Studies on Chemo- and Site-Selective C−H Amination of Aniline and Phenol Derivatives with Dirhodium Catalysts and Catalytic Asymmetric Synthesis of Inherently Chiral Calixarenes

ロジウム二核錯体によるアニリン及びフェノール誘導体の位置及び化学選択的 C-H アミノ化並びに分子不斉カリックスアレーンの触媒的不斉合成に関する研究

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Abbreviation

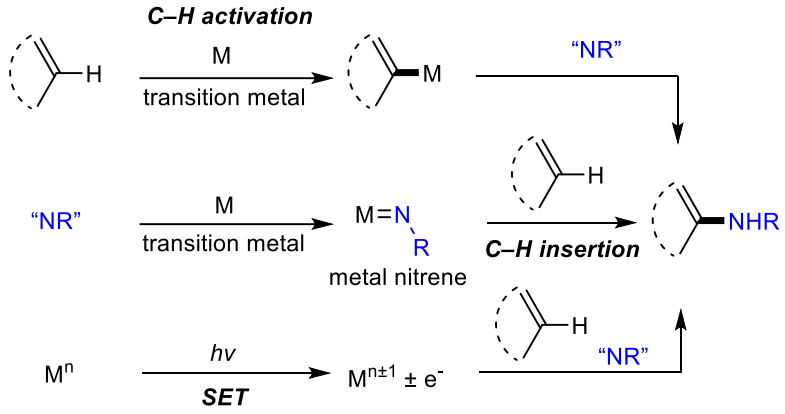
Ac	acetyl
aq.	aqueous
Bn	benzyl
^{t}Bu	*tert*-butyl
cat.	catalyst
CDI	carbonyldiimidazole
de	diastereoselective excess
DFT	density functional theory
ee	enantioselective excess
equiv.	equivalent
ESI	electron spray ionization
G	Gibbs free energy
H	enthapy
h	hour
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
^{i}Pr	isopropyl
^{n}Pr	normalpropyl
IR	infrared
K	equilibrium constant
KIE	kinetic isotope effect
Me	methyl
min	minute
m.p.	melting point
NMR	nuclear magnetic resonance
o	*ortho*-
p	*para*-
Ph	phenyl
r.t.	room temperature
S	entropy
T	temperature
TS	transition state
TIPDS	1,1,3,3-tetraisopropyldisiloxane-1,3-diyl
Troc	2,2,2-trichloroehtoxycarbonyl
THF	tetrahydrofuran
Ts	*p*-toluenesulfonyl

Theoretical Section

Chapter 1 Introduction

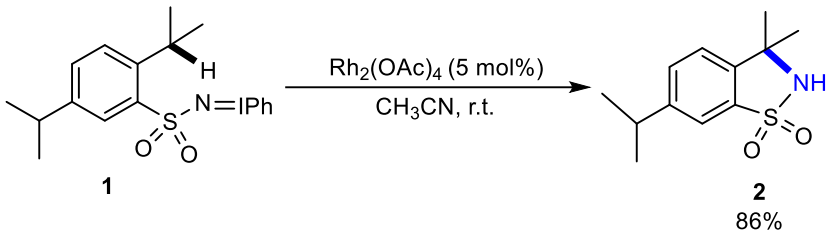
Development of new methods to construct C−N bonds is of great significance in current synthetic organic chemistry because C−N bonds are ubiquitously involved in functional materials and bioactive molecules.[1] From this context, the methods for C−N bond construction such as nucleophilic N-substitution, reductive amination and Buchwald-Hartwig coupling reaction were intensively studied and successfully applied to fine chemical synthesis.[2] Although the above methods are now reliable, preparation of functionality prior to the amination is necessary. In recent years, transition metal-catalyzed C−H amination provides a straightforward access to various amines without any pre-functionalization, offering a great opportunity to the quick access to diverse nitrogen-containing molecules with high efficiency.[3]

In general, transition metal-catalyzed C−H amination reactions can be classified into three categories, C−H activation catalysis, C−H insertion catalysis, and single-electron-transfer (SET) catalysis (Scheme 1.1).[3f] In the mechanism of C−H insertion catalysis, a metal nitrene species is proposed to be generated and interact with a substrate in either a concerted or a stepwise manner to result in C−N bond formation. To date, much efforts have been devoted to develop C−H amination reaction via C−H insertion process, by virtue of various transition metals such as Cu, Ru, Rh, Ag, Ir, and Co.[3b,3f]



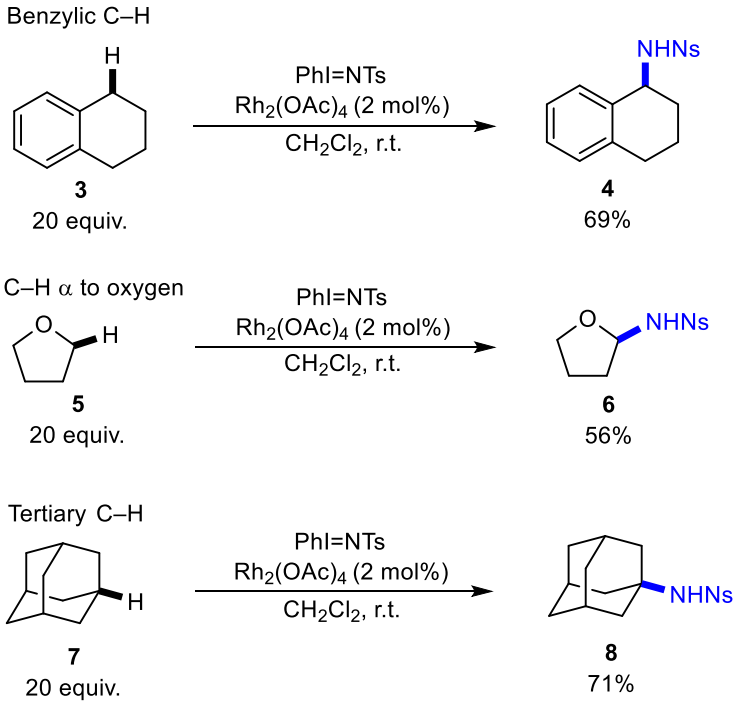
Scheme 1.1 Reaction categories for metal-catalyzed C−H amination.

Dirhodium tetracarboxylates displayed a notable reactivity in the amination of unactivated C(sp^3)−H bonds via formation of dirhodium nitrene complexes and their C−H insertion process.[4] The first example of dirhodium-mediated intramolecular C(sp^3)–H amination was reported by Breslow and Gellman in the early 80s (Scheme 1.2).[4a] After the report, development of efficient reagents and excellent catalysts expanded the utility of dirhodium-catalyzed intramolecular C−H amination and the improved methods have been successfully applied to total synthesis of complex natural products.[5]

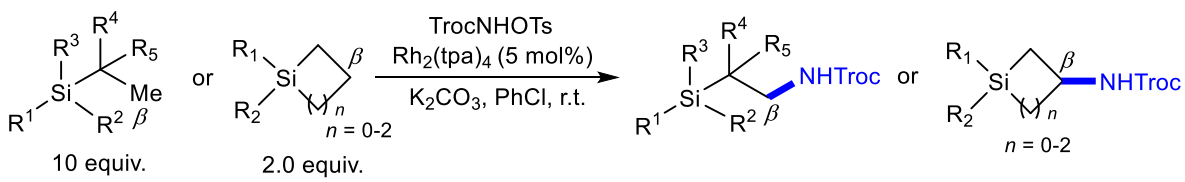


Scheme 1.2 The first example of dirhodium-catalyzed C−H amination.

While the cleavage of C−H bonds is position-limited in intramolecular reactions, control of chemo- and site-selectivity becomes an issue in intermolecular reactions.[6] In 1997, Müller's group reported the first example of intermolecular chemo-selective C(sp^3)–H amination using dirhodium catalysts to reveal that electron rich C(sp^3)–H bonds such as benzylic, allylic, and tertiary C(sp^3)–H bonds and C(sp^3)–H bonds α to oxygen atoms can be selectively converted to C–N bonds (Scheme 1.3).[7] Recently, Ueda, Kawabata and coworkers reported dirhodium-catalyzed site-selective C(sp^3)–H amination of organosilicon compounds directed by *β* effect of the silicon atom (Scheme 1.4).[8]

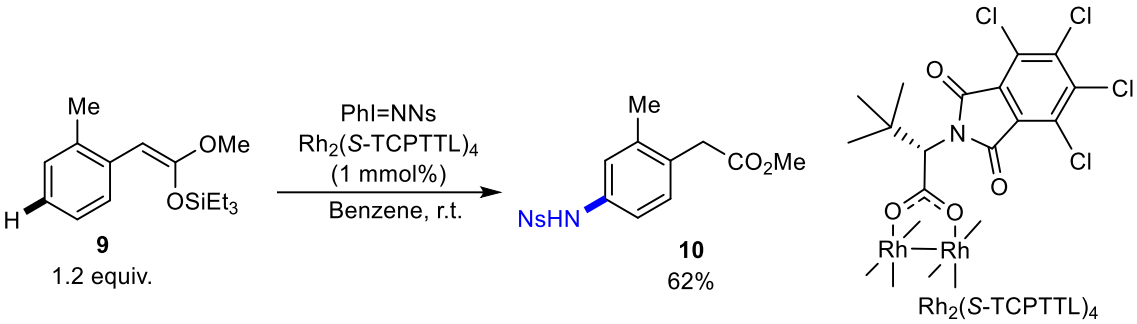


Scheme 1.3 Intermolecular chemoselective C(sp^3)–H amination by dirhodium nitrenes.

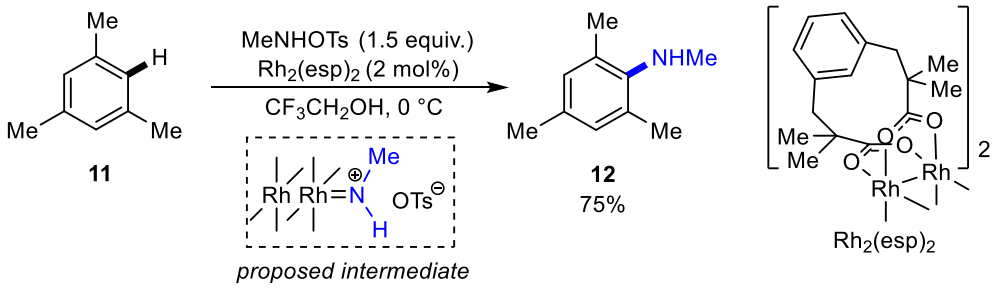


Scheme 1.4 *β*-silicon-effect promoted dirhodium-catalyzed site-selective C(sp^3)–H amination.

Compared to C(sp^3)−H amination, intermolecular C(sp^2)−H amination by dirhodium catalysts was less studied.[9] In 2007, Hashimoto *et al* unexpectedly found that the intermolecular C(sp^2)–H amination took place at *para* position of the silyl ketene acetal moiety of compound **9**, during the study of amination reaction of silyl ketene acetals to provide α-chiral amino acid derivatives (Scheme 1.5).[10] Ten years later, Falck *et al* reported a general method for dirhodium-catalyzed intermolecular C(sp^2)−H amination of various arenes (Scheme 1.6).[11] In this research, it was claimed that nitrenium ion species generated in the acidic medium are the key to the electrophilic aromatic amination.

