PART I: PALLADIUM-CATALYZED RADICAL ALKYLATION OF ARENES

PART II: NICKEL-CATALYZED ASYMMETRIC HYDROGENATION OF QUINOXALINES USING FORMIC ACID

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ABSTRACT

We developed a general procedure for palladium-catalyzed radical alkylation of activated arenes. Electron-deficient benzenes and naphthalene derivatives reacted to give alkylated products in moderate to good yields. The alkyl radicals added to *para* position of strong electron-withdrawing groups on the arenes. This alkylation method complements with traditional Friedel-Crafts alkylation which reacted well with electron-rich and neutral arenes.

We reported asymmetric transfer hydrogenation of 2-substituted quinoxalines using Ni/TangPhos as the catalyst and formic acid as the source of hydrogen. Moderate to good enantioselectivities were obtained depending on the substituents. We also realized a one-pot reductive amination between 1,2-phenylenediamine and substituted glyoxal. The two spontaneously condensed to form quinoxalines. The later was not isolated and subjected to nickel catalyzed asymmetric transfer hydrogenation.

We realized a challenging Heck arylation of *N*-substituted maleimides, which are exceedingly prone to basic hydrolysis. We found a combination of weak base KOAc in ethylene carbonate solvent helped to slow down the ring-opening side reactions of sensitive maleimide to form the Heck product in good yield and with good generality.

Chapter 1: Palladium-catalyzed radical alkylation of arenes

1.1 Introduction

Alkylarene motifs are omnipresent in many drug molecules (Figure 1.1).[1-4] Direct C-H alkylation reactions are the most efficient ways to access to such alkylated arenes. The most conventional alkylation method is Friedel-Crafts alkylation and transition-metal catalyzed cross-coupling reactions. Recently, metal-catalyzed C-H alkylations have also become increasingly popular due to its control of site selectivities.

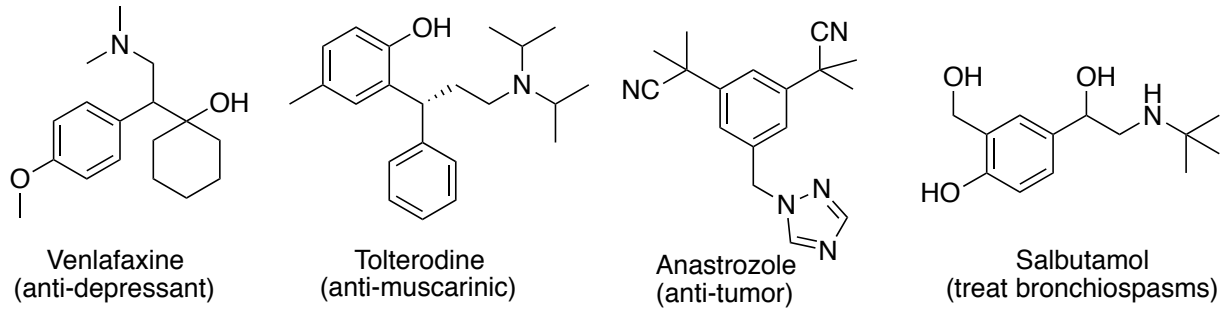
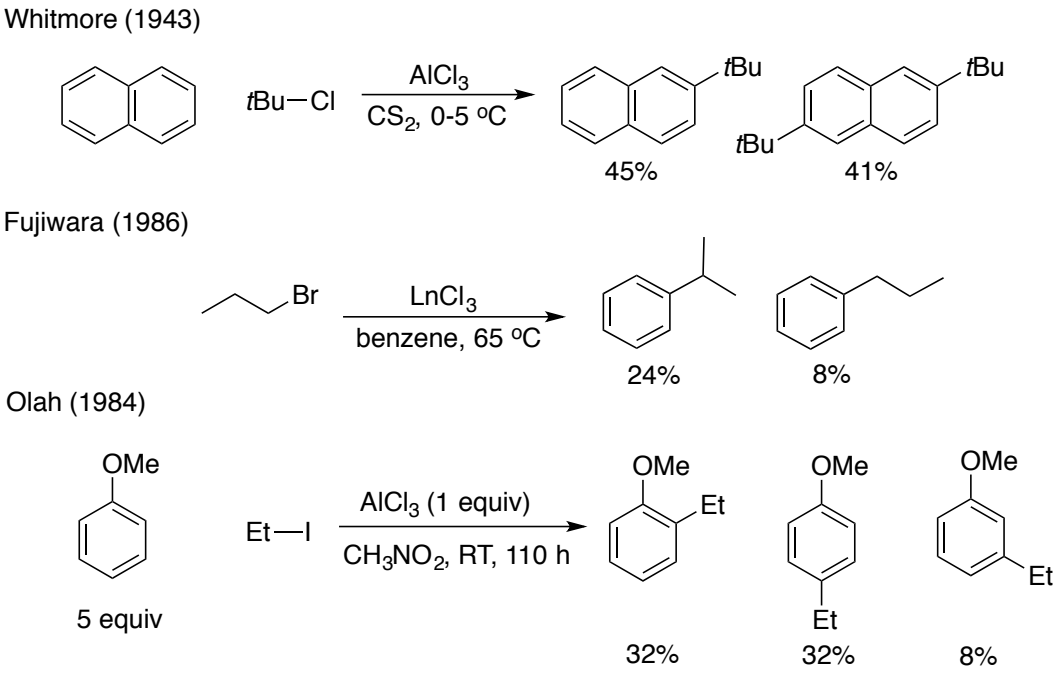


Figure 1.1 Drug molecules containing alkylarene motif

1.2 Friedel-Crafts alkylation

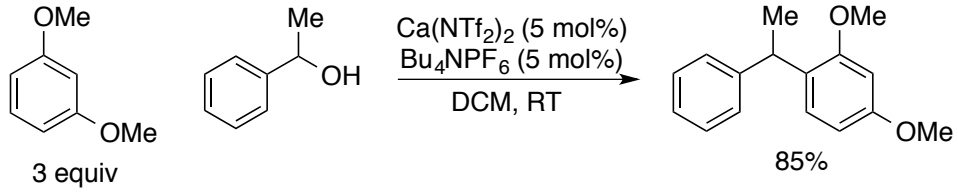
The classical method to obtain alkylated arenes is Friedel-Crafts alkylation.[5,6] Friedel-Crafts reaction alkylates aromatic compounds using alkyl halides in the presence of a Lewis acid catalyst (Scheme 1.2). It is named after Charles Friedel and James Crafts to acknowledged their detailed work published regarding this reaction in 1877.[7]



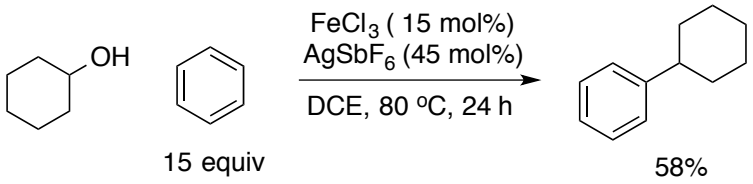
Scheme 1.2 Examples of Friedel-Crafts alkylation of benzene, anisole[8] and naphthalene[9] with alkyl halides[10]

Since its discovery, many metal halides such as $FeCl_3$, $TiCl_4$ $SnCl_4$ and BF_3 and Brønsted acids such as HF and H_2SO_4 have been found to be suitable catalysts for Friedel-Crafts alkylation. Besides alkyl halides, alcohols also proved to be suitable electrophiles for Friedel-Crafts alkylation, providing a greener alternative to alkyl halide (Scheme 1.3). [11,12]

Niggemann (2010)



Cook (2014)



Scheme 1.3 Recent examples of Friedel-Crafts alkylation of arenes

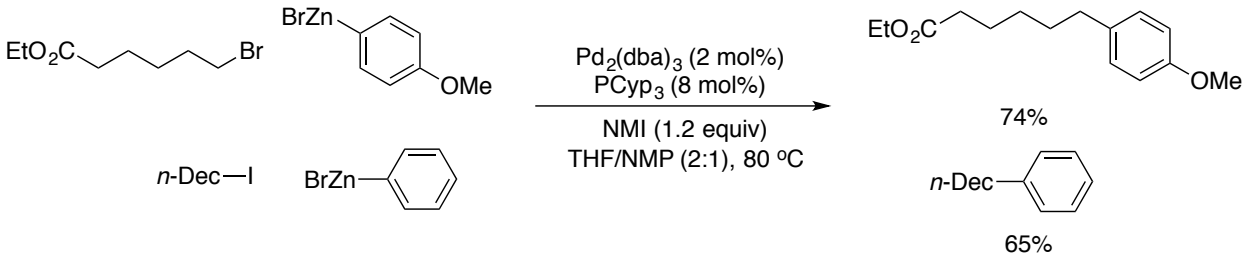
Despite the various milestones achieved, the major drawback of Friedel-Crafts alkylation is the limitation of substrate scope. Friedel-Crafts alkylation works well with electron-neutral or electron-rich arenes, while electron-poor arenes usually react poorly in this reaction. The alkylated products are also prone to overalkylation as it is more nucleophilic than the starting material, and the carbocations formed from primary alkyl halides tend to undergo isomerization. In addition, the regioselectivity of Friedel-Crafts reaction is usually poor when more than one suitable alkylation site is present.

1.3 Alkylation of arenes via cross-coupling reactions using unactivated alkyl halides

Transition-metal catalyzed cross-coupling reactions are effective and reliable ways for C-C bond formation to produce alkylated arenes.[13-15] The formation of aryl-alkyl bonds through cross-coupling reactions are often challenging, especially when the electrophiles are unactivated alkyl halides contains β-hydrogens due to slow oxidative addition and competing side reaction such as β-H elimination. However, in the late 20th century Kochi and Tamara,[16-18] Suzuki,[19] and

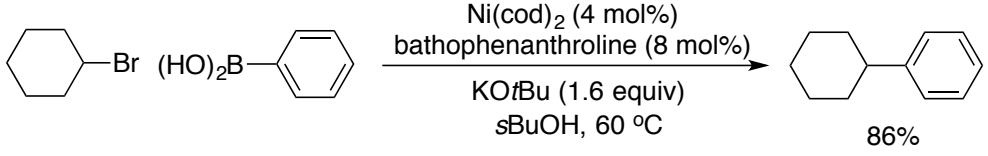
Knochel[20] demonstrated the feasibility of using unactivated alkyl halides as electrophiles in transition-metal catalyzed cross-coupling reactions. At the beginning of the 21st century, there was a surge in the number of publications on cross-coupling reactions of unactivated alkyl halides, contributing to the significant progress in this area.

In 2003, Zhou and Fu reported Negishi coupling with unactivated alkyl halides and tosylates (Scheme 1.4). [21] A wide array of alkyl and alkenylzinc reagents reacted well with $Pd_2(dba)_3/PCyp_3$ or $Pd_2(dba)_3/[HPCyp_3]BF_4$ catalysts in the presence of *N*-methylimidazole (NMI) to give the alkylated product with moderate to good yield. Various functional groups such as ethers, nitriles and esters are well tolerated on both alkyl halides and zinc reagents. Two examples of cross-coupling of alkyl halides with arylzinc reagents were reported with moderate yield.



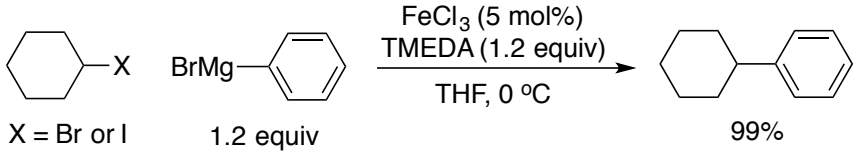
Scheme 1.4 Zhou and Fu's Negishi coupling using unactivated alkyl halides

In 2004, Zhou and Fu developed Suzuki coupling of unactivated secondary alkyl halides (Scheme 1.5).[22] $Ni(cod)_2$/bathophenanthroline effectively catalyzed the cross-coupling of arylboronic acids with unactivated primary and secondary alkyl bromides and iodides to afford the desired alkylated product with moderate to good yield. Electron-rich and electron-poor arylboronic acids reacted smoothly, and some heteroaryl and alkenylboronic acids were tolerated as well.



Scheme 1.5 Zhou and Fu's Suzuki coupling using unactivated alkyl halides

Nakamura and co-workers also reported Fe-catalyzed Kumada cross-coupling of aryl Grignard reagents with unactivated primary and secondary alkyl halides in 2004 (Scheme 1.6).[23] TMEDA is essential as it suppressed olefin formation from alkyl halides, and the slow addition of Grignard reagent and TMEDA to the solution of catalyst and alkyl halides provided high yields of the desired products. Electron-rich aryl Grignard reagents afforded the corresponding alkylated products in near quantitative yield, while electron-poor (4- trifluoromethylphenyl)magnesium bromide only gave the product in 67% yield. Alkyl bromides and iodides reacted equally well, but reactions using alkyl chlorides might require a higher temperature and a greater excess of Grignard reagents.



Scheme 1.6 Nakamura's Fe-catalyzed Kumada coupling of aryl Grignard reagents with unactivated alkyl halides

Since such cross-coupling reactions require aryl metal reagents, it is less atom-economical and extra synthetic steps might be required for the preparation of these aryl metal reagents. It will be more convenient if alkylation can occur directly on the C-H bonds of the arenes.

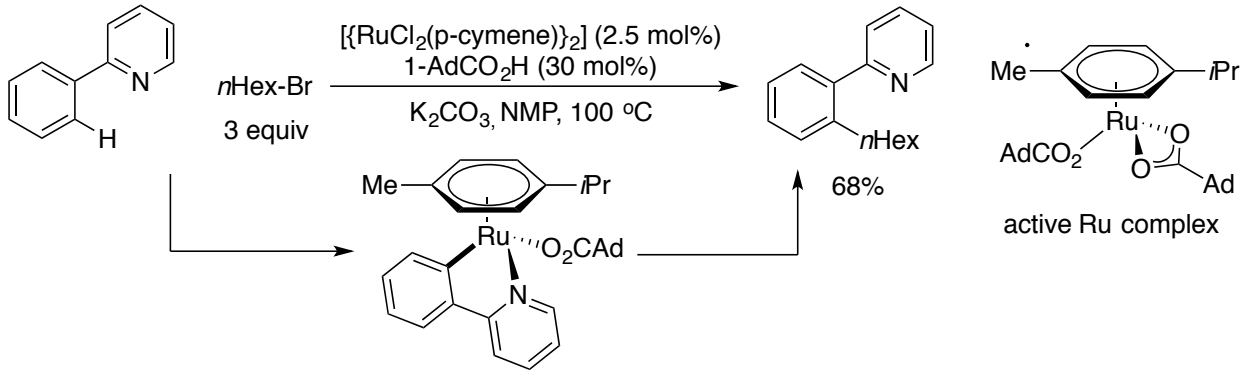
1.4 Transition metal-catalyzed C-H alkylation

Significant success has been achieved with the direct C-H alkylation of arenes using unactivated alkyl halides. Various noble transition metals such as palladium, rhodium, ruthenium and even first row transition metals like nickel, cobalt and iron have been demonstrated to catalyze such transformations. Such metal-catalyzed C-H alkylation reactions can be classified into two major categories: chelation-assisted C-H alkylation and free radical alkylation.

1.4.1 Examples of chelation-assisted C-H alkylation catalyzed by noble metals

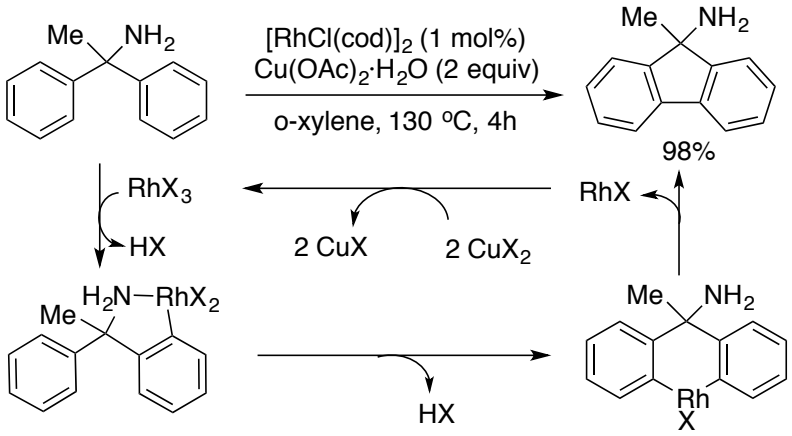
Due to similar bond dissociation energies of different C-H bonds in arenes, it is challenging to achieve site selectivity in C-H alkylation of arenes. In order to overcome this inherent selectivity issue, directing groups are often employed to control the alkylation process. Nitrogen-containing groups are often used as they have higher affinity to metal centers in general, which can in turn direct metal centers to the *ortho* sites. Many examples of the chelation-assisted C-H alkylations of the *ortho* sites have been reported, while reports of the C-H alkylations of other sites remain scarce.

Ackermann et al. reported Ru-catalyzed alkylation of arenes using unactivated alkyl halides (Scheme 1.7). [24] Carboxylic acid was essential to produce a ruthenium carboxylate complex as the active catalyst, and both phenylpyridine and pyrazole derivatives were successfully alkylated at the *ortho*-positions. Primary alkyl bromides reacted with good to excellent yields while secondary alkyl bromides gave lower yields. Neopentyl bromide furnished the desired product in 57% yield without isomerization, indicating that the reaction did not take place via electrophilic aromatic substitution and nucleophilic substitution. If the reaction occurred via electrophilic aromatic substitution or S_N1 nucleophilic substitution, neopentyl cations would be formed and this might result in the isomerization in final product. Also since neopentyl bromide reacted well, S_N2 mechanism could be rule out as neopentyl bromide would react poorly due to steric hindrance from *t*Bu group.



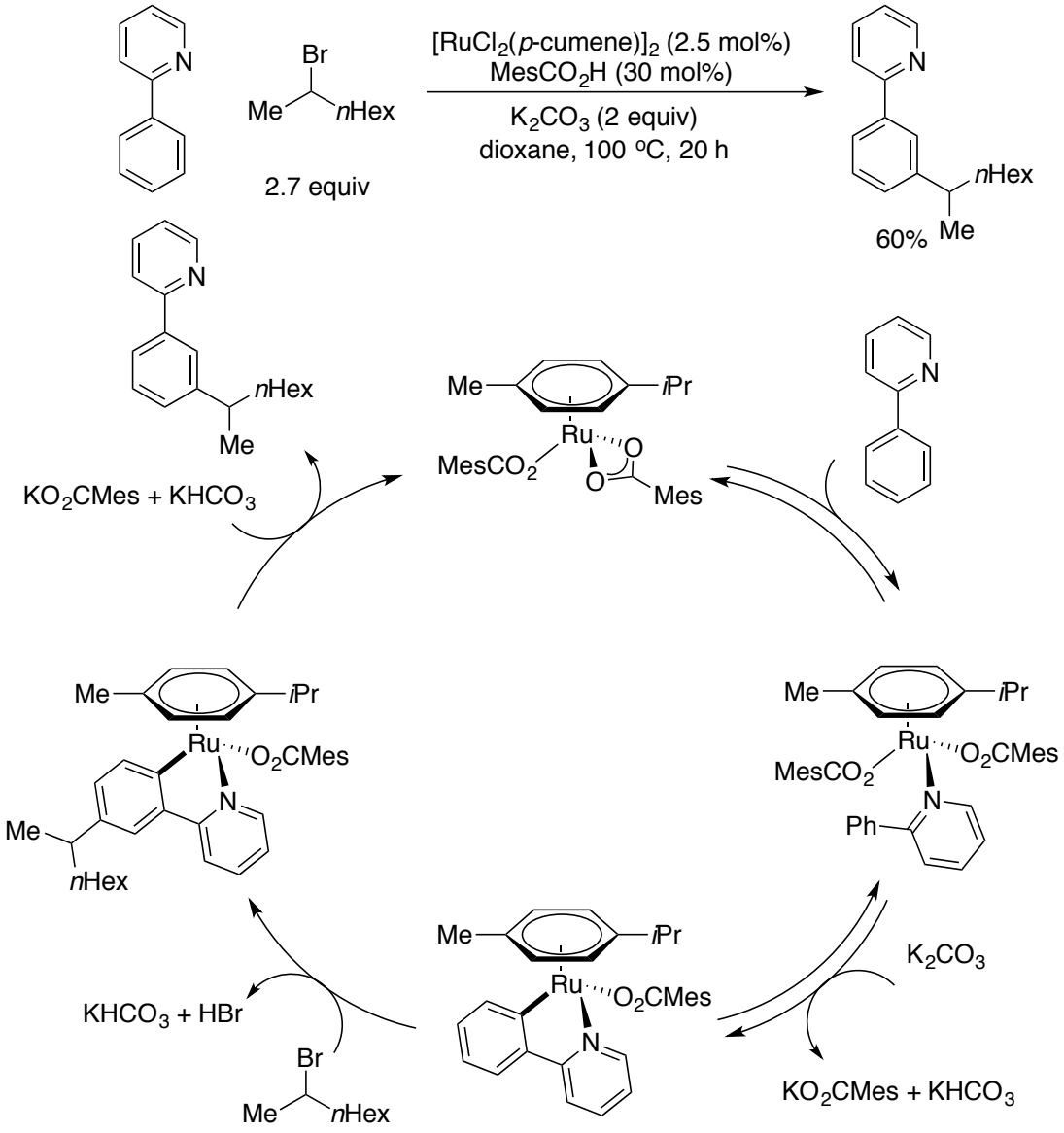
Scheme 1.7 Ackermann's Ru-catalyzed alkylation of arenes with unactivated alkyl halide

In 2012, Miura et al. reported a rhodium-catalyzed dehydrogenative cyclization to form fluorene derivatives (Scheme 1.8).[25] Using amine as directing group, 1-amino-1,1-diarylalkanes cyclized at high temperature of 130 ^{o}C to give fluorene derivatives with good to excellent yields. $Cu(OAc)_2$ first oxidized Rh^{I} to the active Rh^{III} complex, and then amino-group directed the rhodium center to *ortho* site, forming a five-membered rhodacycle. The rhodium center then inserted into the second *ortho* C-H bond, forming a six-membered rhodacycle, followed by reductive elimination to give the cyclized product.



Scheme 1.8 Miura's rhodium-catalyzed dehydrogenative cyclization

In 2013, Ackermann and co-workers reported a Ru-catalyzed *meta*-C-H alkylation of arenes (Scheme 1.9).[26] They successfully alkylated 2-phenylpyridine, 2-phenylpyrimidine and 2-phenylazole at the *meta* positions. Simple cyclic and acyclic secondary alkyl bromides reacted well with moderate to good yields. It was found that when 2-(4-methoxyphenyl)pyridine and 2-(4-fluorophenyl)pyridine were simultaneously present in the reaction, 2-(4-methoxyphenyl)pyridine reacted at a faster rate, indicating that alkyl halides were acting as electrophiles. 2-Phenylpyridine reacted with [(cumene)Ru($MesCO_2$)$_2$] to form a key metalacycle, after which electrophilic alkylation took place at the *meta* site of the arene.

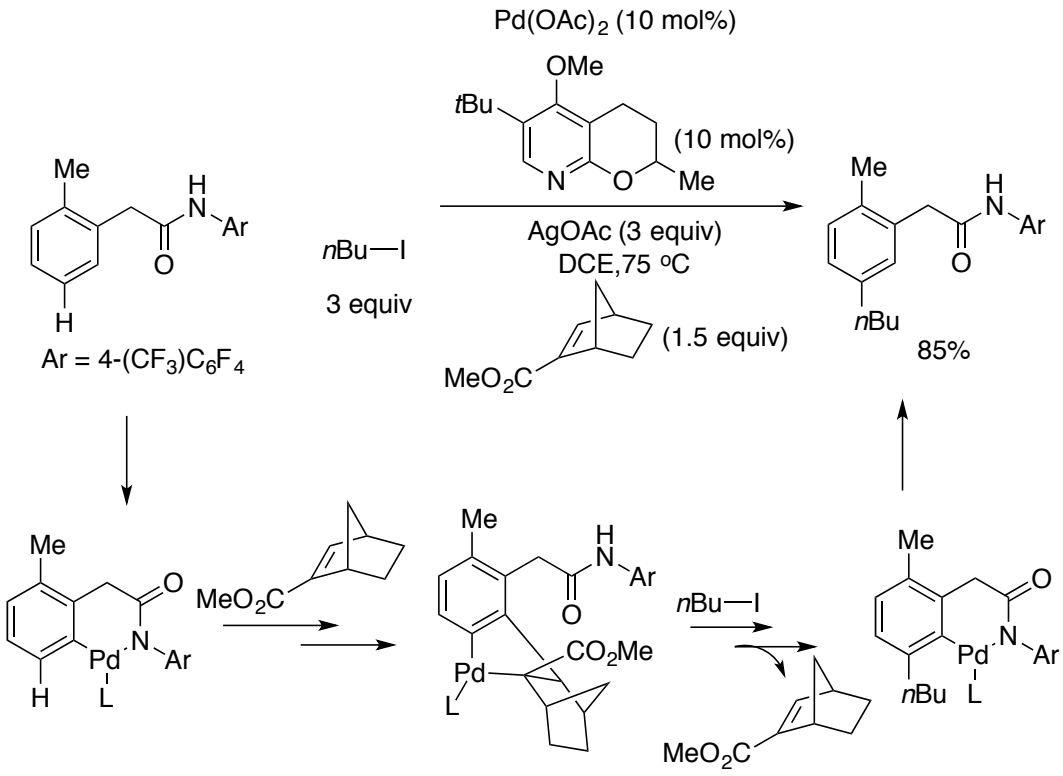


Scheme 1.9 Ackermann's Ru-catalyzed meta-C-H alkylation

Aside from nitrogen-containing functional groups, norbenenes also serve as auxiliaries for C-H activations in Catellani reactions. Catellani reaction is a classical reaction utilizing palladium-catalyzed C-H activation,[27,28] which is developed by Catellani and co-workers in 1997.[29]

In 2015, Yu and co-workers made a major breakthrough in *meta*-C-H activation. Catalyzed by $Pd(OAc)_2$ and a pyridine-based ligand, substrates with *ortho*-directing groups were methylated and benzylated at the remote *meta* position by utilizing norbornene as a transient mediator.[30] His

group later found that the presence of electron-withdrawing ester group on norbornene allowed a wider range of primary alkyl iodides to participate in the reaction, giving the alkylated products in good yields (Scheme 1.10).[31]

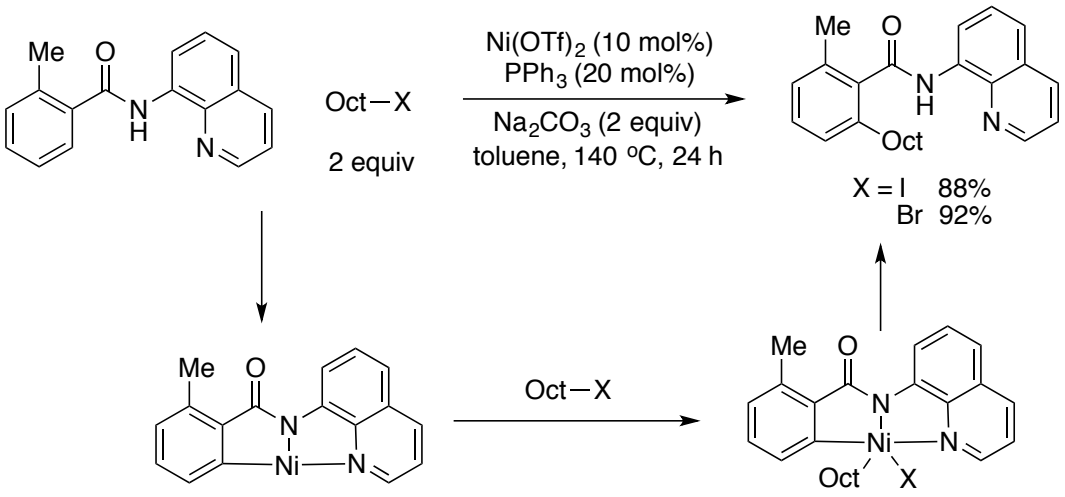


Scheme 1.10 Yu's palladium-catalyzed norbornene-mediated *meta*-C-H alkylation

1.4.2 Examples of chelation-assisted C-H alkylation catalyzed by first-row metals

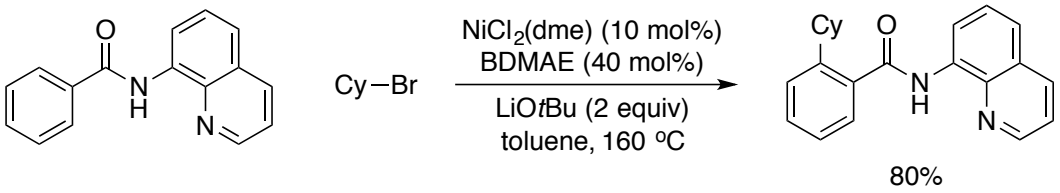
Besides noble metals, first-row transition metals can also effectively catalyze such chelation-assisted C-H alkylations.

In 2003, Chatani and co-workers reported a nickel-catalyzed direct C-H alkylation of benzamides using primary alkyl halides.[32] The C-H alkylation was directed by a bidentate 8-quinolylamide carboxamide and catalyzed by a simple $Ni(OTf)_2/PPh_3$ catalyst. Primary alkyl chlorides, bromides and iodides were suitable substrates for the reaction. A Ni(II)/Ni(IV) catalytic cycle was proposed as shown below (Scheme 1.11). The bidentate auxillary facilitated the formation of a nickelacycle on benzamide after cleavage of the *ortho* C-H bond, and oxidative addition of alkyl halide occurred followed by reductive elimination to give the alkylated product.



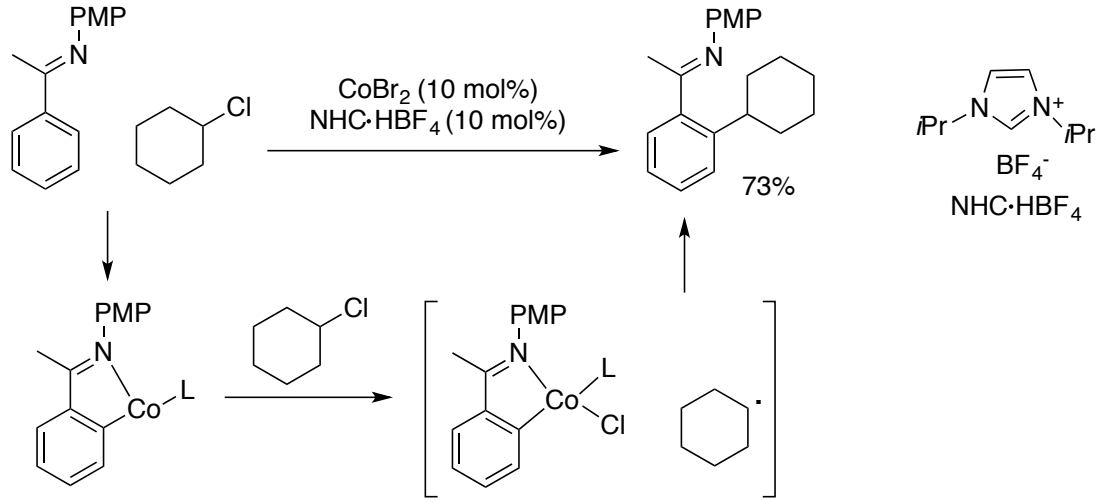
Scheme 1.11 Chatani's Ni-catalyzed bidentate-chelation assisted C-H alkylation of benzamides

Ackermann later reported a similar alkylation of benzamide using secondary alkyl bromides catalyzed by $NiCl_2$(DME) and 2-(dimethylamino)ethyl ether (BDMAE).[33] (Scheme 1.12). Unactivated secondary alkyl bromides and chlorides reacted well to afford the alkylated products in moderate to good yields, and trifluoroethyl iodide is a suitable alkylating agent as well.



Scheme 1.12 Ackermann's Ni-catalyzed chelation assisted secondary alkylation of benzamides

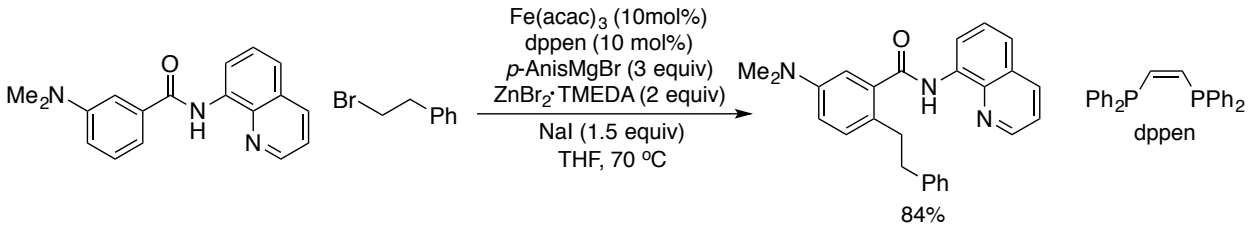
Yoshikai and co-workers published a cobalt/NHC-catalyzed alkylation of ketimines and 2-phenylpyridine with primary and secondary alkyl bromides and chlorides (Scheme 1.13). [34,35] Based their own experimental observations and previous work on cobalt-catalyzed free radical cyclization by Oshima and co-workers, [36] a catalytic process involving a radical intermediate was proposed. The imine group directed insertion of the cobalt centre onto the *ortho* C-H bond and resulted in a cobaltacycle which then reacted with alkyl chloride to give the alkylated product.



