 7.0 Hz, 4H), 3.70-3.77 (m, 1H), 5.10 (d, *J* = 7.0 Hz, 1H), 6.44 (d, *J* = 5.5 Hz, 1H), 7.41 (dd, *J* = 1.0, 8.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.97 (s, 1H), 8.54 (d, *J* = 5.5 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 11.0 (CH_3), 19.6 (CH_3), 23.3 (CH_2), 33.9 (CH_2), 46.2 (CH_2), 47.7 (CH), 52.1 (CH_2), 98.4 (CH), 118.6 (C), 119.7 (CH), 123.7 (CH), 128.1 (t, $J_{C\text{-}D}$ = 22.4 Hz, C), 129.1 (CH), 148.3 (C), 148.9 (C), 150.5 (CH). IR (ATR): 1150, 1330, 1540, 1570, 3250 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{18}H_{26}DN_3$: 286.2268; Found: 286.2265.

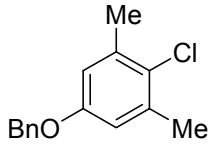
2.6. Synthesis of aryl/heteroaryl chlorides

1-Benzyloxy-4-chlorobenzene (8b).



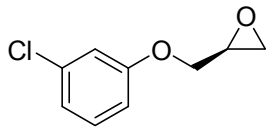
This aryl chloride was prepared based on the previous report.[12] To a mixture of K_2CO_3 (885 mg, 6.4 mmol) and 4-chlorophenol (1.23 g, 9.6 mmol) in dry acetone (6.0 mL) was added benzyl bromide (547 mg, 3.2 mmol) followed by heating to 50 °C overnight. The reaction mixture was then poured into 2 M NaOH solution and extracted with AcOEt. The organic extracts were dried over $MgSO_4$. Concentration and purification through silica gel chromatography (hexane/AcOEt = 10/1) gave 698 mg of the product (3.2 mmol, 99% yield) as white solids of mp 66-67 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.04 (s, 2H), 6.89-6.91 (m, 2H), 7.22-7.26 (m, 2H), 7.32-7.35 (m. 1H), 7.37-7.42 (m. 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 70.2 (CH_2), 116.2 (CH), 125.8 (C), 127.5 (CH), 128.1 (CH), 128.7 (CH), 129.4 (CH), 136.6 (C), 157.4 (C). IR (ATR): 830, 1040, 1240, 1490, 1580 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{13}H_{11}{}^{35}ClO$: 218.0498; Found: 218.0489.

1-Benzyloxy-4-chloro-3,5-dimethylbenzene (8d).



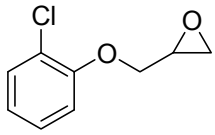
This aryl chloride was prepared from benzyl bromide (6.4 mmol) with the same procedure as **2b**. Silica gel chromatography (hexane/AcOEt = 10/1) gave 1.58 g of the product (6.4 mmol, 99% yield) as white solids of mp 52-53 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.34 (s, 6H), 5.01 (s, 2H), 6.72 (s, 2H), 7.31-7.34 (m, 1H), 7.37-7.42 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.8 (CH_3), 69.9 (CH_2), 114.8 (CH), 126.5 (C), 127.4 (CH), 127.9 (CH), 128.6 (CH), 136.9 (C), 137.1 (C), 156.7 (C). IR (ATR): 700, 750, 850, 1030, 1160, 1590 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{15}H_{15}{}^{35}ClO$: 246.0811; Found: 246.0808.

(*S*)-(+)-2-[(3-Chlorophenoxy)methyl]oxirane (8f).