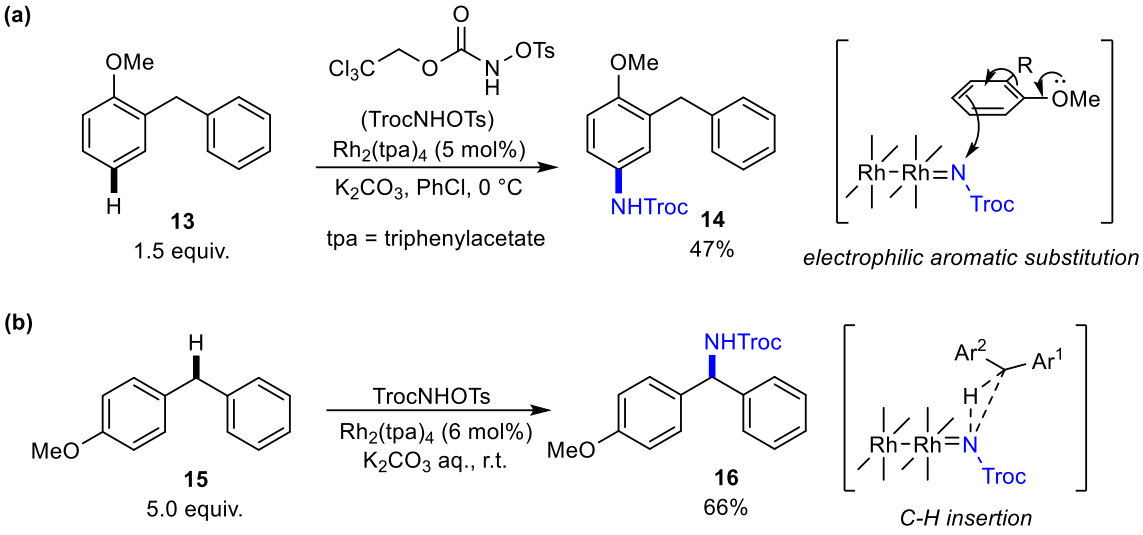


Scheme 1.5 The first example of dirhodium catalyzed intermolecular C(sp^2)−H amination.



Scheme 1.6 Dirhodium-catalyzed C(sp^2)−H amination via dirhodium nitrenium ions.

In 2018, Ueda and Kawabata *et al* reported dirhodium-catalyzed intermolecular chemo- and site-selective C(sp^2)−H amination of alkoxyarenes (Scheme 1.7a).[12] Under the condition, a neutral dirhodium nitrene complex is assumed to be generated to promote C(sp^2)−H amination via electrophilic aromatic substitution. The aromatic C(sp^2)−H amination took place at the *para* position of the oxygen substituent, even in the presence of otherwise reactive benzylic C(sp^3)–H bonds (Scheme 1.7b).[13]



Scheme 1.7 (a) Intermolecular chemo- and site-selective C(sp^2)–H amination via electrophilic aromatic substitution of dirhodium nitrene complex. (b) Intermolecular benzylic C(sp^3)–H amination.

Based on the background, I started investigation for development of other chemo- and site-selective C−H aminations by use of dirhodium catalysts. And also, I tried to apply the method described in Scheme 1.7a to unprecedented enantioselective reactions. The contents of my thesis were outlined below.

In chapter 2, the method for chemo- and site-selective C−H amination of *N*,*N*-dialkylanilines catalyzed by rhodium catalyst was developed. The C−H amination of *N*,*N*-dimethylaniline catalyzed by $Rh_2(oct)_4$ proceeded selectively at C(sp^3)–H bonds α to the nitrogen atom, in the presence of aromatic C(sp^2)–H bonds. C(sp^3)–H amination of the *N*-methyl group of various *N*-alkyl-*N*-methylanilines (alkyl ≠ methyl) was observed exclusively even in the presence of potentially reactive benzylic and tertiary C−H bonds α to the nitrogen atom.[14]

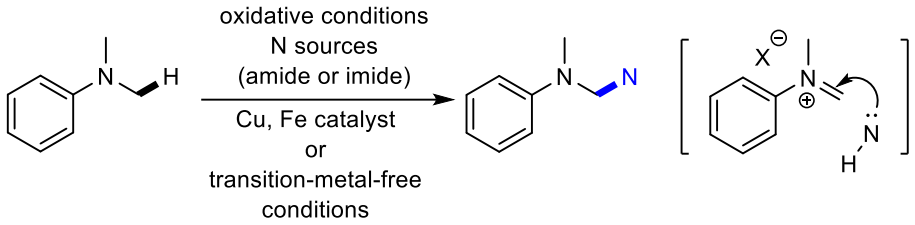
In chapter 3, chemoselectivity in C–H amination of anisole and aniline derivatives was discussed. Experimental and theoretical studies indicated that phenyl rings on the α carbon of the carboxylate ligands of dirhodium complexes strongly affected the efficiency of both C−H amination reactions. In the case of C(sp^3)−H amination of aniline derivatives, the phenyl rings stabilize the coordination state of amine to Rh center to inhibit the reaction strongly. On the other hand, the phenyl rings accelerate the C(sp^2)−H amination of anisole, which suggested that generating δ+ of aromatic ring in the transition state structure would be stabilized by the phenyl rings through cation/π or C–H/π interactions.

In chapter 4, the catalytic asymmetric synthesis of inherently chiral calixarenes (ICCs) was investigated. Use of a chiral dirhodium complex for selective C(sp^2)–H amination of a C_s-symmetric calix[4]arene derivative effectively promoted the chemo-, site- and enantioselective C(sp^2)–H amination to provide the desymmetrized ICC in up to 88% ee. To the best of my knowledge, this is the first efficient example of catalytic asymmetric synthesis of ICCs, using artificial catalysts.

Chapter 2 Development of chemo- and site-selective C−H amination of *N*,*N*-dialkylanilines

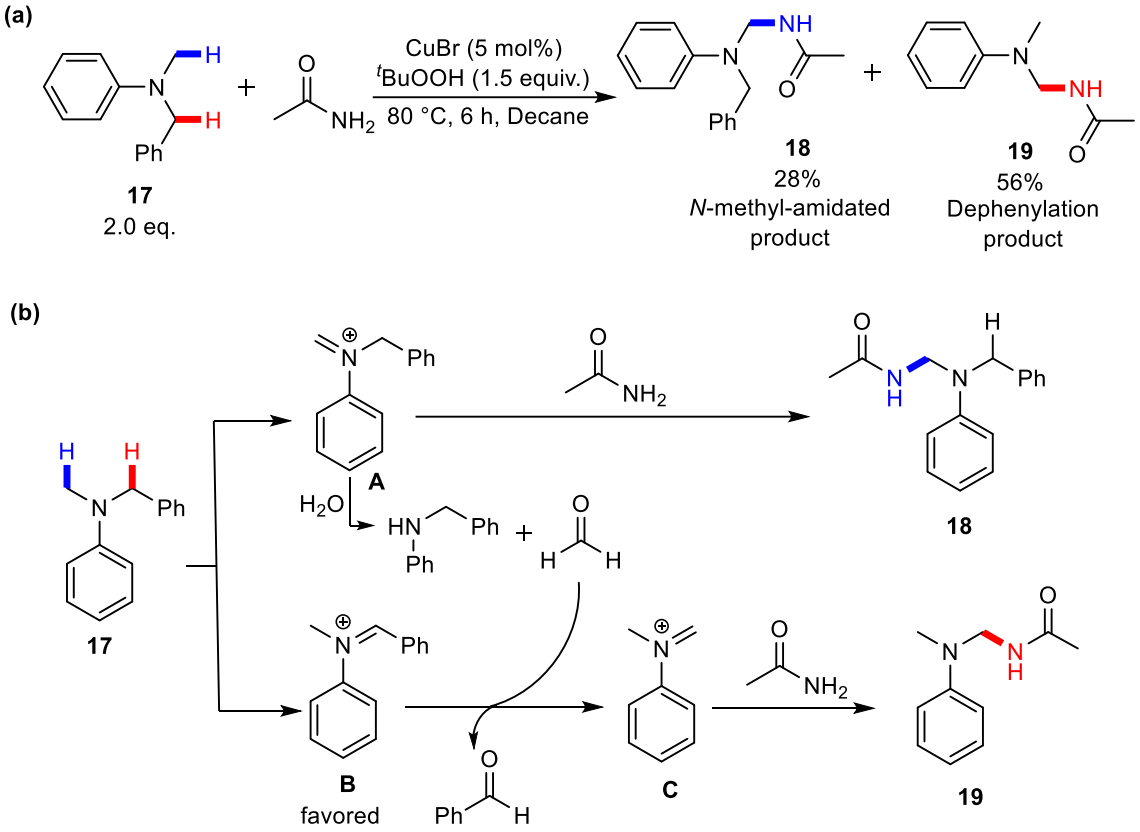
2.1 Background

Since arylamine motifs are privileged structural units for the development of functional materials and bioactive molecules,[15] C–H bond functionalization of aniline derivatives have been extensively studied.[16] In the past few decades, considerable achievements have been made in C–H amidation of *N*,*N*-dimethylaniline derivatives *via* cross dehydrogenative coupling between amides and C(sp^3)–H bonds α to a nitrogen atom (Scheme 2.1).[17-20] For example, Fu and co-workers developed Cu-catalyzed C(sp^3) – H amidation of *N*,*N*-dimethylaniline with amides and imides in the presence of *tert*-butyl hydroperoxide as an oxidant.[17a] Fe-catalyzed oxidative protocols as well as transition-metal-free C(sp^3)–H amidation have also been developed.



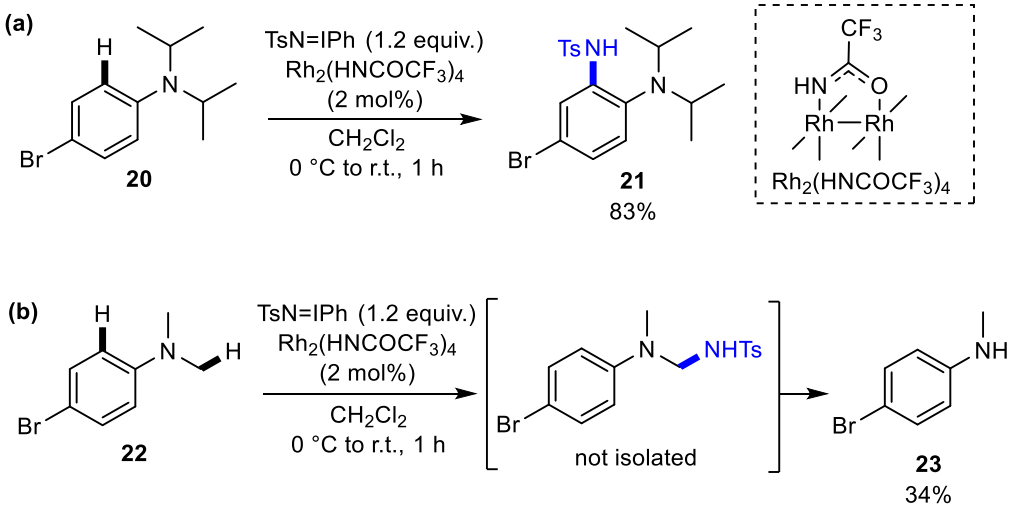
Scheme 2.1 Oxidative C(sp^3)−H amidation of *N*,*N*-dimethylanilines via iminium intermediates.

While various types of C−H amidation reaction of *N*,*N*-dimethylaniline derivatives were reported, control of the site selectivity is still an unsolved problem in C(sp^3)−H amidation of *N*,*N*-dialkylanilines with two different alkyl groups. Fu and coworkers reported that treatment of *N*-benzyl-*N*-methylaniline (**17**) with copper bromide and *tert*-butyl hydroperoxide provided the desired *N*-methyl-amidated product **18** in 28% yield along with the undesired dephenylated product **19** as a major product in 56% yield (Scheme 2.2a).[17a] The possible reaction paths were described in Scheme 2.2b. The primary C−H bond cleavage provided the iminium intermediate **A** and following nucleophilic addition of acetamide to **A** gave **18**. On the other hand, the benzylic C−H bond cleavage provided the favored iminium intermediate **B**. Hydrolysis of **B** and condensation with formaldehyde, derived from hydrolysis of **A**, generated the iminium intermediate **C** to afford undesired **19** by reaction with acetamide.