Scheme 1.13 Yoshikai's cobalt/NHC-catalyzed alkylation of phenyl imines and 2-phenylpyridine with simple alkyl halides

Nakamura and co-workers also reported an iron-catalyzed alkylation of olefins, arenes and heteroarenes with alkyl tosylates and halides, using 8-aminoquinolyl carboxamide group as auxiliary (Scheme 1.14).[37] The use of *p*-AnisMgBr together with $ZnBr_2$·TMEDA suppressed unwanted side coupling of the Grignard reagents with alkyl tosylates or halides and the

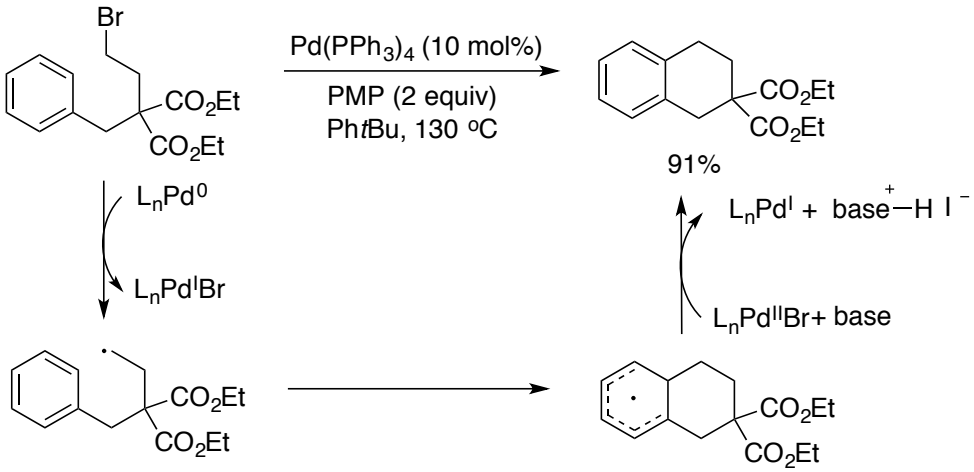
homocoupling of the Grignard reagents. Desired alkylated products were obtained in moderate to excellent yields.



Scheme 1.14 Nakamura's Fe-catalyzed alkylation of olefins, arenes and heteroarenes

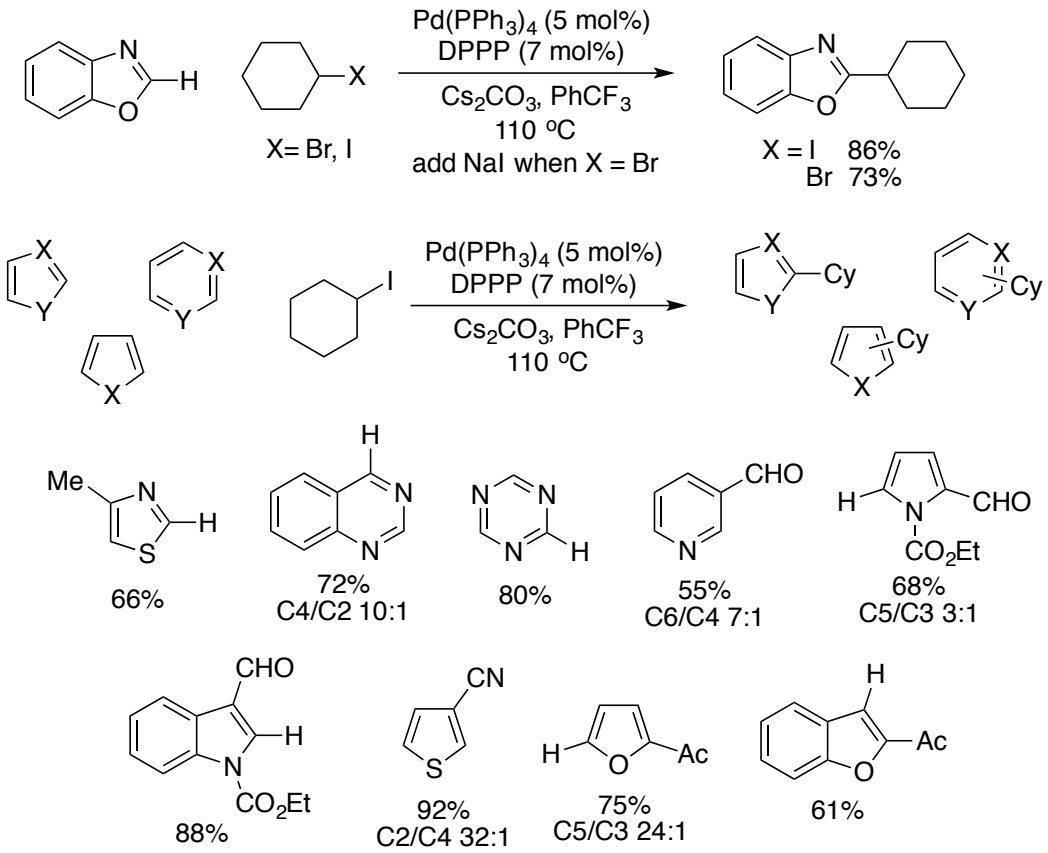
1.4.3 Palladium-catalyzed free radical alkylation of arenes and heteroarenes

In 2015, Alexanian et al. reported a palladium-catalyzed intramolecular free radical alkylation of arenes and heteroarenes with pendant alkyl halides to produce the corresponding products in high yields (Scheme 1.15).[38] The reaction was catalyzed by commercially available $Pd(PPh_3)_4$, and 1,2,2,6,6-pentamethylpiperidine (PMP) was used as the base for reactions of alkyl bromides whereas K_3PO_4 was used for those of alkyl iodides. The alkyl halide first reacted with $Pd(PPh_3)_4$ to generate an alkyl radical. The alkyl radical then attacked the adjacent aryl ring, and the radical then rearomatization to form the cyclized product. The desired products were obtained in moderate to excellent yields despite the high reaction temperature.



Scheme 1.15 Alexanian's palladium-catalyzed intramolecular alkylation of unactivated alkyl halides

In the recent years, Dr. Xiaojin Wu from our group reported a versatile palladium-catalyzed free radical alkylation of heteroarenes (Scheme 1.16).[39] Using benzoxazole as a model substrate in the presence of $Pd(PPh_3)_4$/DPPP catalyst, Dr. Wu found that a wide array of secondary and tertiary alkyl bromides and iodides reacted well to give alkylated products with moderate to good yields. When alkyl bromides were used, sodium iodide was added to afford the alkylated products in moderate to good yields. It is suggested that sodium iodide facilitated the formation of alkyl iodides from alkyl bromides, which were the actual reactants of the reaction. A wide variety of heterocycles, such as pyridines, pyrroles, furans and thiophenes were successfully alkylated, and the presence of electron-withdrawing groups such as aldehydes, acetates and nitriles were crucial for substrate activations and site selectivities.



Scheme 1.16 Zhou's palladium-catalyzed alkylation of benzoxazole and other heteroarenes

1.5 Results and discussion

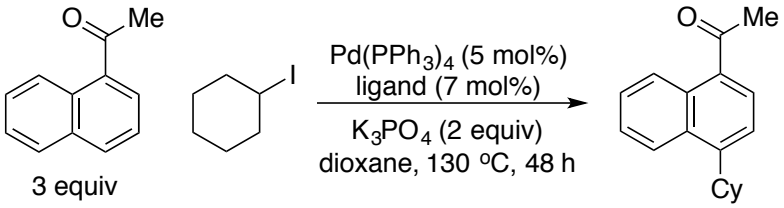
Friedel-Crafts alkylation and transition-metal catalyzed cross-couplings are two common methods to prepare alkylated arenes. However, the substrate scope of Friedel-Crafts alkylation is generally limited to electron-rich arenes and cross-coupling reactions require the preactivation of the aryl substrates. Transition-metal catalyzed C-H alkylation provides an atom-economical alternative for the synthesis of alkylated arenes. In the recent years, there have been many publications on chelation-assisted C-H alkylations. However, they require the presence of directing groups and site selectivities are often limited to *ortho* position. We envisioned that the less explored transition-metal catalyzed free radical C-H alkylation can provide a more versatile

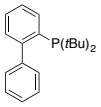
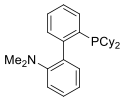
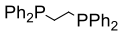
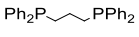
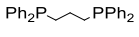
method for the synthesis of alkylated arenes as no directing groups are needed and the alkylations are possible at the *ortho*, *meta* and *para* sites. Inspired by the previous work in our lab by Dr. Xiaojin Wu, we attempted to expand our palladium-catalyzed free radical alkylation reaction to apply to activated benzene and naphthalene derivatives.

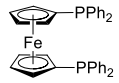
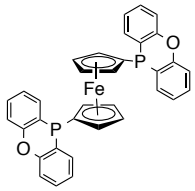
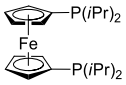
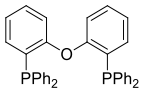
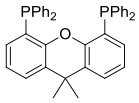
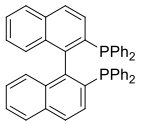
1.5.1 Condition optimization of Pd-catalyzed alkylation of isophthalaldehyde

Based on our previous experience on alkylation of unsaturated heterocycles, electron-deficient aromatic compounds should be more susceptible to radical alkylation. Using isophthalaldehyde and iodocyclohexane as model substrates, we began to find a suitable ligand for palladium catalysis. Commercially available phosphine ligands such as Buchwald ligands, PPh_3, PCy_3 and DPEPhos all gave good yields of the desired product (Table 1.3). Notably, good yield was obtained even without added phosphines (Table 1.3, entry 20). However, upon testing the alkylations of other arenes, we found that a homemade ferrocene-based ligand, DPxPF, was the best ligand as it enabled the alkylation of a wide range of arenes (Table 1.1 and 1.2). For the alkylation of methyl benzoate, low yields of 15-41% were obtained and crude ^{1}H NMR revealed cyclohexene as the by-product.

Table 1.1 Effect of ligands for alkylation of 1-acetonaphthone

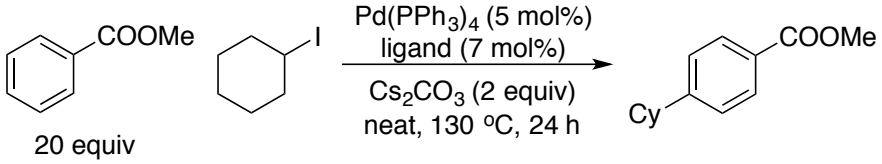


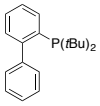
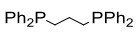
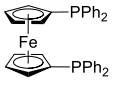
Entry	Ligand	Conversion of iodocyclohexane (based on 100%)	Conversion of acetonaphthone (based on 300%)	GC Yield (%)	C4/C2 Selectivity
1	no ligand	100	98	41	8.4:1
2	 JohnPhos	100	98	49	8.5:1
3	 DavePhos	100	104	42	8.9:1
4	PCy_3	100	131	56	8.3:1
5	tBu$_3$PHBF$_4$	100	122	40	9.3:1
6	 DPPE	100	147	68	8.2:1
7	 DPPP	100	156	75	8.8:1
8	 DPPB	100	118	76	7.9:1

9	 DPPF	100	106	60	6.8:1
10	 **DPxPF**	**100**	**121**	**87**	**9.1:1**
11	 D*i*PPF	100	109	65	6.9:1
12	 DPEPhos	100	122	79	8.7:1
13	 Xantphos	100	105	62	7.1:1
14	 rac-BINAP	100	117	70	7.7:1
15	DPxPF (110 ^{o}C)	100	118	81	9.2:1
16	DPxPF Arene (1.5 equiv)	100	86/150	69	9.1:1

	CyI (1 equiv)				
17	DPxPF				
	Arene (1 equiv)	150/150	79/100	75	9.1:1
	CyI (1.5 equiv)				

Table 1.2 Effect of ligands for alkylation of methyl benzoate



Entry	Ligand	Conversion of iodocyclohexane (based on 100%)	GC Yield (%)
1	no ligand	58	18
2	 JohnPhos	66	16
3	PCy_3	88	30
4	tBu$_3$PHBF$_4$	97	15
5	 DPPB	82	32
6	 DPPF	96	40

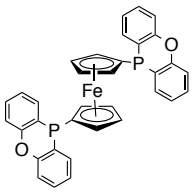
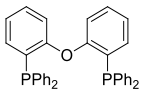
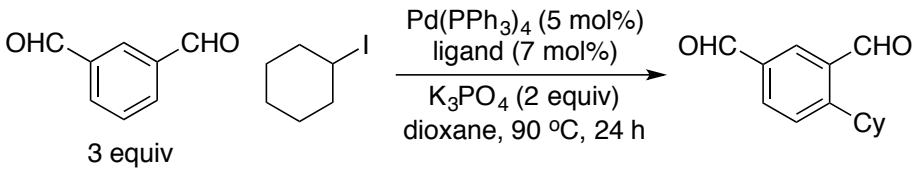
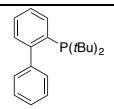
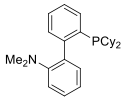
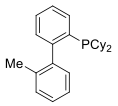
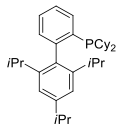
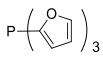
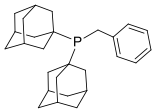
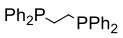
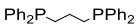
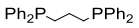
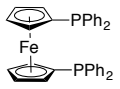
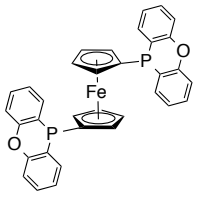
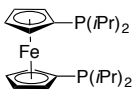
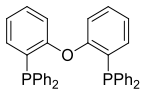
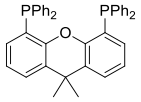
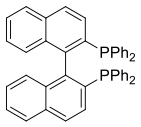
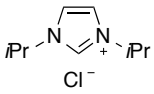
7	 **DPxPF**	**97**	**36**
8	 DPEPhos	96	41

Table 1.3 Effect of ligands for alkylation of isophthalaldehyde



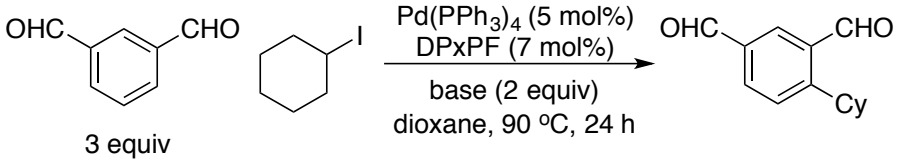
Entry	Ligand	Conversion of iodocyclohexane (based on 100%)	Conversion of isophthalaldehyde (based on 300%)	GC Yield (%)
1	 JohnPhos	100	96	88
2	 DavePhos	99	158	72
3	 MePhos	100	126	88

4	 XPhos	100	105	87
5	PPh_3	100	93	88
6		100	105	88
7	PCy_3	100	89	88
8	tBu$_3$PHBF$_4$	100	113	86
9		100	114	77
10	 DPPE	99	156	72
11	 DPPP	96	138	84
12	 DPPB	96	131	84
13	 DPPF	98	136	80
14	 **DPxPF**	**100**	**105**	**86**

15		98	165	61
	D*i*PPF			
16		100	98	87
	DPEPhos			
17		95	133	79
	Xantphos			
18		100	137	65
	rac-BINAP			
19		91	165	57
20	no ligand	100	92	87

Screening of bases showed that K_3PO_4, K_2CO_3 and even weak inorganic bases such as $KHCO_3$ and CsF gave the product in good yield (Table 1.4, entries 1, 3, 4 and 12). No products were obtained when strong bases such as NaOMe, NaO*t*Bu and KO*t*Bu were used (Table 1.4, entries 8-10).

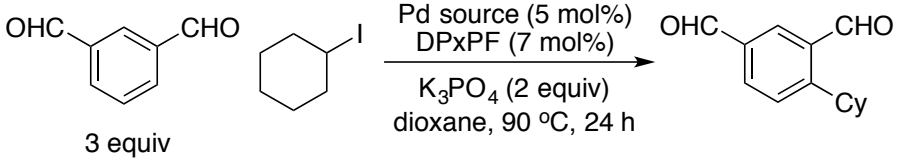
Table 1.4 Effect of bases in alkylation of isophthalaldehyde



Entry	Base	Conversion of iodocyclohexane (based on 100%)	Conversion of isophthalaldehyde (based on 300%)	GC Yield (%)
1	**K_3PO_4**	**100**	**105**	**88**
2	K_3PO_4.•H_2O	100	147	78
3	K_2CO_3	100	99	85
4	$KHCO_3$	98	87	82
5	Cs_2CO_3	99	178	54
6	CsOPiv	100	118	60
7	NaOH	94	273	34
8	NaOMe	100	291	0
9	NaO*t*Bu	100	300	0
10	KO*t*Bu	100	300	0
11	CsOH•H_2O	98	278	61
12	CsF	100	90	83
13	Et_3N	71	53	21
14	*i*Pr_2NEt	29	26	13

In alkylation reactions of isophthalaldehyde, we found that the alkylated products were obtained in good yields with either palladium(0) or palladium(II) precatalysts. $Pd(PPh_3)_4$ was chosen for further studies since it gave the best yield (Table 1.5, entry 1).

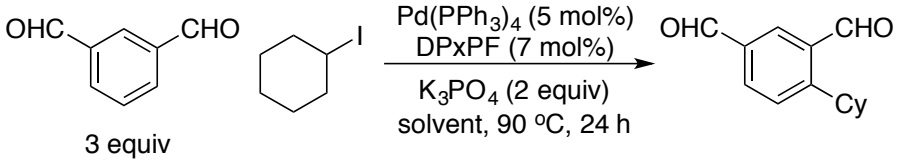
Table 1.5 Effect of palladium sources in alkylation of isophthalaldehyde



Entry	Palladium source	Conversion of iodocyclohexane (based on 100%)	Conversion of isophthalaldehyde (based on 300%)	GC Yield (%)
1	**$Pd(PPh_3)_4$**	**100**	**104**	**87**
2	$Pd(dba)_2$	59	62	52
3	$Pd_2(dba)_3$	94	97	70
4	$Pd(OAc)_2$	88	108	71
5	$Pd(TFA)_2$	95	99	82
6	$Pd(hfacac)_2$	89	92	78
7	$PdCl_2$	29	224	13

In model reactions of isophthalaldehyde and iodocyclohexane, we established that ethereal solvents, such as dioxane, THF and diglyme, and some aromatic solvents worked best. We chose dioxane as the the optimal solvent, which gave the highest yield among all.

Table 1.6 Effect of solvents in alkylation of isophthalaldehyde

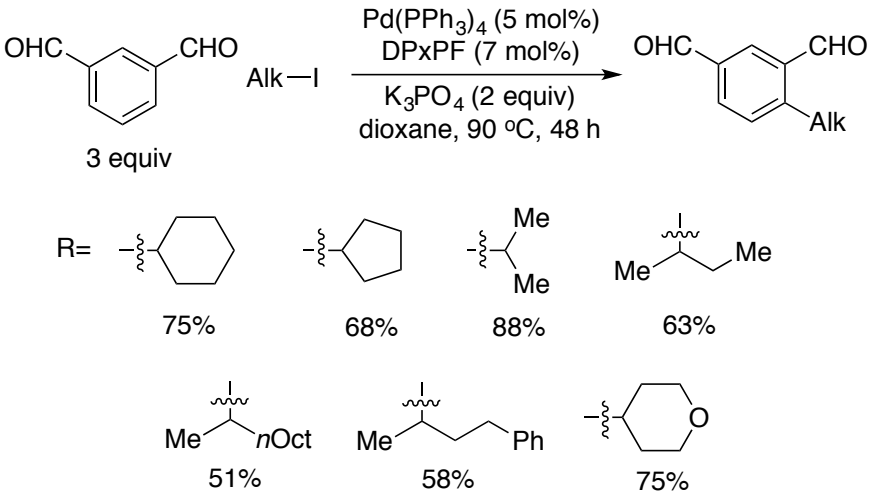


Entry	Solvent	Conversion of iodocyclohexane (based on 100%)	Conversion of isophthalaldehyde (based on 300%)	GC Yield (%)
1	dioxane	95	100	89
2	THF	100	123	75
4	CPME	75	90	58
5	diglyme	100	153	52
6	triglyme	100	165	23
7	PhOMe	98	104	86
8	PhMe	77	80	65
9	$PhCF_3$	89	94	71
10	DMF	86	212	25
11	DMA	100	261	12
12	DMSO	100	215	3

1.5.2 Substrate scope of Pd-catalyzed alkylation of arenes

With the optimized conditions in hand, we tested different secondary alkyl iodides and arenes to investigate the substrate scope of the reaction. Both cyclic and acyclic secondary alkyl iodides reacted well with isophthalaldehyde to give the desired product in moderate to good yields (Scheme 1.17). The oxygen-containing 4-iodotetrahydropyran also reacted well to give a

good yield of 75%. Alkylation of isophthalaldehyde with 1-iodohexane and 2-iodo-2-methylpropane were attempted, and only trace amount of alkylated products (<10%) were detected for both instances. Alkylation between isophthalaldehyde and bromocyclohexane was also attempted with NaI or KI as additive, but only a trace amount of alkylated product was detected and most of the bromocyclohexane remained unreacted.



Scheme 1.17 Substrate scope of alkyl iodides

To investigate the selectivity of the reaction, the LUMO of isophthalaldehyde was calculated using the Hartree-Fock method (Figure 1.18). It is noted that the cyclohexyl radical added to the position having the largest atomic coefficient in the LUMO of the aromatic ring.

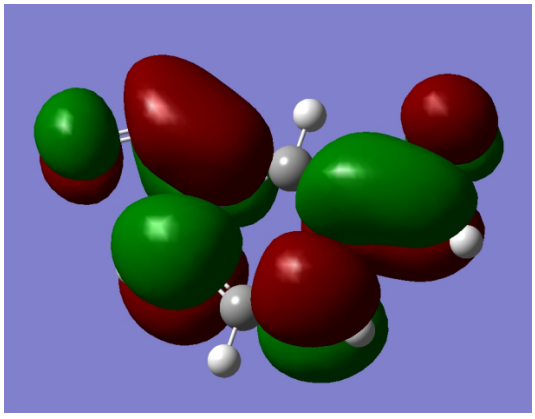
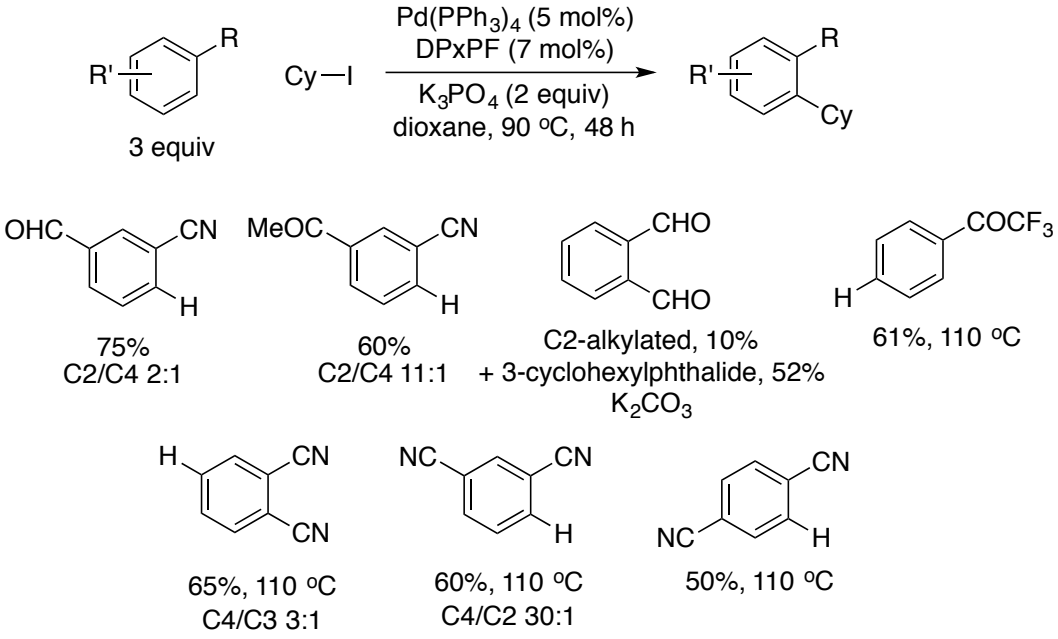


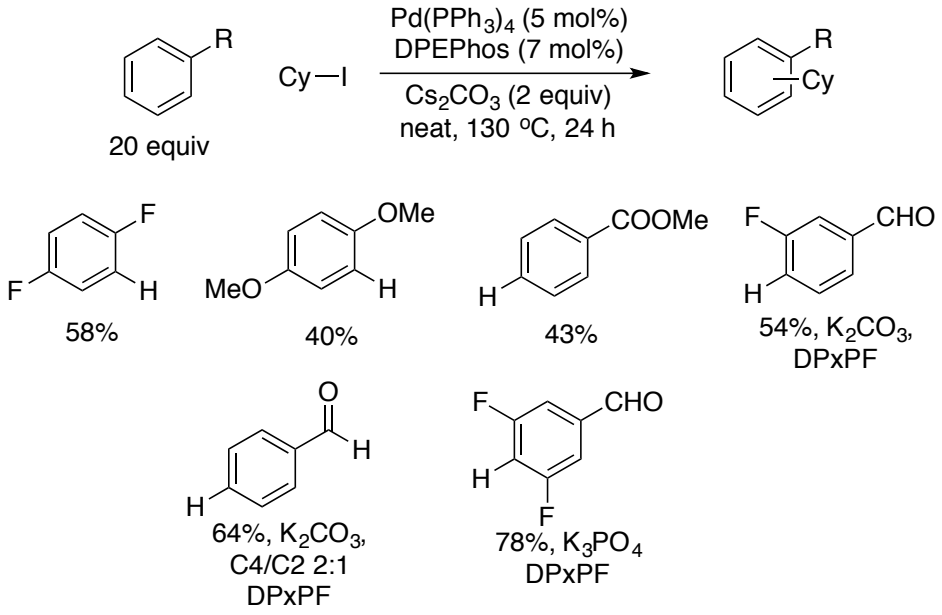
Figure 1.18 LUMO of isophthalaldehyde was calculated using the Hartree-Fock method

Various doubly activated benzene derivatives reacted under the reaction conditions to give the alkylated products with moderate to good selectivity. Functional groups such as aldehydes, ketones and nitrile were well-tolerated. The selectivity was predominantly determined by electronic and steric factors of electron-withdrawing groups. For 1,3-disubstituted arenes such as 3-formylbenzonitrile and 3-acetylbenzonitrile, the alkyl chain underwent addition predominantly to the para positions of the aldehyde and ketone groups (Scheme 1.19).



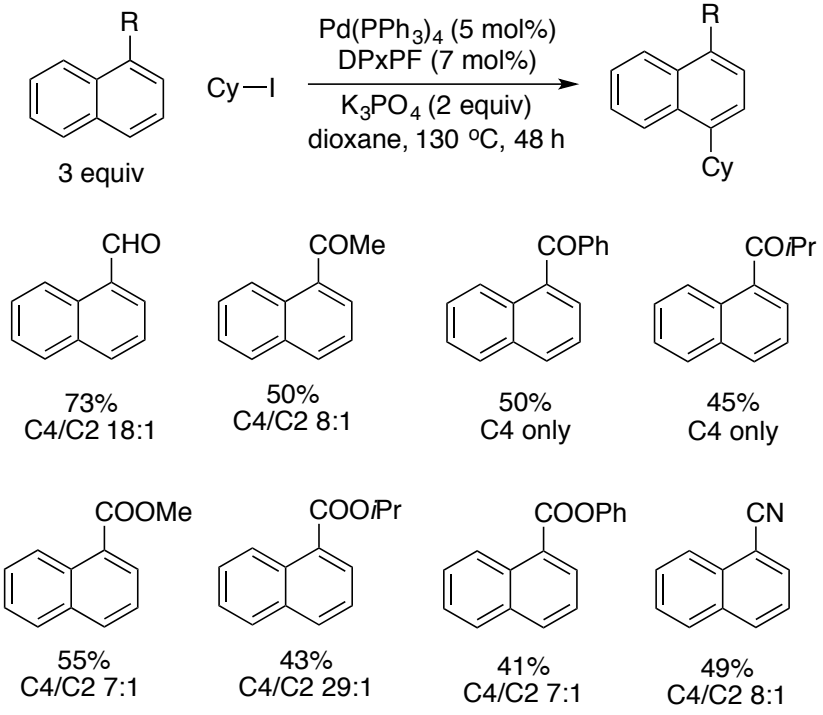
Scheme 1.19 Substrate scope of doubly activated arenes under standard optimum condition

For less reactive arenes, the reaction was carried out under neat condition using DPxPF or DPEPhos with 20 equivalents of arenes. Electron-rich and electron-deficient arenes reacted to give the alkylated products with moderate to good yields. For methyl benzoate and 3-fluorobenzaldehyde, the C4 alkylated products were exclusively formed. For benzaldehyde, *para* position is slightly preferred to the *ortho* position with a selectivity of 2:1 (Scheme 1.20).



Scheme 1.20 Substrate scope of activated arenes under neat condition

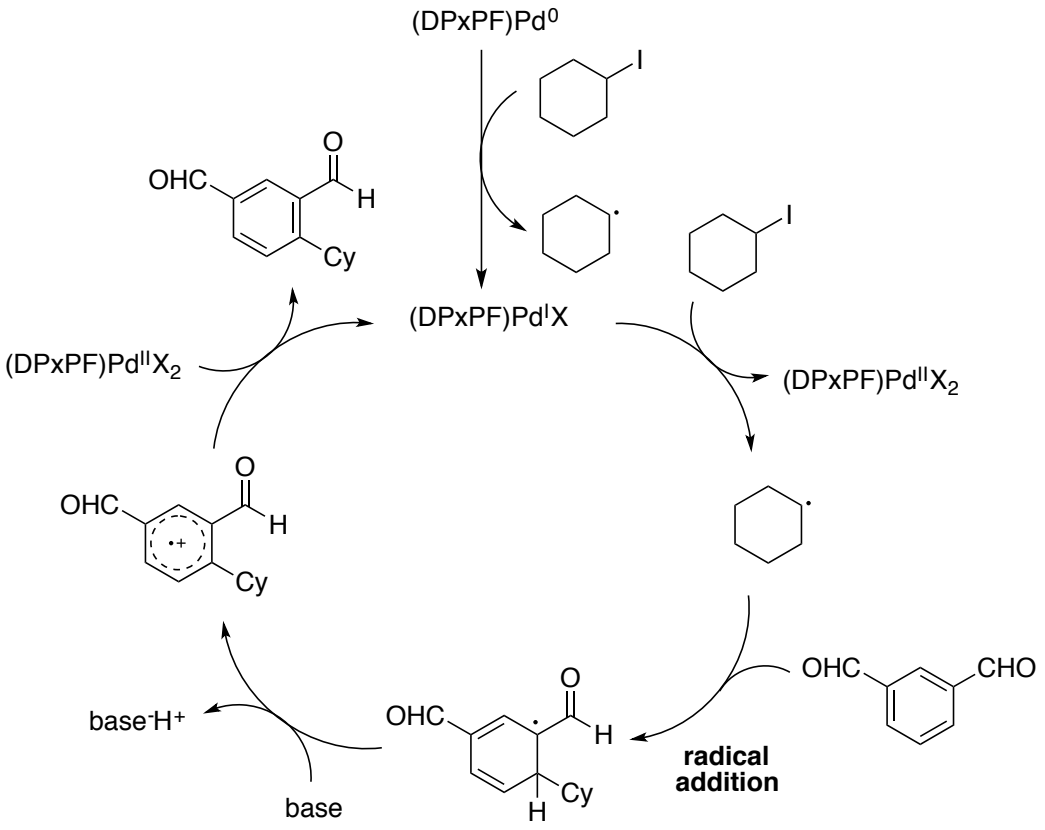
1-Substituted naphthalenes also reacted well to give C4-alkylated products as major products in moderate to good yields (Scheme 1.21). The selectivities increased along with the increase of the electron-withdrawing abilities of the substituents. For example, when the substituents were esters and nitriles, the regioselectivity was <10:1. In comparison, substrates bearing ketone and aldehyde groups exhibited higher selectivities in general.



Scheme 1.21 Examples of alkylation of activated naphthalenes

1.5.3 Proposed mechanism for Pd-catalyzed alkylation of arenes

The radical mechanism of alkylation is proposed as follows (Scheme 1.22).

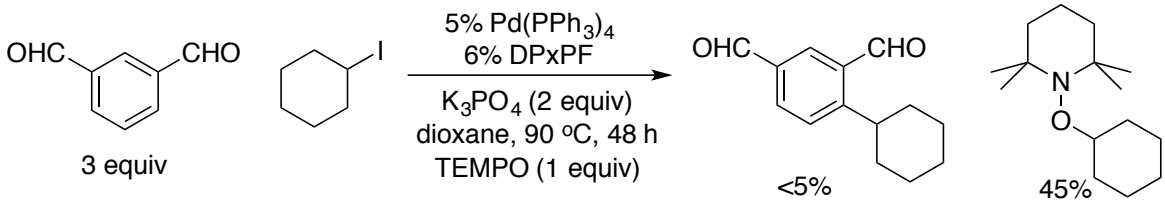


Scheme 1.22 A proposed catalytic cycle of Pd-catalyzed free radical alkylation of arenes

Iodocyclohexane first reacts with (DPxPF)Pd^0 via halogen abstraction to generate a cyclohexyl radical. A second halogen abstraction results in the formation of (DPxPF)$Pd^{II}X$, and a second cyclohexyl radical. Cyclohexyl radical then adds to isophthalaldehyde selectively to the C2-position. The alkylated arene radical is then deprotonated by the base to form a radical anion. The latter transfers an electron back to (DPxPF)$Pd^{II}X^2$ to generate (DPxPF)$Pd^{I}X$.