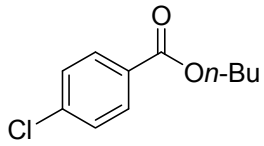
This aryl chloride was prepared based on the previous report.[13] A solution of 3-chlorophenol (1.13 g, 8.8 mmol) in dry DMF (7.4 mL) was added to a suspension of NaH (60% in mineral oil, 420 mg, 10.5 mmol) in dry DMF (29 mL) slowly at room temperature. Within a period of 10 minutes, the turbid mixture became a clear solution. After this clear solution was stirred for 30 min, a solution of (2*S*)-(+)-glycidyl tosylate (1.83 g, 8.0 mmol) in dry DMF (5.4 mL) was added slowly. The resulting mixture was stirred for 15 h at room temperature and quenched with saturated NH_4Cl. The two-phase mixture was diluted with water and extracted with *i*-Pr_2O. The combined organic extracts were washed with saturated $NaHCO_3$ and brine, and then dried over Na_2SO_4. Concentration and purification through silica gel column chromatography (hexane/benzene = 1/1) gave 1.00 g (5.4 mmol, 68% yield) of the product as colorless oil. $[\alpha]^{22}_{D}$ +11.8 (*c* 9.41, EtOH). 91% *ee* (HPLC: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 200/1, 1.0 mL/min, 254 nm, (*S*)-isomer 17.3 min and (*R*)-isomer 15.3 min). ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.76 (dd, *J* = 3.0, 4.8 Hz, 1H), 2.92 (dd, *J* = 4.2, 4.8 Hz, 1H), 3.33-3.36 (m, 1H), 3.93 (dd, *J* = 5.8, 11.0 Hz, 1H), 4.23 (dd, *J* = 3.0, 11.0 Hz, 1H), 6.82 (ddd, *J* = 0.8, 2.0, 8.3 Hz, 1H), 6.93 (t, *J* = 2.0 Hz, 1H), 6.96 (ddd, *J* = 0.8, 2.0, 8.0 Hz, 1H), 7.20 (dd, *J* = 8.0, 8.3 Hz, 1H). ^{13}C- NMR (100 MHz, $CDCl_3$): δ 44.4 (CH_2), 49.8 (CH), 68.9 (CH_2), 113.1 (CH), 115.0 (CH), 121.4 (CH), 130.3 (CH), 134.8 (C), 159.2 (C). IR (ATR): 770, 1070 1280, 1590 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_9H_9{}^{35}ClO_2$: 184.0291; Found: 184.0289.

2-[(2-Chlorophenoxy)methyl]oxirane (8e).



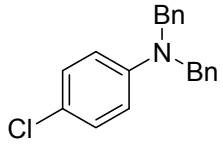
This aryl chloride was prepared based on the previous report.[14] To a solution of 2-chlorophenol (1.0３ g, 8 mmol) in dry acetone (21 mL) were added K_2CO_3 (3.31 g, 23.9 mmol) and epi-chlorohydrin (2.96 g, 31.9 mmol). The reaction mixture was refluxed for 24 h. Additional epi-chlorohydrin (2.96 g, 31.9 mmol) was added and the solution was refluxed for 24 h. The mixture was cooled to room temperature, and the solids were filtered off. The solvent was removed under reduced pressure and the resulting oil was taken up in toluene (20 mL). The organic layer was washed with H_2O, 1 M NaOH solution, and H_2O. The organic layer was dried over Na_2SO_4. Silica gel chromatography (hexane/AcOEt = 10/1) gave 1.40 g of the product (7.6 mmol, 95% yield) as colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.83 (dd, *J* = 3.1, 5.0 Hz, 1H), 2.92 (t, *J* = 5.0 Hz, 1H), 3.39-3.42 (m, 1H), 4.07 (dd, *J* = 5.3, 11.3 Hz, 1H), 4.30 (dd, *J* = 3.1, 11.3 Hz, 1H), 6.93 (dt, *J* = 1.5, 8.0 Hz, 1H), 6.97 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.19-7.23 (m, 1H), 7.37 (dd, *J* = 1.5, 8.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 44.4 (CH_2), 49.9 (CH), 69.5 (CH_2), 114.0 (CH), 122.0 (CH), 123.1 (C), 127.7 (CH), 130.3 (CH), 154.0 (C). IR (ATR): 740, 1060, 1280, 1590 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_9H_9{}^{35}ClO_2$: 184.0291; Found: 184.0294.

l**Butyl 4-chlorobenzoate (8h).**



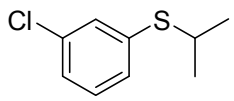
This aryl chloride was prepared based on the previous report.[15] To a solution of 4-chlorobenzoyl chloride (1.31 g, 7.5 mmol) in dry THF (24 mL) was added butanol (838 mg, 11.3 mmol). The reaction was refluxed for 12 h and cooled to room temperature. Water was added, and then the resulting mixture was extracted with *i*-Pr_2O. The combined organic layers were washed with water and brine, and then dried over Na_2SO_4. Concentration and purification through silica gel chromatography (hexane/ AcOEt = 50/1) gave 1.59 g of the product (7.4 mmol, 99% yield) as colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.98 (t, *J* = 7.4 Hz, 3H), 1.44-1.51 (m, 2H), 1.72-1.78 (m, 2H), 4.32 (t, *J* = 6.7 Hz, 2H), 7.40-7.42 (m, 2H), 7.96-7.99 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.6 (CH_3), 19.1 (CH_2), 30.6 (CH_2), 64.9 (CH_2), 128.6 (CH), 128.9 (C), 130.9 (CH), 139.2 (C), 165.8 (C). IR (ATR): 760, 1090, 1170, 1720 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{11}H_{13}{}^{35}ClO_2$: 212.0604; Found: 212.0602.