Scheme 2.2 The problem of site-selectivity in copper-catalyzed C(sp^3)–H amidation.

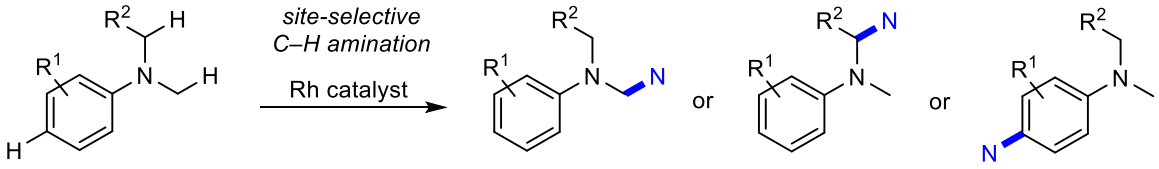
C−H insertion of metal nitrene complexes is considered as an alternative method for C−H amidation reaction to solve the problem about site selectivity, while metal nitrene-mediated C(sp^3)−H amidation α to a nitrogen atom has been relatively unexplored.[21]



Scheme 2.3 (a) Dirhodium-catalyzed *ortho* C(sp^2)−H amidation of *N*,*N*-diisopropylaniline derivative. (b) Side reaction in the reaction of *N*,*N*-dimethylaniline derivative.

Ito and Sugiyama *et al* reported dirhodium-catalyzed *ortho*-selective C(sp^2)−H amidation of *N*,*N*-diisopropylaniline derivatives **20** (Scheme 2.3a).[22] In this report, when *N*,*N*-dimethylaniline derivative **22** was used as a substrate, demethylated product **23** was obtained as a side product, which indicated that competitive C(sp^3)−H amidation took place and the unstable aminal structure was decomposed during the reaction or purification process (Scheme 2.3b). In addition, the *para* position of the amino group was substituted to inhibit the *para*-C(sp^2)−H amidation.

Based on the background, there is remained uncertainty that which C−H bond of *N*,*N*-dialkylanilines is the most reactive in dirhodium-nitrene-mediated C−H amination reaction. To check the reactivity, I started examination of the previously reported condition to C−H amination of *N*,*N*-dimethylanilines and *N*-alkyl-*N*-methylanilines (alkyl ≠ methyl) (Scheme 2.4).

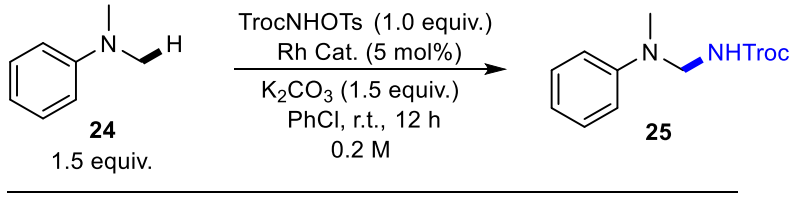


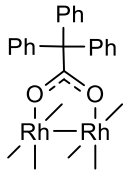
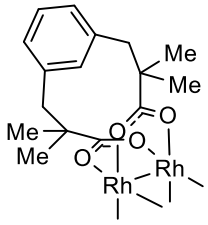
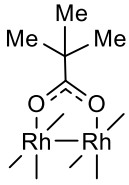
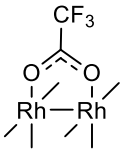
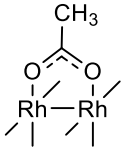
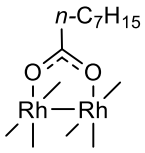
Scheme 2.4 Rhodium catalyzed chemo- and site-selective C−H amination of aniline derivatives.

2.2 Catalyst screening

The study was commenced with C−H amination of *N*,*N*-dimethylaniline (**24**) as a substrate in the presence of various dirhodium catalysts (Table 2.1). According to the previously optimized conditions for C−H amination of anisole derivatives[12] and organosilanes[8], 1.5 equiv. of **24** were treated with *N*-trichloroethoxycarbonyl-*O*-tosylhydroxylamine (TrocNHOTs) in the presence of $Rh_2(tpa)_4$ and K_2CO_3 in chlorobenzene at r.t., which gave no C−H aminated products. Instead, in the presence of $Rh_2(esp)_2$, amination of C(sp^3)−H α to the nitrogen atom selectively took place to give **25** in 39% yield as a single regioisomer. Screening of catalysts demonstrated that $Rh_2(oct)_4$ promoted the C(sp^3)−H amidation most effectively to provide **25** in 46% yield. In all cases, C(sp^2)−H aminated product was not obtained at all.

Table 2.1 Catalyst screening for C−H amination of *N*,*N*-dimethylaniline.



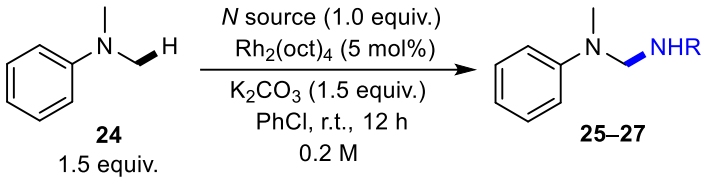
		
$Rh_2(tpa)_4$ 0% yield[a]	$Rh_2(esp)_2$ 39% yield[a]	$Rh_2(piv)_4$ 40% yield[a]
		
$Rh_2(tfa)_4$ 36% yield[a]	$Rh_2(OAc)_4$ 42% yield[a]	$Rh_2(oct)_4$ 46% yield[a]

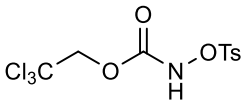
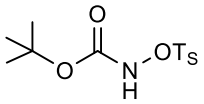
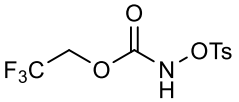
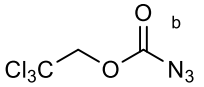
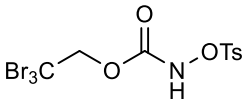
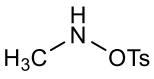
[a] Determined by crude ^{1}H NMR, using 1,3-dinitrobenzene as an internal standard.

2.3 Optimization of reaction condition

With $Rh_2(oct)_4$ as a catalyst, the effects of aminating reagents were investigated (Table 2.2). Use of the trifluoroethoxy analogue and the tribromoethoxy analogue of TrocNHOTs provided C(sp^3)–H aminated product **26** and **27** in the comparable yields. Treatment of **24** with *N*-*tert*-butoxycarbonyl-*O*-tosylhydroxylamine and $TrocN_3$ gave only trace amount of the C–H aminated product. *N*-Methyl-*O*-tosylhydroxylamine[23] did not provide any C–H aminated product.

Table 2.2 Aminating agents screening in the amination of *N*,*N*-dimethylaniline.

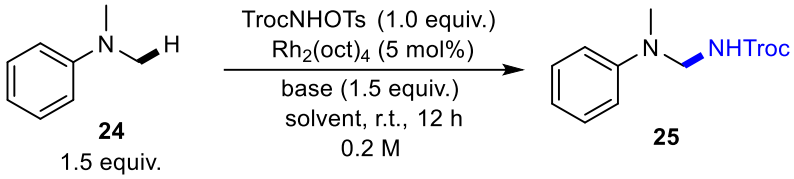


Aminating agent	Product[a]	Aminating agent	Product[a]
	**25** (R = Troc) 46% yield		Trace
	**26** ($R = CO_2CH_2CF_3$) 39% yield		Trace
	**27** ($R = CO_2CH_2CBr_3$) 43% yield		Trace

[a] Determined by crude ^{1}H NMR analysis, using 1,3-dinitrobenzene as an internal standard.
[b] Without base.

Then, the effects of solvents and bases were investigated (Table 2.3). Although the solvent did not affect the efficiency of the reaction, CH_2Cl_2 and toluene were found most suitable for the present purpose (entries 1–7). It is worth noting that the primary benzylic C(sp^3)–H bonds of toluene were totally intact for amination reaction, even when toluene was used as a solvent (entry 7). The use of Li_2CO_3, Na_2CO_3, Cs_2CO_3, Rb_2CO_3, or KOAc instead of K_2CO_3 did not improve the yield of the aminated product **25** (entry 7 vs 8–12). Finally, the yield of **25** was improved by use of 10 equiv. of the substrate **24** to afford **25** in 79% yield (entry 13).

Table 2.3 Effects of solvents and bases.



Entry	Solvent	Base	Yield (%)[a]
1	EtOAc	K_2CO_3	40
2	CH_2Cl_2	K_2CO_3	60
3	$CHCl_3$	K_2CO_3	49
4	PhH	K_2CO_3	51
5	PhF	K_2CO_3	52
6	$PhCF_3$	K_2CO_3	48
7	PhMe	K_2CO_3	60
8	PhMe	Li_2CO_3	44
9	PhMe	Na_2CO_3	30
10	PhMe	Cs_2CO_3	41
11	PhMe	Rb_2CO_3	54
12	PhMe	KOAc	40
13[b]	PhMe	K_2CO_3	79(70)[c]

[a] Determined by crude ^{1}H NMR analysis, using 1,3-dinitrobenzene as an internal standard. [b] 10 equiv. of **24** was used. [c] Isolated yield in parentheses.

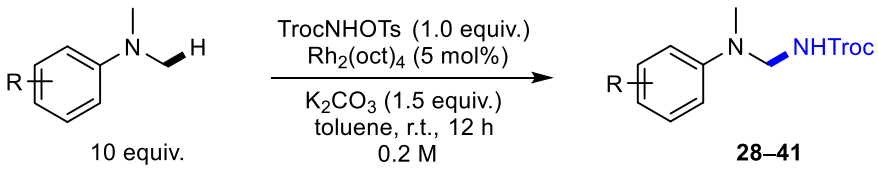
2.4 Investigation for substrate scope

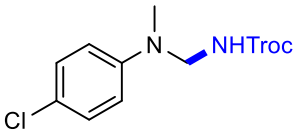
Substrate scope was then investigated with various *N*,*N*-dimethylarylamines under the optimized conditions for the C−H amination reaction (Table 2.4). Substrates with chloro, bromo, and iodo groups, respectively at C(4) successfully gave the corresponding aminated products **28**, **29**, and **30** in high yields. Treatment of 4,*N*,*N*-trimethylaniline with the present protocol gave **31** as a single product, while the primary benzylic C(sp^3)−H bonds amination was not observed. Either an electron-withdrawing or electron-donating group at C(4) did not affect the efficiency of the C(sp^3)−H amination reaction (**32**−**34**). The present procedure was found applicable to aniline derivatives with various substituents at the C(2), which can be seen in products **35**–**39**. The compound containing fluorescent dansyl group was found also to undergo selective amination of the C(sp^3)−H bond α to the nitrogen atom to give the product **41**. With all substrates examined here, highly chemoselective C(sp^3)−H amination was observed in the presence of aromatic C(sp^2)−H bonds. In all cases, TrocNHOTs was almost completely consumed and the formation of $TrocNH_2$ was observed, which indicated partial decomposition of the aminating reagent under the reaction conditions.[13, 24-26] When slight excess amounts (1.5 equiv.) of the substrates were employed, moderate yields of the desired products were observed in some cases (**28**, **30**, **32**, and **33**).

Site-selectivity of the C−H amination was investigated using several *N*-alkyl-*N*-methylanilines (alkyl ≠ methyl) (Table 2.5). Treatment of *N*-ethyl-*N*-methylaniline by the present protocol provided the *N*-methyl-aminated product **42** as a single regioisomer. Potential reactivity of the *N*-ethyl group toward the C−H amination might be missed because of the instability of the aminal structure of the product generated at the *N*-ethyl group if any. However, *N*-methylaniline, assumed to be generated from the decomposition of the aminal structure,[22] was not obtained under the condition. This result clearly showed that amination of *N*-ethyl-*N*-methylaniline took place site-selectively at the primary C(sp^3)−H bond adjacent to the nitrogen atom. Similarly, C(sp^3)−H amidation of substrates with an *n*-butyl and an *n*-octyl group provided *N*-methyl-amidated products **43** and **44**, respectively, as the single regioisomers. Notably, substrates with tertiary and benzylic C(sp^3)−H bonds α to the nitrogen atom underwent amination at the primary C(sp^3)−H bond selectively, to give **45** and **46**, respectively. The present method was also applicable to *N*-methyl-selective C−H amination of indoline derivative with an electronically reactive tertiary C(sp^3)−H bond adjacent to a nitrogen atom (**47**).