A radical trapping experiment was conducted to investigate the mechanism of the reaction (Scheme 1.23). The alkylation of isophthalaldehyde was effectively inhibited when one equivalent of TEMPO was added to the reaction. *N*-Cyclohexyl-TEMPO was afforded in significant amount

and only a trace amount of the desired alkylated product was detected. This supports our claim in which the reaction proceeds via a radical mechanism.



Scheme 1.23 Radical trapping experiment using TEMPO

1.6 Conclusion

We have reported a selective radical alkylation of electron-deficient arenes catalyzed by a palladium complex. Benzene and naphthalene derivatives bearing one electron-withdrawing group reacted to give the alkylated products in moderate to good yields. Alkyl radicals underwent addition selectively to the *para* positions to electron-withdrawing groups in most cases. This radical alkylation method complements with traditional Friedel-Crafts alkylation, which is generally limited to electron-neutral and electron-rich arenes.[40]

1.7 Experimental

1.7.1 General

^{1}H NMR spectra were acquired on Bruker 400 MHz spectrometers and chemical shifts were recorded relative to tetramethylsilane (δ 0.00) or residual protiated solvent ($CDCl_3$: δ 7.26). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH. Coupling constants were reported as a *J* value in Hz. ^{13}C NMR spectra were obtained at 100 MHz on 400 MHz and chemical

shifts were recorded relative to solvent resonance ($CDCl_3$:δ 77.16). $^{31}P\{^1H\}$ NMR spectra were obtained at 162 MHz on 400 MHz instrument. Proof of purity of new compounds was demonstrated with copies of ^1H, ^{13}C, $^{31}P\{^1H\}$ and $^{19}F\{^1H\}$ NMR spectra.

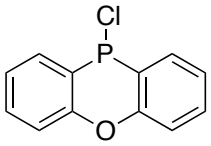
Glassware was dried in an oven at 120 ^oC for at least 2 hours before use. Anhydrous dioxane was purchased from Sigma Aldrich and was stored over activated 4 Å molecular sieve beads in an argon-filled glovebox before use. Dry hexane, diethyl ether and dichloromethane were collected from a solvent purification system containing a column of activated alumina (1 m x 2) under argon. Dry THF was freshly distilled from sodium/benzophenone under argon before use. All of anhydrous solvents were stored in Schlenk tubes in an argon-filled glove box.

Unless noted otherwise, commercially available chemicals were used without further purification. Anhydrous K_3PO_4 is obtained from Sigma-Aldrich (catalog number: RDD019 SIGMA). Dry diisopropylethylamine (DIPEA) and triethylamine were distilled from CaH_2 under argon before use. The GC standard, *n*-tetradecane was degassed with argon bubbling and dried over activated 4 Å molecular sieve beads for a few days in the glovebox before use.

Thin-layer chromatography (TLC) was conducted with Merck 60 F254 coated silica gel plate (0.2 mm thickness). Flash chromatography was performed using Merck silica gel 60 (0.040-0.063 mm).

Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with Agilent J & W GC column DB-5MS-UI. GCMS analysis was conducted on a Thermo Scientific DSQ II single quadrupole GC/MS instrument with Agilent J & W GC column DB-5MS-UI. ESI/MS analysis was conducted on a ThermoFinnigan LCQ Fleet MS spectrometer.

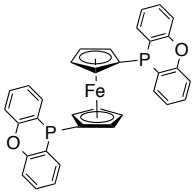
1.7.2 Synthesis of DPxPF



10-Chlorophenoxaphosphine [95725-42-1]. This compound was synthesized with slight modification from van Leeuwen's procedure.[41] In an argon-filled glovebox, $AlCl_3$ (2.0 g, 15 mmol), diphenyl ether (1.6 mL, 10 mmol) and PCl_3 (3.5 mL, 40 mmol) was added to a 25 mL dry Schlenk tube. The tube was capped tightly and stirred at 100 ^oC for 8 h. After which, the reaction was cooled to room temperature and PCl_3 was removed *in vacuo*. Dry toluene (20 mL) was added to dissolve the foamy orange solid obtained and pyridine (2.4 mL, 30 mmol) was then added dropwise at room temperature. The reaction was stirred at room temperature for an additional hour. (The reaction was heated using a heat gun from time to time for easy stirring as it turned very viscous after stirring.) After stirring was completed, the reaction was filtered in an argon-filled glovebox to remove the sticky solids formed, and toluene from the filtrate was removed *in vacuo*. Pale yellow solid (981 mg, 41%) was obtained. The crude product was used directly for the next step.

^1H NMR (400 MHz, $CDCl_3$): δ 7.85-7.80 (m, 2H), 7.60-7.56 (m, 2H), 7.36 (pseudo d, J = 8.4 Hz, 2H), 7.31-7.261 (m, 2H).

$^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ 33.8



1,2-Bisphenoxaphosphinoferrocene. This compound is synthesized using a modified procedure from Kamer and van Leeuwen's synthesis of 1,2-Bis(1,10 -

dimethylphenoxaphosphino)ferrocene.[42] In an argon-filled glovebox, a 25 mL dry Schlenk tube was charged with ferrocene (186 mg, 1.0 mmol) and dry hexane (5 mL). To the orange solution obtained, TMEDA (0.33 mL, 2.2 mmol) and *n*BuLi (1.1 mL, 2.2 mmol, 2.0 M in cyclohexane) was added. The reaction was stirred at room temperature for 24 h. Then the reaction was cooled to -78 ^{o}C in a dry ice-acetone bath, and a solution of 10-chlorophenoxaphosphine (493 mg, 2.1 mmol) in freshly distilled THF (4 mL) was added dropwise at -78 ^{o}C. After addition, the reaction was warmed up to room temperature and stirred at room temperature for 24 h. Solvent was evaporated, DCM (10 mL) and water (10 mL) were added. The organic layer was separated and the aqueous layer was washed with DCM (10 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 , and Na_2SO_4 was filtered off. The filtrate was concentrated, and the crude product was purified by flash chromatography using DCM/hexanes (1:8) as the eluent. Orange solid (248 mg, 41%) was obtained.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.54 (m, 4H), 7.39-7.35 (m, 4H), 7.18-7.11 (m, 8H), 4.04 (t, J = 1.7 Hz, 4H), 3.82 (pseudo d, J = 1.8 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 135.0 (d, J_{CP}= 37.9 Hz), 131.0, 123.6 (d, J_{CP}= 12.3 Hz), 119.8 (d, J_{CP}= 2.5 Hz), 117.9, 71.9 (d, J_{CP}= 14.8 Hz), 71.59, 71.55.

^{31}P{^{1}H} NMR (121 MHz, $CDCl_3$): δ -68.5.

MS (ESI): Calcd for $C_{34}H_{24}FeO_2P_2$: 582.4. Found [M+1]: 583.0.

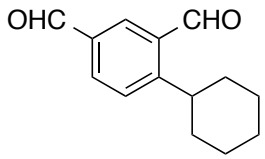
1.7.3 Condition Optimization of Pd-catalyzed alkylation of arenes

Typical procedure for condition optimization: In an argon-filled glovebox, a dry 10 mL Schlenk tube containing a magnetic stir bar was charged with $Pd(PPh_3)_4$ (5 mol%, 5.8 mg, 0.005 mmol), DPxPF (7 mol%, 0.007 mmol, 4.1 mg) and anhydrous dioxane (0.3 mL). After stirring at

room temperature for 10 min, *n*-tetradecane (10 μL), K_3PO_4 (2 equiv, 0.15 mmol, 42.4 mg), isophthalaldehyde (3 equiv, 0.3 mmol, 40.2 mg) and iodocyclohexane (1 equiv, 0.1 mmol, 21.0 mg) were added sequentially. The tube was tightly capped and the mixture was stirred vigorously in a preheated 90 ^oC oil bath. After 48 h, aliquots were taken from the reaction mixture in the glovebox and were passed through a short plug of silica gel with ethyl acetate washings. The filtrate was subjected to GC analysis to determine the conversion of iodocyclohexane and the calibrated GC yield of the product.

1.7.4 Pd-catalyzed alkylation of isophthalaldehyde

Typical procedure for the alkylation of isophthalaldehyde with alkyl iodides: In an argon-filled glovebox, a dry 10 mL Schlenk tube containing a magnetic stir bar was charged with $Pd(PPh_3)_4$ (5 mol%, 0.025 mmol, 28.9 mg), DPxPF (7 mol%, 0.035 mmol, 20.4 mg) and anhydrous dioxane (1.5 mL). The reaction mixture was stirred for 10 min, after which *n*-tetradecane (30 μL), K_3PO_4 (2 equiv, 1 mmol, 212 mg), isophthalaldehyde (3 equiv, 1.5 mmol, 201 mg) and alkyl iodide (1.0 equiv, 0.5 mmol) were added. The tube was capped tightly and the mixture was vigorously stirred in a preheated 110 ^oC oil bath. After iodocyclohexane was fully consumed (monitored by GC), the reaction mixture was passed through a short plug of silica gel with EA/hexanes (1:5) washings to remove the Pd catalyst. The filtrate was concentrated on a rotary evaporator, and the resulting residue was purified by silica gel flash chromatography. The structure of the product obtained was confirmed by ^1H and ^{13}C NMR spectroscopy of the purified sample.

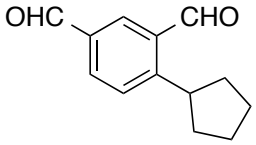


4-Cyclohexylisophthalaldehyde. The product was purified by flash chromatography (THF/hexanes 1:20) to afford a pale yellow solid (80.8 mg, 75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.43 (s, 1H), 10.06 (s, 1H), 8.31 (d, *J* = 1.7 Hz, 1H), 8.05 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 3.63-3.58 (m, 1H), 1.91-1.81 (m, 5H), 1.59-1.45 (m, 4H), 1.35-1.26 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 191.1, 157.1, 134.6, 133.8, 133.6, 133.4, 127.9, 39.0, 34.3, 26.8, 26.1.

GCMS (EI): Calcd for $C_{14}H_{16}O_2$: 216.3. Found: 216.1.

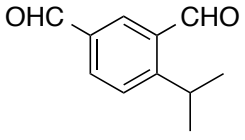


4-Cyclopentylisophthalaldehyde. The product was purified by flash chromatography (THF/hexanes 1:20) to afford a colourless oil (69.0 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.44 (s, 1H), 10.04 (s, 1H), 8.28 (d, *J* = 1.5 Hz, 1H), 8.04 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 4.01 (pseudo quintet, *J* = 8.4 Hz, 1H), 2.18-2.10 (m, 2H), 1.89-1.64 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 191.1, 156.0, 134.6, 134.5, 133.5, 133.1, 128.0, 40.5, 34.9, 26.0.

GCMS (EI): Calcd for $C_{13}H_{14}O_2$: 202.3. Found: 201.1.



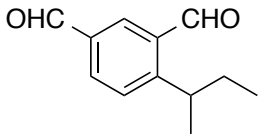
4-Isopropylisophthalaldehyde. The product was purified by flash chromatography

(THF/hexanes 1:20) to afford a colourless oil (77.0 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.42 (s, 1H), 10.05 (s, 1H), 8.30 (d, *J* = 1.6 Hz, 1H), 8.06 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 4.03 (pseudo septet, *J* = 6.9Hz, 1H), 1.34 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 191.1, 158.0, 134.7, 133.7, 133.5, 127.4, 28.5, 23.7.

GCMS (EI): Calcd for $C_{11}H_{12}O_2$: 176.2. Found: 176.1.

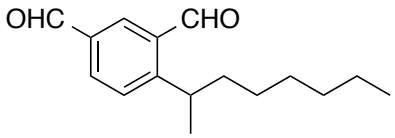


4-(*Sec*-butyl)isophthalaldehyde. The product was purified by flash chromatography (THF/hexanes 1:20) to afford a colourless oil (60.3 mg, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.43 (s, 1H), 10.05 (s, 1H), 8.31 (d, *J* = 1.4 Hz, 1H), 8.06 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 3.79 (pseudo sextet, *J* = 7.0 Hz, 1H), 1.74-1.67 (m, 2H), 1.32 (d, *J* = 6.9 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 191.1, 157.2, 134.7, 134.3, 133.4, 133.3, 128.0, 35.1, 31.0, 21.5, 12.2.

GCMS (EI): Calcd for $C_{12}H_{14}O_2$: 190.2. Found: 190.1.



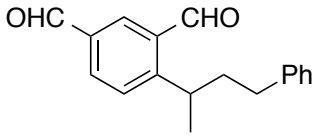
4-(Octan-2-yl)isophthalaldehyde. The product was purified by flash chromatography (THF/hexanes 1:20) to afford a colourless oil (62.5 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.43 (s, 1H), 10.05 (s, 1H), 8.31 (d, *J* = 1.7 Hz, 1H), 8.06 (dd, *J*

= 8.1, 1.7 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 3.87 (pseudo sextet, *J* = 7.0 Hz, 1H), 1.69- 1.63 (m, 2H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.27-1.16 (m, 8H), 0.84 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.2, 191.1, 157.6, 134.6, 134.2, 133.4, 133.3, 128.0, 38.2, 33.5, 31.8, 29.4, 27.7, 22.7, 22.0, 14.1.

GCMS (EI): Calcd for $C_{16}H_{22}O_2$: 246.4. Found: 246.1.

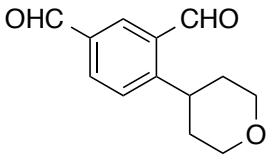


4-(4-Phenylbutan-2-yl)isophthalaldehyde. The product was purified by flash chromatography (THF/hexanes 1:17) to afford a colourless oil (76.7 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.26 (s, 1H), 10.06 (s, 1H), 8.31 (d, *J* = 1.7 Hz, 1H), 8.08 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.25 (pseudo t, *J* = 7.4 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 7.3 Hz, 2H), 3.91 (pseudo sextet, *J* = 7.0 Hz, 1H), 2.64-2.52 (m, 2H), 2.09-1.95(m, 2H), 1.37 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 191.0, 156.7, 141.6, 134.8, 134.3, 133.5, 133.4, 128.6, 128.4, 128.0, 126.2, 39.6, 33.9, 32.9, 22.1.

GCMS (EI): Calcd for $C_{18}H_{18}O_2$: 266.3. Found: 266.1.



4-(tetrahydropyran-4-yl)isophthalaldehyde. The product was purified by flash chromatography (EA/hexanes 1:5) to afford a white solid (61.2 mg, 56%).

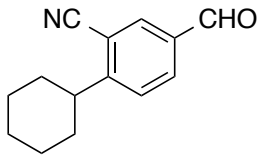
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.34 (s, 1H), 10.07 (s, 1H), 8.31 (d, *J* = 1.8 Hz, 1H), 8.08 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.65 (d, *J* =8.1 Hz, 1H), 4.11 (pseudo dd, *J* = 11.5, 4.1 Hz, 2H), 3.98 (tt, *J* = 11.8, 3.6 Hz, 1H), 3.62 (td, *J* = 11.7, 2.0 Hz, 2H), 1.94-1.83 (m, 2H), 1.79-1.75 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.8, 190.8, 154.6, 135.0, 134.9, 134.2, 133.9, ws44128.1, 68.3, 36.5, 33.5.

GCMS (EI): Calcd for $C_{13}H_{14}O_3$: 218.5. Found: 218.0.

1.7.5 Pd-catalyzed alkylation of substituted arenes using dioxane as solvent

Typical procedure for the alkylation of substituted arenes with iodocyclohexane: In an argon-filled glovebox, a dry 10 mL Schlenk tube containing a magnetic stir bar was charged with $Pd(PPh_3)_4$ (5 mol%, 0.015 mmol, 17.3 mg), DPxPF (7 mol%, 0.021 mmol, 12.2 mg) and anhydrous dioxane (0.3 mL). The reaction mixture was stirred for 10 min, after which K_3PO_4 (1.5 equiv, 0.45 mmol, 95 mg), arene (3.0 equiv, 0.9 mmol), iodocyclohexane (1.0 equiv, 0.3 mmol, 63 mg) and *n*-tetradecane (30 μL) were added. The tube was capped tightly and the mixture was vigorously stirred in a preheated 110 ^{o}C oil bath. After iodocyclohexane was almost fully consumed (monitored by GC), the reaction mixture was passed through a short plug of silica gel with DCM washings to remove the Pd catalyst. The filtrate was concentrated on a rotary evaporator, and the resulting residue was purified by silica gel flash chromatography. The structure of the product obtained was confirmed by ^{1}H and ^{13}C NMR spectroscopy of the purified sample.



2-Cyclohexyl-5-formylbenzonitrile. The regioselectivity of C2 and C4 alkylation is determined to be 2:1 by GC and GC-MS. The crude compound was purified by was purified by flash chromatography (THF/hexanes 1:30).

The C2-alkylated product was obtained as a pale yellow solid (49.2 mg, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 8.12 (d, *J* = 1.7 Hz, 1H), 8.04 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 3.10-3.04 (m, 1H), 1.95-1.81 (m, 5H), 1.56-1.43 (m, 4H), 1.34-1.27 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 158.0, 134.8, 134.6, 133.4, 127.7, 117.2, 113.3, 43.4, 33.6, 26.6, 26.0.

GCMS (EI): Calcd for $C_{17}H_{18}O$: 213.3. Found: 213.1.

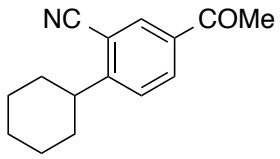
4-Cyclohexyl-3-formylbenzonitrile.

The C4-alkylated product was obtained as a pale yellow oil (30.9 mg, 29%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.37 (s, 1H), 8.11 (d, *J* = 1.8 Hz, 1H), 7.79 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 3.58-3.52 (m, 1H), 1.91-1.80 (m, 5H), 1.55-1.44 (m, 4H), 1.32-1.26 (m, 1H),

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.1, 155.4, 136.7, 134.7, 133.9, 128.2, 118.1, 110.8, 38.9, 34.3, 26.8, 26.1.

GCMS (EI): Calcd for $C_{17}H_{18}O$: 213.3. Found: 213.1.

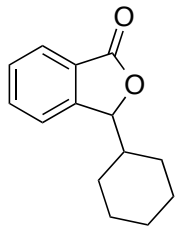


5-Acetyl-2-cyclohexylbenzonitrile. The regioselectivity of C2 and C4 alkylation is determined to be 11:1 by GC and GC-MS. The product was purified by flash chromatography (THF/hexanes 1:20) to afford an orange solid (41 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 1.8 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 3.06-3.00 (m, 1H), 2.60 (s, 3H), 1.95-1.87 (m, 4H), 1.83-1.78 (m, 1H), 1.55- 1.40 (m, 4H), 1.32-1.29 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 156.4, 135.4, 133.2, 132.5, 127.2, 117.5, 112.7, 43.1, 33.6, 26.6, 25.9.

GCMS (EI): Calcd for $C_{17}H_{18}O$: 227.3. Found: 227.1.



3-Cyclohexylphthalide [92251-57-5]. The reaction is set up using $Pd(PPh_3)_4$ (34.7 mg, 0.03 mmol), DPxPF (24.4 mg, 0.042 mmol), phthalaldehyde (241 mg, 1.8 mmol), iodocyclohexane (126 mg, 0.6 mmol), K_2CO_3 (166 mg, 1.2 mmol) and dioxane (1.8 mL). The product was purified by flash chromatography (EA/hexanes 1:40) to afford 3-cyclohexylphthalide as the major product and 3-cyclohexylphthalaldehyde as the minor product. 3-Cyclohexylphthalide was obtained as a white solid (67.4 mg, 52%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.6 Hz, 1H), 7.65 (pseudo td, *J* = 7.5, 1.0 Hz, 1H), 7.50 (pseudo t, *J* = 7.5 Hz, 1H), 7.44 (dd, *J* = 7.6, 1.0 Hz, 1H), 5.32 (d, *J* = 3.7 Hz, 1H), 1.96-1.77 (m, 3H), 1.71-1.64 (m, 2H), 1.37-1.21 (m, 3H), 1.12-1.03 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 149.1, 134.1, 129.3, 127.0, 125.9, 122.5, 85.7, 42.4, 29.5, 26.5, 26.34, 26.31, 26.2.

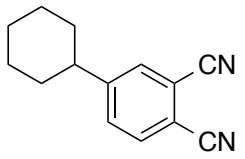
GCMS (EI): Calcd for $C_{17}H_{18}O$: 216.3. Found: 216.0.

3-Cyclohexylphthalaldehyde. 3-Cyclohexylphthalaldehyde was obtained as a yellow oil (12.7 mg, 10%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.57 (s, 1H), 10.47 (s, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 1.7 Hz, 1H), 7.60 (dd, *J* = 7.9, 1.8 Hz, 1H), 2.70-2.64 (m, 1H), 1.93-1.87 (m, 4H), 1.81-1.77 (m, 1H), 1.53-1.37 (m, 4H), 1.34-1.26 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0, 192.4, 155.2, 137.0, 134.7, 132.5, 132.2, 129.8, 45.0, 34.3, 26.9, 26.2.

GCMS (EI): Calcd for $C_{17}H_{18}O$: 216.3. Found: 216.1.



4-Cyclohexylphthalonitrile [1104380-62-2]. The reaction was carried out at 110 ^{o}C The regioselectivity of C4 and C3 alkylation is determined to be 3:1 by GC and GC-MS. The product was purified by flash chromatography (THF/hexanes 1:30).

The C4-alkylated product is obtained as colorless oil (32 mg, 51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 1.7 Hz, 1H), 7.56 (dd, *J* = 8.1, 1.7 Hz, 1H), 2.64-2.60 (m, 1H), 1.88-1.83 (m, 4H), 1.78-1.75 (m, 1H), 1.46-1.33 (m, 4H), 1.29-1.24 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 133.6, 132.2, 132.0, 115.9, 115.8, 115.7, 113.0, 44.5, 33.8, 26.4, 25.7.

GCMS (EI): Calcd for $C_{14}H_{14}N_2$: 210.3. Found: 210.1.

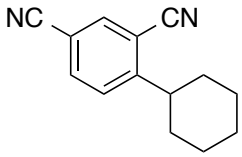
3-Cyclohexylphthalonitrile [1332460-96-4].

The C3-alkylated product is obtained as colorless oil (9 mg, 15%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.61 (m, 3H), 3.08-3.00 (m, 1H), 1.92-1.88 (m, 4H), 1.83-1.79 (m, 1H), 1.55-1.39 (m, 4H), 1.34-1.21 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.7, 133.1, 131.1, 131.0, 116.5, 116.0, 115.2, 114.8, 43.2, 33.6, 26.5, 25.8.

GCMS (EI): Calcd for $C_{14}H_{14}N_2$: 210.3. Found: 210.1.

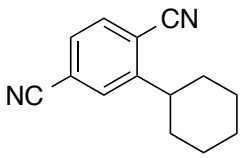


4-Cyclohexylisophthalonitrile [1104380-66-6]. The reaction was carried out at 110 ^{o}C. The regioselectivity of C4 and C2 alkylation is determined to be 30:1 by GC and GC-MS. The product was purified by flash chromatography (THF/hexanes 1:30) to afford the product as white solid (38 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 1.5 Hz, 1H), 7.80 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 3.06-3.00 (m, 1H), 1.92-1.89 (m, 4H), 1.83-1.79 (m, 1H), 1.50-1.42 (m, 4H), 1.29-1.25 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 136.4, 136.1, 127.9, 117.0, 116.1, 113.7, 111.1, 43.3, 33.4, 26.4, 25.8.

GCMS (EI): Calcd for $C_{14}H_{14}N_2$: 210.3. Found: 210.1.

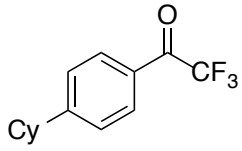


2-Cyclohexylterephthalonitrile [192128-43-1]. The reaction was carried out at 110 ^{o}C. The product was purified by flash chromatography (THF/hexanes 1:30) to afford the product as white solid (32 mg, 50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 1.1 Hz, 1H), 7.57 (dd, *J* = 8.0, 1.5 Hz, 1H), 3.05-2.99 (m, 1H), 1.93-1.80 (m, 5H), 1.55-1.23 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 133.6, 130.6, 129.8, 117.6, 116.9, 116.6, 116.4, 42.8, 33.6, 26.5, 25.8.

GCMS (EI): Calcd for $C_{14}H_{14}N_2$: 210.3. Found: 210.1.



1-(4-Cyclohexylphenyl)-2,2,2-trifluoroethan-1-one [252552-35-5]. The reaction mixture is heated at 110 ^{o}C. The product was purified by flash chromatography (THF/hexanes 1:20) to afford a colorless oil (47 mg, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 2.64-2.57 (m, 1H), 1.89-1.88 (m, 4H), 1.80-1.77 (m, 1H), 1.50-1.36 (m, 4H), 1.32-1.26 (m, 1H).

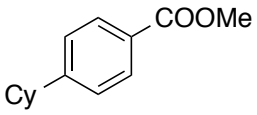
^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 130.6 (q, J_{CF} = 2.0 Hz), 127.9, 127.8, 45.1, 34.1, 26.8, 26.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ -71.3.

GCMS (EI): Calcd for $C_{14}H_{15}F_3O$: 256.3. Found: 256.0.

1.7.6 Pd-catalyzed alkylation of substituted arenes using neat condition

Typical procedure for the alkylation of substituted arenes with iodocyclohexane in neat condition: In an argon-filled glovebox, a dry 10 mL Schlenk tube containing a magnetic stir bar was charged with $Pd(PPh_3)_4$ (5 mol%, 0.05 mmol, 57.8 mg), DPEPhos (7 mol%, 0.07 mmol, 37.7 mg), Cs_2CO_3 (1.5 equiv, 1.5 mmol, 489 mg), substituted arene (20 equiv, 20 mmol), iodocyclohexane (1.0 equiv, 1.0 mmol, 210 mg) and *n*-tetradecane (0.1 mL). The tube was capped tightly and the mixture was vigorously stirred in a preheated 130 ^{o}C oil bath. After iodocyclohexane was almost fully consumed (monitored by GC), the reaction mixture was passed through a short plug of silica gel with DCM washings to remove the Pd catalyst. The filtrate was concentrated on a rotary evaporator, and the excess arene was then distilled out using Kugelrohr distillation. The resulting residue from the distillation was purified using silica gel flash chromatography. The structure of the product obtained was confirmed by ^{1}H and ^{13}C NMR spectroscopy of the purified sample.

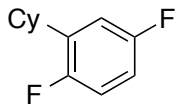


Methyl 4-cyclohexylbenzoate [92863-34-8]. The yield was determined by GC analysis (43%) from the crude product. The product was purified by flash chromatography (THF/hexanes 1:10) after Kugelrohr distillation to afford a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2Hz, 2H), 3.89 (s, 1H), 2.57-2.52 (m, 1H), 1.89-1.83 (m, 4H), 1.77-1.74 (m, 1H), 1.48-1.34 (m, 4H), 1.30-1.24 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3 153.6, 129.8, 127.9, 127.0, 52.0, 44.8, 34.3, 26.9, 26.2.

GCMS (EI): Calcd for $C_{17}H_{18}O$: 218.3. Found: 218.1.



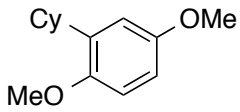
2-Cyclohexyl-1,4-difluorobenzene [1478701-11-9]. The yield is determined by GC analysis (58%) from the crude product. The product was purified by flash chromatography (hexanes) after Kugelrohr distillation to afford a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96-6.89 (m, 2H), 6.83-6.78 (m, 1H), 2.86-2.81 (m, 1H), 1.86-1.83 (m, 4H), 1.78-.175 (m, 1H), 1.44-1.33 (m, 4H), 1.29-1.23 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1 (dd, J_{CF} = 240.9, 1.8 Hz), 156.6 (dd, J_{CF} = 239.8, 2.2 Hz), 136.5 (dd, J_{CF} = 17.4, 7.1 Hz), 116.1 (dd, J_{CF} = 26.2, 8.7 Hz), 114.3 (dd, J_{CF} = 23.9, 5.5 Hz), 113.2 (dd, J_{CF} = 24.0, 8.7 Hz), 37.2, 33.1, 26.8, 26.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -119.4 (d, J = 17.7 Hz), -125.7 (d, J = 17.7 Hz).

GCMS (EI): Calcd for $C_{17}H_{18}O$: 196.2. Found: 196.0.

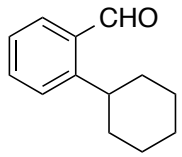


2-Cyclohexyl-1,4-dimethoxybenzene [52033-84-8]. The yield is determined by GC analysis (40%) from the crude product. The product was purified by flash chromatography (EA/hexanes 1:40) after Kugelrohr distillation to afford a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.80-6.77 (m, 2H), 6.69-6.66 (m, 1H), 3.79 (s, 1H), 3.78 (s, 1H), 2.96-2.91 (m, 1H), 1.84-1.82 (m, 4H), 1.77-1.74 (m, 1H), 1.48-1.24 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.9, 151.2, 137.9, 113.7, 111.5, 110.1, 56.3, 55.8, 37.1, 33.4, 27.2, 26.5.

GCMS (EI): Calcd for $C_{17}H_{18}O$: 220.3. Found: 220.1.



2-Cyclohexylbenzaldehyde [128323-04-6]. The yield is determined by GC analysis (72%) from the crude product. The product was purified by flash chromatography (THF/hexanes 1:30) followed by preparative thin layer chromatography (THF/hexanes 1:7) to obtain the desired product as colourless oil. The regioselectivity of C2 and C4 alkylation is determined to be 1.3:1 by GC and GC-MS.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.37 (s, 1H), 7.82 (dd, J = 7.7, 1.4 Hz, 1H), 7.54 (td, J = 7.6, 1.4 Hz, 1H), 7.43 (pseudo d, J = 7.6 Hz, 1H), 7.34 (pseudo t, J = 7.5 Hz, 1H), 3.56-3.52 (m, 1H), 1.88-1.78 (m, 5H), 1.59-1.43 (m, 4H), 1.29-1.26 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 150.7, 134.1, 133.3, 131.4, 126.8, 126.2, 38.4, 34.6, 27.0, 26.3.

GCMS (EI): Calcd for $C_{17}H_{18}O$: 188.3. Found: 188.1.

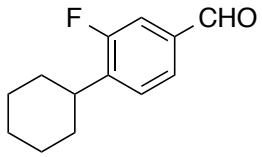
When DPxPF is used, the GC yield is 64% and the C2/C4 selectivity is 1:1.9.

4-Cyclohexylbenzaldehyde [27634-89-5].

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 2.62-2.55 (m, 1H), 1.90-1.85 (m, 4H), 1.80-1.75 (m, 1H), 1.50-1.35 (m, 4H), 1.32-1.27 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.2, 155.5, 134.7, 130.1, 127.7, 45.1, 34.2, 26.8, 26.2.

GCMS (EI): Calcd for $C_{17}H_{18}O$: 188.3. Found: 188.1.



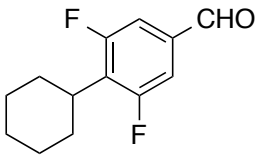
4-Cyclohexyl-3-fluorobenzaldehyde [1553946-12-5]. DPxPF (40.7 mg) and K_2CO_3 (276 mg) was used instead of DPEPhos and K_2CO_3. The yield is determined by GC analysis (66%) from the crude product. The product was purified by flash chromatography (THF/hexanes 1:30) followed by preparative thin layer chromatography (THF/hexanes 1:7) to obtain the desired product as colourless oil. Only one isomer is detected by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (d, J_{HF} = 1.7 Hz, 1H), 7.61 (dd, J_{HF} = 7.8, 1.0 Hz, 1H), 7.50 (dd, J_{HF} = 10.1, 1.2 Hz, 1H), 7.41 (pseudo t, *J* = 7.4 Hz, 1H), 2.95-2.90 (m, 1H), 1.88-1.77 (m, 5H), 1.51- 1.39 (m, 4H), 1.32-1.26 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 161.0 (d, J_{CF} = 247.9 Hz), 142.1 (d, J_{CF} = 15.4 Hz), 136.1 (d, J_{CF} = 6.8 Hz), 128.5 (d, J_{CF} = 5.2 Hz), 126.3 (d, J_{CF} = 3.1 Hz), 115.4 (d, J_{CF} = 23.9 Hz), 37.8, 32.9, 26.8, 26.1.

^{19}F NMR (376 MHz, $CDCl_3$): -117.7.

GCMS (EI): Calcd for $C_{17}H_{18}O$: 206.3. Found: 206.1.



4-Cyclohexyl-3,5-difluorobenzaldehyde [1553946-12-5]. DPxPF (40.7 mg) and K_2CO_3 (424 mg) was used instead of DPEPhos and K_2CO_3. The yield is determined by GC analysis (78%) from the crude product. The product was purified by flash chromatography (THF/hexanes 1:30) followed by preparative thin layer chromatography (THF/hexanes 1:7) to obtain the desired product as colourless oil. Only one isomer is detected by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (t, J_{HF} = 1.6 Hz, 1H), 7.34 (d, J_{HF} = 8.4 Hz, 2H), 3.04 (tt, J = 3.9 Hz, 1H), 1.86-1.73 (m, 7H), 1.43-1.25 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6, 161.9 (d, J_{CF} = 250.2, 9.1 Hz), 135.8 (t, J_{CF} = 8.5Hz), 129.6 (t, J_{CF} = 18.3 Hz), 112.5 (d, J_{CF} = 28.1 Hz), 35.6, 30.8, 26.9, 25.9.