4-Chloro-*N*,*N*-dibenzylbenzeneamine (8j).



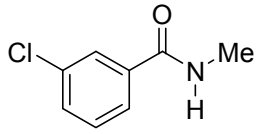
This aryl chloride was prepared based on the previous report.[16] To a mixture of 4-chloroaniline (1.28 g, 10 mmol) and K_2CO_3 (2.76 g, 20 mmol) in dry CH_3CN (10 mL) was added benzyl bromide (4.10 g, 24 mmol). The reaction mixture was stirred at 120 ºC for 5 h and cooled to room temperature. Water was added, and then the resulting mixture was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4. Concentration and purification through silica gel chromatography (hexane/ *i*-Pr_2O = 50/1) gave 2.80 g of the product (9.1 mmol, 91% yield) as white solid of mp 98-99 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.63 (s, 4H), 6.62-6.65 (m, 2H), 7.07-7.10 (m, 2H), 7.22 (d, *J* = 7.1 Hz, 4H), 7.24-7.27 (m, 2H), 7.31-7.34 (m, 4H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 54.4 (CH_2), 113.7 (CH), 121.5 (C), 126.6 (CH), 127.1 (CH), 128.7 (CH), 129.0 (CH), 138.1 (C), 147.7 (C). IR (ATR): 800, 1090, 1170, 1350 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{20}H_{18}{}^{35}ClN$: 307.1128; Found: 307.1118.

Isopropyl 3-chlorophenyl sulfide (8k).



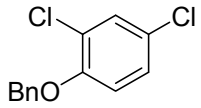
This aryl chloride was prepared based on the previous report.[17] To a solution of NaOEt (20% in ethanol, 11 mmol) was added 3-chlorobenzenethiol (1.45 g, 10 mmol). The reaction mixture was stirred at room temperature for 30 min and treated with 2-iodopropane (2.04 g, 12 mmol). The reaction mixture was stirred for 16 h at room temperature and water was added, and then the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were washed with 2 M NaOH solution and brine, and then dried over Na_2SO_4. Concentration and purification through silica gel chromatography (hexane/*i*-Pr_2O = 100/1) gave 1.80 g of the product (9.6 mmol, 96% yield) as colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.31 (d, *J* = 6.7 Hz, 6H), 3.40 (septet, *J* = 6.7 Hz, 1H), 7.17-7.26 (m, 3H), 7.36 (t, *J* = 1.6 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 22.9 (CH_3), 37.9 (CH), 126.5 (CH), 129.2 (CH), 129.8 (CH), 130.7 (CH), 134.4 (C), 138.0 (C). IR (ATR): 680, 1080, 1580 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_9H_{11}{}^{35}ClS$: 186.0270; Found: 186.0273.

3-Chloro-*N*-methylbenzamide (8m).



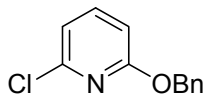
This aryl chloride was prepared based on the previous report.[18] To a solution of 3-chlorobenzoyl chloride (1.75 g, 10 mmol) in dry Et_2O (20 mL) was added $MeNH_2$ (40% in methanol, 15 mmol) and Et_3N (2.02 g, 20 mmol). The reaction mixture was stirred for 1 h at room temperature. The resulting mixture was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4. Concentration and purification through silica gel chromatography (hexane/AcOEt = 1/1) gave 1.69 g of the product (9.9 mmol, 99% yield) as white solids of mp 68-69 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.02 (d, *J* = 4.9 Hz, 3H), 6.11 (brs, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.47 (ddd, *J* = 1.2, 2.0, 7.8 Hz, 1H), 7.61-7.63 (m, 1H), 7.75 (t, *J* = 2.0, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 26.7 (CH_3), 125.0 (CH), 127.3 (CH), 129.6 (CH), 131.2 (CH), 134.4 (C), 136.2 (C), 167.3 (C). IR (ATR): 680, 1080, 1170, 1550, 1640, 3310 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_8H_8{}^{35}ClNO$: 169.0294; Found: 169.0298.

1-Benzyloxy-2,4-dichlorobenzene (8n).