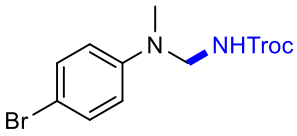
Although amination of some trialkylamines such as *N*,*N*-dimethylbenzylamine (**48**) under the optimized condition was examined, the desired C(sp^3)−H amination did not proceed to give only recovered starting materials (Scheme 2.5). The present protocol could not be applied for C(sp^3)−H amination of aliphatic trialkylamines.

Table 2.4 Chemoselective C(sp^3)–H amination of *N*,*N*-dimethylarylamine.

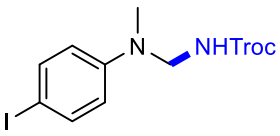




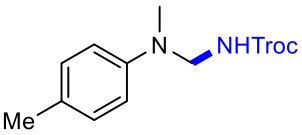
28, 75%[a] (47%)[b]



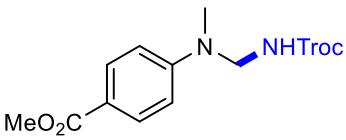
29, 71%[a]



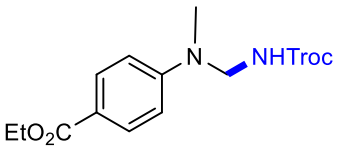
30, 69%[a] (46%)[b]



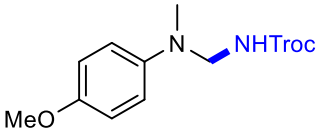
31, 41%[a]



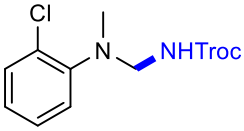
32, 73%[a] (45%)[b]



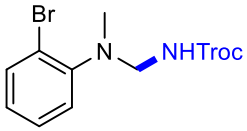
33, 63%[a] (49%)[b]



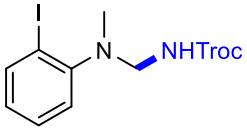
34, 53%[a]



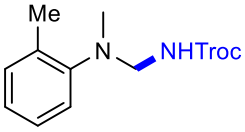
35, 44%[a]



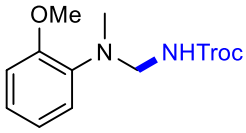
36, 59%[a]



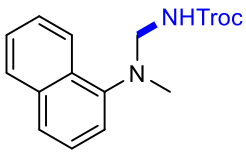
37, 52%[a]



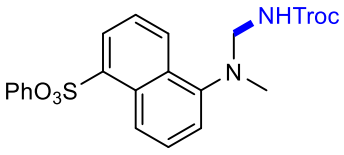
38, 43%[a]



39, 54%[a]



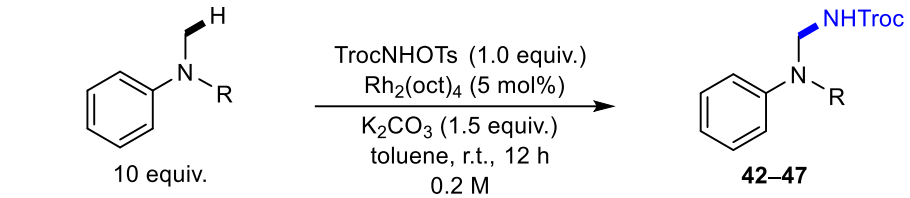
40, 48%[a]

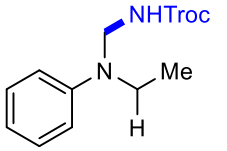


41, 59%[a]

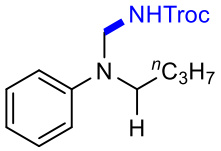
[a] Isolated yields. [b] The number in parentheses is yield with 1.5 equiv. of substrate used, it was determined by crude ^{1}H NMR analysis, using 1,3-dinitrobenzene as an internal standard.

Table 2.5 Site selectivity profiles of C(sp^3)–H amination of *N*-alkyl-*N*-methylaniline derivatives.

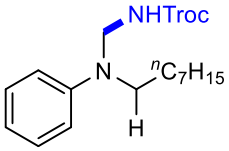




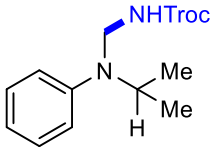
42, 33%[a]



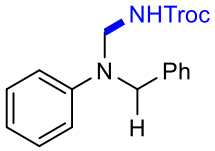
43, 43%[a]



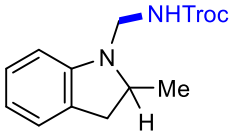
44, 40%[a]



45, 42%[a]

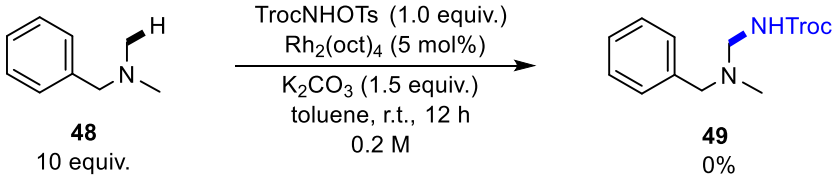


46, 37%[a]



47, 33%[a]

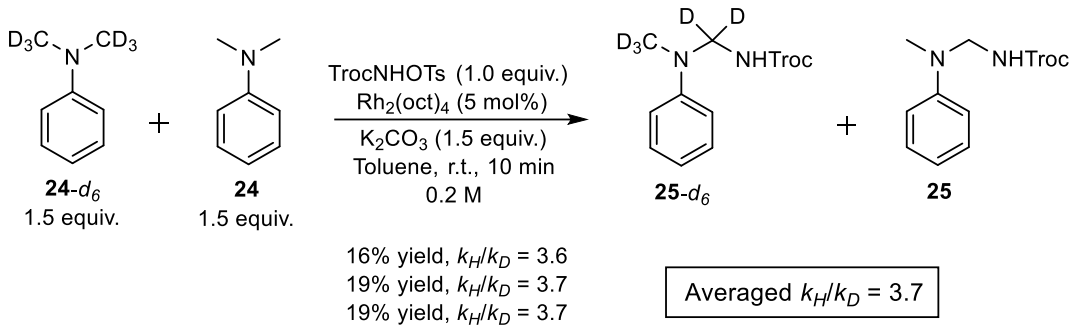
[a] Isolated yields.



Scheme 2.5 C(sp^3)–H amination of *N*,*N*-dimethylbenzylamine.

2.5 Mechanistic investigation

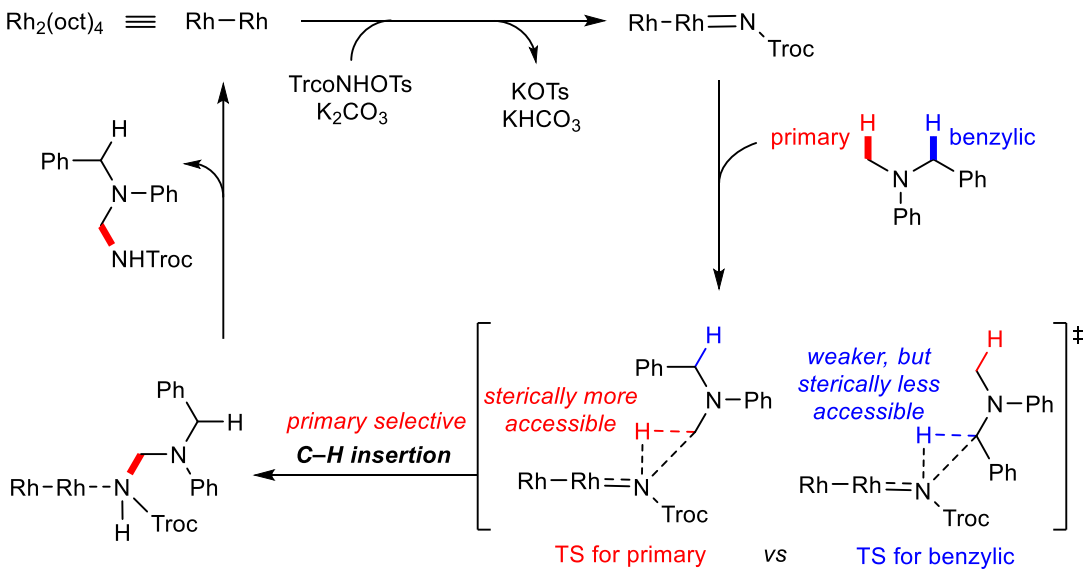
To get insights into the reaction mechanism, the KIE of the reaction was measured (Scheme 2.6). Under the competitive reaction of a 1:1 mixture of **24** and **24**-d_6, the C−H amination of **24** took place faster than that of **24**-d_6. The KIE value was estimated by the three times experiment of the competitive reaction to be k_H/k_D = 3.7. This result indicated that the C−H bond cleavage is involved in the product-determining step.



Scheme 2.6 Determination of KIE by competitive reaction between **24** and **24**-d_6.

A possible reaction pathway for the C(sp^3)−H amination is described in Scheme 2.7. The dirhodium nitrene complex is assumed to be generated from $Rh_2(oct)_4$, TrocNHOTs, and K_2CO_3 according to the previous reports for dirhodium-catalyzed C(sp^3)−H amination.[13, 25-26] The C−H insertion of the nitrene species would take place to form the N−H bond and C−N bond in an asynchronous concerted manner, which should be the product-determining step in this reaction according to the KIE experiment. At last, the product was released from the rhodium center and the regenerated $Rh_2(oct)_4$ was participated to the next catalytic cycle.

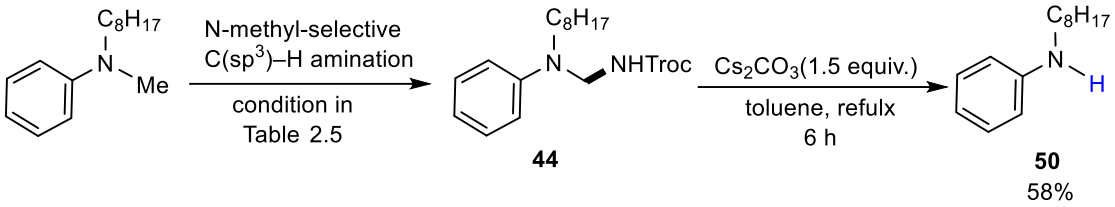
The reacting C−H bonds were selected at the C−H insertion step. For example, *N*-benzyl-*N*-methylaniline has two possible reaction sites, the primary C(sp^3)−H bonds and the secondary benzylic C(sp^3)−H bonds. Although the secondary benzylic C(sp^3)−H bonds have the less bond dissociation energy, the sterically more accessible primary methyl C(sp^3)−H bonds adjacent to the nitrogen atom was expected to be selectively converted to the C−N bond. Similar site selectivity was observed in *β*-selective C(sp^3)−H amination of organosilicon compounds via C−H insertion of dirhodium nitrene complexes.[8]



Scheme 2.7 A possible catalytic cycle.

2.6 Application to two-step demethylation

An application to two-step demethylation of the *N*-methyl aniline derivative *N*-methyl-*N*-octylaniline was demonstrated (Scheme 2.8). Treatment of **44,** obtained by C(sp^3)−H amination of *N*-methyl-*N*-octylaniline, with Cs_2CO_3 in toluene under reflux condition afforded the desired N-demethylated product, phenyloctylamine **50**, in 58% isolated yield. Development of N-demethylation reaction under mild condition has great significance because conventional methods for N-demethylation requires relatively harsh conditions.[27] The present method is assumed to be potentially useful for the application to late-stage functionalization of bioactive molecules containing aromatic *N*-methyl group.