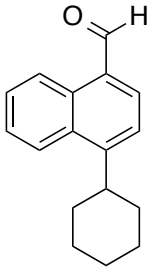
^{19}F NMR (376 MHz, $CDCl_3$): -110.7.

GCMS (EI): Calcd for $C_{13}H_{14}F_2O$: 224.3. Found: 224.0.

1.7.7 Pd-catalyzed alkylation of 1-substituted naphthalenes

Typical procedure for the alkylation of 1-substituted naphthalenes with iodocyclohexane: In an argon-filled glovebox, a dry 10 mL Schlenk tube containing a magnetic stir bar was charged with $Pd(PPh_3)_4$ (5 mol%, 17.3 mg, 0.015 mmol), DPxPF (7 mol%, 0.021 mmol, 12.2 mg) and anhydrous dioxane (0.9 mL). The reaction mixture was stirred for 10 min, and K_3PO_4 (2.0 equiv, 0.6 mmol, 127 mg), 1-substituted naphthalene (3.0 equiv, 0.9 mmol), iodocyclohexane (1.0 equiv, 0.3 mmol, 63 mg) and *n*-tetradecane (30 μL). The tube was capped tightly and the mixture was vigorously stirred in a preheated 130 ^oC oil bath. After iodocyclohexane was almost fully

consumed (monitored by GC), the reaction mixture was passed through a short plug of silica gel with EA/hexanes (1:5) washings to remove the Pd catalyst. The filtrate was concentrated on a rotary evaporator, and the resulting residue was purified using silica gel flash chromatography followed by preparative thin layer chromatography to obtain the desired product. The structure of the product obtained was confirmed by ^{1}H and ^{13}C NMR spectroscopy of the purified sample.

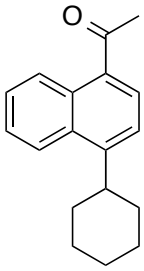


4-Cyclohexyl-1-naphthaldehyde [86586-11-0]. The product was purified by flash chromatography (THF/hexanes 1:7) to obtain the desired product as colourless oil (52.1 mg, 72%). The regioselectivity of the C4 and C2 alkylation is determined to be 18:1 by GC and GC-MS.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.33 (s, 1H), 9.35 (dd, J = 8.5, 0.8 Hz, 1H), 8.20 (d, J = 8.4Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.69-7.59 (m, 2H), 7.55 (d, J = 7.5 Hz, 1H), 3.42-3.37 (m, 1H), 2.05-1.85 (m, 5H), 1.64-1.52 (m, 4H), 1.42-1.28 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 152.2, 137.2, 131.7, 131.3, 129.7, 128.5, 126.9, 125.8, 123.6, 121.8, 40.2, 34.2, 27.2, 26.5.

GCMS (EI): Calcd for $C_{17}H_{18}O$: 238.3. Found: 238.1.

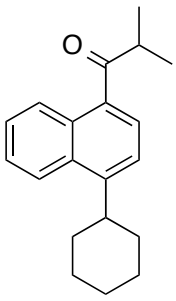


1-Acetyl-4-cyclohexylnaphthalene [78227-14-2]. The product was purified by flash chromatography (THF/hexanes 1:7) to obtain the desired product as colourless oil (37.8 mg, 50%). The regioselectivity of the C4 and C2 alkylation is determined to be 8:1 by GC and GC-MS.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83-8.81 (m, 1H), 8.19-8.17 (m, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.61-7.55 (m, 2H), 7.42 (d, *J* = 7.6 Hz, 1H), 3.40-3.35 (m, 1H), 2.74 (s, 3H), 2.05-1.85 (m, 5H), 1.63-1.52 (m, 4H), 1.43-1.34 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9, 149.4, 133.7, 131.9, 130.8, 128.9, 127.4, 127.0, 126.3, 123.5, 121.1, 39.8, 34.2, 30.1, 27.3, 26.6.

GCMS (EI): Calcd for $C_{18}H_{20}O$: 252.4. Found: 252.1.



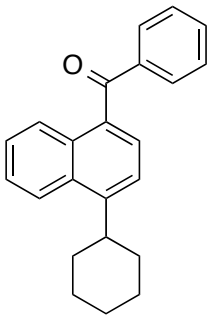
1-(4-Cyclohexyl-1-naphthalenyl)-2-methyl-propan-1-one [86586-13-2]. The product was purified by flash chromatography (THF/hexanes 1:7) to obtain the desired product as colourless oil (37.8 mg, 45%). Only one isomer is detected by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36-8.33 (m, 1H), 8.17-8.15 (m, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.56-7.51 (m, 2H), 7.21 (d, *J* = 7.6 Hz, 1H), 3.52 (hep, *J* = 7.0 Hz, 1H), 3.38-3.33 (m, 1H), 2.04-

1.84 (m, 5H), 1.63-1.50 (m, 4H), 1.40-1.31 (m, 1H), 1.24 (d, J = 6.9 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.3, 148.0, 135.2, 131.9, 131.1, 127.0, 126.7, 126.2, 126.1, 123.5, 121.1, 39.7, 39.6, 34.2, 27.3, 26.6, 19.0.

GCMS (EI): Calcd for $C_{20}H_{24}O$: 280.4. Found: 280.1.

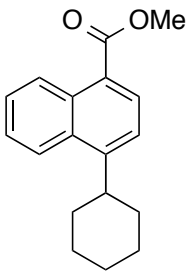


(4-Cyclohexylnaphthalen-1-yl)(phenyl)methanone. The product was purified by flash chromatography (THF/hexanes 1:7) to obtain the desired product as colourless oil (47 mg, 50%). Only one isomer is detected by GC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22-8.16 (m, 2H), 7.88-7.86 (m, 2H), 7.61-7.45 (m, 7H), 3.43-3.37 (m, 1H), 2.08-1.95 (m, 4H), 1.89-1.85 (m, 1H), 1.65-1.54 (m, 5H), 1.41-1.31 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 147.8, 138.8, 134.5, 133.2, 131.8, 131.6, 130.6, 128.5, 128.2, 126.8, 126.7, 126.3, 123.6, 121.0, 39.8, 34.3, 27.3, 26.6.

GCMS (EI): Calcd for $C_{23}H_{22}O$: 314.4. Found: 314.1.

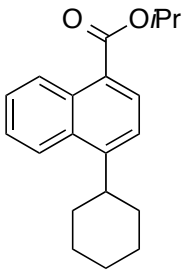


Methyl 4-cyclohexyl-1-naphthoate. The product was purified by flash chromatography (THF/hexanes 1:7) to obtain the desired product as colourless oil (44 mg, 55%). The regioselectivity of the C4 and C2 alkylation is determined to be 7:1 by GC and GC-MS.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97-8.95 (m, 1H), 8.18 -8.11 (m, 2H), 7.61-7.52 (m, 2H), 7.40 (d, *J* = 7.7 Hz, 1H), 3.98 (s, 3H), 3.39-3.33 (m, 1H), 2.03-1.83 (m, 5H), 1.62-1.50 (m, 4H), 1.41-1.35 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 149.6, 131.9, 131.8, 130.2, 127.1, 126.7, 126.0, 125.3, 123.6, 121.4, 52.2, 39.9, 34.2, 27.3, 26.6.

GCMS (EI): Calcd for $C_{18}H_{20}O_2$: 268.4. Found: 268.1.

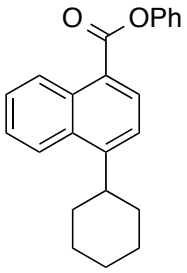


Isopropyl 4-cyclohexyl-1-naphthoate. The product was purified by flash chromatography (THF/hexanes 1:7) to obtain the desired product as colourless oil (38 mg, 43%). Only one isomer is detected in the reaction mixture by GCMS.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94-8.92 (m, 1H), 8.19-8.16 (m, 1H), 8.09 (d, *J* = 7.7 Hz, 1H), 7.61-7.53 (m, *J* = 7 Hz, 1H), 5.36 (hep, *J* = 6.2 Hz, 1H), 3.40-3.34 (m, 1H), 2.03-1.84 (m, 5H), 1.63-1.54 (m, 4H), 1.43 (d, *J* = 6.2Hz, 6H), 1.39-1.33 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 149.2, 131.8, 131.7, 129.8, 127.0, 126.7, 126.3, 126.0, 123.6, 121.4, 68.4, 39.8, 34.2, 27.3, 26.6, 22.2.

GCMS (EI): Calcd for $C_{20}H_{24}O_2$: 296.4. Found: 296.1.

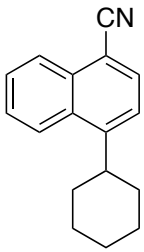


Phenyl 4-cyclohexyl-1-naphthoate. The product was purified by flash chromatography (THF/hexanes 1:7) to obtain the desired product as colourless oil (41 mg, 41%). The regioselectivity of the C4 and C2 alkylation was determined to be 8:1 by GC and GC-MS.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15-9.13 (m, 1H), 8.48-8.45 (m, 1H), 8.27-8.25 (m, 1H), 7.68-7.61 (m, 2H), 7.55-7.48 (m, 3H), 7.35-7.33 (m, 3H), 3.48-3.43 (m, 1H), 2.11-1.90 (m, 5H), 1.69-1.58 (m, 4H), 1.45-1.38 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 151.3, 150.8, 132.3, 131.9, 131.3, 129.7, 127.6, 126.7, 126.3, 126.0, 124.0, 123.7, 122.1, 121.5, 40.0, 34.2, 27.3, 26.6.

GCMS (EI): Calcd for $C_{23}H_{22}O_2$: 330.4. Found: 330.1.



4-Cyclohexyl-1-naphthonitrile. The product was purified by flash chromatography (THF/hexanes 1:7) to obtain the desired product as colourless oil (35 mg, 49%). The regioselectivity of the C4 and C2 alkylation is determined to be 8:1 by GC and GC-MS.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29-8.26 (m, 1H), 8.20 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.69-7.61 (m, 2H), 7.44 (d, J = 7.6 Hz, 1H), 3.40-3.35 (m, 1H), 2.02-1.85 (m, 5H), 1.61-1.50

(m, 4H), 1.39-1.32 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 132.9, 132.8, 131.2, 128.0, 127.3, 126.3, 124.1, 121.9, 118.5, 108.3, 39.9, 34.1, 27.2, 26.4.

GCMS (EI): Calcd for $C_{17}H_{17}N$: 235.3. Found: 235.1.

Chapter 2: Nickel-catalyzed asymmetric hydrogenation of substituted quinoxalines using formic acid

2.1 Introduction

1,2,3,4-Tetrahydroquinoxaline derivatives exhibit a wide range of biological activities and some of them are also drug precusors.[43-47] Some derivatives of 1,2,3,4-tetrahydroquinoxaline have found to be potent vasopressin receptor antagonists[44] which are commonly used to treat hyponatremia[48], a condition whereby the sodium level in one's blood is abnormally low. Other 1,2,3,4-tetrahydroquinoxaline derivatives also show promising activities in inhibiting cholesteryl ester transfer protein (CETP), which can be potentially used to treat atherosclerosis[47], a condition caused by the narrowing of arteries due to fatty deposits (Figure 2.1).

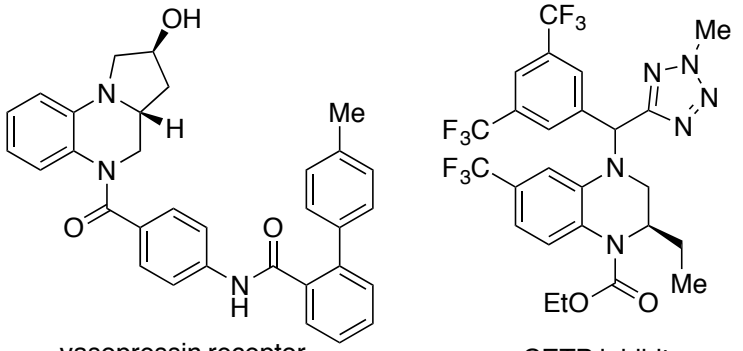


Figure 2.1 Examples of biologically active 1,2,3,4-tetrahydroquinoxaline derivatives

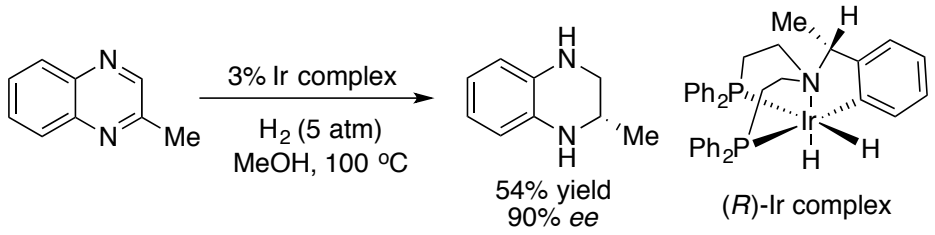
Asymmetric hydrogenation of quinoxalines is probably the simplest way to access to chiral 1,2,3,4-tetrahydroquinoxalines.[49-52] Today several noble metal catalysts are available for the hydrogenation with high level of asymmetric induction.

2.2 Transition metal-catalyzed hydrogenation of 2-substituted quinoxalines

Asymmetric hydrogenation of quinoxalines is the most common method to access 1,2,3,4-tetrahydroquinoxalines. Such hydrogenation is usually performed by precious transition metal catalysts such as iridium[53-57] and ruthenium.[58,59]

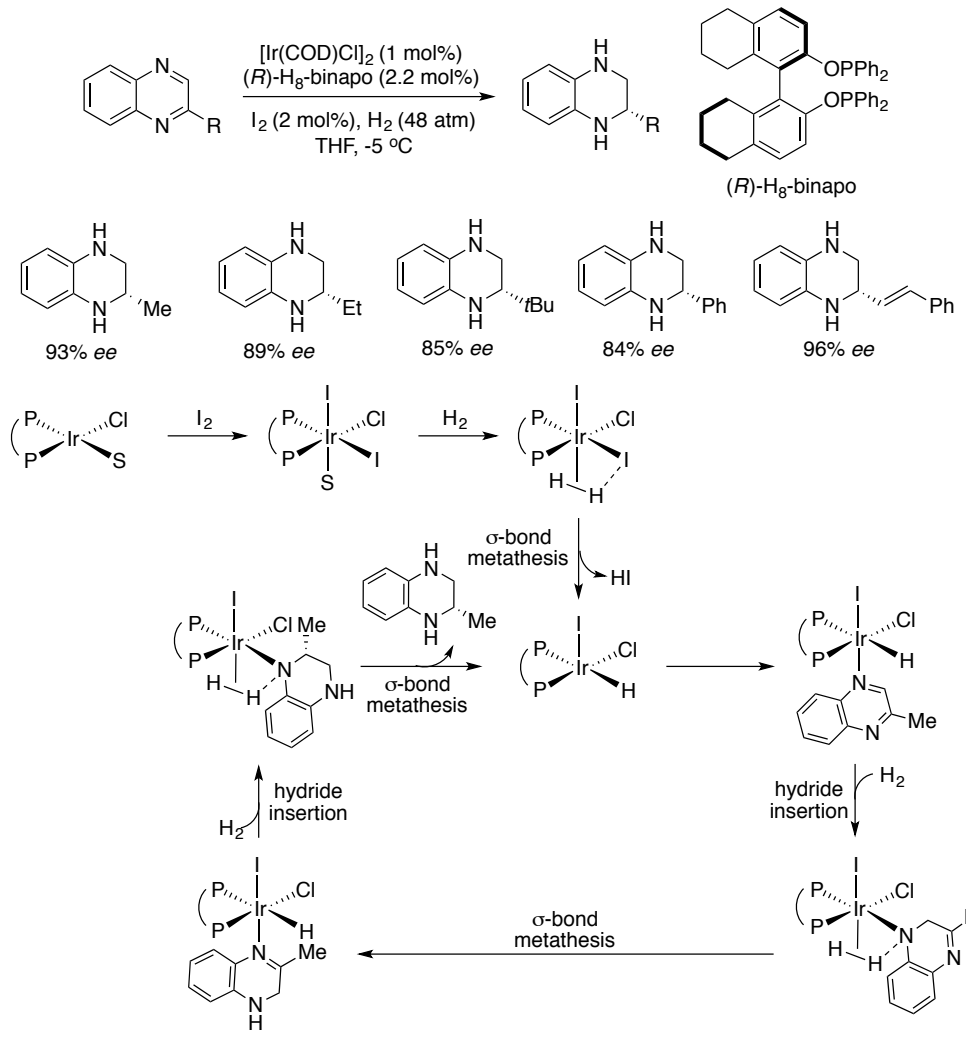
2.2.1 Iridium-catalyzed hydrogenation of 2-substituted quinoxalines

The first Ir-catalyzed hydrogenation of 2-methyl quinoxaline was reported by Bianchini and co-workers in 1998. [53] They used an *ortho*-metalated iridium dihydride complex, which yielded the desired 2-methyl-1,2,3,4-tetrahydroquinoxaline in 90% *ee*. Only one example of 2-methylquinoxaline was demonstrated (Scheme 2.2).



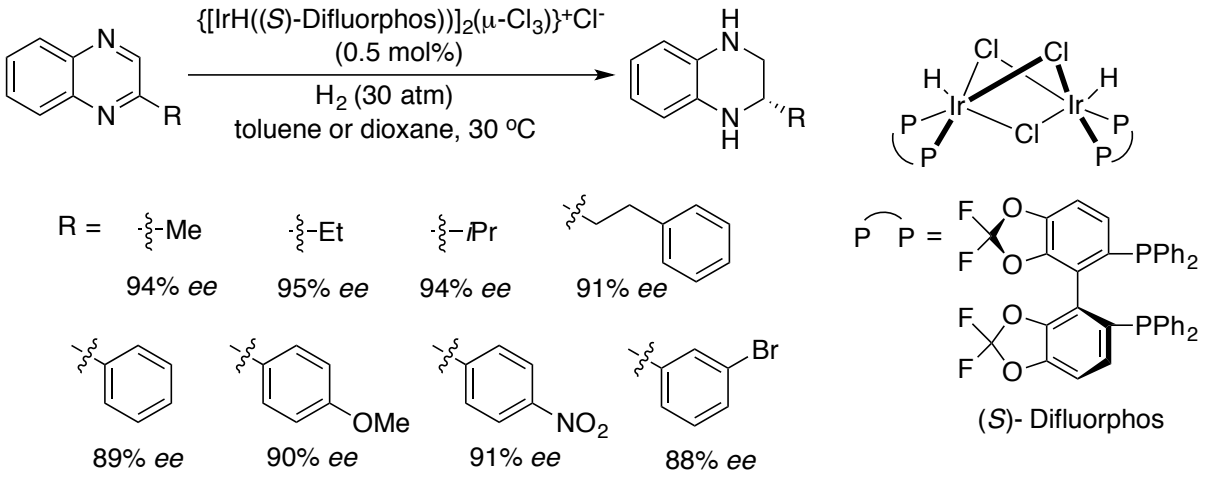
Scheme 2.2 Bianchini's Ir-catalyzed asymmetric hydrogenation of 2-methylquinoxaline

In 2009, Tang and co-workers reported a $[Ir(COD)Cl]_2$/(R)-H_8-binapo catalyst, which effectively reduced a wide range of 2-substituted quinoxalines with good to excellent enantioselectivities.[54] Iodine played a key role in the catalytic cycle, by *in situ* producing chloroiodoiridium(III) hydride as the active species.[60] Without the iodine additive, the hydrogenated product was obtained in 32% *ee* with a low conversion of 28% in the model reaction. It is noted that the *ee* values of the hydrogenated product decreased as the size of C2 substituent increased (Scheme 2.3).



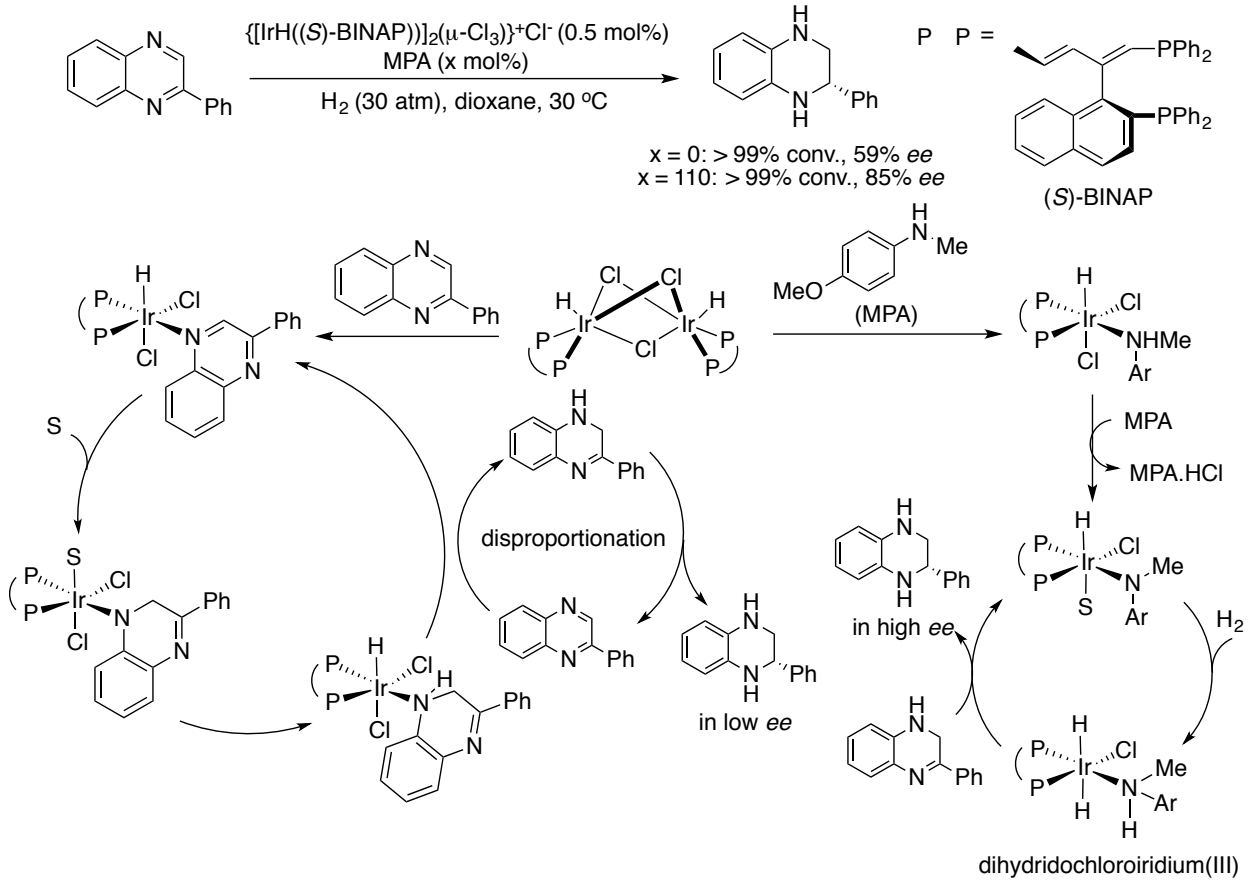
Scheme 2.3 Tang's Ir-catalyzed asymmetric hydrogenation of 2-substituted quinoxalines

Ohshima, Mashima and Ratovelomanana-Vidal reported an Ir/Difluorophos-catalyzed asymmetric hydrogenation of 2-substituted quinoxalines.[56,57] The cationic dinuclear iridium complex effectively reduced a wide range of 2-substituted quinoxalines with good to excellent enantioselectivities, including 2-arylquinoxalines. The presence of the bridging chloride ions in the iridium complex was essential for the high enantioselectivity, as replacing the chloride with bromide or iodide ions resulted in a decline of the *ee* values (Scheme 2.4).



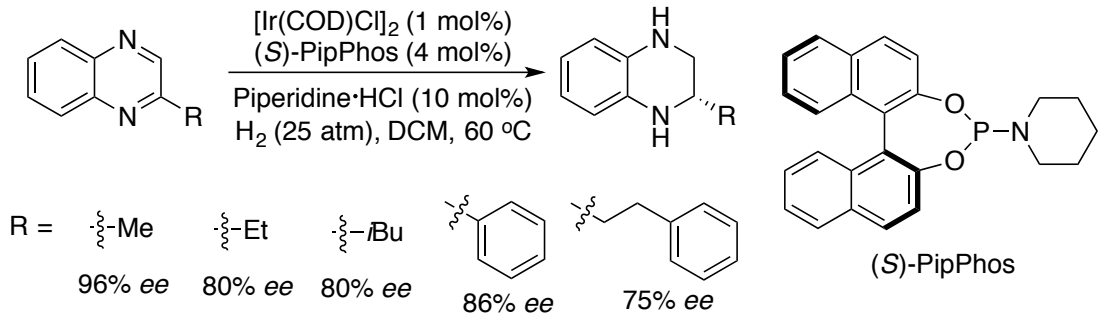
Scheme 2.4 Vidal's Ir-catalyzed asymmetric hydrogenation of 2-alkyl- and 2-arylquinoxalines

Mashima et al. later conducted a detailed mechanistic study on the effects of amine additives on the asymmetric hydrogenation of quinoxalines catalyzed by similar iridium complexes.[61] It was discovered that the presence of *N*-methyl-*p*-anisidine (MPA) improved the enantioselectivity of hydrogenated product from 59% *ee* to 85% *ee*. Mechanistic studies showed that 2-phenylquinoxaline is first reduced at the less hindered C=N bond. 3-phenyl-1,2-dihydroquinoxaline however can undergo an undesired Ir-catalyzed disproportionation, simultaneously producing 2-phenylquinoxaline and 2-phenyl-1,2,3,4-tetrahydroquinoxaline with low enantioselectivity. The addition of MPA can effectively deterred the undesirable disproportionation reaction, which significantly improved the enantioselectivity of the 1,2,3,4-tetrahydrogenated product (Scheme 2.5).



Scheme 2.5 Mashima's proposed mechanism of Ir-catalyzed asymmetric hydrogenation of quinoxalines in the presence of MPA

Minnaard, Feringa and de Vries reported an asymmetric hydrogenation of quinoxalines catalyzed by $[Ir(COD)Cl]_2$/(*S*)-PipPhos.[55] It was the first example to make use of a monodentate phosphoramidite ligand. The addition of piperidine hydrochloride led to an increase in the *ee* value for 2-methylquinoxaline. 2-Methylquinoxaline was hydrogenated to give an excellent *ee* value of 96%, but the *ee* values for other alkyl and phenyl substituents were only moderate (Scheme 2.6).

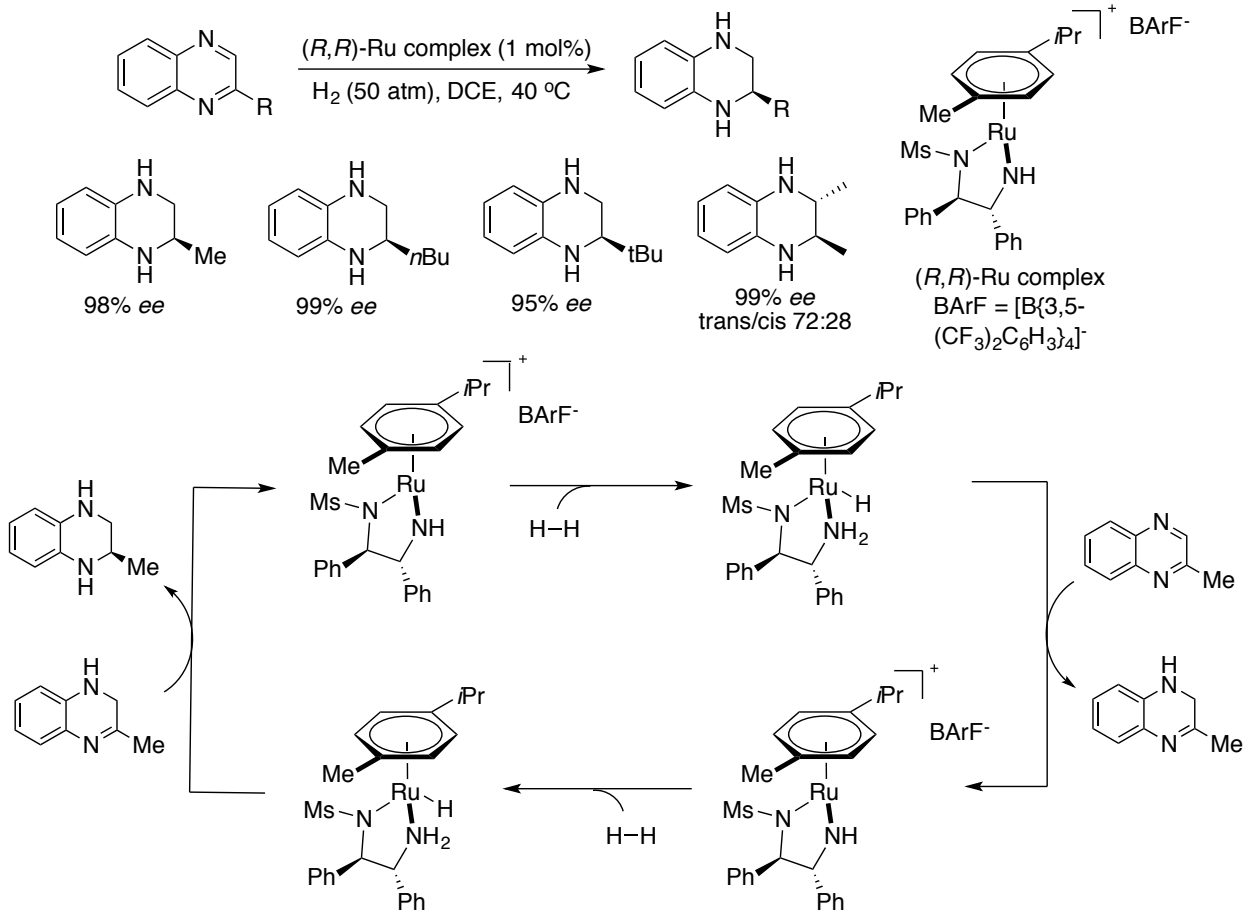


Scheme 2.6 $[Ir(COD)Cl]_2$/(*S*)-PipPhos-catalyzed asymmetric hydrogenation of 2-substituted quinoxalines

2.2.2 Ruthenium-catalyzed hydrogenation of 2-substituted quinoxalines

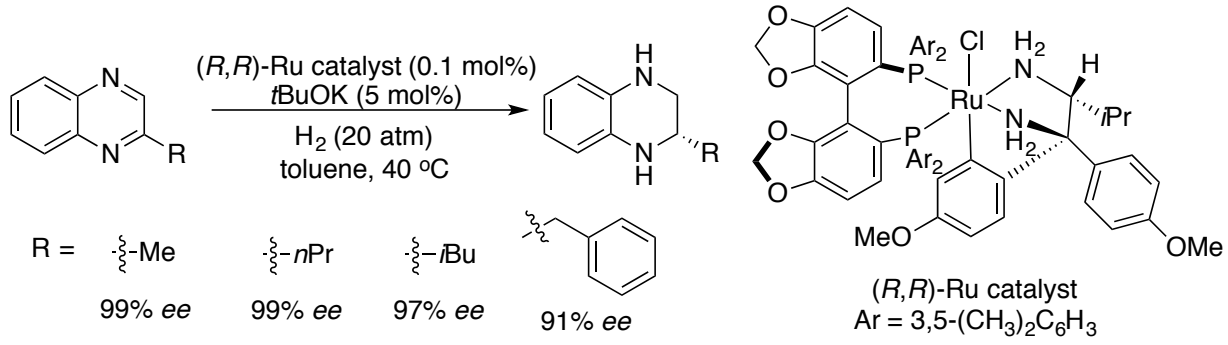
Besides iridium complexes, ruthenium complexes were also efficient catalysts for the hydrogenation of 2-substituted quinoxalines.

In 2011, Fan and co-workers reported asymmetric hydrogenation of substituted quinoxalines catalyzed using ruthenium diamine complexes developed by Noyori[62,63] at 50 atm of hydrogen gas (Scheme 2.7).[58] The robust Ru complexes effectively reduced both 2-substituted quinoxalines and the more sterically hindered 2,3-disubstituted quinoxalines. The resulting 1,2,3,4-tetrahydroquinoxalines were obtained with good to excellent enantioselectivities and moderate diastereoselectivities. The Ru complex first coordinated with hydrogen molecule to produce the active monohydride complex. 2-Methylquinoxaline then bound to the active Ru complex, and hydride transfer occurred to give 3-methyl-1,2-dihydroquinoxaline. 3-Methyl-1,2-dihydroquinoxaline then underwent a second hydrogenation to give the chiral tetrahydrogenated product.