This aryl chloride was prepared based on the previous report.[19] To a solution of 2,4-dichlorophenol (1.63 g, 10 mmol) and Cs_2CO_3 (6.52 g, 20 mmol) in dry DMF (27 mL) was added benzyl bromide (1.71 g, 10 mmol). The reaction mixture was stirred for 30 min at room temperature and water was added, and then the resulting mixture was extracted with Et_2O. The combined organic layers were washed with water and brine, and dried over $MgSO_4$. Concentration and purification through silica gel chromatography (hexane/*i*-Pr_2O = 100/1) gave 2.51 g of the product (9.9 mmol, 99% yield) as colorless solids of mp 33-34 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.14 (s, 2H), 6.88 (d, *J* = 8.8 Hz, 1H), 7.14 (dd, *J* = 2.6, 8.8 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.38-7.41 (m, 3H), 7.43-7.45 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 71.0 (CH_2), 114.8 (CH), 124.1 (C), 126.0 (C), 127.1 (CH), 127.5 (CH), 128.1 (CH), 128.7 (CH), 130.0 (CH), 136.1 (C), 153.0 (C). IR (ATR): 730, 1000, 1060, 1270 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{13}H_{10}{}^{35}Cl_2O$: 252.0109; Found: 252.0107.

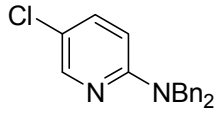
2-Benzyloxy-6-chloropyridine (10c).



This heteroaryl chloride was prepared based on the previous report.[20] A mixture of 6-chloro-2-hydroxypyridine (4.66 g, 36 mmol) and NaH (60% in mineral oil, 1.44 g, 36 mmol) in DMF (144 mL) was stirred for 30 min followed by adding benzyl chloride (4.56 g, 36 mmol) and further stirring for 3 h at room temperature. Water was added, and then the resulting mixture

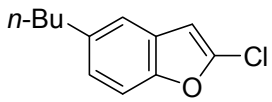
was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. Concentration and purification through silica gel chromatography (hexane/AcOEt = 4/1) gave 2.53 g of the product (11.6 mmol, 32% yield) as colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.36 (s, 2H), 6.70-6.72 (m, 1H), 6.91-6.93 (m, 1H), 7.32-7.35 (m, 1H), 7.37-7.40 (m, 2H), 7.46-7.47 (m, 2H), 7.51-7.54 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 68.2 (CH_2), 109.3 (CH), 116.4 (CH), 128.0 (CH), 128.2 (CH), 128.5 (CH), 136.6 (C), 140.7 (CH), 148.2 (C), 163.2 (C). IR (ATR): 790, 1160, 1260, 1590 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{12}H_{10}{}^{35}ClNO$: 219.0451; Found: 219.0451.

2-(Dibenzylamino)-5-chloropyridine (10d).



This heteroaryl chloride was prepared based on the previous report.[21] NaH (60% in mineral oil, 2.72 g, 68 mmol) was suspended in dry DMF (60 mL) and cooled in an ice bath. 2-Amino-5-chloropyridine (3.86 g, 30 mmol) was added, and the mixture was stirred for 15 min. Then, benzyl bromide (1.16 g, 68 mmol) was added, and the reaction mixture was allowed to warm slowly to room temperature with the control of exotherm and gas evolution. Stirring at room temperature was continued for 1 h. DMF was evaporated and the residue was extracted with AcOEt. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration and purification through silica gel chromatography (hexane/AcOEt = 20/1) gave 4.36 g of the product (14 mmol, 47% yield) as colorless solids of mp 83-84 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.77 (s, 4H), 6.38 (d, *J* = 9.1 Hz, 1H), 7.20-7.22 (m, 4H), 7.24-7.26 (m, 2H), 7.29-7.32 (m, 5H), 8.12-8.13 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 51.2 (CH_2), 106.7 (CH), 119.2 (C), 127.0 (CH), 127.1 (CH), 128.7 (CH), 137.1 (CH), 138.0 (C), 146.3 (CH), 157.0 (C). IR (ATR): 690, 730, 1140, 1360, 1490 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{19}H_{17}{}^{35}ClN_2$: 308.1080; Found: 308.1069.

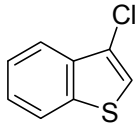
5-Butyl-2-chlorobenzofuran (10h).