Scheme 2.8 Two-step demethylation of *N*-methyl-*N*-octylaniline.

Chapter 3 Studies on chemoselectivity in C−H amination of anisole and aniline derivatives

In chapter 2, development of C(sp^3)−H amination of aniline derivatives was described, where $Rh_2(oct)_4$ was an effective catalyst and $Rh_2(tpa)_4$ was totally ineffective. On the other hand, C−H amination of anisole under similar condition took place selectively at *para* postion of the methoxy group, where $Rh_2(oct)_4$ was totally ineffective and $Rh_2(tpa)_4$ was an effective catalyst. Chemoselectivities in the C−H amination reaction under similar conditions were totally different depending on the substrates. In addition, ligand effects were complementary to each chemoselective reactions. Interested in the reactivity difference and effects of the catalysts, a detailed study, especially about ligand effects on each reaction, was conducted in this chapter to elucidate the origin of the chemoselectivity and reactivity differences. The ligand effect of dirhodium catalysts with different number of phenyl rings on the α carbon of the carboxylate group was tested in both C(sp^3)−H amination of aniline derivatives and C(sp^2)−H amination of anisole. In combination with NMR experiments and DFT calculation, the possible ligand effect was proposed in each reaction, in which the resting state or transition state structure were affected by the ligand structure. Based on the proposal, a new catalyst was designed and tested to improve the efficiency of C(sp^2)−H amination of anisole.

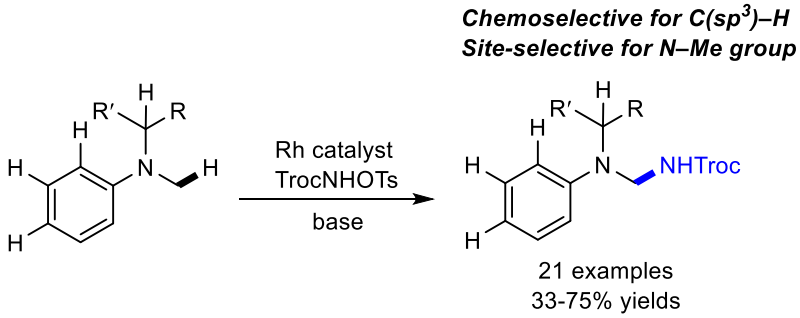
Chapter 4 Catalytic asymmetric synthesis of inherently chiral calixarenes by enantioselective C(sp^2)−H amination

The application of the chemo- and site-selective C–H amination of phenol derivatives to an unprecedented enantioselective reaction was examined. Due to the bowl-shaped 3D structure, calix[4]arene have a non-classical chirality (named, inherent chirality) depending on the arrangement of achiral substituents. While several examples of asymmetric synthesis of inherently chiral calix[4]arene (ICCs) were reported by virtue of chiral auxiliaries, there is only one report on catalytic asymmetric synthesis of ICCs using enzymatic acylation reaction. In this chapter, after various modification of lower rim and upper rim of the substrate, a new C_s-symmetric calix[4]arene derivative with modification on both upper rim and lower rim was found underwent enantioselective C–H aminative desymmetrization successfully, catalyzed by a chiral dirhodium complex. Conditions screening such as aminative agents, solvents, bases, and temperature were conducted and the stereochemistry was discussed.

Conclusion and outlook

By utilizing rhodium metal as catalyst and TrocNHOTs as nitrogen source, rhodium nitrene intermediated was generated, and the highly chemo and site- or stereo-selective C−H amination of different substrates were achieved. The results are summarized below.

Chapter 2. An optimal condition for dirhodium catalyzed C−H amination of aniline derivatives proceeded at C(sp^3)−H bonds α to the nitrogen atom was established, in a chemo and site-selective manner. Mechanistic study shows that the C−H bond cleavage was involved in the product-determining step in the concerted asynchronous C−H insertion process. The application of this amination to a two steps N-demethylation was demonstrated. This method provides an alternative way to the site-selective amination of *N*-methylaniline derivatives and will be possibly used in the N-demethylation of functional molecules.



Chapter 3. The origin of the chemoselectivity in C–H amination of anisole and aniline derivatives was discussed. It was proved by experimental results and DFT calculation that the phenyl rings on the α carbon of the carboxylate ligands of dirhodium complexes strongly affected the efficiency of both C−H amination reactions. In the case of C(sp^3)−H amination of aniline derivatives, the phenyl rings stabilize the resting state of amine to Rh center by multiple C–H/π interactions to inhibit the reaction strongly. On the other hand, the phenyl rings accelerate the C(sp^2)−H amination of anisole, which suggested cation/π or C–H/π interactions stabilize the generating δ+ of aromatic ring in the transition state structure.

Chapter 4. Catalytic desymmetrization of C_s-symmetric calix[4]arene derivatives by enantioselective C(sp^2)−H amination was investigated. Various modification of lower and upper rim of the substrates to find one good condition for the purpose. The C(sp^2)−H amination of the calix[4]arene derivative with substituents on both upper rim and lower rim was achieved in high enantioselectivity, with a chiral dirhodium complex catalyst constituting of amino acid derivatives. To the best of my knowledge, this is the first example of catalytic asymmetric synthesis of inherently chiral calix[4]arene by rhodium catalyzed amination. Although highly selective amination was achieved about only one substrate and the absolute configuration of the product has not been determined yet, this achievement is expected to expand the methodology for catalytic asymmetric synthesis of ICCs and applications of ICCs for unique host-guest chemistry.

Experimental section

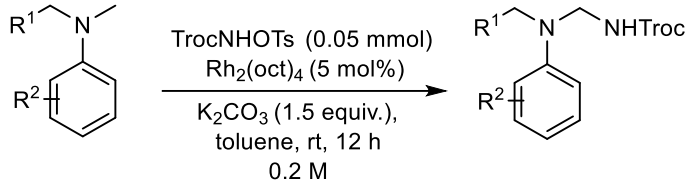
1. General information

^{1}H NMR spectra were recorded on JEOL ECX-400 (400 MHz) and are reported in ppm using solvent resonance as the internal standard ($CDCl_3$ at 7.26 ppm, acetone-d_6 at 2.05 ppm). When peak multiplicities are reported, the following abbreviations are used: s = singlet; d = doublet; dd = doublet doublet; t = triplet; q = quartet; sep = septet; m = multiplet; br = broad. ^{13}C NMR spectra were recorded on JEOL ECX-400 (100 MHz) or JEOL ECX-600 (150 MHz) and are reported in ppm using solvent resonance as the internal standard ($CDCl_3$ at 77.16 ppm, acetone-d_6 at 29.84 ppm). Unless otherwise noted, NMR spectra were recorded at 293 K. IR spectra were recorded with a JASCO FT/IR-4200 spectrometer. Mass spectra were obtained on Bruker Impact HD mass spectrometers or Bruker timsTOF mass spectrometer (IMS-QTOF) for ESI. Melting points were measured using a Yamagimoto micro point apparatus. Specific rotation was measured with JASCO P-2200 polarimeters. Analytic HPLC was run with a JASCO PU-2089 Plus instrument, equipped with Daicel CHIRAL PAK IB or COSMOSIL CHiRAL 5A columns, and a JASCO UV-2075 Plus UV/Vis detector at 254 nm. Recycle HPLC was run with a JASCO PU-2086 Plus instrument, equipped with a COSMOSIL 5SL column and a JASCO UV-2075 Plus UV/Vis detector at 254mn. Purification of reaction products was carried out by column chromatography on silica gel 60N (spherical, neutral, KANTO) or preparative thin layer chromatography on precoated plates (0.5 mm, Merck). Analytical thin layer chromatography was performed on precoated plates (0.25 mm, Merck). Visualization was accomplished with UV light.

TrocNHOTs, 2,2,2-trifluoroethyl-*N*-tosyloxycarbamate, $Rh_2(tpa)_4$ and $Rh_2(piv)_4$ were prepared according to literature procedure. $Rh_2(oct)_4$ and $Rh_2(OAc)_4$ were purchased from TCI. $Rh_2(tfa)_4$ and $Rh_2(esp)_2$ were purchased from Sigma-Aldrich. Li_2CO_3, K_2CO_3, Na_2CO_3, Cs_2CO_3, Rb_2CO_3, and KOAc were purchased from Wako Chemical. Anhydrous chlorobenzene, benzotrifluoride and 2,2,2-tribromoethanol were purchased from Sigma-Aldrich. Anhydrous toluene, chloroform, ethyl acetate and benzene were purchased from Wako Chemical. Anhydrous dichloromethane was purchased from Kanto Kagaku. Fluorobenzene was purchased from TCI. Anhydrous DMF and acetonitrile were purchased from Nacalai tesque. All chemical reagents were commercially purchased and used without further purification.

2. Chapter 2

General procedure for dirhodium-catalyzed intermolecular C−H amination of *N,N*-dialkylanilines



To a suspension of *N,N*-diakylanilines (0.5 mmol, 10 equiv. or 0.075 mmol, 1.5 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.) and K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.) in toluene (0.25 mL) were added $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) at r.t.. After being stirred for 12 h, the reaction was quenched by addition of water and extracted with EtOAc. The organic layer was washed with brine, and dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by preparative TLC or column chromatography to afford the aminated product. The product exists as a mixture of rotamers due to its carbamoyl moiety. For coalescence of the signals of the rotamers, ^{1}H NMR of product was measured at 323K.

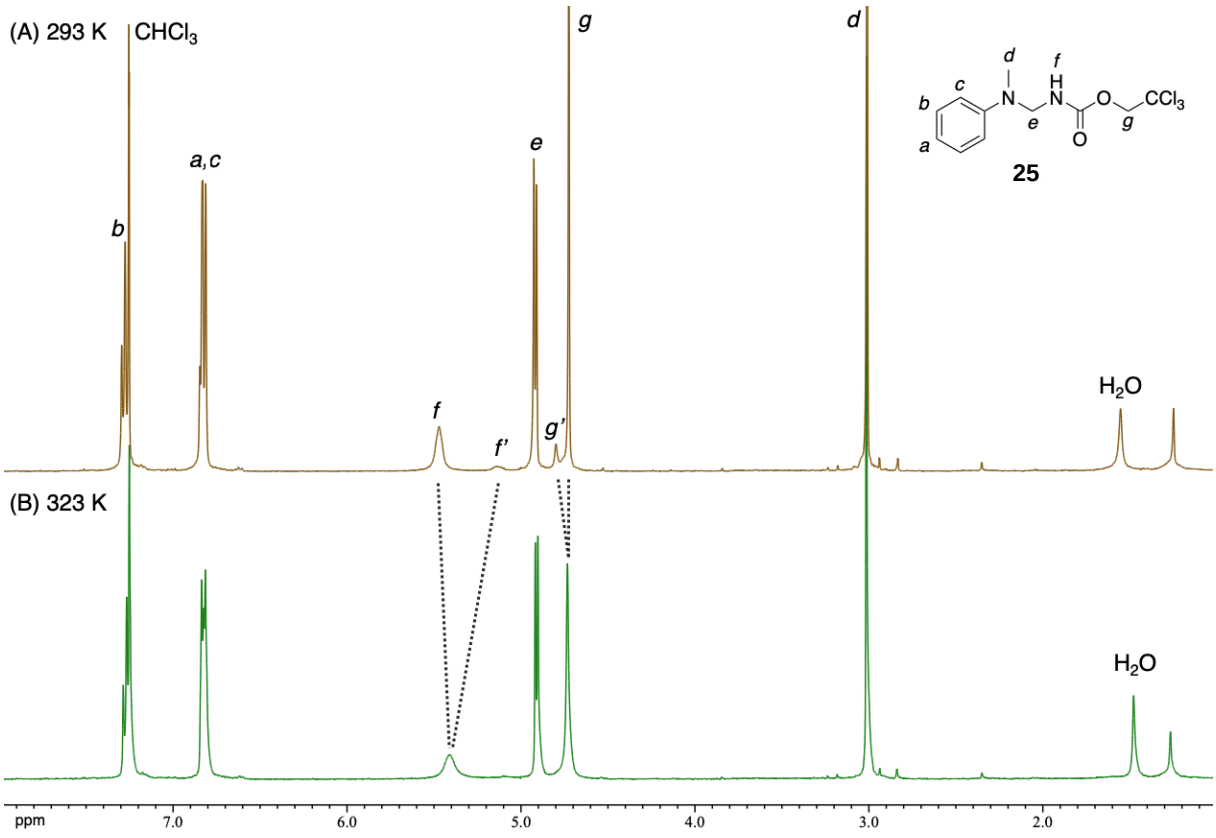
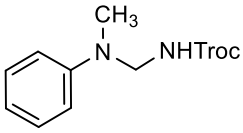


Figure S1. VT-^{1}H NMR spectra of **25** in $CDCl_3$ (A) at 293 K (B) at 323K.