Scheme 2.7 Fan's attempt on Ru-catalyzed asymmetric hydrogenation of 2-substituted and 2,3-substituted quinoxalines

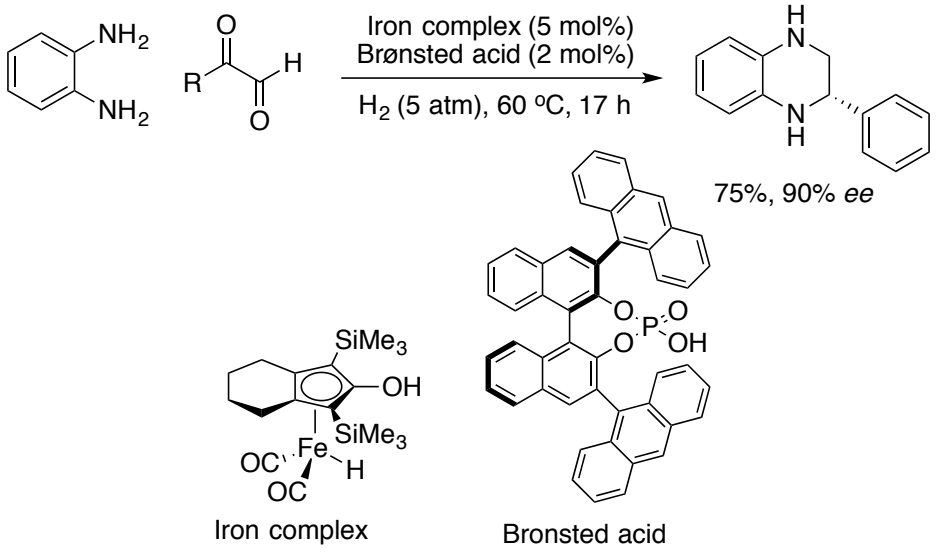
Later, Ohkuma and co-workers also attempted the asymmetric hydrogenation of 2-alkylquinoxalines using chiral ruthenabicyclic complexes (Scheme 2.8).[59] Only 0.1 mol% of catalyst loading was needed, and the presence of the bulky 3,5-xylyl groups on the phosphine ligands were crucial in obtaining the desired hydrogenated products in high enantioselectivities. However, 2-phenylquinoxaline was unreactive under this reaction condition.



Scheme 2.8 Ohkuma's Ru-catalyzed asymmetric hydrogenation of 2-alkylquinoxalines

2.2.3 Iron-catalyzed one-pot synthesis of chiral tetrahydroquinoxalines

Beller and co-workers reported a single example of one-pot synthesis of 2-phenyl-1,2,3,4-tetrahydroquinoxalines catalyzed by a combination of an achiral iron complex and a chiral Brønsted acid.[64] 2-Phenylquinoxaline was formed from 1,2-phenylenediamine and phenylglyoxal. The latter was activated by the binding of chiral Brønsted acid, then the iron complex hydrogenated the activated substrate to give 2-phenyl-1,2,3,4-tetrahydroquinoxaline in 90% *ee* (Scheme 2.9).

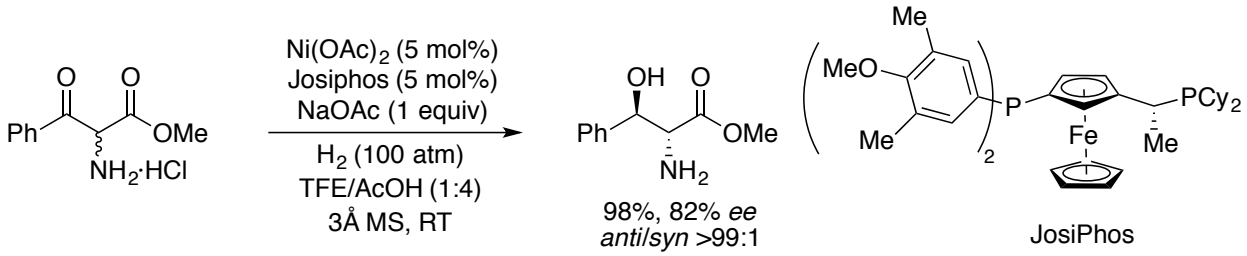


Scheme 2.9 Beller's one-pot synthesis of chiral 2-phenyl-1,2,3,4-tetrahydroquinoxaline

2.2.4 Nickel-catalyzed asymmetric hydrogenation and transfer hydrogenation of olefins

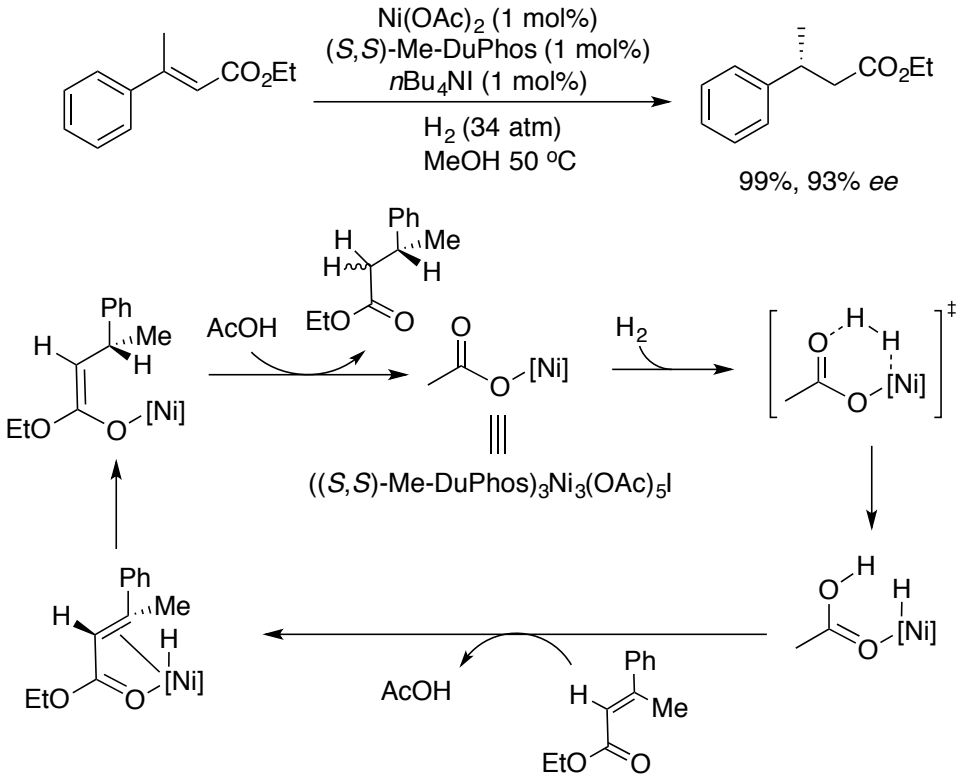
Nickel is a cheap and abundant first-row transition metal and it has a longstanding history in catalyzing hydrogenation. The most classical nickel catalyst used for hydrogenation would be Raney nickel. Asymmetric heterogeneous hydrogenation of methyl acetoacetate catalyzed by nickel tartrate complex has been well-studied since 1979.[65-67] In the recent decade, examples of homogeneous Ni-catalyzed asymmetric hydrogenation have also been reported.

Hamada and co-workers successfully reduced α-amino-β-ketoester[68] and α-aminoketone hydrochlorides[69] via the nickel-catalyzed dynamic kinetic resolution. Using $Ni(OAc)_2$ and JosiPhos ligands with hydrogen gas, the hydrogenated product was produced with good diastereoselectivities and moderate to good enantioselectivities (Scheme 2.10).



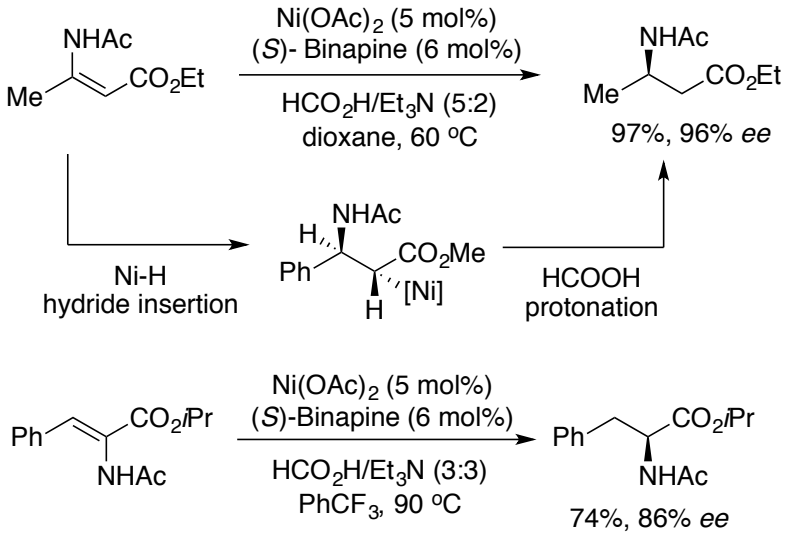
Scheme 2.10 Hamada's Ni-catalyzed asymmetric hydrogenation of α-amino-β-ketoester hydrochlorides

Chirik and co-workers described an asymmetric hydrogenation using $Ni(OAc)_2$/(*S*,*S*)-Me-DuPhos and hydrogen gas (Scheme 2.11).[70] α,β-Unsaturated olefins were successfully reduced to generate β-stereocenters with good enantioselectivities. The use of $Ni(OAc)_2$ in combination with $n$$Bu_4NI$ is critical to achieve high reactivity and selectivity. $n$$Bu_4NI$ provided a source of I^- for the formation of active nickel catalyst, $((S,S)\text{-Me-DuPhos})_3Ni_3(OAc)_5I$, whereas the acetate ligand helps in the cleavage of the H-H bond.



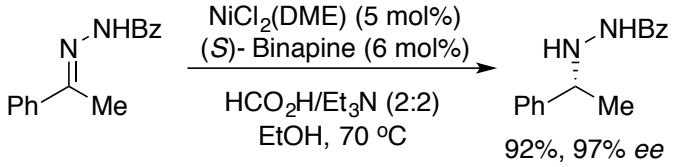
Scheme 2.11 Chirik's attempt on Ni-catalyzed asymmetric hydrogenation of α,β-unsaturated olefins

In the recent years, our group has been committed to develop more economical and environment-friendly methods for asymmetric hydrogenation via nickel catalysis and has achieved promising results. In 2014, Dr. Peng Yang and Haiyan Xu from our group reported an efficient nickel-catalyzed asymmetric transfer hydrogenation for the synthesis of β-acylamidoesters and α-acetamidoesters (Scheme 2.12).[71] Formic acid is used as hydrogen source to avoid the safety hazards that arises from the use and storage of hydrogen gas. $Ni(OAc)_2$ when combined with (*S*)-Binapine, a bulky electron-rich bisphosphine ligand developed by Xumu Zhang[72], created a potent catalyst to give the hydrogenated products in good to excellent enantioselectivities. Deuterium-labelling experiments showed that suggested that the formate ion underwent decarboxylation to form a nickel hydride species, and the hydride was added to the *β*-position.



Scheme 2.12 Ni-catalyzed asymmetric transfer hydrogenation of olefins by Zhou's group

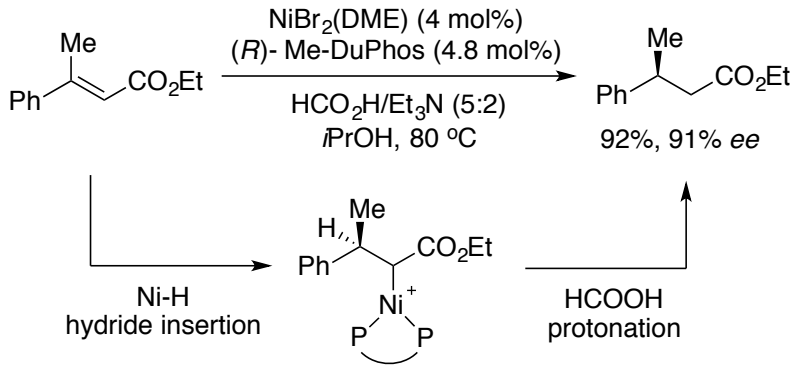
Haiyan Xu from our group later developed an effective system for the asymmetric transfer hydrogenation of hydrazones in the following year (Scheme 2.13).[73] $NiCl_2$(DME)/(*S*)-Binapine effectively reduced the hydrazones in the presence of HCOOH and Et_3N in alcoholic solvents to give the hydrogenated products in good to excellent enantioselectivites. ONIOM-DFT calculation results suggested that a cationic Ni(II) hydride was the active catalyst and formate ions underwent Ni-catalyzed decarboxylation to form nickel hydride complex.



Scheme 2.13 Ni-catalyzed asymmetric transfer hydrogenation of hydrazones by Zhou's group

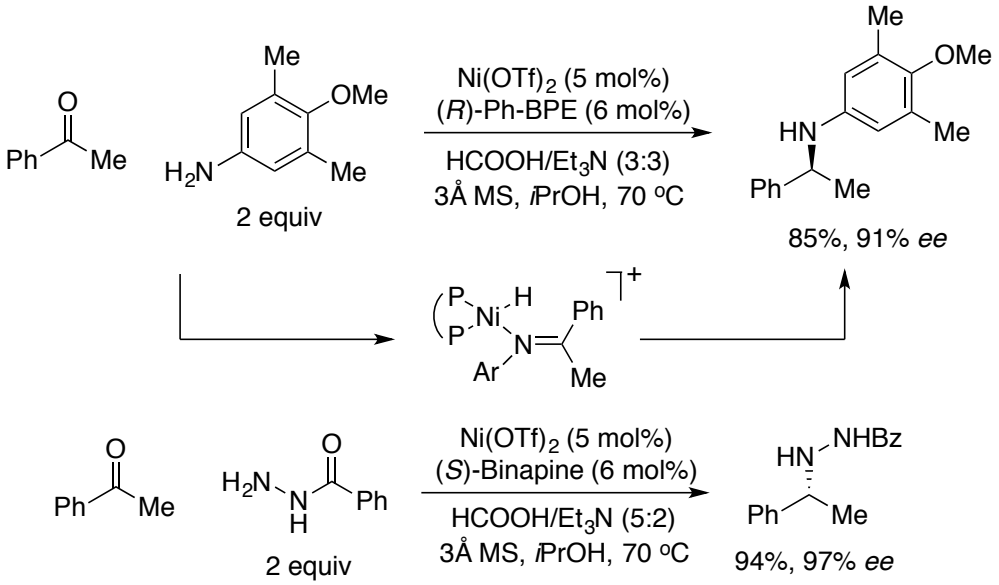
Siyu Guo from our group also reported the asymmetric transfer hydrogenation of conjugated olefins[74](Scheme 2.14). $NiBr_2$(DME)/(*R*)-Me-DuPhos catalytic system can effectively reduced (*E*)-cinnamates in the presence of HCOOH/Et_3N and *i*PrOH to afford the hydrogenated products in good enantioselectivities and yields. Electron-donating and electron-withdrawing

groups can be tolerated, as well as thiophene and pyridine rings. It is interesting to note that no directing group is necessary, the ester group can be replaced by nitrile or amide groups.



Scheme 2.14 Ni-catalyzed asymmetric transfer hydrogenation of conjugated olefins by Zhou's group

In our most recent publications on nickel-catalyzed asymmetric hydrogenation, Dr. Peng Yang reported an efficient enantioselective reductive amination of ketones with arylamines and benzhydrazide (Scheme 2.15).[75] The ketimines or hydrazones were first formed by stirring the ketones with arylamines or benzhydrazide in the presence of molecular sieve and *i*PrOH, and were subsequently reduced by $Ni(OTf)_2$/(*R*)-Ph-BPE or $Ni(OTf)_2$/(*S*)-Binapine to give the hydrogenated products in good to excellent yields and enantioselectivities. Calculations by the ONIOM-DFT method revealed that the reaction was likely to proceed via a nickel(II) hydride intermediate.



Scheme 2.15 Nickel-catalyzed asymmetric reductive amination of ketones with arylamines and benzhydrazide

2.3 Results and discussions

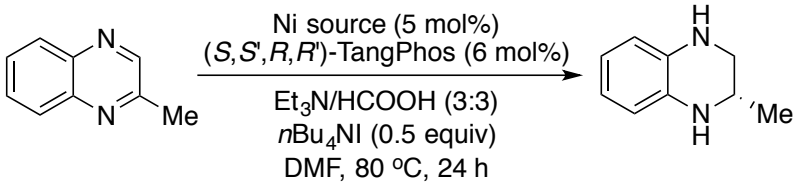
As shown by the previous work, the asymmetric hydrogenation of 2-substituted quinoxalines were often catalyzed by precious transition metals using high pressure of hydrogen gas. There is a need to develop a more user friendly method to access to the chiral derivatives of 1,2,3,4-tetrahydroquinoxalines with cheaper first-row transition metals. Encouraged by our previous work, we envisioned to apply our catalytic system to hydrogenation of 2-substituted quinoxalines. This will also be the first example of metal-catalyzed asymmetric transfer hydrogenation of 2-substituted quinoxalines.

2.3.1 Optimization of catalysts and conditions

We examined the effect of various nickel salts in a model asymmetric hydrogenation of 2-methylquinoxaline. Many nickel(II) salts generated the product in good to excellent yields, among

which $NiCl_2$(DME) produced the desired 1,2,3,4-tetrahydroquinoxaline in 91% yield and 79% *ee* (Table 2.1, entry 1). To our surprise, the reaction did not proceed when anhydrous $NiCl_2$ was used, probably due to the low solubility of $NiCl_2$ in DMF.

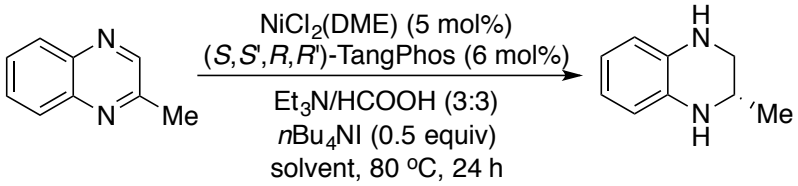
Table 2.1 Effect of nickel sources



Entry	Nickel salts	Conversion (%)	GC Yield (%)	Ee (%)
1	**$NiCl_2$(DME)**	**92**	**91**	**79**
2	$NiCl_2$	5	0	-
3	$NiBr_2$(DME)	90	83	73
4	NiI_2	95	90	69
5	$Ni(OAc)_2$	88	78	70
6	$Ni(OTf)_2$	94	93	67
7	$NiSO_4 \cdot 6H_2O$	64	52	57
8	$Ni(COD)_2$	46	24	40

Next, various solvents were screened. Polar solvents such as DMF, DMA and NMP worked well to give the hydrogenated products in good yields (Table 2.2, entries 1-3), while alcoholic solvents gave the hydrogenated products in slightly lower yields (Table 2.2, entries 5-7). Ethers and aromatic solvents provided poor yields in this reaction. Overall, DMF provided the highest *ee* value of 79%.

Table 2.2 Effect of solvents

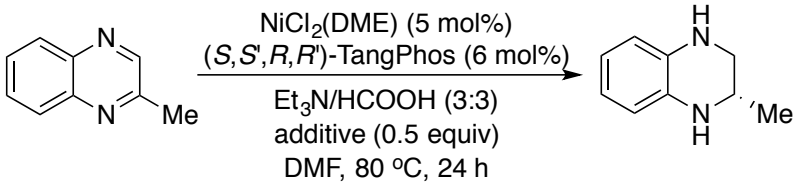


Entry	Solvents	Conversion (100%)	GC Yield (%)	Ee (%)
1	**DMF**	**87**	**84**	**79**
2	**DMA**	**78**	**57**	**72**
3	**NMP**	**81**	**73**	**71**
4	DMSO	83	57	67
5	EtOH	49	36	68
6	*n*PrOH	45	37	70
7	***i*PrOH**	**52**	**35**	**73**
8	PhMe	72	23	49
9	PhOMe	67	36	51
10	$PhCF_3$	78	46	54
11	dioxane	63	35	36
12	CPME	67	11	49
13	DME	77	42	52

The addition of halides had proven to be beneficial in the previous work of Chirik et al. on nickel-catalyzed hydrogenation of α,β-unsaturated olefins.[70] Hence, a range of halide additives were screened in the effort to improve the enantioselectivity of this reaction. The addition of

*n*Bu$_4$NI slightly elevated the enantioselectivity of the product by 2% in DMF (Table 2.3, entry 4), while other halides caused a drop in the enantioselectivity (Table 2.3, entries 2, 3 and 5). Upon reexamination of solvents in the presence of *n*Bu$_4$NI, we found that the addition of 0.5 equiv of *n*Bu$_4$NI in *i*PrOH improved the *ee* value to 83% (Table 2.3, entry 8).

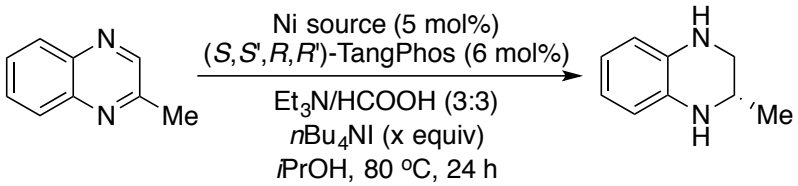
Table 2.3 Effect of additives



Entry	Additives	Conversion (100%)	GC Yield (%)	Ee (%)
1	none	92	90	79
2	*n*Bu$_4$NBr	85	70	75
3	*n*Bu$_4$NCl	70	54	57
4	***n*Bu$_4$NI**	**88**	**75**	**81**
5	KI	65	32	16
6	*n*Bu$_4$NI in DMA	79	69	70
7	*n*Bu$_4$NI in NMP	74	64	73
8	***n*Bu$_4$NI in *i*PrOH**	**96**	**94**	**83**

Upon readjusting the amount of additives, we found that 3 equivalents of *n*Bu$_4$NI boosted the *ee* of the model reaction further to 91% (Table 2.4, entry 4). Further increment of the amount of *n*Bu$_4$NI did not improve the enantioselectivity further.

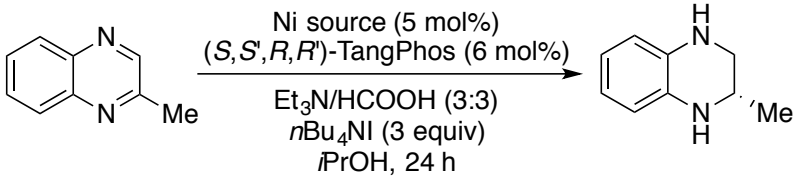
Table 2.4 Effect of equivalents of nBu$_4$NI



Entry	Equiv of nBu$_4$NI	Conversion (100%)	Yield (%)	Ee (%)
1	0.2	95	91	81
2	0.5	96	93	83
3	1.0	96	93	85
4	**3.0**	**96**	**92**	**91**
5	10.0	95	93	90

We also examined the effect of reaction temperature. The change in temperature only affected the enantioselectivity to a small extent. The optimal *ee* value of 92% was achieved at 90 ^{o}C (Table 2.5, entry 4).

Table 2.5 Effect of reaction temperature

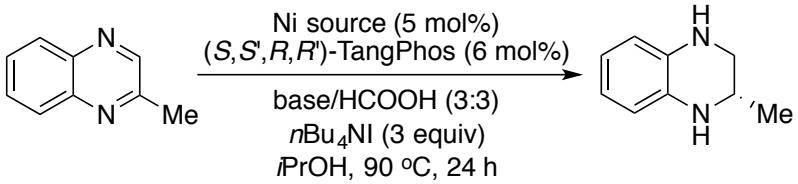


Entry	Temperature	Conversion (100%)	GC Yield (%)	Ee (%)
1	60 ^{o}C	58	50	89
2	70 ^{o}C	96	95	89

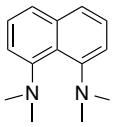
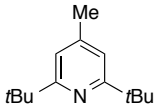
3	80 °C	97	96	89
4	**90 °C**	**97**	**95**	**92**
5	100 °C	97	95	88

The effect of different bases was also investigated. Reactions using Et_3N as the base produced the desired product with an excellent *ee* value of 93% (Table 2.6, entry 1) Other amine bases such as Cy_2NMe, iPr_2NEt and nBu_3N can also be used as well (Table 2.6, entries 2, 4 and 5). However, bulky 2,6-di-*tert*-butyl-4-methylpyridine led to a poor *ee* of 16% (Table 2.6, entry 7). While reactions using *N*-methylmorpholine as the base produced the product with only 68% *ee* (Table 2.6, entry 8), and reactions using the bulky Proton Sponge give the product in 87% *ee* (Table 2.6, entry 6). The difference in enantioselectivities may be due to the interaction of proton on the conjugate acids of the amines with the nitrogen on partially hydrogenated product.

Table 2.6 Effect of organic bases

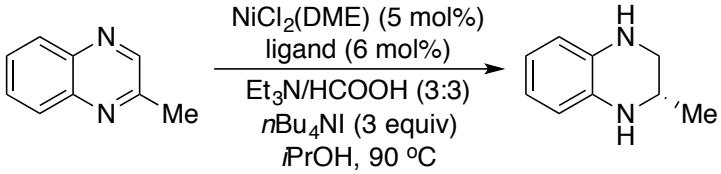


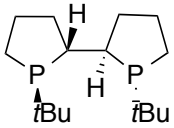
Entry	Organic bases	Conversion (100%)	Yield (%)	Ee (%)
1	**Et_3N**	**95**	**94**	**93**
2	nBu_3N	95	92	89
3	$nOct_3N$	93	92	85
4	Cy_2NMe	95	94	92
5	iPr_2NEt	94	92	92

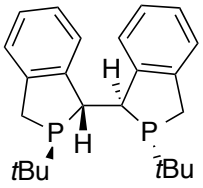
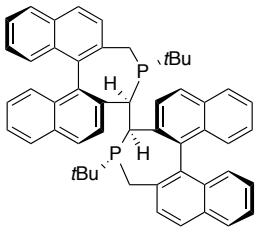
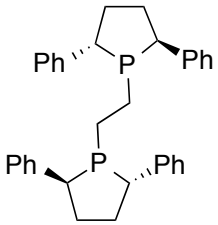
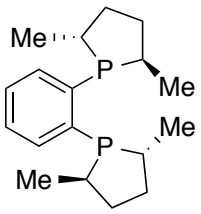
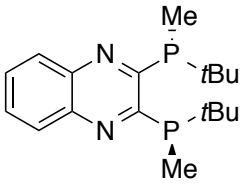
6	 Proton Sponge	94	93	87
7		53	24	16
8	*N*-Methylmorpholine	95	93	68

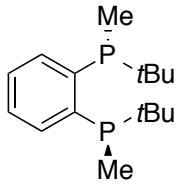
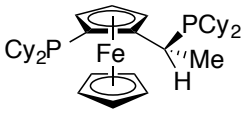
With the optimal conditions in hand, we re-examined the effect of chiral bisphosphines in the model reaction. Previously, our group determined that bis(arylphosphine)s such as BINAP, SEGPHOS and Chiraphos had no catalytic activity together with nickel salts. We found that (*S*,*S*',*R*,*R*')-TangPhos gave the highest *ee* value of 92% (Table 2.7, entry 1). Other ligands like (*R*)-BenzP* and (*R*)-QuinoxP* also gave moderate enantioselectivities of 77% *ee* and 79% *ee* respectively (Table 2.7, entries 6 and 7). It is interesting to note that in the presence of bulky (*S*)-Binapine, a nearly racemic mixture of the hydrogenated product was obtained (Table 2.7, entry 3).

Table 2.7 A sampling of ligand effect



Entry	Ligands	Conversion (100%)	GC Yield (%)	Ee (%)
1		**96**	**94**	**92**

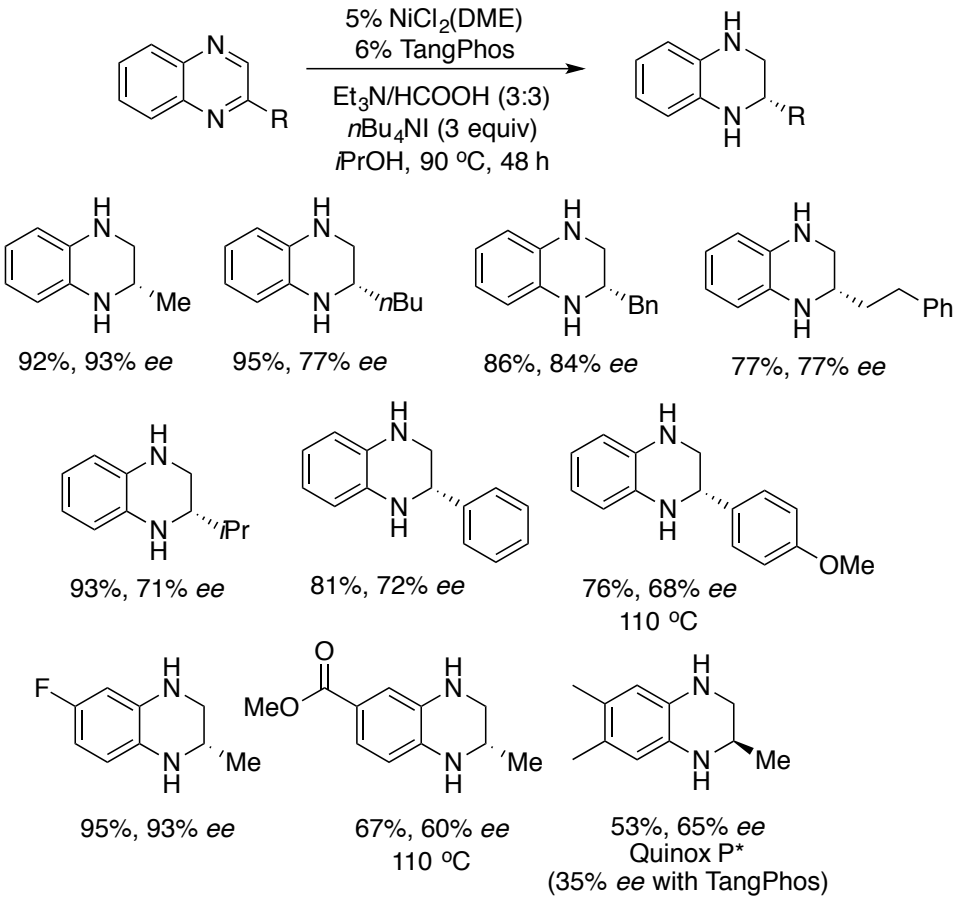
	(*S*,*S*',*R*,*R*')-TangPhos			
2		85	59	50
	(1*R*,1'*R*, 2*S*,2'*S*)-DuanPhos			
3		86	63	<5
	(*S*)-Binapine			
4		68	54	46
	(*S*,*S*)-Ph-BPE			
5		78	70	23
	(*R*,*R*)-Me-DuPhos			
6		82	77	77
	(*R*)-QuinoxP*			

7	 (*R*)-BenzP*	79	76	79
8		17	4	-

2.3.2 Substrate scope of nickel-catalyzed asymmetric transfer hydrogenation of 2-substituted quinoxalines

Under the optimal conditions, 2-methylquinoxaline gave the hydrogenated product in 93% *ee*. However, as the bulkiness of the C2-substituent increased, the *ee* value declined. For example, 2-isopropylquinoxaline yielded 71% *ee* whereas 2-phenylquinoxaline gave only 72% *ee* (Scheme 2.16).

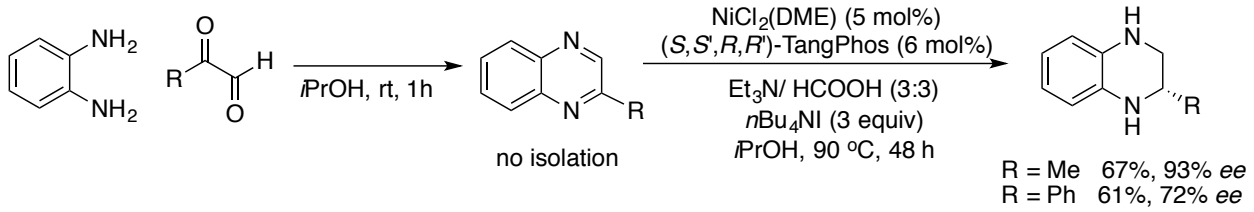
Substituents on the benzofused rings also caused a reduction in the enantioselectivities. For instance, 2,6,7-trimethylquinoxaline and methyl 2-methylquinoxaline-6-carboxylate give 35% *ee* and 60% *ee* when (*S*,*S*',*R*,*R*')-TangPhos was used. The enantioselectivities of 6,7-dimethyltetrahydroquinoxaline was improved to 65% ee when the ligand was changed to QuinoxP*.



Scheme 2.16 Examples of nickel-catalyzed asymmetric transfer hydrogenation of 2-substituted quinoxalines.