This heteroaryl chloride was prepared based on the previous report.[3] To a solution of 5-butylbenzofuran[22] (888 mg, 5.1 mmol) in dry THF (27 mL) at –78 °C was added *n*-BuLi (1.6 M in hexane, 6.2 mmol) dropwise. After 30 min, hexachloroethane (5.1 mmol) was added. The resulting mixture was warmed to room temperature over 1 h, and then quenched by slow addition of saturated NH_4Cl. The crude product was extracted with AcOEt, washed with water, and then

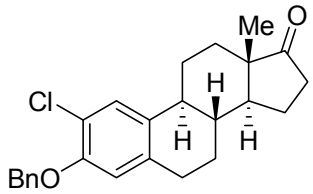
dried over $MgSO_4$. Concentration and purification through silica gel chromatography (hexane/*i*-Pr_2O = 400/1) gave 1.04 g of the product (5.0 mmol, 98% yield) as colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.3 Hz, 3H), 1.32-1.39 (m, 2H), 1.59-1.65 (m, 2H), 2.67 (t, *J* = 7.9 Hz, 2H), 6.51 (s, 1H), 7.07-7.09 (m, 1H), 7.27 (s, 1H), 7.32 (d, *J* = 8.5 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.8 (CH_3), 22.2 (CH_2), 34.1 (CH_2), 35.5 (CH_2), 103.0 (CH), 110.4 (CH), 119.5 (CH), 124.9 (CH), 128.4 (C), 138.2 (C), 141.3 (C), 152.7 (C). IR (ATR): 790, 930, 1190, 1460 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{12}H_{13}{}^{35}ClO$: 208.0655; Found: 208.0655.

3-Chlorobenzothiophene (10k).



This heteroaryl chloride was prepared based on the previous report.[23] A mixture of 3-chloro-benzo[*b*]thiophene-2-carboxylic acid (1.70 g, 8.0 mmol), copper (254 mg, 4.0 mmol), and quinoline (19.6 g, 152 mmol) was stirred for 3 h at 150 °C and cooled to room temperature. Hexane was added and then the copper was removed by filtration. The filtrate was washed with 6 M HCl solution, 1 M HCl solution, and brine, and then dried over $MgSO_4$. Concentration and purification through silica gel chromatography (hexane/*i*-Pr_2O = 400/1) gave 1.16 g of the product (6.88 mmol, 86% yield) as colorless oil. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.31 (s, 1H), 7.40-7.44 (m, 1H), 7.45-7.49 (m, 1H), 7.83-7.87 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): 120.7 (CH), 121.1 (C), 121.8 (CH), 122.8 (CH), 124.8 (CH), 125.3 (CH), 136.1 (C), 138.4 (C). IR (ATR): 720, 750, 1060, 1420 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_8H_5{}^{35}ClS$: 167.9800; Found: 167.9803.

(8*R*,9*S*,13*S*,14*S*)-3-Benzyloxy-2-chloro-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren (12a).



This aryl chloride was prepared based on the previous report.[24] To a mixture of 2-chloroestrone[25] (183 mg, 0.6 mmol) and K_2CO_3 (331 mg, 2.4 mmol) in dry acetone (3.0 mL) was added benzyl bromide (188 mg, 1.1 mmol). The reaction mixture was refluxed for 2 h and cooled to room temperature. The resulting mixture was filtered with CH_2Cl_2 and the filtrate was collected. Concentration and purification through silica gel chromatography (hexane/AcoEt =

8/1) gave 216 mg of the product (0.55 mmol, 91% yield) as white solids of mp 194-195 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.91 (s, 3H), 1.37-1.66 (m, 6H), 1.93-2.07 (m, 3H), 2.11-2.18 (m, 1H), 2.20-2.25 (m, 1H), 2.33-2.37 (m, 1H), 2.50 (dd, *J* = 8.1, 19.3 Hz, 1H), 2.83-2.85 (m, 1H), 5.12 (s, 2H), 6.70 (s, 1H), 7.29 (s, 1H), 7.30-7.34 (m, 1H), 7.37-7.40 (m, 2H), 7.46-7.48 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 13.7 (CH_3), 21.4 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 29.1 (CH_2), 31.3 (CH_2), 35.7 (CH_2), 37.9 (CH), 43.6 (CH), 47.8 (C), 50.2 (CH), 70.7 (CH_2), 114.4 (CH), 120.4 (C), 127.0 (CH), 127.2 (CH), 127.9 (CH), 128.5 (CH), 133.5 (C), 136.1 (C),136.8 (C), 152.0 (C), 220.7 (C). IR (ATR): 740, 1060, 1250, 1730 cm^{-1}. HRMS (EI) *m/z*: (M^+) Calcd for $C_{25}H_{27}{}^{35}ClO_2$: 394.1700; Found: 394.1686.

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