Specific Procedures and Characterization Data

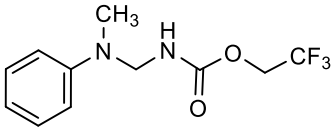
2,2,2-Trichloroethyl ((methyl(phenyl)amino)methyl)carbamate (25)



Following the general procedure, *N*,*N*-dimethylaniline (63 μL, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by sequential preparative TLC (1st EtOAc/hexane = 1/9, 2nd $CHCl_3$/hexane = 1/1) to afford **25** as colorless oil (11.0 mg, 71%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.29−7.26 (m, 2H), 6.84−6.82(m, 3H), 5.42 (br s, 1H), 4.92 (d, *J* = 5.6 Hz, 2H), 4.74 (s, 2H), 3.02 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 154.9, 147.7 129.6, 118.7, 113.9, 95.6, 74.7, 59.7, 37.8; **IR** (neat, cm^{-1}): 3326, 2952, 1722, 1598, 1499, 1367, 1220, 1132, 1041, 993, 817, 750; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{11}H_{14}Cl_3N_2O_2$ $[M+H]^+$ 311.0115; found, 311.0115.

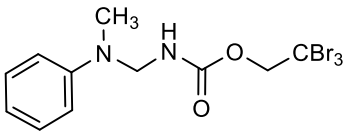
2,2,2-Trifluoroethyl ((methyl(phenyl)amino)me9thyl)carbamate (26)



Following the general procedure, *N*,*N*-dimethylaniline (10 μL, 0.075 mmol, 1.5 equiv), 2,2,2-trifluoroethyl (tosyloxy)carbamate (15.6 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in chlorobenzene (0.25 mL) for 12 h. The crude material was purified by sequential preparative TLC (1st EtOAc/hexane = 1/9, 2nd $CHCl_3$/hexane = 1/1) to afford **26** as colorless oil (4.8 mg, 37%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.29−7.26 (m, 2H), 6.85−6.81 (m, 3H), 5.36 (br s, 1H), 4.88 (d, *J* = 5.6 Hz, 2H), 4.46 (q, *J* = 8.0 Hz, 2H), 3.01 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 154.8, 147.7 129.6, 123.1 (q, *J* = 276.5 Hz), 118.7, 113.9 and 113.6 (rotamers), 61.1 (q, *J* = 36.2 Hz), 59.7, 37.9; **IR** (neat, cm^{-1}): 3339, 2916, 1729, 1602, 1531, 1507, 1292, 1232, 1176, 973, 758, 694; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{11}H_{14}F_3N_2O_2$ $[M+H]^+$ 263.1002; found, 263.1007.

2,2,2-Tribromoethyl ((methyl(phenyl)amino)methyl)carbamate (27)

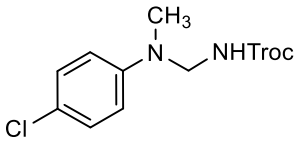


Following the general procedure, *N*,*N*-dimethylaniline (10 μL, 0.075 mmol, 1.5 equiv.), 2,2,2-tribromoethyl (tosyloxy)carbamate (24.8 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in chlorobenzene (0.25 mL) for 12 h. The crude material was purified by sequential preparative TLC (1st EtOAc/hexane = 1/9, 2nd $CHCl_3$/hexane

= 1/1) to afford **27** as colorless oil (8.0 mg, 36%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.30−7.26 (m, 2H), 6.85−6.81 (m, 3H), 5.46 (br s, 1H), 4.94−4.93 (m, 4H), 3.03 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 154.8, 147.8 129.6, 119.0 and 118.7 (rotamers), 113.9 and 113.7 (rotamers), 79.4, 60.4 and 59.7 (rotamers), 37.9, 37.2; **IR** (neat, cm^{-1}): 3318, 2920, 1725, 1598, 1495, 1359, 1216, 1129, 1041, 993, 750, 699, 635; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{11}H_{14}{}^{79}Br_2{}^{81}BrN_2O_2$ $[M+H]^+$ 444.8580; found, 444.8583.

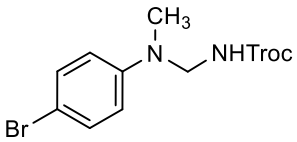
2,2,2-Trichloroethyl (((4-chlorophenyl)(methyl)amino)methyl)carbamate (28)



Following the general procedure, 4-chloro-*N*,*N*-dimethylaniline (78 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by sequential preparative TLC (1st EtOAc/hexane = 1/5, 2nd $CHCl_3$/hexane = 1/1) to afford **28** as colorless oil (13.0 mg, 75%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.21 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 5.42 (br s, 1H), 4.88 (d, *J* = 6.0 Hz, 2H), 4.74 (s, 2H), 3.00 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 154.9, 146.4, 129.4, 123.7, 115.1 and 114.9 (rotamers), 95.5, 74.7, 59.8, 38.0; **IR** (neat, cm^{-1}): 3331, 2920, 1725, 1499, 1363, 1216, 1140, 1005, 809, 722; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{11}H_{13}Cl_4N_2O_2$ $[M+H]^+$ 344.9726; found, 344,9725.

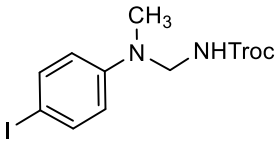
2,2,2-Trichloroethyl (((4-bromophenyl)(methyl)amino)methyl)carbamate (29)



Following the general procedure, 4-bromo-*N*,*N*-dimethylaniline (100 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by sequential preparative TLC (1st EtOAc/hexane = 1/9, 2nd $CHCl_3$/hexane = 1/1) to afford **29** as colorless oil (13.8 mg, 71%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.35 (d, *J* = 9.2 Hz, 2H), 6.70 (d, *J* = 9.2 Hz, 2H), 5.43 (br s, 1H), 4.87 (d, *J* = 6.0 Hz, 2H), 4.74 (s, 2H), 2.99 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 154.9, 146.8, 132.3, 115.5 and 115.3 (rotamers), 110.9, 95.5, 74.7, 59.6, 38.0; **IR** (neat, cm^{-1}): 3326, 2948, 1725, 1598, 1495, 1363, 1208, 1132, 1052, 1000, 813, 722; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{11}H_{13}BrCl_3N_2O_2$ $[M+H]^+$ 388.9220; found, 388.9218.

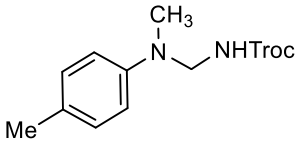
2,2,2-Trichloroethyl (((4-iodophenyl)(methyl)amino)methyl)carbamate (30)



Following the general procedure, 4-iodo-*N*,*N*-dimethylaniline (124 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by sequential preparative TLC (1st EtOAc/hexane = 1/9, 2nd $CHCl_3$/hexane = 1/1) to afford **30** as colorless oil (15.0 mg, 69%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.52 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 5.45 (br s, 1H), 4.87 (d, *J* = 5.6 Hz, 2H), 4.74 (s, 2H), 2.99 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 154.9, 147.4, 138.2, 115.8, 95.5, 80.1, 74.7, 59.4, 37.9; **IR** (neat, cm^{-1}): 3335, 2948, 1722, 1590, 1490, 1359, 1224, 1140, 1052, 809, 727; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{11}H_{13}Cl_3IN_2O_2$ $[M+H]^+$ 436.9082; found, 436.9079.

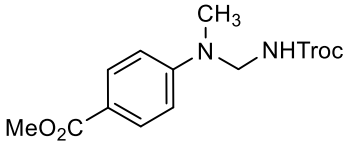
2,2,2-Trichloroethyl ((methyl(*p*-tolyl)amino)methyl)carbamate (31)



Following the general procedure, *N*,*N*,4-trimethylaniline (68 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by sequential preparative TLC (1st EtOAc/hexane = 1/9, 2nd $CHCl_3$/hexane = 1/1) to afford **31** as light yellow oil (6.7 mg, 41%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.09 (d, *J* = 7.2 Hz, 2H), 6.75 (d, *J* = 7.2 Hz, 2H), 5.39 (br s, 1H), 4.88 (d, *J* = 6.0 Hz, 2H), 4.74 (s, 2H), 2.98 (s, 3H), 2.28 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 155.0, 145.6, 130.1, 128.2, 114.4 and 114.2 (rotamers), 95.6, 74.9 and 74.6 (rotamers), 60.0, 37.8, 20.4; **IR** (neat, cm^{-1}): 3331, 2920, 1718, 1514, 1363, 1212, 1136, 1049, 957, 813, 730; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{12}H_{16}Cl_3N_2O_2$ $[M+H]^+$ 325.0272; found, 325.0272.

Methyl 4-(methyl((((2,2,2-trichloroethoxy)carbonyl)amino)methyl)amino)benzoate (32)

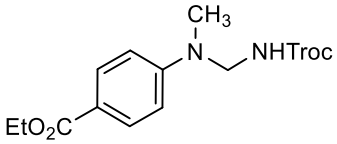


Following the general procedure, methyl 4-(dimethylamino)benzoate (90 mg, 0.5 mmol, 10 equiv.),

TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (EtOAc/hexane = 1/5) to afford **32** as a white solid (13.4 mg, 73%).

White solid: **m.p.** 152 °C; **^{1}H NMR** (400 M Hz, $CDCl_3$, 323 K) δ: 7.95 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 5.51 (br s, 1H), 4.95 (d, *J* = 6.0 Hz, 2H), 4.75 (s, 2H), 3.87 (s, 3H), 3.11 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 167.3, 154.9, 151.2, 131.7, 119.5, 111.9, 95.4, 774.8, 58.9, 51.9, 38.2; **IR** (KBr, cm^{-1}): 3351, 2955, 1741, 1693, 1618, 1527, 1290, 1186, 1005, 831, 767; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{13}H_{16}Cl_3N_2O_4$ $[M+H]^+$ 369.0170; found, 369.0171.

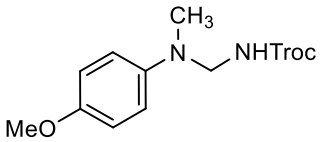
Ethyl 4-(methyl((((2,2,2-trichloroethoxy)carbonyl)amino)methyl)amino)benzoate (33)



Following the general procedure, ethyl 4-(dimethylamino)benzoate (97 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (EtOAc/hexane = 1/5) to afford **33** as a white solid (12.0 mg, 63%).