2.3.3 Ni-catalyzed one-pot asymmetric reductive amination to access chiral 1,2,3,4-tetrahydroquinoxalines

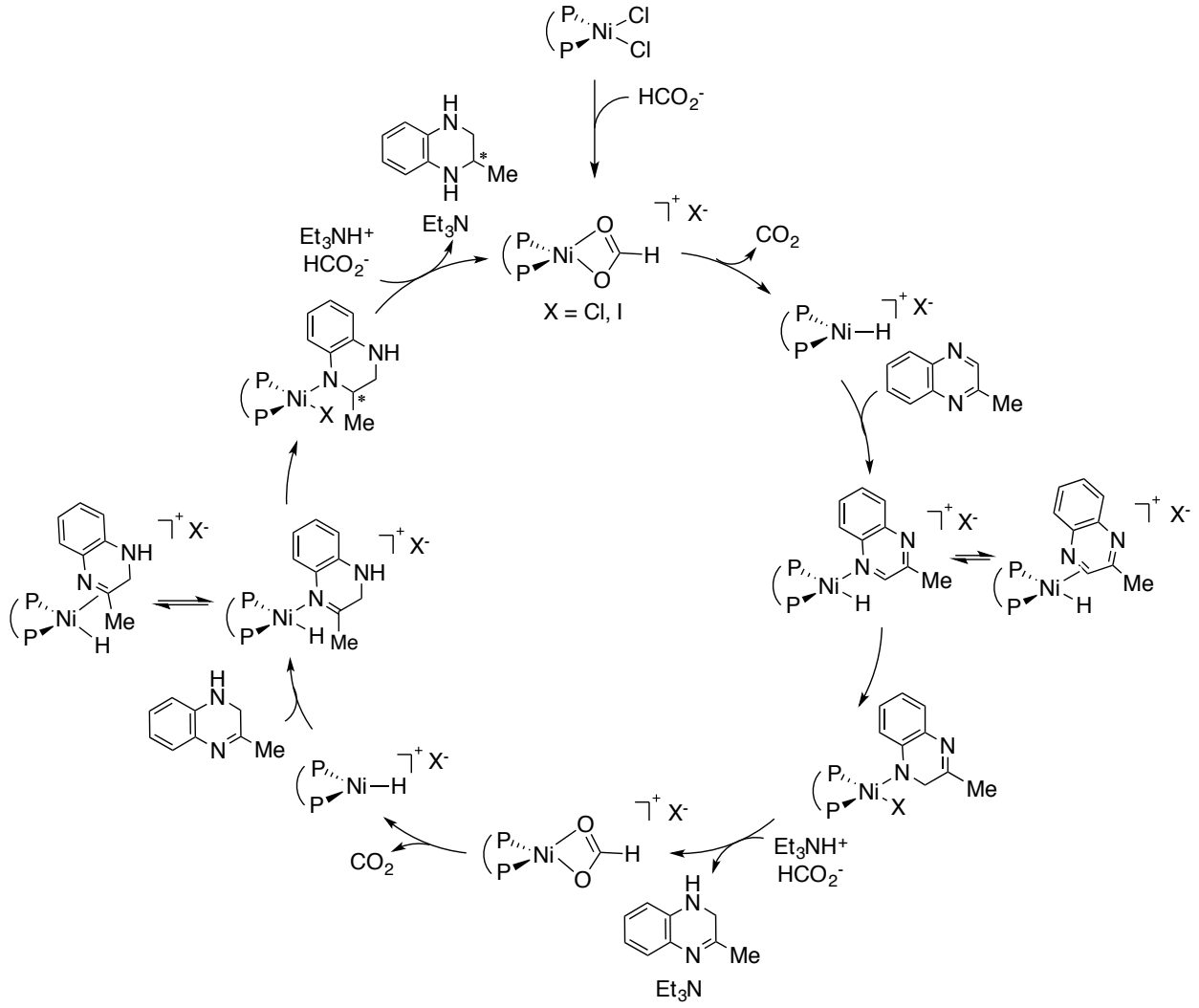
We performed a one-pot synthesis of chiral 1,2,3,4-tetrahydroquinoxalines using our Ni-catalyzed hydrogenation procedure. 1,2-Phenylenediamine and substituted glyoxal reacted in *i*PrOH to form 2-substituted quinoxalines spontaneously, even in the absence of molecular sieve. The quinoxalines then underwent hydrogenation to produce chiral 1,2,3,4-tetrahydroquinoxalines (Scheme 2.17). This part of the work was published in a recent article.[75]



Scheme 2.17 Nickel-catalyzed one-pot synthesis of chiral 2-substituted 1,2,3,4-tetrahydroquinoxalines

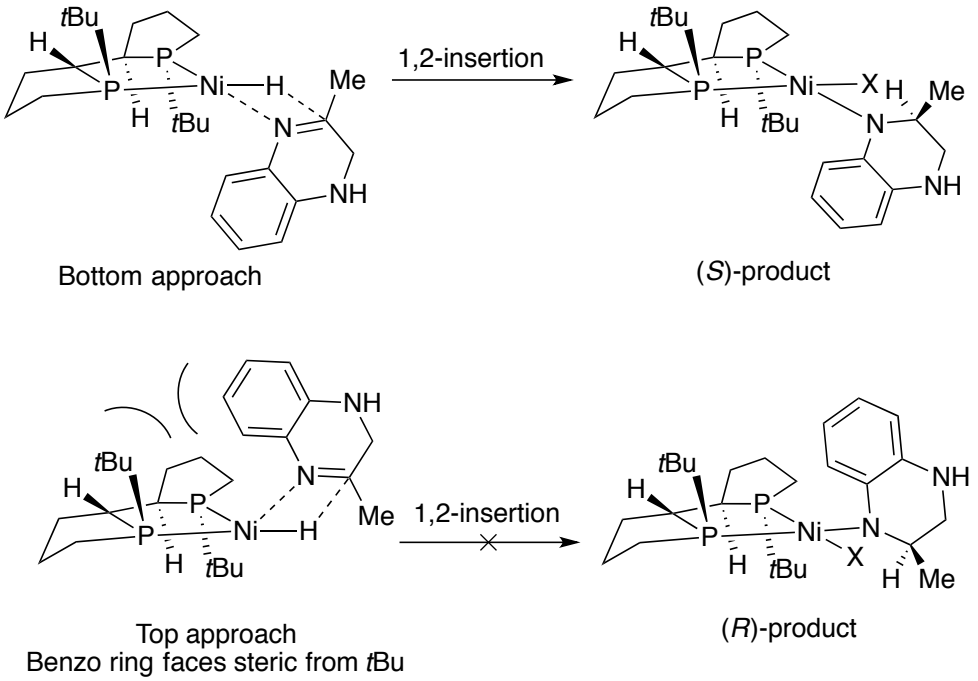
2.3.4 Proposed catalytic cycle for nickel-catalyzed asymmetric hydrogenation of 2-substituted quinoxalines

The catalytic cycle is proposed as follows (Scheme 2.18).



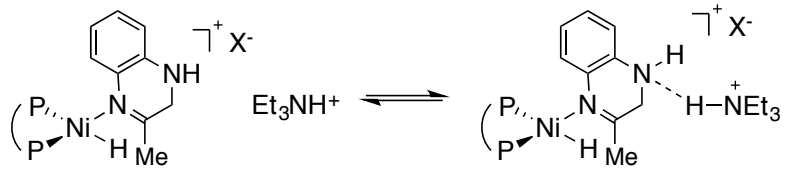
Scheme 2.18 Proposed catalytic cycle for Ni-catalyzed asymmetric hydrogenation of 2-substituted quinoxalines

A nickel(II) formate species, formed from the nickel(II) chloride precatalyst and a formate anion, undergo decarboxylation to give a nickel hydride species. 2-Methylquinoxaline then coordinates to the nickel center followed by 1,2-insertion to reduce the less sterically hindered C=N bond first. The nitrogen on the amine formed is then protonated by Et_3NH^+, and the 3-methyl-1,2-dihydroquinoxaline formed is displaced by a formate anion. The more sterically hindered C=N bond is reduced in a similar manner next, generating a tertiary stereocenter.



Scheme 2.19 Possible configuration for the reduction of the second C=N bond

During the reduction of the second C=N, the substrate preferentially approaches from the bottom with the benzo ring facing down, and 1,2-insertion to form the (*S*)-product. It is not favourable for the substrate to approach from the top with the benzo ring facing up as the benzo ring would face steric from the upward pointing *t*-butyl group on the ligand (Scheme 2.19).



Scheme 2.20 Hydrogen bond formation between Et_3NH^+ and the amine formed

At the start of the reaction, there is a significant concentration of Et_3NH^+ and HCO_2^- in the reaction mixture due to acid-base neutralization. The proton on Et_3NH^+ may form a hydrogen bond with the basic nitrogen on the amine resulted from the first C=N hydrogenation (Scheme 2.20). This affects the hydrogenation of the second C=N hydrogenation to a small degree, and hence resulting in a slightly lower *ee*. We hypothesized that nBu$_4$NI provides a source of I^- anions to bind with Et_3NH^+ cations, prevent the formation of aforementioned hydrogen bond, preventing the corrosion of enantioselectivity. *i*PrOH is the optimum solvent in this reaction as it can better dissolve nBu$_4$NI, resulting in a higher percentage of dissociation of nBu4$^+$ and I^- ions, providing a larger pool of I^- anions.

2.4 Conclusion

In conclusion, we have developed an efficient method for the hydrogenation of 2-substituted quinoxalines using Ni/TangPhos as the catalyst with moderate to good enantioselectivity. We also found that 2-substituted 1,2,3,4-tetrahydroquinoxalines can be obtained by a one-pot reaction of 1,2-phenylenediamine and glyoxal.

2.5 Experimental data

2.5.1 General

^{1}H NMR spectra were acquired on Bruker 400 MHz spectrometers and chemical shifts were recorded relative to tetramethylsilane (δ 0.00) or residual protiated solvent ($CDCl_3$: δ 7.26). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH. Coupling constants were reported as a *J* value in Hz. ^{13}C NMR spectra were obtained at 100 MHz on 400 MHz and chemical shifts were recorded relative to solvent resonance ($CDCl_3$: δ 77.16). Proof of purity of new compounds was demonstrated with copies of ^{1}H, ^{13}C and ^{19}F NMR spectra.

Glassware was dried in an oven at 120^{o}C for at least 2 hours before use. Isopropanol was distilled from sodium under argon before use. Unless noted otherwise, commercially available chemicals were used without further purification. The GC standard, *n*-tetradecane was degassed with argon bubbling and dried over activated 4 Å molecular sieve beads for a few days in the glovebox before use.

Thin-layer chromatography (TLC) was conducted with Merck 60 F254 coated silica gel plate (0.2 mm thickness). Flash chromatography was performed using Merck silica gel 60 (0.040-0.063 mm).

Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with Agilent J & W GC column DB-5MS-UI. GCMS analysis was conducted on a Thermo Scientific DSQ II single quadrupole GC/MS instrument with Agilent J & W GC column DB-5MS-UI. Chiral HPLC analysis was performed on a Shimadzu LC-20AD instrument using Daicel CHIRALPAK® and CHIRALCEL® columns at 25°C and a mixture of HPLC-grade hexanes and

isopropanol as eluent. Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm and the concentration of samples was denoted as *c*.

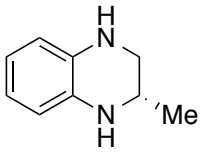
2.5.2 Condition optimization of Ni-catalyzed asymmetric hydrogenation of 2-methylquinoxaline

A typical procedure for condition optimization: In an argon-filled glovebox, a dry 10 mL Schlenk tube containing a magnetic stir bar was charged with $NiCl_2$(DME) (5 mol%, 0.005 mmol, 1.1mg), (*S*,*S*',*R*,*R*')-TangPhos (6 mmol%, 0.006 mmol, 1.7 mg) and *i*PrOH (0.3 mL). The reaction was stirred for 10 min at RT. Then, *n*-tetradecane (10 μL), *n*BuNI (3 equiv, 0.3 mmol, 111 mg), 2-methylquinoxaline (1 equiv, 0.1 mmol, 14.4 mg), Et_3N (3 equiv, 0.3 mmol, 42 μL) and HCOOH (0.3 equiv, 0.3 mmol, 11 μL) were added. The tube was tightly capped and the mixture was stirred in a preheated 90 ^oC oil bath. After 24 h, aliquots were taken from the reaction mixture and passed through a short plug of silica gel with ethyl acetate washings. The filtrate was subjected to GC analysis to determine the conversion of 2-methylquinoxaline and the calibrated GC yield of the product. To determine the enantioselectivity of the product, the filtrate was dissolved in 1:5 *i*PrOH/hexanes and subjected to chiral HPLC analysis (Daicel CHIRALPAK® IC; 1% *i*PrOH in hexanes; flow rate 1.0 mL/min).

2.5.3 Ni-catalyzed asymmetric hydrogenation of 2-substituted quinoxalines

A typical procedure for Ni-catalyzed asymmetric hydrogenation of 2-substituted quinoxalines: In an argon-filled glovebox, a dry 10 mL Schlenk tube containing a magnetic stir bar was charged with $NiCl_2$.glyme (3.3 mg, 0.015 mmol), (*S*,*S*',*R*,*R*')-TangPhos (5.1 mg, 0.018 mmol) and *i*PrOH (0.9 mL) and the reaction was stirred at RT for 10 min. Then, *n*-tetradecane (30 μL), *n*Bu_4NI (333 mg, 0.9 mmol), 2-substituted quinoxaline (0.3 mmol), Et_3N (126 μL, 0.9 mmol)

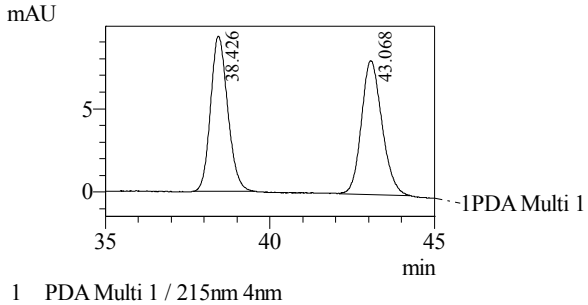
and HCOOH (33 μL, 0.9 mmol) were added. The tube was tightly capped and the mixture was stirred in a preheated 90 ^{o}C oil bath for 48 h (monitored by GC). The reaction is then concentrated and the crude product was purified by flash chromatography using ethyl acetate/hexanes as eluent. The enantioselectivity (*ee*) of the purified product was determined by chiral HPLC analysis using Daicel CHIRALPAK® and Daicel CHIRALCEL® columns.



(*S*)-2-Methyl-1,2,3,4-tetrahydroquinoxaline [24463-31-8]. The product was isolated by flash chromatography (EA/ hexanes 1:5) as pale yellow solid. Yield: 41 mg, 92%.

$[\alpha]_D^{22}$= -16.3˚(*c* = 0.38, $CHCl_3$). [Lit.[54] $[\alpha]_D^{24}$= -34.4˚(*c* = 0.065, CH_2Cl_2), 93% ee, (*S*)]

Ee: 94%. Daicel CHIRALPAK® IC, *n*-hexane/isopropanol 99/1, flow rate = 1.0 mL/min.



1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

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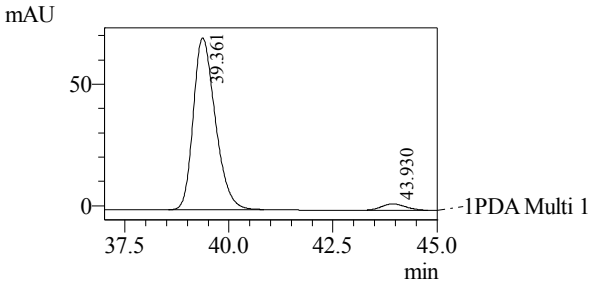
2	43.068	347928	50.748
Total		685600	100.000



1 PDA Multi 1 / 215nm 4nm

PeakTable

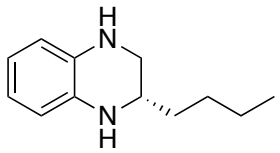
PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	39.361	2603735	96.271
2	43.930	100847	3.729
Total		2704582	100.000

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60-6.57 (m, 2H), 6.52-6.49 (m, 2H), 3.57 (br s, 2H), 3.56-3.48 (m, 1H), 3.32 (dd, *J* = 10.7, 2.8 Hz, 1H), 3.04 (dd, *J* = 10.6, 8.3 Hz, 1H), 1.19 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 133.7, 133.3, 118.84, 118.83, 114.61, 114.57, 48.4, 45.9, 20.0.

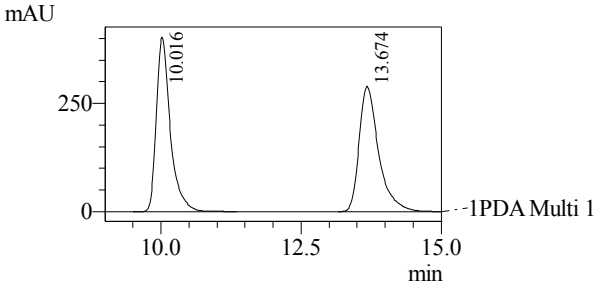
GCMS (EI): Calcd for $C_9H_{12}N_2$: 148.2. Found: 148.1.



(*S*)-2-Butyl-1,2,3,4-tetrahydroquinoxaline [1203947-90-3]. The product was isolated by flash chromatography (EA/ hexanes 1:5) as orange solid. Yield: 54 mg, 95%.

$[\alpha]_D^{21}$= -33.7˚(*c* = 3.3, $CHCl_3$). [Lit.[54] $[\alpha]_D^{24}$= -30.4˚(*c* = 0.15, CH_2Cl_2), 93% ee, (*S*)]

Ee: 72%. Daicel CHIRALCEL® OD, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.



1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

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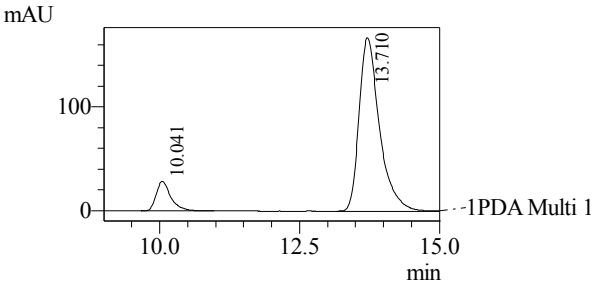
2	13.674	6985538	50.017
Total		13966412	100.000



1 PDA Multi 1 / 215nm 4nm

PeakTable

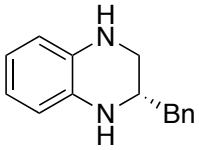
PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	10.041	521554	10.944
2	13.710	4244240	89.056
Total		4765795	100.000

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62-6.57 (m, 2H), 6.54-6.49 (m, 2H), 3.52 (br s, 2H), 3.38-3.33 (m, 2H), 3.07 (pseudo dd, *J* = 11.2, 8.4 Hz, 1H), 1.51-1.35 (m, 6H), 0.97-0.93 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 133.6, 133.5, 118.8, 118.7, 114.6, 114.5, 50.4, 46.8, 34.1, 27.9, 22.9, 14.1.

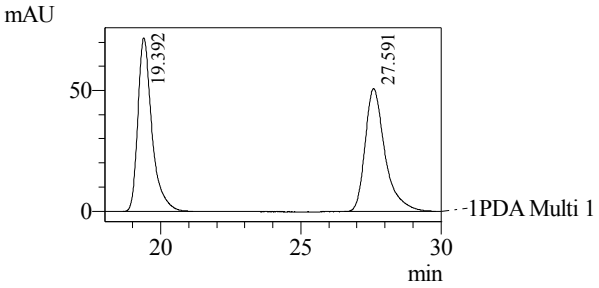
GCMS (EI): Calcd for $C_{12}H_{18}N_2$: 190.3. Found: 190.1.



(*S*)-2-Benzyl-1,2,3,4-tetrahydroquinoxaline [1360631-94-2]. The product was isolated by flash chromatography (EA/ hexanes 1:5) as dark red oil. Yield: 58 mg, 86%.

$[\alpha]_D^{21}$= -80.6˚(*c* = 1.4, $CHCl_3$).

Ee: 84%. Daicel CHIRALCEL® OD, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.

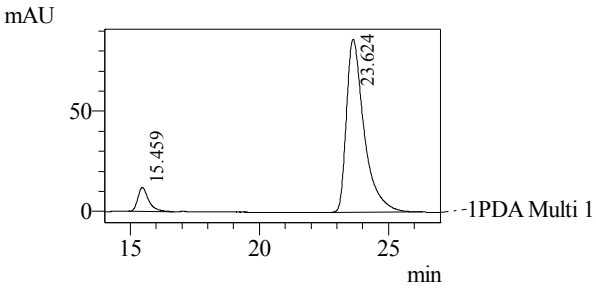


1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	19.392	2503971	49.908
2	27.591	2513163	50.092
Total		5017134	100.000



1 PDA Multi 1 / 215nm 4nm

PeakTable

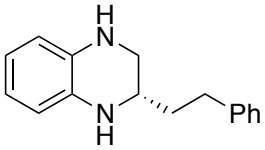
PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	15.459	348725	7.818
2	23.624	4112002	92.182
Total		4460727	100.000

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.31 (m, 2H), 7.27-7.22 (m, 3H), 6.60-6.54 (m, 2H), 6.52-6.49 (m, 1H), 6.44-6.41 (m, 1H), 3.63-3.57 (m, 1H), 3.46 (br s, 2H), 3.39 (dd, *J* = 10.8, 2.8 Hz, 1H), 3.17 (dd, *J* = 10.7, 7.1 Hz, 1H), 2.84 (dd, *J* = 13.3, 5.6 Hz, 1H), 2.72 (dd, *J* = 13.3, 8.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 133.4, 133.2, 129.4, 128.8, 126.7, 118.92, 118.85, 114.7, 114.5, 51.4, 46.4, 40.7.

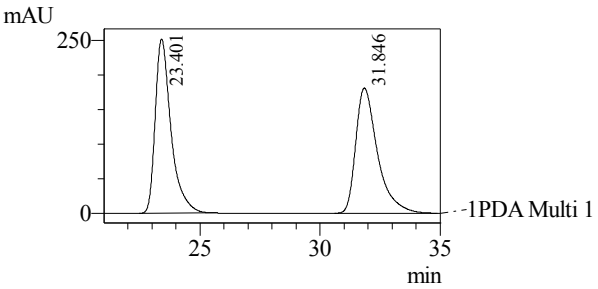
GCMS (EI): Calcd for $C_{15}H_{16}N_2$: 224.3. Found: 224.1.



(*S*)-2-Phenethyl-1,2,3,4-tetrahydroquinoxaline [1360631-94-2]. The product was isolated by flash chromatography (EA/ hexanes 1:5) as orange solid. Yield: 55 mg, 77%.

$[\alpha]_D^{21}$= -35.1˚(*c* = 3.6, $CHCl_3$). [Lit.[58] $[\alpha]_D^{24}$= +49.8˚(*c* = 1.0, CH_2Cl_2), 98% ee, (*S*)]

Ee: 77%. Daicel CHIRALCEL® OD, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.

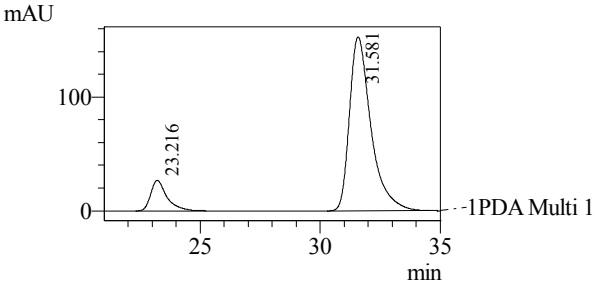


1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	23.401	11564430	50.281
2	31.846	11435088	49.719
Total		22999519	100.000



1 PDA Multi 1 / 215nm 4nm

PeakTable

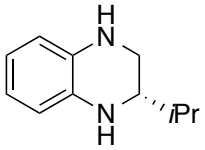
PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	23.216	1256056	11.674
2	31.581	9502923	88.326
Total		10758980	100.000

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.27 (m, 2H), 7.21-7.17 (m, 3H), 6.59-6.55 (m, 2H), 6.49-6.44 (m, 2H), 3.47 (br s, 2H), 3.40-3.32 (m, 2H), 3.08 (pseudo dd, *J* = 10.4, 7.2 Hz, 1H), 2.74-2.70 (m, 2H), 1.83-1.80 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.6, 133.44, 133.39, 128.6, 128.4, 126.2, 118.9, 118.8, 114.7, 114.5, 49.9, 46.5, 35.9, 32.2.

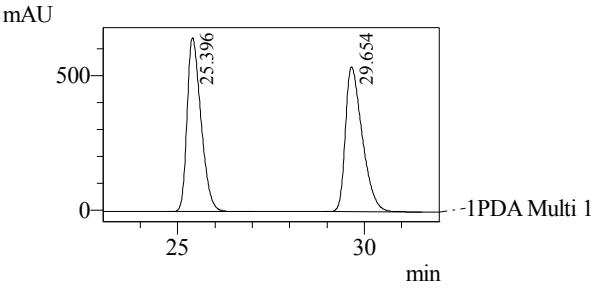
GCMS (EI): Calcd for $C_{16}H_{18}N_2$: 238.3. Found: 238.1.



(*S*)-2-Isopropyl-1,2,3,4-tetrahydroquinoxaline [1252875-58-3]. The product was isolated by flash chromatography (EA/ hexanes 1:5) as pale yellow solid. Yield: 49 mg, 93%.

$[\alpha]_D^{22}$= -21.4˚(*c* = 1.1, $CDCl_3$). [Lit.[57] $[\alpha]_D^{24}$= -36.2˚(*c* = 1.0, CH_2Cl_2), 94% ee, (*S*)]

Ee: 71%. Daicel CHIRALPAK® IC, *n*-hexane/isopropanol 99/1, flow rate = 1.0 mL/min.

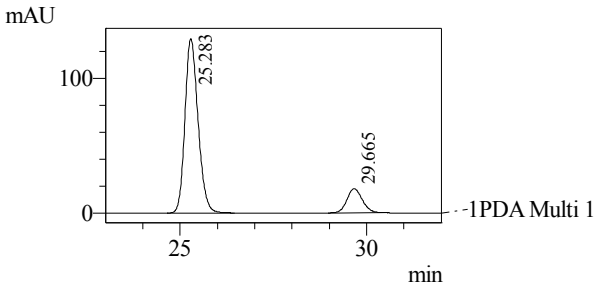


1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	25.396	16733194	49.768
2	29.654	16888878	50.232
Total		33622072	100.000



1 PDA Multi 1 / 215nm 4nm

PeakTable

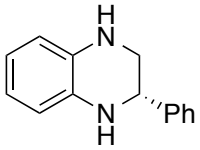
PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	25.283	3168165	85.983
2	29.665	516487	14.017
Total		3684652	100.000

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.63-6.56 (m, 2H), 6.53-6.50 (m, 2H), 3.59 (br, 2H), 3.37 (dd, *J* = 10.0, 2.2 Hz, 1H), 3.19-3.09 (m, 2H), 1.75 (pseudo octet, *J* = 6.7 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.0, 133.5, 118.9, 118.5, 114.42, 114.39, 56.1, 44.1, 31.1, 18.8, 18.7.

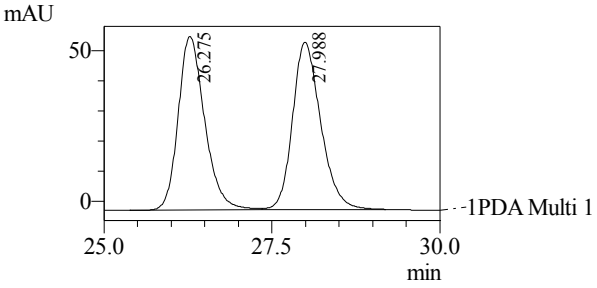
GCMS (EI): Calcd for $C_{11}H_{16}N_2$: 176.3. Found: 176.1.



(*S*)-2-Phenyl-1,2,3,4-tetrahydroquinoxaline [1203948-11-1]. The product was isolated by flash chromatography (EA/ hexanes 1:5) as pale yellow solid. Yield: 51 mg, 81%.

$[\alpha]_D^{22}$= -80.2˚(*c* = 1.0, $CHCl_3$). [Lit.[58] $[\alpha]_D^{20}$= +96.3˚(*c* = 1.0, $CHCl_3$), 94% ee, (*S*)]

Ee: 72%. Daicel CHIRALPAK® IC, *n*-hexane/isopropanol 99/1, flow rate = 1.0 mL/min.

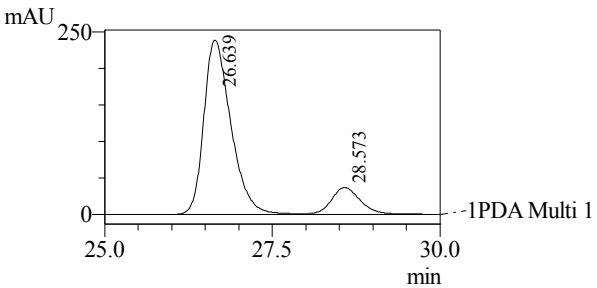


1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	26.275	1580265	49.383
2	27.988	1619746	50.617
Total		3200010	100.000



1 PDA Multi 1 / 215nm 4nm

PeakTable

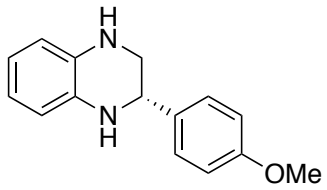
PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	26.639	6711292	85.896
2	28.573	1101951	14.104
Total		7813243	100.000

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.33 (m, 5H), 6.69-6.65 (m, 2H), 6.62-6.59 (m, 2H), 4.49 (dd, *J* = 8.2, 3.0 Hz, 1H), 3.85 (br, 1H), 3.47 (dd, *J* = 11.0, 3.1 Hz, 1H), 3.34 (dd, *J* = 11.0, 8.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 134.2, 132.9, 128.7, 128.0, 127.1, 119.0, 118.9, 114.8, 114.5, 54.8, 49.2.

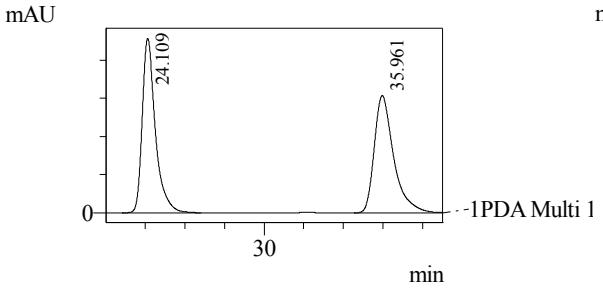
GCMS (EI): Calcd for $C_{14}H_{14}N_2$: 210.3. Found: 210.1.



(S)-2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoxaline [1253208-06-8]. The reaction was heated at 110 ^{o}C for 48h. The product was isolated by flash chromatography (EA/ hexanes 1:5) as orange solid. Yield: 55 mg, 76%.

$[\alpha]_D^{21}$= +58.5˚(c = 2.9, $CHCl_3$). [Lit.[58] $[\alpha]_D^{20}$= +90.1˚(c = 1.0, $CHCl_3$), 94% ee, (*S*)]

Ee: 68%. Daicel CHIRALCEL® OD, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.

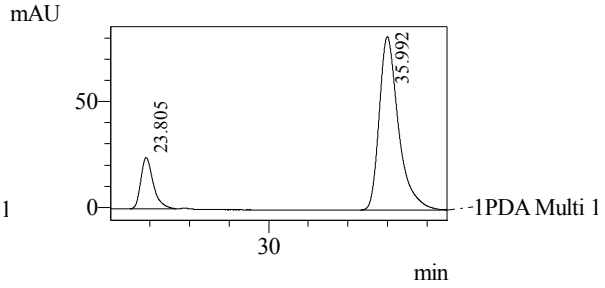


1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	24.109	10559731	50.182
2	35.961	10483112	49.818
Total		21042843	100.000



1 PDA Multi 1 / 215nm 4nm

PeakTable

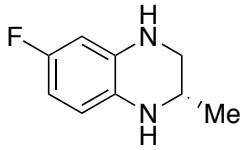
PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	23.805	1057302	16.068
2	35.992	5522930	83.932
Total		6580232	100.000

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.30 (m, 2H), 6.94-6.91 (m, 2H), 6.67-6.63 (m, 2H), 6.60-6.56 (m, 2H), 4.43 (dd, J = 8.3, 3.0 Hz, 1H), 3.83 (s, 1H), 3.71 (br s, 2H), 3.42 (dd, J = 11.0, 3.1 Hz, 1H), 3.31 (dd, J = 11.0, 8.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 134.3, 134.0, 132.9, 128.2, 118.9, 118.8, 114.7, 114.5, 114.1, 55.4, 54.2, 49.4.

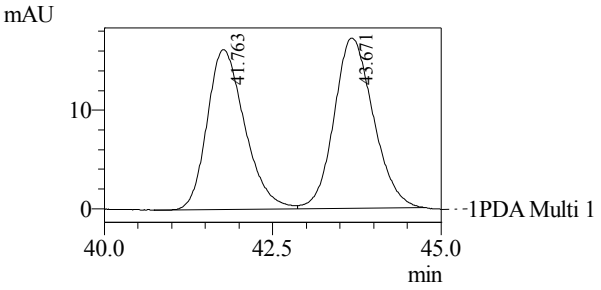
GCMS (EI): Calcd for $C_{15}H_{16}N_2$: 240.3. Found: 240.1.



(*S*)-6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoxaline [1513142-66-9]. The product was isolated by flash chromatography (EA/ hexanes 1:5) as orange solid. Yield: 47 mg, 95%.

$[\alpha]_D^{21}$= -26.8˚(*c* = 1.7, $CHCl_3$).

Ee: 93%. Daicel CHIRALPAK® IC, *n*-hexane/isopropanol 99/1, flow rate = 1.0 mL/min.

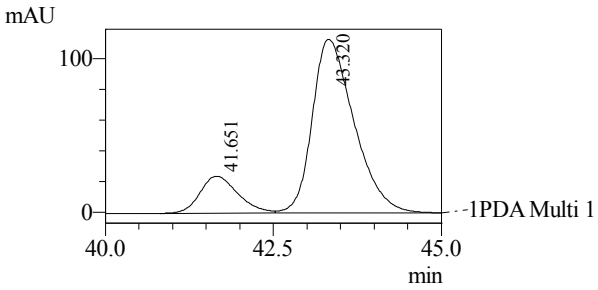


1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	41.763	629158	47.360
2	43.671	699290	52.640
Total		1328448	100.000



1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

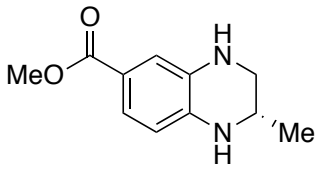
Peak#	Ret. Time	Area	Area %
1	41.651	948811	16.216
2	43.320	4902238	83.784
Total		5851049	100.000

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41 (dd, *J* = 8.5, 5.4, 1H), 6.28-6.20 (m, 2H), 3.55-3.47 (m, 1H), 3.37 (br s, 2H), 3.28 (dd, *J* = 10.8, 2.9 Hz, 1H), 2.97 (dd, *J* = 12.2, 8.1 Hz, 1H), 1.18 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1 (d, J_{CF} = 234.2 Hz), 134.9, (d, J_{CF} = 10.3 Hz), 128.9, 115.0 (d, J_{CF} = 9.2 Hz), 104.0 (d, J_{CF} = 22.6 Hz), 101.2 (d, J_{CF} = 25.8 Hz), 48.2, 46.0, 19.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -125.5.