White solid: **m.p.** 120 °C; **^{1}H NMR** (400 M Hz, $CDCl_3$, 323 K) δ: 7.95 (d, *J* = 9.2 Hz, 2H), 6.77 (d, *J* = 9.2 Hz, 2H) 5.53 (br s, 1H), 4.95 (d, *J* = 6.0 Hz, 2H), 4.75 (s, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 3.11 (s, 3H), 1.37 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 166.8, 154.9, 151.1, 131.6, 119.8, 111.9, 95.4, 74.7, 60.6, 58.9, 38.1, 14.6; **IR** (KBr, cm^{-1}): 3343, 2965, 1729, 1682, 1518, 1295, 1184, 1106, 817, 722; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{14}H_{18}Cl_3N_2O_4$ $[M+H]^+$ 383.0327; found, 383.0324.

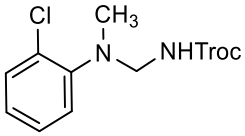
2,2,2-Trichloroethyl (((4-methoxyphenyl)(methyl)amino)methyl)carbamate (34)



Following the general procedure, 4-methoxy-*N*,*N*-dimethylaniline (75 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (EtOAc/hexane = 1/9) to afford **34** as colorless oil (8.9 mg, 53%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 6.87−6.81 (m, 4H), 5.36 (br s, 1H), 4.83 (d, *J* = 6.4 Hz, 2H), 4.73 (s, 2H), 3.77 (s, 3H), 2.93 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 155.0, 153.3, 142.1, 116.7 and 116.3 (rotamers), 115.0, 95.6, 74.6, 61.0, 55.8, 38.0; **IR** (neat, cm^{-1}): 3326, 2920, 1722, 1518, 1243, 1129, 1037, 822, 722; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{12}H_{16}Cl_3N_2O_3$ $[M+H]^+$ 341.0221; found, 341.0220.

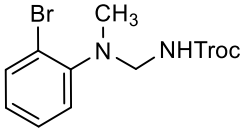
2,2,2-Trichloroethyl (((2-chlorophenyl)(methyl)amino)methyl)carbamate (35)



Following the general procedure, 2-chloro-*N*,*N*-dimethylaniline (77 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (EtOAc/hexane = 1/9) to afford **35** as colorless oil (7.6 mg, 44%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.38 (d, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 7.1 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.00 (t, *J* = 8.0 Hz, 1H), 5.37 (br s, 1H), 4.74 (s, 2H), 4.68 (d, *J* = 6.8 Hz, 2H), 2.90 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 155.0, 146.5, 130.9, 128.5, 127.6 and 127.2 (rotamers), 124.6 and 124.4 (rotamers), 122.7 and 122.3 (rotamers), 95.7, 74.8 and 74.5 (rotamers), 61.9 and 61.6 (rotamers), 38.4; **IR** (neat, cm^{-1}): 3339, 2960, 1722, 1514, 1479, 1224, 1120, 1049, 718; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{11}H_{13}Cl_4N_2O_2$ $[M+H]^+$ 344.9726; found, 344.9738.

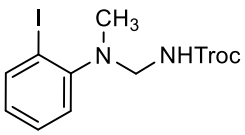
2,2,2-Trichloroethyl (((2-bromophenyl)(methyl)amino)methyl)carbamate (36)



Following the general procedure, 2-bromo-*N*,*N*-dimethylaniline (100 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (EtOAc/hexane = 1/9) to afford **36** as colorless oil (11.1 mg, 59%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.59 (d, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 5.38 (br s, 1H), 4.74 (s, 2H), 4.65 (d, *J* = 6.4 Hz, 2H), 2.88 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 155.0 and 154.3 (rotamers), 147.9 and 147.6 (rotamers), 134.1, 128.6 and 128.3 (rotamers), 125.3 and 125.2 (rotamers), 123.3 and 123.0 (rotamers), 120.0 and 119.7 (rotamers), 95.7, 74.8 and 74.5 (rotamers), 62.4 and 62.0 (rotamers), 38.5; **IR** (neat, cm^{-1}): 3339, 2948, 1725, 1515, 1479, 1232, 1156, 722; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{11}H_{13}BrCl_3N_2O_2$ $[M+H]^+$ 388.9220; found, 388.9219.

2,2,2-Trichloroethyl (((2-iodophenyl)(methyl)amino)methyl)carbamate (37)

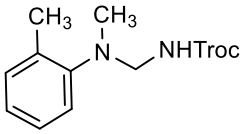


Following the general procedure, 2-iodo-*N*,*N*-dimethylaniline (124 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified

by preparative TLC (EtOAc/hexane = 1/9) to afford **37** as colorless oil (11.4 mg, 52%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.87 (d, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.83 (t, *J* = 7.6 Hz, 1H), 5.37 (br s, 1H), 4.74 (s, 2H), 4.57 (d, *J* = 6.0 Hz, 2H), 2.84 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 155.0, 150.7, 140.4, 129.2, 126.3, 123,2, 98.2, 95.7, 74.5, 62.8, 39.0; **IR** (neat, cm^{-1}): 3339, 2920, 1729, 1510, 1463, 1236, 1125, 718; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{11}H_{13}Cl_3IN_2O_2$ $[M+H]^+$ 436.9082; found, 436.9081.

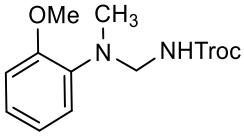
2,2,2-Trichloroethyl ((methyl(*o*-tolyl)amino)methyl)carbamate (38)



Following the general procedure, *N*,*N*,2-trimethylaniline (68 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (EtOAc/hexane = 1/9) to afford **38** as light yellow oil (7.0 mg, 43%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.25−7.14 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.02 (t, *J* = 7.2 Hz, 1H), 5.21 (br s, 1H), 4.73 (s, 2H), 4.51 (d, *J* = 6.4 Hz, 2H), 2.81 (s, 3H), 2.32 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 155.0, 148.4, 133.1, 131.5, 126.6, 124.1, 121,7 and 121,5 (rotamers), 95.7, 74.8 and 74.5 (rotamers), 61.9, 38.9, 18.4; **IR** (neat, cm^{-1}): 3335, 2952, 1738, 1594, 1503, 1316, 1224, 1049, 806, 727; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{12}H_{16}Cl_3N_2O_2$ $[M+H]^+$ 325.0272; found, 325.0257.

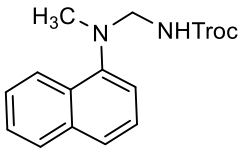
2,2,2-Trichloroethyl (((2-methoxyphenyl)(methyl)amino)methyl)carbamate (39)



Following the general procedure, 2-methoxy-*N*,*N*-dimethylaniline (76 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (EtOAc/hexane = 1/3) to afford **39** as colorless oil (9.1 mg, 54%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.02−6.88 (m, 4H), 5.38 (br s, 1H), 4.73 (s, 2H), 4.71 (d, *J* = 6.4 Hz, 2H), 3.89 (s, 3H), 2.91 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 155.2, 152.0, 138.4, 123.3, 121.1, 120.2 and 120.0 (rotamers), 111.4, 95.8, 74.5, 61.2, 55.7, 38.4; **IR** (neat, cm^{-1}): 3339, 2948, 1733, 1598, 1503, 1455, 1232, 1105, 809, 722; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{12}H_{16}Cl_3N_2O_3$ $[M+H]^+$ 341.0221; found, 341.0219.

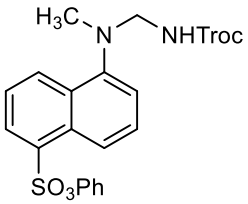
2,2,2-Trichloroethyl ((methyl(naphthalen-1-yl)amino)methyl)carbamate (40)



Following the general procedure, *N*,*N*-dimethylnaphthalen-1-amine (85 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by column chromatography (EtOAc/hexane = 1/9) to afford **40** as yellow oil (8.6 mg, 48%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 8.19 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.51−7.47 (m, 2H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 5.22 (br s, 1H), 4.76−4.74 (m, 4H), 2.98 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 155.0, 146.3 and 145.9 (rotamers), 134.9, 129.1, 128.6, 126.2, 125.9, 125.6, 124.5, 123.5, 117.9 and 117.6 (rotamers), 95.7, 74.7 and 74.5 (rotamers), 63.2 and 62.7 (rotamers), 39.1 and 39.0 (rotamers); **IR** (neat, cm^{-1}): 3326, 3051, 2956, 2920, 1725, 1510, 1395, 1224, 1136, 1037, 933, 806, 781; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{15}H_{16}Cl_3N_2O_2$ $[M+H]^+$ 361.0272; found, 361.0272.

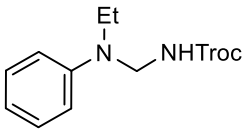
Phenyl 5-(methyl((((2,2,2-trichloroethoxy)carbonyl)amino)methyl)amino)naphthalene-1-sulfonate (41)



Following the general procedure, phenyl 5-(dimethylamino)naphthalene-1-sulfonate (164 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by column chromatography (EtOAc/hexane = 1/3) to afford **41** as light yellow oil (15.3 mg, 59%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 8.62 (d, *J* = 8.8 Hz, 1H), 8.60 (d, *J* = 6.4 Hz, 1H), 8.12 (d, *J* = 7.2 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.23−7.16 (m, 3H), 6.92 (d, *J* = 7.2 Hz, 2H), 5.30 (br s, 1H), 4.74−4.70 (m, 4H), 3.00 (s, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 155.0, 149.8, 147.4, 131.6, 131.5, 131.3, 130.3, 130.2, 129.7, 128.8, 127.3, 123.9, 122.2, 121.5, 119.3, 95.6, 74.8 and 74.6 (rotamers), 63.2, 39.5; **IR** (neat, cm^{-1}): 3402, 2952, 1738, 1518, 1367, 1192, 1052, 862, 730; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{21}H_{20}Cl_3N_2O_5S$ $[M+H]^+$ 517.0153; found, 517.0143.

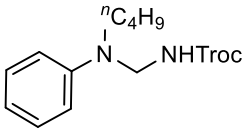
2,2,2-Trichloroethyl ((ethyl(phenyl)amino)methyl)carbamate (42)



Following the general procedure, *N*-ethyl-*N*-methylaniline (68 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (EtOAc/hexane = 1/9) to afford **42** as colorless oil (5.3 mg, 33%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.28−7.24 (m, 2H), 6.81−6.79 (m, 3H), 5.40 (br s, 1H), 4.90 (d, *J* = 5.2 Hz, 2H), 4.75 (s, 2H), 3.47 (q, *J* = 6.8 Hz, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 154.7, 146.6, 129.7, 118.1, 113.7 and 113.3 (rotamers), 95.6, 74.6, 58.0, 44.8, 13.2; **IR** (neat, cm^{-1}): 3318, 2965, 1725, 1503, 1372, 1200, 1140, 997, 822, 727; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{12}H_{16}Cl_3N_2O_2$ $[M+H]^+$ 325.0272; found, 325.0274.

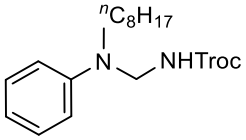
2,2,2-Trichloroethyl ((butyl(phenyl)amino)methyl)carbamate (43)



Following the general procedure, *N*-butyl-*N*-methylaniline (81 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (EtOAc/hexane = 1/9) to afford **43** as colorless oil (7.6 mg, 43%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.27−7.24 (m, 2H), 6.81−6.78 (m, 3H), 5.37 (br s, 1H), 4.89 (d, *J* = 5.2 Hz, 2H), 4.75 (s, 2H), 3.38 (t, *J* = 7.2 Hz, 2H), 1.64−1.58 (m, 2H), 1.41−1.35 (m, 2H), 0.96 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 154.7, 146.8, 129.7, 118.1, 113.6 and 113.2 (rotamers), 95.6, 74.6, 58.4, 50.4, 30.1, 20.4, 14.1; **IR** (neat, cm^{-1}): 3326, 2960, 2864, 1733, 1602, 1503, 1367, 1232, 1184, 817, 722; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{14}H_{20}Cl_3N_2O_2$ $[M+H]^+$ 353.0585; found, 353.0586.

2,2,2-Trichloroethyl ((octyl(phenyl)amino)methyl)carbamate (44)

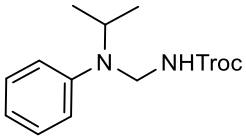


Following the general procedure, *N*-methyl-*N*-octylaniline (110 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (EtOAc/hexane = 1/9) to afford **44** as colorless oil (8.2 mg, 40%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.27−7.23 (m, 2H), 6.81−6.77 (m, 3H), 5.37 (br s, 1H), 4.89 (d, *J* = 5.6 Hz, 2H), 4.75 (s, 2H), 3.36 (t, *J* = 7.2 Hz, 2H), 1.68−1.58 (m, 2H), 1.35−1.21 (m, 10H), 0.89 (t, *J* = 6.0 Hz, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 154.7, 146.8, 129.7, 118.1, 113.5 and 113.2 (rotamers),

95.6, 74.6, 58.4, 50.7, 31.9, 29.6 and 29.4 (rotamers), 28.0, 27.3, 22.8, 14.3; **IR** (neat, cm^{-1}): 3335, 2956, 2857, 1729, 1602, 1503, 1367, 1224, 997, 817, 722; **HRMS-ESI**$^+$ (m/z): Calcd. for $C_{18}H_{28}Cl_3N_2O_2$ $[M+H]^+$ 409.1211; found, 409.1209.

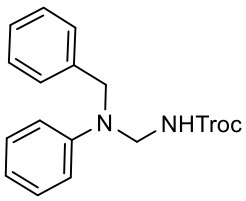
2,2,2-Trichloroethyl ((isopropyl(phenyl)amino)methyl)carbamate (45)



Following the general procedure, *N*-isopropyl-*N*-methylaniline (75 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (EtOAc/hexane = 1/9) to afford **45** as colorless oil (7.1 mg, 42%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.28−7.24 (m, 2H), 6.87−6.80 (m, 3H), 5.19 (br s, 1H), 4.87 (d, *J* = 5.2 Hz, 2H), 4.75 (s, 2H), 4.06 (sep, 1H), 1.27 (d, *J* = 6.4 Hz, 6H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 153.9, 147.3, 129.8 and 129.5 (rotamers), 118.4, 114.0 and 113.7 (rotamers), 95.6, 74.8 and 74.5 (rotamers), 52.9, 48.0, 20.8; **IR** (neat, cm^{-1}): 3315, 2965, 1725, 1499, 1323, 1192, 1116, 1045, 822, 727; **HRMS-ESI**$^+$ (m/z): Calcd. for $C_{13}H_{18}Cl_3N_2O_2$ $[M+H]^+$ 339.0428; found, 339.0429.

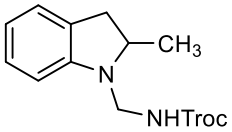
2,2,2-Trichloroethyl ((benzyl(phenyl)amino)methyl)carbamate (46)



Following the general procedure, *N*-benzyl-*N*-methylaniline (100 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (EtOAc/hexane = 1/9) to afford **46** as colorless oil (7.2 mg, 37%).

^{1}H NMR (400 M Hz, $CDCl_3$, 323 K) δ: 7.33−7.21 (m, 7H), 6.85−6.80 (m, 3H), 5.45 (br s, 1H), 4.98 (d, *J* = 6.0 Hz, 2H), 4.73 (s, 2H), 4.65 (s, 2H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 154.8, 147.2, 138.4, 129.7, 128.8, 127.2, 126.8, 118.7, 113.6, 95.5, 74.7, 58.4, 54.3; **IR** (neat, cm^{-1}): 3335, 3028, 1725, 1602, 1499, 1363, 1236, 1172, 809, 727; **HRMS-ESI**$^+$ (m/z): Calcd. for $C_{17}H_{18}Cl_3N_2O_2$ $[M+H]^+$ 387.0428; found, 387.0428.

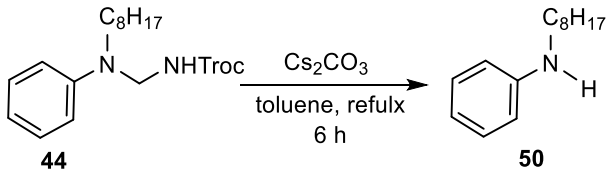
2,2,2-trichloroethyl ((2-methylindolin-1-yl)methyl)carbamate (47)



Following the general procedure, 1,2-dimethylindoline (75 mg, 0.5 mmol, 10 equiv.), TrocNHOTs (18.1 mg, 0.05 mmol, 1.0 equiv.), K_2CO_3 (10.4 mg, 0.075 mmol, 1.5 equiv.), and $Rh_2(oct)_4$ (1.9 mg, 0.05 equiv.) were stirred at r.t. in toluene (0.25 mL) for 12 h. The crude material was purified by preparative TLC (EtOAc/hexane = 1/9) to afford **47** as a white solid (5.6 mg, 33%).

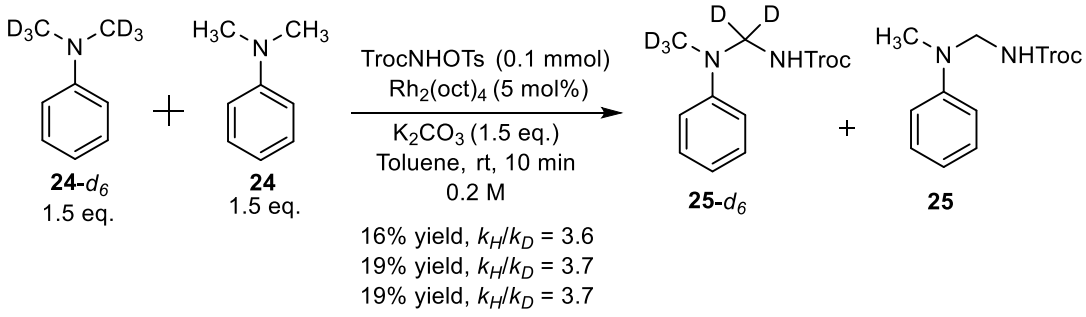
White solid: **m.p.** 79 ℃; **^{1}H NMR** (400 M Hz, $CDCl_3$, 323 K) δ: 7.10−7.06 (m, 2H), 6.73 (t, *J* = 7.6 Hz, 1H), 6.56 (d, *J* = 7.6 Hz, 1H), 5.38 (br s, 1H), 4.86−4.72 (m, 4H), 3.84−3.74 (m, 1H), 3.13 (dd, *J* = 8.8 Hz and 15.6 Hz, 1H), 2.64 (dd, *J* = 10.4 Hz and 15.2 Hz, 1H), 1.41 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 M Hz, $CDCl_3$) δ: 155.2, 149.9, 129.7, 127.6, 124.9, 119.3, 107.3, 95.6, 74.7, 57.7, 52.0, 37.3, 19.2; **IR** (KBr, cm^{-1}): 3343, 2968, 1718, 1527, 1372, 1236, 1148, 989, 730; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{13}H_{16}Cl_3N_2O_2$ $[M+H]^+$ 337.0272; found, 337.0253.

Procedure for Decomposition of Aminal 50



Cs_2CO_3 (78 mg, 0.24 mmol, 1.5 equiv.) was added to a solution of **44** (65 mg, 0.16 mmol, 1.0 equiv.) in toluene (1.6 mL) and the resulting mixture was allowed stirring under reflux condition. After being stirred for 6 h, the reaction was quenched by addition of 1N HCl and extracted with EtOAc. The organic layer was washed with brine, and dried over Na_2SO_4, filtered, and concentrated. The NMR yield of the product **50** (75%) was determined by ^{1}H NMR using 1,3-dinitrobenzene as an internal standard. The residue was purified by preparative TLC (EtOAc/hexane = 1/20) to afford the product **50** (19 mg, 58% yield) as colorless oil. The spectral data were identical to the reported data.[28]

KIE Measurements

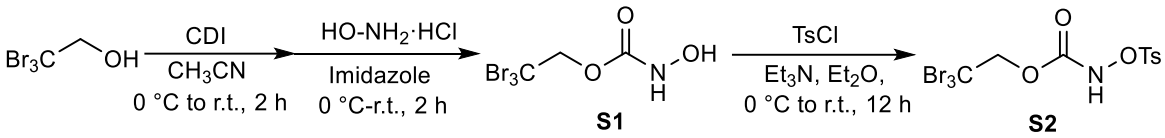


To a suspension of *N*,*N*-dimethylaniline (**24**; 18 mg, 0.15 mmol, 1.5 equiv.), *N*,*N*-bis(methyl-d_3)aniline (**24**-d_6; 19 mg, 0.15 mmol, 1.5 equiv.), TrocNHOTs (36.2 mg, 0.10 mmol, 1.0 equiv.) and K_2CO_3 (20.8 mg, 0.15 mmol, 1.5 equiv.) in toluene (0.5 mL) was added $Rh_2(oct)_4$ (4.0 mg, 0.005 mmol, 0.05 equiv.)

at r.t.. After being stirred for 10 min, the reaction was quenched by addition of water and extracted with EtOAc. The organic layer was washed with brine, and dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative TLC purification (EtOAc/hexane =1/9) to afford a mixture of **25** and **25**-d_6. KIE was calculated from the comparison of the integrals between an aromatic signal (δ 6.84−6.82 ppm, 3H of **25** and **25**-d_6) and a methylene (δ 4.92 ppm, 2H of **25**) in ^{1}H NMR of a solution of **25** and **25**-d_6 ($CDCl_3$). The experiments were performed three times and the determined KIE was the average of three runs.

Synthesis of reagents

2,2,2-tribromoethyl-*N*-tosyloxycarbamate (**S2**) was synthesized by the method described below.



To a solution of 2,2,2-tribromoethanol (424 mg, 1.5 mmol, 1.0 equiv.) in CH_3CN (7.5 mL) was added CDI (267 mg, 1.6 mmol, 1.1 equiv.) at 0 °C. After being stirred for 2 h at r.t., the solution was cooled to 0 °C. Imidazole (306 mg, 4.5 mmol, 3.0 equiv.) and hydroxylamine hydrochloride (417 mg, 6 mmol, 4.0 equiv.) were added to the reaction mixture. The reaction mixture was stirred at r.t. for 2 h and acidified with 1 N HCl. The resulting mixture was extracted with diethylether, the organic layer was washed with brine, and dried over Na_2SO_4, filtered, and concentrated in vacuo. The yellow oil was solidified to a yellow solid. After recrystallization from $CHCl_3$/Hexane, the desired **S1** was obtained (220 mg, 43%) as a white solid.

To a solution of **S1** (170 mg, 0.5 mmol, 1.0 equiv.) in diethylether (10 mL) at 0 °C were added *p*-toluenesulfonyl chloride (105 mg, 0.55 mmol, 1.1 equiv.) and triethylamine (76 μL, 0.55 mmol, 1.1 equiv.). The resulting white suspension was stirred at r.t. for 2 h. The reaction was quenched by addition of water and extracted with diethylether. The organic layer was washed with brine, and dried over Na_2SO_4, filtered, and concentrated in vacuo. The desired product **S2** was obtained as a white solid (110 mg, 44% yield) after recrystallization from $CHCl_3$/Hexane.

White solid, **m.p.** 171 °C; **^{1}H NMR** (400 M Hz, acetone-d_6) δ: 11.1 (br s, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 4.92 (s, 2H), 2.46 (s, 3H); **^{13}C NMR** (100 M Hz, acetone-d_6) δ: 155.1, 147.2, 131.6, 130.8, 130.4, 78.1, 36.3, 21.6; **IR** (KBr, cm^{-1}): 3247, 2948, 1765, 1594, 1447, 1383, 1280, 1232, 1180, 1101, 1052, 817, 730, 547; **HRMS-ESI$^+$** (m/z): Calcd. for $C_{10}H_{10}{}^{79}Br_2{}^{81}BrNO_5SNa$ $[M+Na]^+$ 517.7702; found, 517.7716.

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