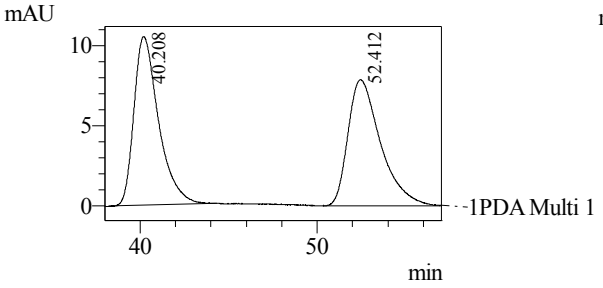
GCMS (EI): Calcd for $C_9H_{11}FN_2$: 166.2. Found: 166.1.



Methyl (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline-6-carboxylate [1893551-36-4]. The product was isolated by flash chromatography (EA/ hexanes 1:5) as orange solid. Yield: 41 mg, 67%.

$[\alpha]_D^{21}$= -32.7˚(*c* = 2.2, $CDCl_3$).

Ee: 60%. Daicel CHIRALCEL® OD, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.

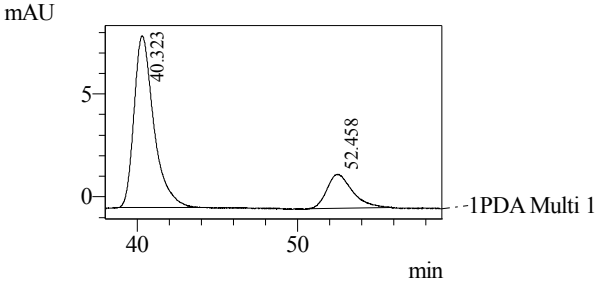


1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	40.208	1017832	50.203
2	52.412	1009608	49.797
Total		2027441	100.000



1 PDA Multi 1 / 215nm 4nm

PeakTable

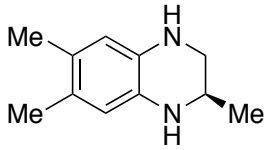
PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	40.323	715248	79.458
2	52.458	184913	20.542
Total		900161	100.000

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.18 (d, *J* = 1.8 Hz, 1H), 6.41 (d, *J* = 8.2 Hz, 1H), 4.02 (br s, 2H), 3.82 (s, 3H), 3.63-3.54 (m, 1H), 3.31 (dd, *J* = 10.7, 3.1 Hz, 1H), 2.98 (dd, *J* = 10.7, 7.9 Hz, 1H), 1.14 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 138.4, 132.1, 121.8, 119.3, 115.3, 112.6, 51.6, 47.6, 46.0, 19.9.

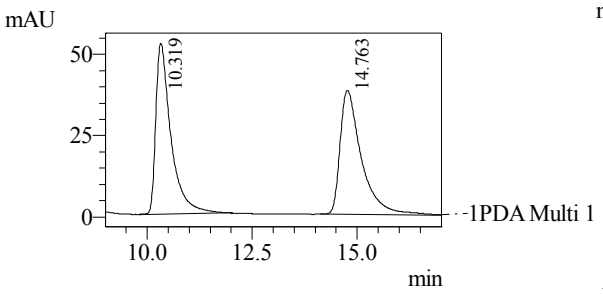
GCMS (EI): Calcd for $C_{11}H_{14}N_2O_2$: 206.3. Found: 206.1.



(*R*)-2,6,7-trimethyl-1,2,3,4-tetrahydroquinoxaline [1203948-03-1]. (*R*)-QuinoxP* (6.0 mg) was used instead of (*S*,*S*',*R*,*R*') TangPhos. The product was isolated by flash chromatography (EA/ hexanes 1:5) as brown solid. Yield: 28 mg, 53%.

$[\alpha]_D^{22}$= -11.0˚(*c* = 3.4, $CHCl_3$). [Lit.[54] $[\alpha]_D^{24}$= -26.5 (*c* = 0.15, CH_2Cl_2), 87% ee, (*S*)]

Ee: 65%. Daicel CHIRALCEL® OD, *n*-hexane/isopropanol 90/10, flow rate = 1.0 mL/min.

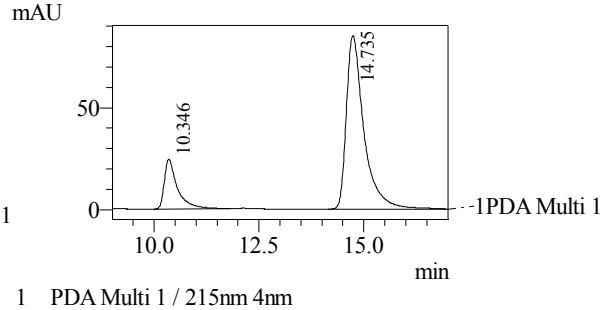


1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	10.319	1316550	49.419
2	14.763	1347486	50.581
Total		2664036	100.000



1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	10.346	528424	17.550
2	14.735	2482545	82.450
Total		3010969	100.000

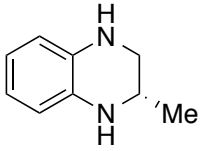
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.35 (d, *J* = 3.8 Hz, 2H), 3.48-3.28 (m, 4H), 3.01 (pseudo t, *J* = 9.3 Hz, 1H), 2.13 (s, 6H), 1.19 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 131.5, 131.1, 126.54, 126.47, 116.5, 48.7, 46.1, 20.0, 19.0.

GCMS (EI): Calcd for $C_{11}H_{16}N_2$: 176.3. Found: 176.1.

2.5.4 Ni-catalyzed one pot asymmetric reductive amination to access chiral 1,2,3,4-tetrahydroquinoxalines

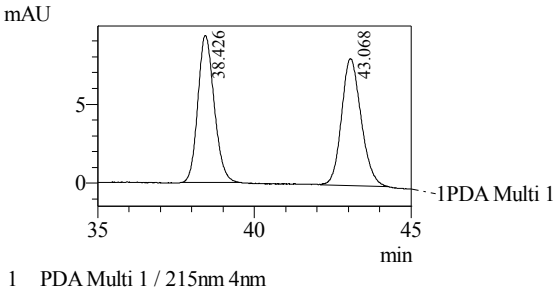
A typical procedure for one pot asymmetric reductive amination: In an argon-filled glovebox, a dry 10 mL Schlenk tube containing a magnetic stir bar was charged with 1,2-phenylenediamine (32.4 mg, 0.3 mmol), α-ketoaldehyde (0.3 mmol) and *i*PrOH (0.9 mL). The reaction was stirred at RT for 1 h (monitered with TLC). After the reaction is completed, $NiCl_2$.glyme (3.3 mg, 0.015 mmol), (*S*,*S*',*R*,*R*')-TangPhos (5.1 mg, 0.018 mmol) was added and the reaction was stirred at RT for 10 min. Then, *n*-tetradecane (30 μL), *n*Bu_4NI (333 mg, 0.9 mmol), Et_3N (126 μL, 0.9 mmol) and HCOOH (33 μL, 0.9 mmol) were added. The tube was tightly capped and the mixture was stirred in a preheated 90 ^oC oil bath for 48 h (monitored by GC). The reaction is then concentrated and the crude product was purified by flash chromatography using EA/hexanes as eluent. The enantioselectivity (*ee*) of the purified product was determined by chiral HPLC analysis using Daicel CHIRALPAK® and CHIRALCEL® columns.



(*S*)-2-Methyl-1,2,3,4-tetrahydroquinoxaline [24463-31-8]. Pyruvic aldehyde (21.6 mg, 0.3 mmol, 35% w/w in H_2O) was used. The product was isolated by flash chromatography (EA/ hexanes 1:5) as pale yellow solid. Yield: 30 mg, 67%.

$[\alpha]_D^{22}$= -16.2˚(*c* = 0.38, $CHCl_3$). [Lit.[54] $[\alpha]_D^{24}$= -34.4˚(*c* = 0.065, CH_2Cl_2), 93% ee, (*S*)]

Ee: 93%. Daicel CHIRALPAK® IC, *n*-hexane/isopropanol 99/1, flow rate = 1.0 mL/min.



1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

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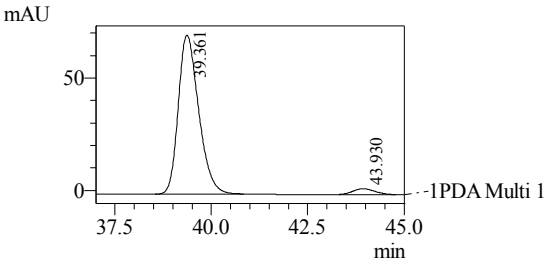
2	43.068	347928	50.748
Total		685600	100.000



1 PDA Multi 1 / 215nm 4nm

PeakTable

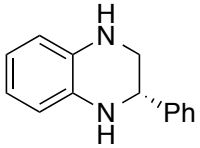
PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	39.361	2603735	96.271
2	43.930	100847	3.729
Total		2704582	100.000

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61-6.57 (m, 2H), 6.53-6.49 (m, 2H), 3.58 (br, 2H), 3.55-3.48 (m, 1H), 3.32 (dd, *J* = 10.7, 2.9 Hz, 1H), 3.04 (dd, *J* = 10.6, 8.2 Hz, 1H), 1.19 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 133.7, 133.3, 118.83, 118.82, 114.61, 114.56, 48.4, 45.9, 20.0.

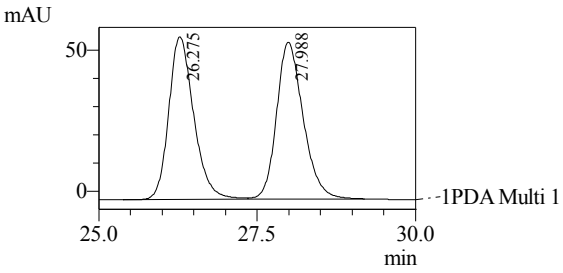
GCMS (EI): Calcd for $C_9H_{12}N_2$: 148.2. Found: 148.1.



(*S*)-2-Phenyl-1,2,3,4-tetrahydroquinoxaline [1203948-11-1]. Phenylglyoxal monohydrate (45.6 mg, 0.3 mmol) was used. The product was isolated by flash chromatography (EA/ hexanes 1:5) as yellow solid. Yield: 38 mg, 61%.

$[\alpha]_D^{22}$= +73.0^o (*c* = 1.0, $CHCl_3$). [Lit.[58] $[\alpha]_D^{20}$= +96.3 ° (*c* = 1.0, $CHCl_3$), 94% ee, (*S*)]

Ee: 72%. Daicel CHIRALPAK® IC, *n*-hexane/isopropanol 99/1, flow rate = 1.0 mL/min.



1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

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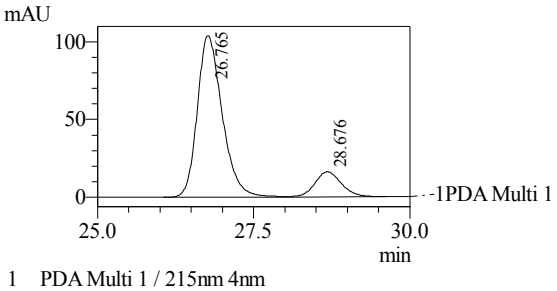
2	27.988	1619746	50.617
Total		3200010	100.000



1 PDA Multi 1 / 215nm 4nm

PeakTable

PDA Ch1 215nm 4nm

Peak#	Ret. Time	Area	Area %
1	26.765	2883367	85.759
2	28.676	478790	14.241
Total		3362157	100.000

^{1}H NMR (400 MHz, CDCl3): δ 7.42-7.33 (m, 5H), 6.70-6.58 (m, 4H), 4.49 (dd, *J* = 8.1, 3.1 Hz, 1H), 3.81 (br, 2H), 3.47 (dd, *J* = 11.0, 3.1 Hz, 1H), 3.34 (dd, *J* = 11.0, 8.2 Hz, 1H).

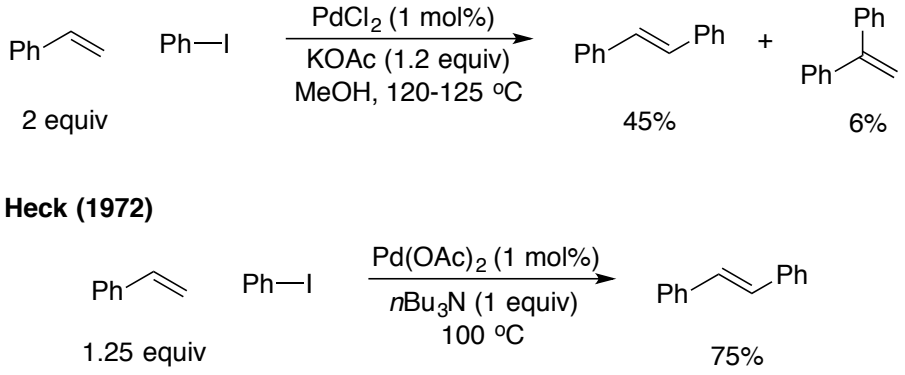
^{13}C NMR (100 MHz, CDCl3): δ 142.0, 134.2, 132.9, 128.7, 128.0, 127.1, 119.0, 118.9, 114.8, 114.5, 54.8, 49.2.

GCMS (EI): Calcd for $C_{14}H_{14}N_2$: 210.3. Found: 210.1.

Chapter 3: A challenging Heck reaction of maleimides

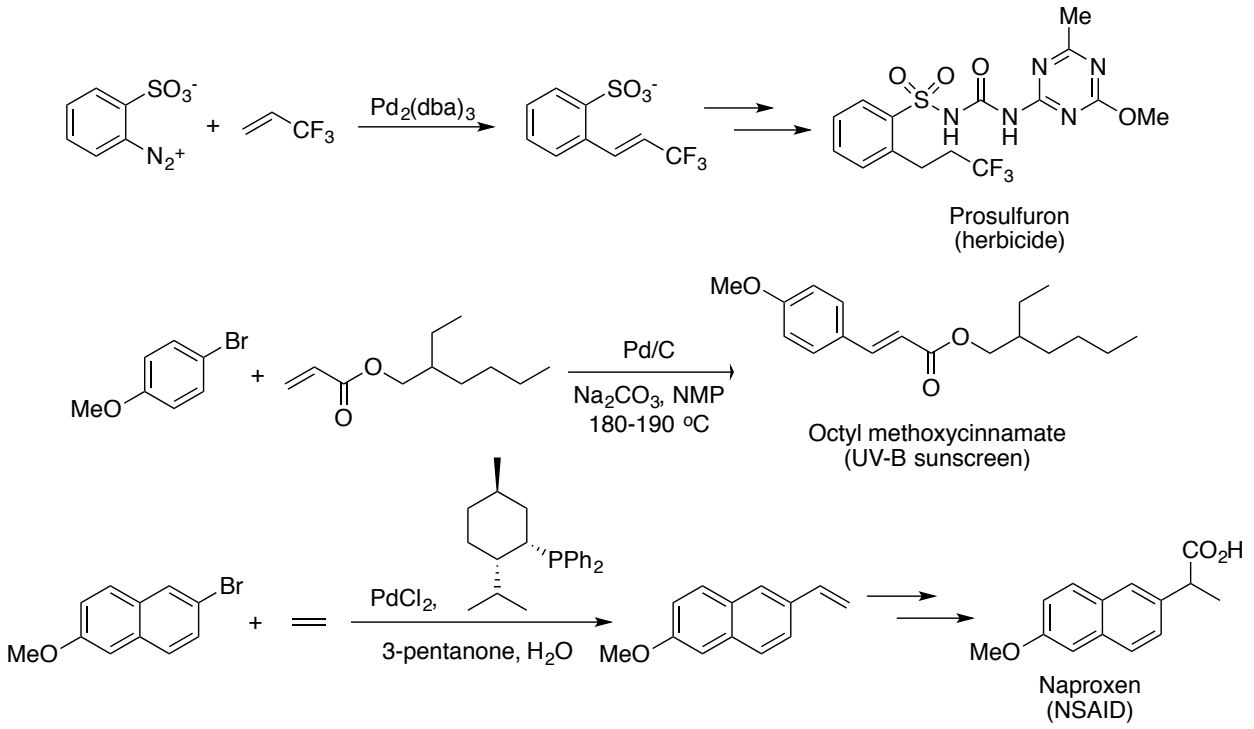
3.1 General introduction of Mizoroki-Heck reaction

The palladium-catalyzed arylation and vinylation of olefins was first independently reported by Tsutomu Mizoroki[76] and Richard Heck[77] in the 1970s (Scheme 3.1).



Scheme 3.1 Discovery of catalytic Mizoroki-Heck reaction

Since then, Mizoroki-Heck reaction[78,79] has served as a versatile tool for forming new C-C bonds through arylation or vinylation of olefins. Today, it is commonly used in the production of pharmaceuticals, agrochemicals, fragrance and advanced materials.[80] Some well-known applications of Heck reaction in industry include the manufacturing of Prosulfuron, octyl methoxycinnamate and Naproxen, a nonsteroidal antiinflammatory drug (NSAID) (Scheme 3.2).

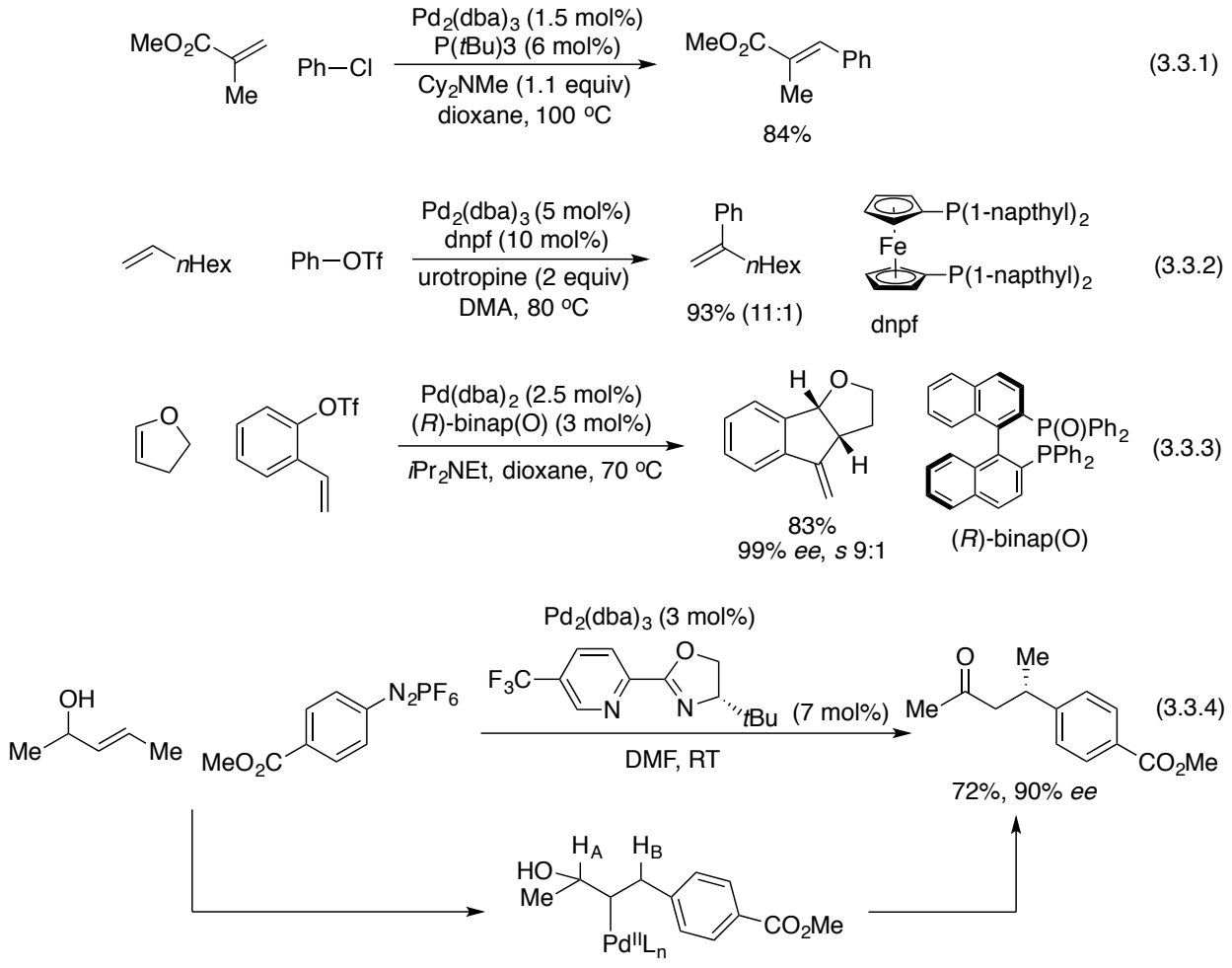


Scheme 3.2 Industrial application of Heck reaction

Since its discovery in the 1970s, Mizoroki-Heck reaction has been well-studied by research groups worldwide. Novel catalysts and ligands have been invented to tackle long standing issues in Heck reaction such as control of the regioselectivities and activation of unreactive substrates. The substrate scope of Mizoroki-Heck reaction encompasses a wide range of olefins, and is constantly expanding to meet its needs in the real world application. Substrates that were once considered infeasible yesterday are now made feasible owing to incessant development and improvement of catalysts and reaction conditions.

Fu et al. reported a versatile Heck reaction catalyzed by $Pd_2(dba)_3/P(t\text{Bu})_3$ in 2001 with a good generality in term of substrate scope (Scheme 3.5.1).[81] Various aryl chloride and bromides react well with a wide range of olefins, giving the Heck product in good to excellent yields. Our group also developed a ligand, dnpf, for Heck reaction of aliphatic olefins with aryl triflates (Scheme 3.5.2). [2] The desired branch Heck products were obtained in good to excellent yield with

high internal selectivity.[82] Sigman et al. described an asymmetric Heck reaction of alkenyl alcohols with aryldiazonium salts in the presence of $Pd_2(dba)_3$ and a PyrOx ligand (Scheme 3.3.4), in which H_A underwent β-elimination selectively to produce the desired ketone product in good enantioselectivities. Our group also reported a Pd/(*R*)-binap(O) catalyzed enantioselective intermolecular cyclization using aryl triflates and cyclic alkenes to obtain tricyclic products in high enantioselectivities (Scheme 3.3.3).



Scheme 3.3 Selected publications on Heck reactions

Despite the progress achieved in Heck reaction, Heck arylation of maleimides remains a challenge as maleimides are prone to hydrolysis under high temperature and in the presence of strong bases.[83]

3.2 Existing arylation methods of maleimides and its applications

Maleimides are a class of particularly useful and versatile compounds. The maleimide motif can be found in many natural products, including Staurosporine, Rebeccamycin, Arcyriaflavin, Hinaimide, Polycitrin and Showdomycin (Figure 3.4).[84-90] They have been particularly of interest to the pharmaceutical industry as they exhibit many beneficial biological activities, such as antibiotic and antitumor properties. Even the simple *N*-methyl-3-phenylmaleimide proved to be a potent monoamine oxidase B inhibitor.[91] Maleimides are also precursor to several bioactive compounds.[92-95]

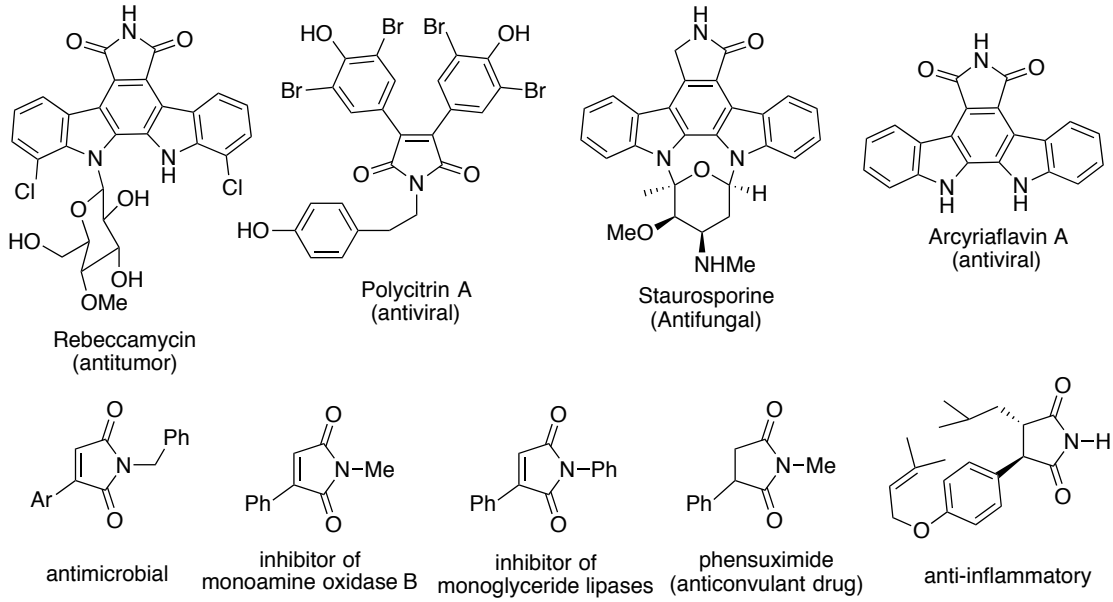


Figure 3.4 Natural products containing the maleimides motifs and biologically active maleimides

Aside from medicinal values, maleimides can also be used to prepare polymers. They also exhibit interesting chemiluminescence properties, which shows their potential to be used as labelling agents in living cells (Figure 3.5).[96,97]

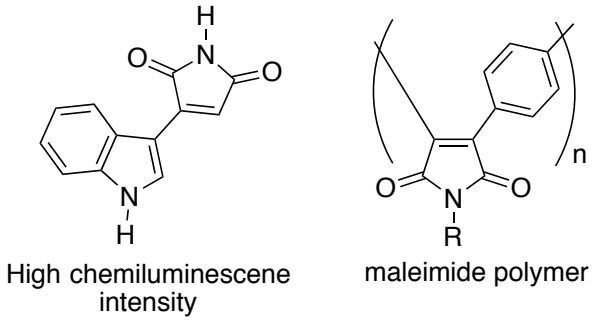


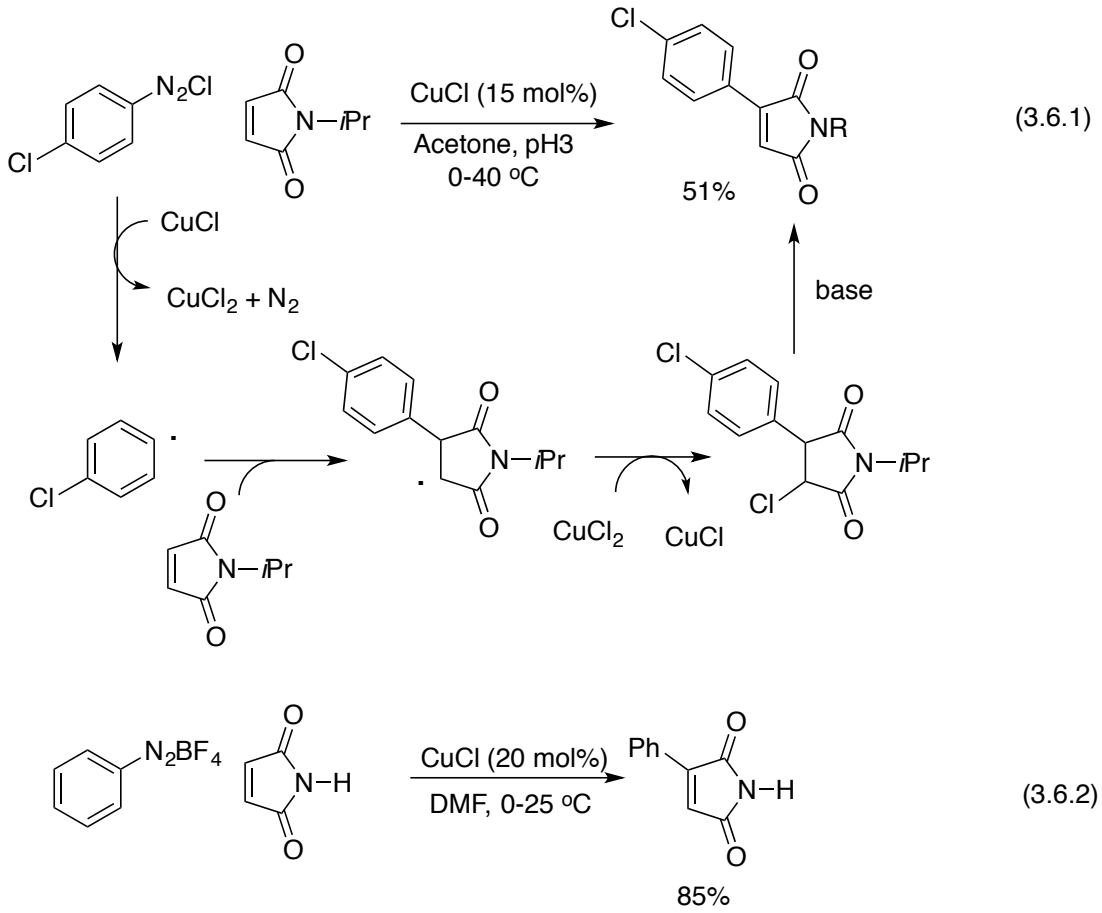
Figure 3.5 Maleimide with high chemiluminescence property and maleimide polymer

3.2.1 Meerwein arylation of maleimides

One of the classical methods to prepare arylmaleimides is Meerwein arylation, a copper-catalyzed reaction using arenediazonium salts as aryl electrophiles.

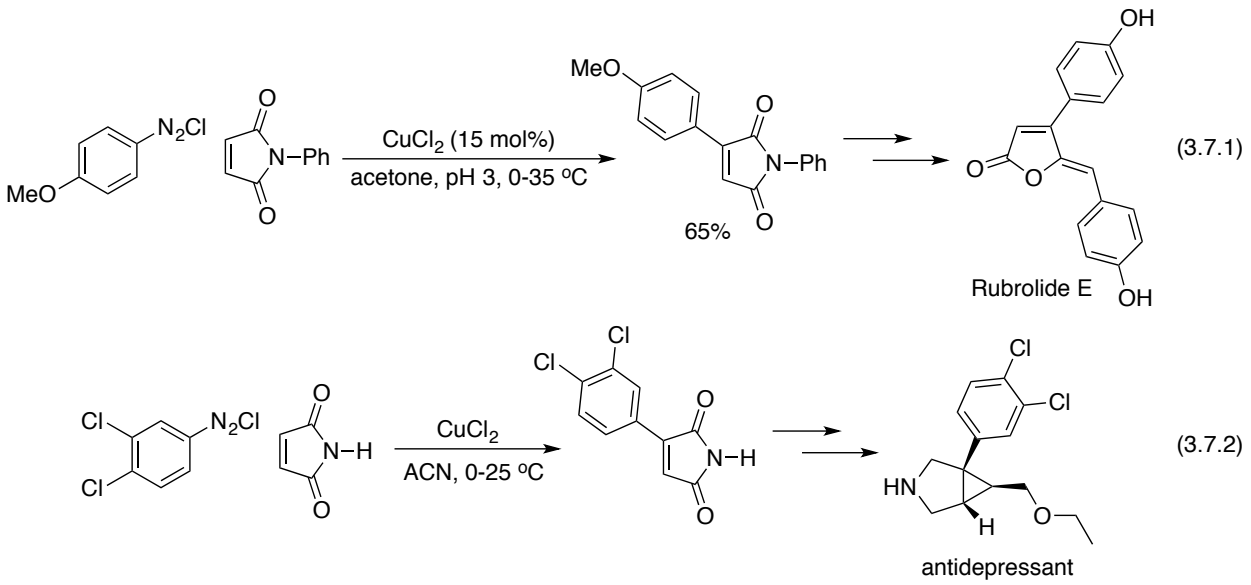
The first example of the direct arylation of maleimides was reported by Rondestvedt and co-workers in 1955. Maleimides reacted with arenediazonium chloride in the presence of $CuCl_2$ at pH 3 to give the monoarylated product.[98,99] The yields were, however, low to moderate in most cases and small amounts of diarylated by-products were detected (Scheme 3.6.1).

Recently, Zhao et al. reported a versatile Cu-catalyzed Meerwein arylation of maleimides with arenediazonium tetrafluoroborate in DMF to produce 3-arylmaleimides. [100]Both electron-rich and electron-deficient substituents on the arenediazonium tetrafluoroborate were tolerated, and no diarylated by-products were detected (Scheme 3.6.2).



Scheme 3.6 Meerwein arylation of maleimides

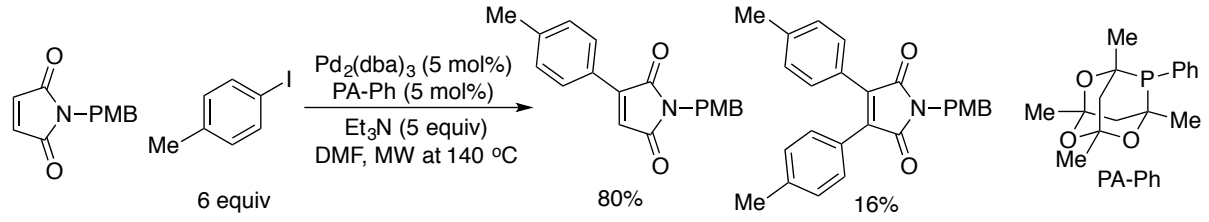
Meerwein arylation has been commonly used to access to 3-arylated maleimides in synthesis of bioactive compounds. Argade et al. applied Meerwein arylation to his synthesis of *N*-phenyl-2-(4-methoxyphenyl)maleimide, [92] which was converted to Rubrolide E, a biologically active marine ascidian metabolites that exhibits potent antibiotic activities towards *Methicillin-resistant Staphylococcus aureus* and *Enterococcus faecalis*[101] (Scheme 3.7.1). Micheli and co-workers also reported synthesis of an antidepressant via Meerwein arylation (Scheme 3.7.2). [93] This target molecule can effectively inhibits uptake of serotonin, norepinephrine, and dopamine transporters, and is promising as powerful antidepressant.



Scheme 3.7 Synthesis of drugs and natural products via Meerwein arylation of maleimides

3.2.2 Heck reaction and cross-coupling reactions of maleimides and halomaleimides

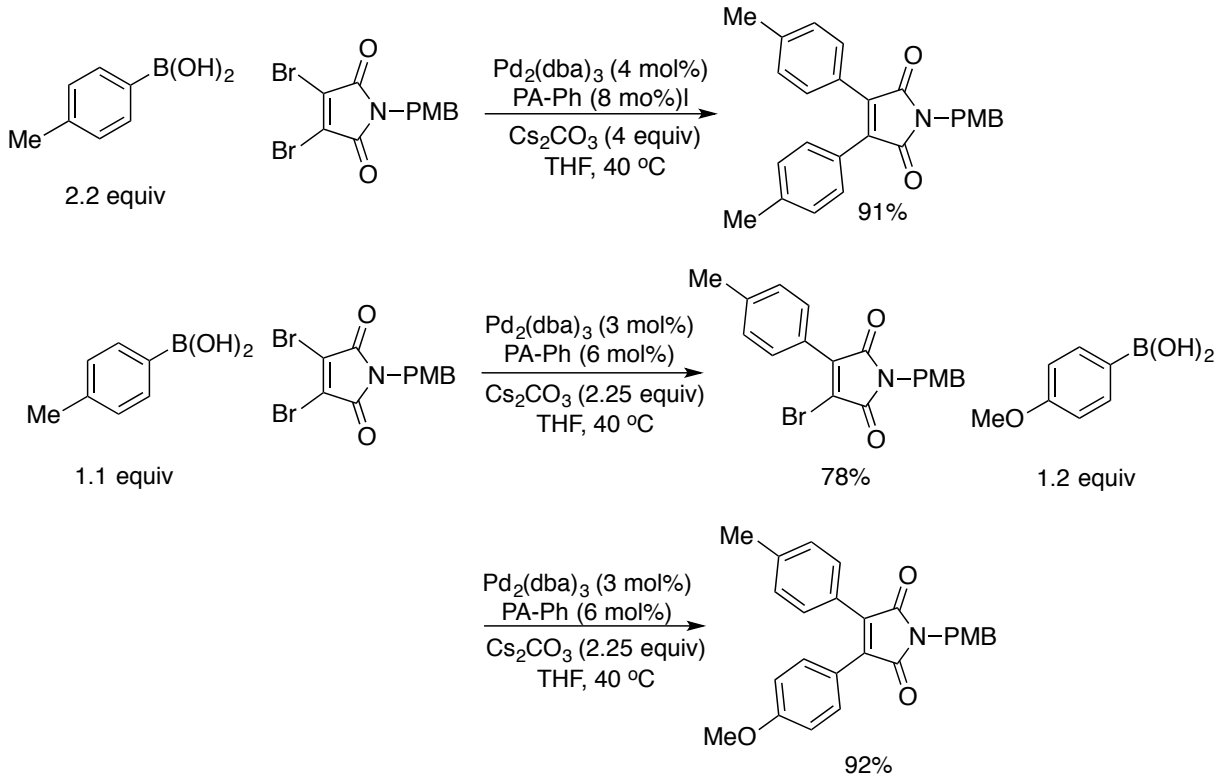
Capretta et al. explored the synthesis of 3,4-diarylmaleimides with the aim to synthesize selective kinase inhibitors containing maleimide structures.[102] Initially, Capretta and co-workers attempted to generate diarylmaleimides through Heck reaction. However, the major product was the monoarylated product despite using 6 equivalents of 4-iodotoluene. Only one example of the Heck reaction was reported (Scheme 3.8).



Scheme 3.8 Capretta's Heck reaction of maleimides

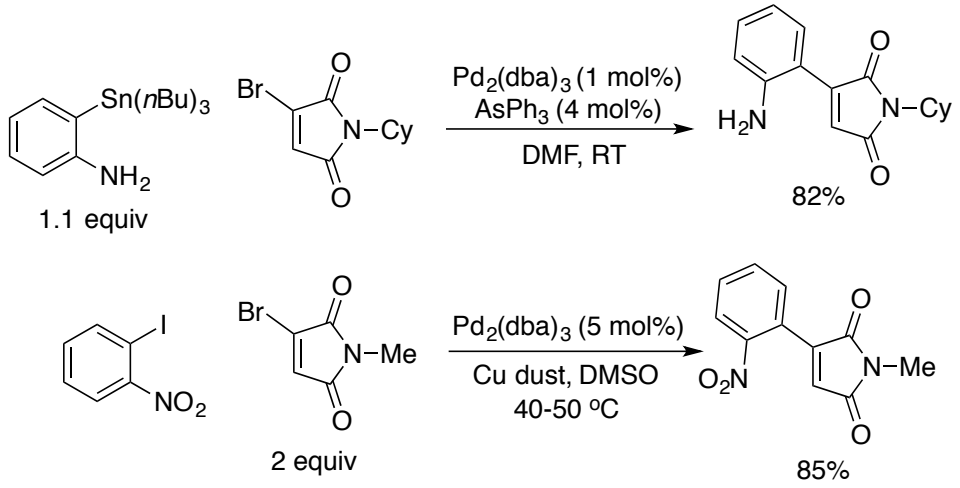
Capretta et al. then switched to explore the palladium-catalyzed Suzuki coupling of 3,4-dibromomaleimides with arylboronic acids. Both symmetrical and unsymmetrical 3,4-diarylated maleimides were produced in excellent yield (Scheme 3.9). The synthesis of substituted

maleimides through Suzuki coupling have been also applied to synthesis of bioactive compounds[95] and fluorescent and chemiluminescent compounds[96,97].



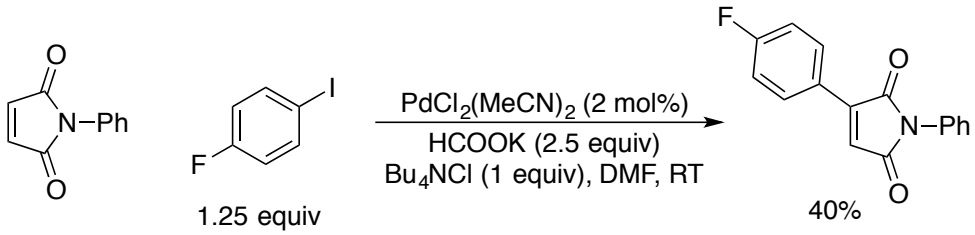
Scheme 3.9 Capretta's Suzuki coupling of *N*-protected 3,4-dibromomaleimide with arylboronic acids

Other than Meerwein arylation and Suzuki cross-coupling, Hoye and Banwell also reported the synthesis of 3-arylmaleimides via Stille[103] and Ullman[104] couplings, but arylstannane and aryl iodide for both reactions were limited to those bearing *o*-nitro or *o*-amino substituents (Scheme 3.10).



Scheme 3.10 Synthesis of monoarylated maleimides via Stille and Ullman coupling

In 2008, Roshchin reported the first example of Heck reaction of maleimides.[105] Aryl iodide can couple with maleimides to give the Heck product using catalytic amounts of $PdCl_2(MeCN)_2$ in the presence of Bu_4NCl and HCOOK. However, the yields were generally poor and the presence of electron-withdrawing groups (CO_2Me and NO_2) on aryl iodides resulted in low yield or no Heck product (Scheme 3.11).

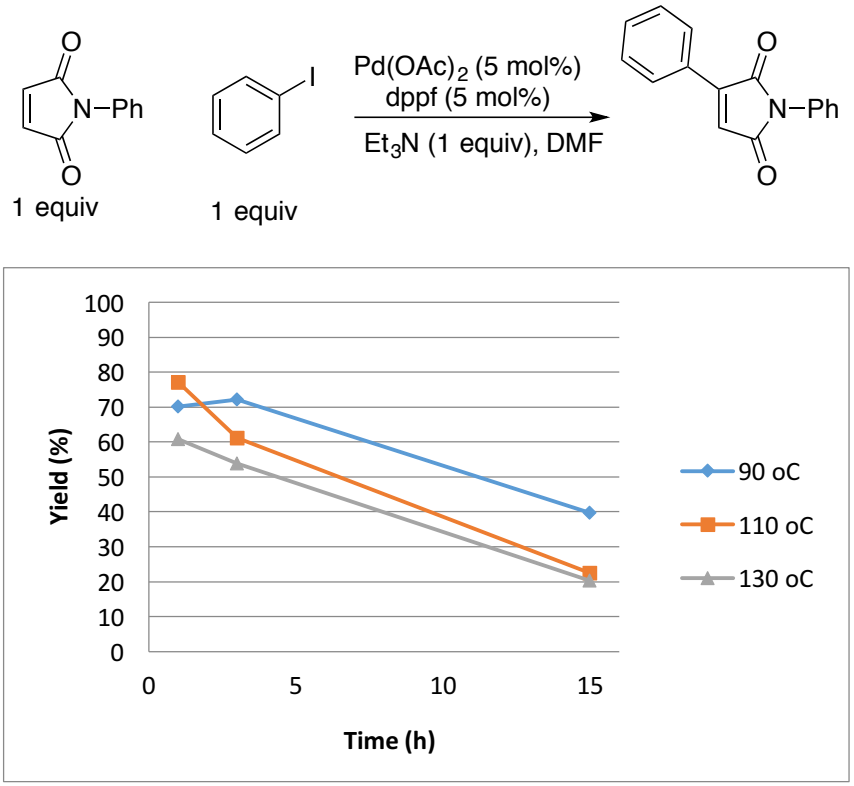


Scheme 3.11 Roshchin's attempt on Heck reaction of maleimides

3.3 Results and discussions

3.3.1 Challenge of fast ring opening of maleimides

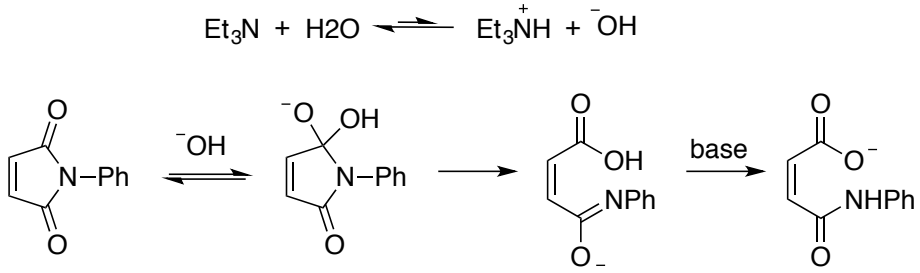
The biggest challenge of Heck reaction of maleimides is the facile basic hydrolysis of maleimides. During our initial screening, we noted that when the reaction was carried out in DMF in the presence of triethylamine, the yield of the product decreased with prolonged heating. This suggested that the arylated maleimide was unstable under the reaction condition (Scheme 3.12).



Scheme 3.12 Instability of arylated maleimide towards bases

Maleimides are known to undergo ring opening to form maleic acid derivatives in basic reaction conditions, and the hydrolysis is directly proportional to the pH of the solution. [83]

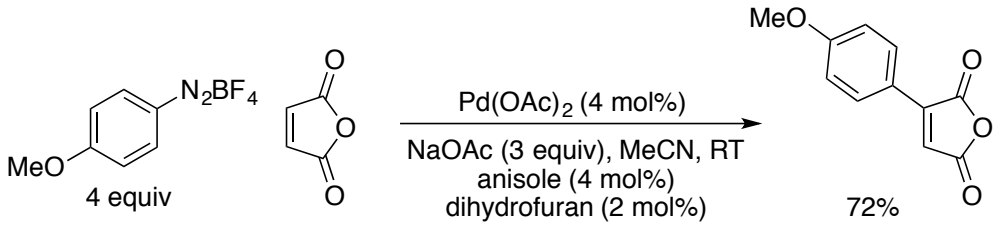
We speculated that self-ionization of a trace amount of water in the presence of triethylamine produced hydroxide ions, which caused the ring-opening of the maleimide (Scheme 3.13). Hence, it is crucial to find a suitable condition that can prevent or minimize the decomposition of maleimides under Heck condition.



Scheme 3.13 Hydrolysis of *N*-phenylmaleimides in the presence of triethylamine

3.3.2 Solution to hydrolysis: weak inorganic base

To find a solution to prevent the hydrolysis of maleimide, we searched the literature to find a suitable base that can be tolerated by maleimides. Although maleic anhydride is more prone to basic hydrolysis than maleimides, examples of Heck arylation of maleic anhydride were reported by Correia and co-workers.[106,107] Using NaOAc as the base, maleic anhydride underwent palladium-catalyzed Heck-Matsuda arylation with aryldiazonium tetrafluoroborates to give monoarylated Heck products in good yields. They noted that a weak inorganic base such as NaOAc or Li_2CO_3 was essential. When strong bases were used, only trace amounts of the Heck products were obtained[106] (Scheme 3.14).

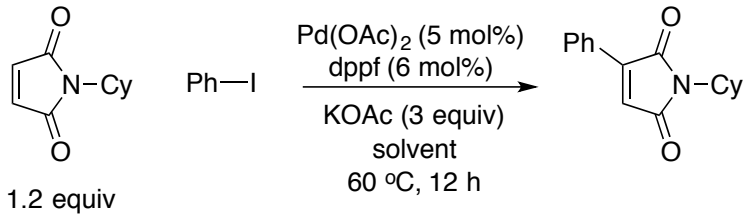


Scheme 3.14 Correia's Heck-Matsuda arylation of maleic anhydride

3.3.3 Condition Optimization

Prompted by the above study of Correia, we employed KOAc as the base and investigated the effect of various solvents in a model Heck reaction of *N*-cyclohexylmaleimide. We have changed the model substrate from *N*-phenylmaleimide to *N*-cyclohexylmaleimide as *N*-alkylmaleimides are generally more resistant towards hydrolysis than *N*-arylmaleimide.[108] To our delight, we found that in ethylene carbonate the Heck product was obtained in 88% yield after 12 h at 60 ^{o}C (Table 3.1, entry 1). Notably, the conversion of maleimides was higher in other polar solvents (Table 3.1, entry 14-16). The polar solvents can better solvate the cations of bases and left acetate anion more exposed and thus more nucleophilic. This can lead to the faster hydrolysis of both the starting maleimide and the product.

Table 3.1 Effect of solvents on Heck reaction of *N*-cyclomaleimide with iodobenzene

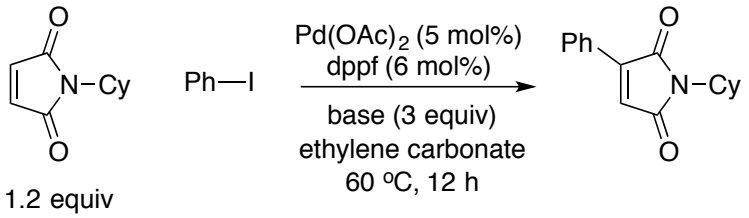


Entry	Solvent	Conversion of PhI (based on 100%)	Conversion of maleimide (based on 120%)	GC Yield (%)
1	**ethylene carbonate**	**100**	**112**	**88**
2	dimethyl carbonate	84	85	67
3	diethyl carbonate	61	65	50
4	EA	87	86	74

5	diglyme	97	102	64
6	triglyme	99	107	63
7	dioxane	82	85	69
8	THF	85	92	62
9	DCM	22	27	15
10	DCE	55	56	46
11	PhMe	26	35	15
12	$PhCF_3$	69	73	55
13	PhOMe	23	33	14
14	DMF	66	120	38
15	DMA	96	108	64
16	DMSO	8	120	0

Using ethylene carbonate as the solvent, we tested a variety of bases for their compatibility with this reaction. Weak inorganic bases such as KOAc, $NaHCO_3$ and $KHCO_3$ (Table 3.2, entries 3-5) furnished the product in good yields after 12 h at 60 ^oC, while organic bases and strong inorganic bases (Table 3.2, entries 8, 9, 12 and 13) gave the monoarylated product in moderate to poor yields despite high conversion of the starting maleimide. Thus, strong bases accelerated hydrolysis of both the starting material and the product.

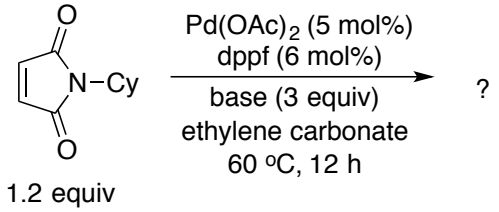
Table 3.2 Effect of bases on Heck reaction of *N*-cyclomaleimide with iodobenzene



Entry	Base	Conversion of PhI (based on 100%)	Conversion of maleimide (based on 120%)	GC Yield (%)
1	LiOAc	25	57	17
2	NaOAc	40	89	31
3	**KOAc**	**100**	**116**	**87**
4	$NaHCO_3$	91	116	71
5	$KHCO_3$	100	120	80
6	Li_2CO_3	9	98	5
7	Na_2CO_3	49	74	41
8	K_2CO_3	21	120	4
9	Cs_2CO_3	35	120	0
10	K_3PO_4	88	119	49
11	KF	80	120	52
12	Et_3N	72	119	30
13	$i Pr_2NEt$	97	119	36

In order to investigate the stability of *N*-substituted maleimides in our basic condition, *N*-cyclohexylmaleimide was heated to 60 ºC for 12 h in the presence of base and ethylene glycol only (Table 3.3). The ratio of N-cyclohexylmaleimide to base is kept at 1.2: 3 for fair comparison to other sets of data. After 12 h, only trace amount of *N*-cyclohexylmaleimide remained when KOAc was used and *N*-cyclohexylmaleimide were completely depleted when heated with Cs_2CO_3 and Et_3N, demonstrating the instability of *N*-substituted maleimides in basic reaction conditions. However, no significant by-product peaks were observed on GC analysis of all three samples did not show. All three reaction mixtures were then sent for ^1H NMR analysis in the effort to identify any by-products, unfortunately the results were inconclusive as the spectrums only showed complicated peaks at 1.5-2.5 ppm and 4-5 ppm region.

Table 3.3 Effect of bases on Heck reaction of *N*-cyclomaleimide with iodobenzene

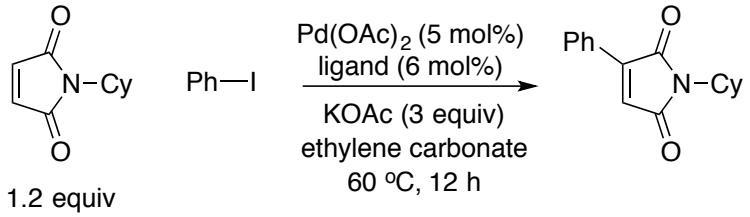


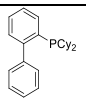
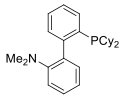
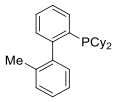
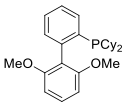
Entry	Base	Conversion of maleimide (based on 100%)
1	KOAc	99
2	Cs_2CO_3	100
3	Et_3N	100

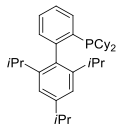
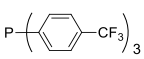
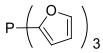
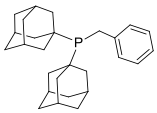
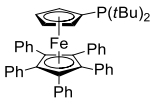
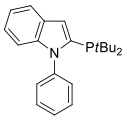
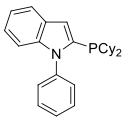
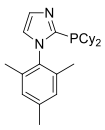
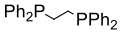
Using KOAc in ethylene carbonate, we tested different ligands. Many phosphine ligands such as SPhos, MePhos, Q-Phos, PCy_3, DPPE, DPPF and DPEPhos (Table 3.4, entries 3, 4, 13,

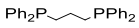
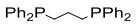
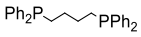
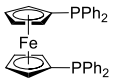
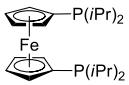
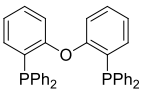
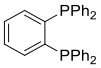
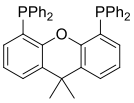
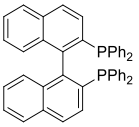
17, 21, 23) gave the product in good to excellent yields. DPPF was chosen as the ligand in subsequent studies due to its low cost and generality. In the absence of phosphines, the reaction also proceeded to give a moderate yield of 64% (Table 3.4, entry 27).

Table 3.4 Effect of ligands on Heck reaction of *N*-cyclomaleimide with iodobenzene



Entry	Ligand	Conversion of PhI (based on 100%)	Conversion of maleimide (based on 120%)	GC Yield (%)
1	 Cy-JohnPhos	100	115	61
2	 DavePhos	50	117	33
3	 MePhos	100	112	93
4	 SPhos	100	111	92

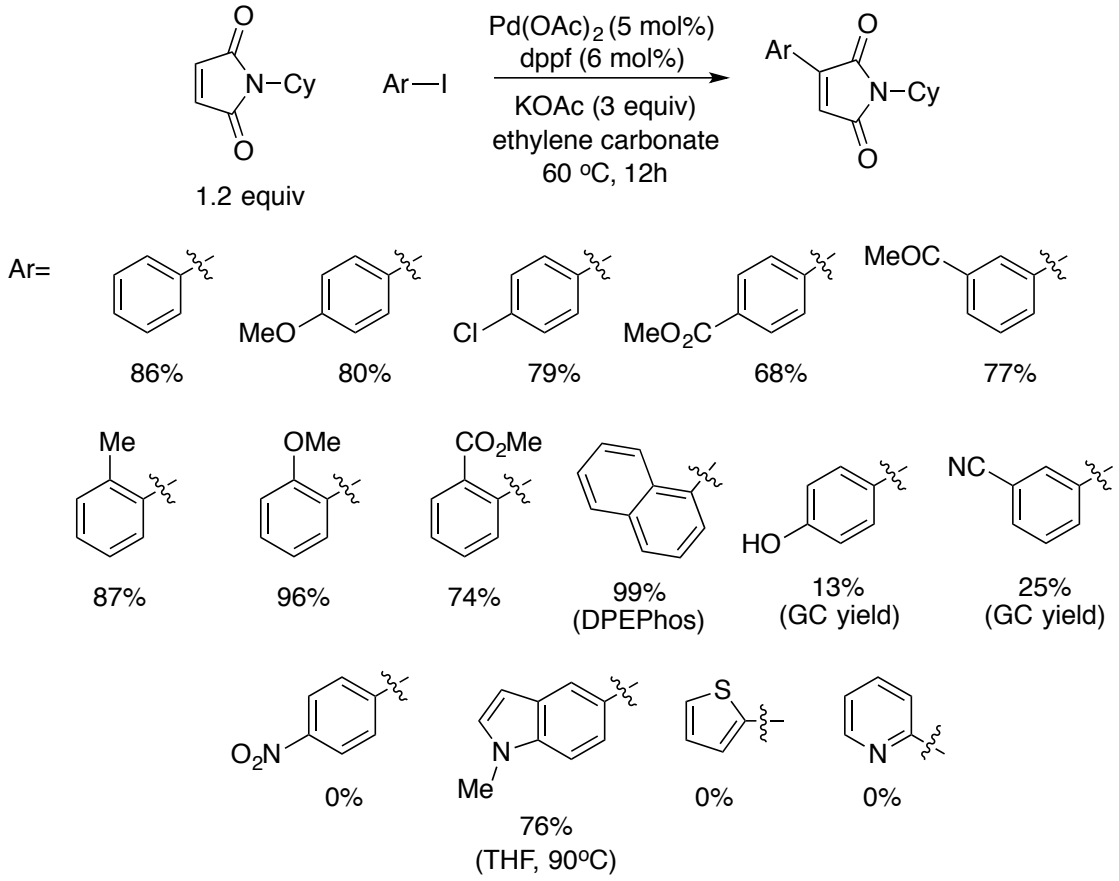
5	 XPhos	99	116	61
6		100	113	63
7	PPh_3	100	117	60
8		95	107	73
9	PCy_3	100	120	90
10	tBu$_3$PHBF$_4$	17	79	11
11	tBu$_3$PHBF$_4$ + 6% KOtBu	69	114	45
12		97	112	78
13	 CTC-Q-Phos	98	106	97
14		83	116	70
15		2	118	0
16		0	118	0
17		100	116	89

	DPPE			
18		57	119	39
	DPPP			
19		87	116	63
	DPPB			
20		88	116	65
	DPPPPE			
21		100	106	90
	DPPF			
22		97	115	87
	D*i*PPF			
23		100	105	96
	DPEPhos			
24		8	117	1
	dppbz			
25		96	108	78
	Xantphos			
26		5	80	1
	rac-BINAP			

27	no ligand	85	100	64

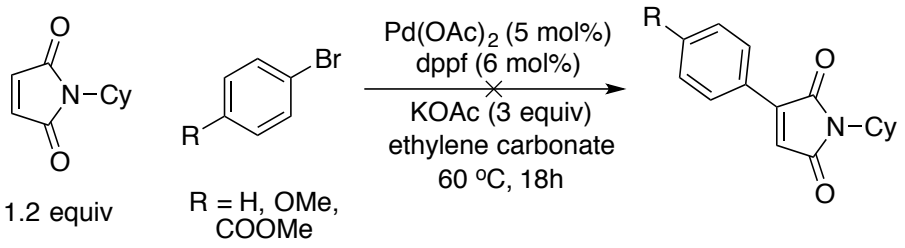
3.3.4 Substrate scope of Heck arylation of maleimides

Using the optimal condition, we explored the scope of aryl iodides (Scheme 3.15). Both electron-rich and electron-deficient aryl iodides smoothly participated in the reaction, although the presence of electron-withdrawing groups on aryl iodide led to slightly lower yield. Notably, high yields were obtained for aryl iodides with *ortho*-substituents, which may be due to the retardation of hydrolysis of 3-arylated maleimide. Unfortunately, aryl iodides containing cyano, hydroxyl and nitro groups were unsuitable substrates for this reaction. Among iodoheterocycles tested, only indolyl iodide reacted smoothly in THF at 90 °C to give the monoarylated product. Both 2-iodothiophene and 2-iodopyridine remained unreactive under the reaction conditions.



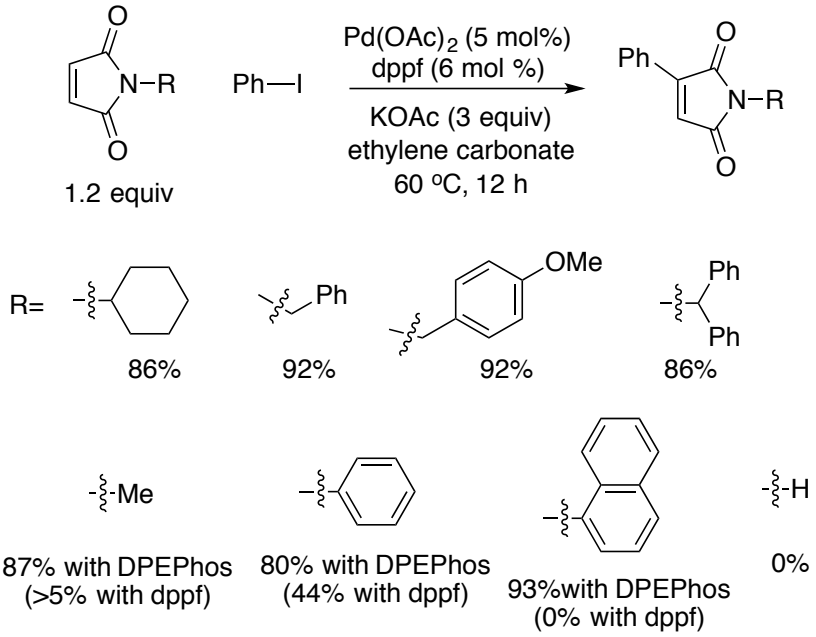
Scheme 3.15 Scope of aryl iodides in Heck reaction of *N*-cyclohexylmaleimide

The Heck reaction was also attempted using aryl bromides. Unfortunately, aryl bromides were unreactive in our reaction condition, no desired Heck products were detected (Scheme 3.16).



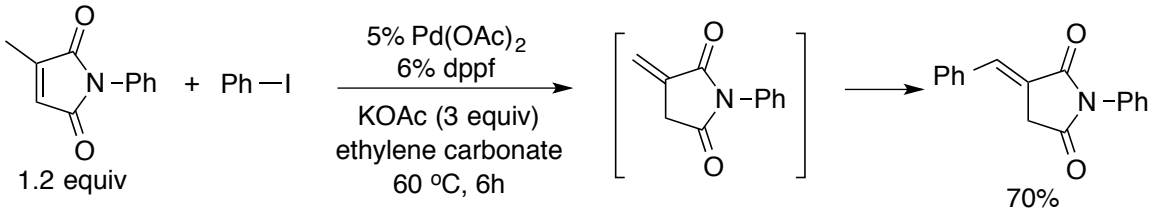
Scheme 3.16 Aryl bromides failed to react in Heck reaction of *N*-cyclohexylmaleimide

The *N*-substituent on the maleimide can be either alkyl or aryl. Good to excellent yields were obtained when *N*-substituents were secondary alkyl or benzylic groups. However, for *N*-aryl maleimides, the ligand must be switched from dppf to DPEPhos to achieve good to excellent yield. For the unprotected maleimide, no desired Heck product was observed, probably due to N-H deprotonation by the base or phosphine (Scheme 3.17).



Scheme 3.17 Scope of maleimides in the Heck reaction with iodobenzene

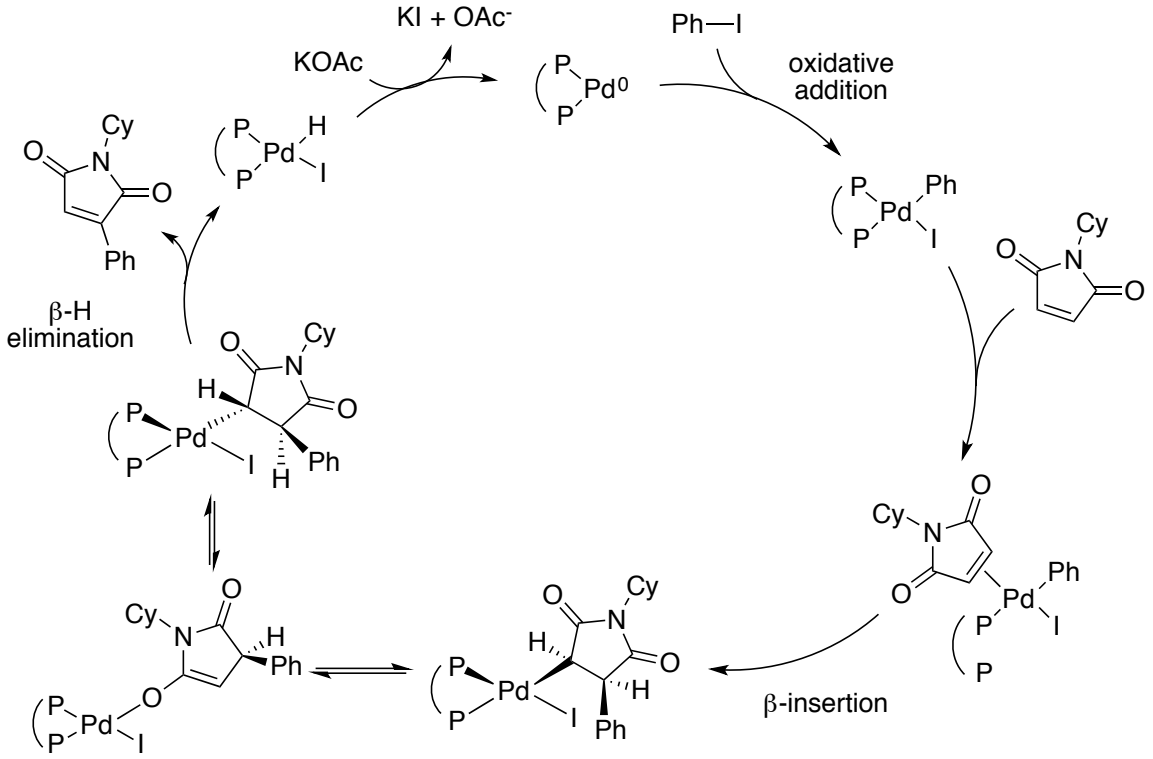
It is interesting to note that when *N*-phenyl-2-methylmalemide afforded *N*-phenyl-2-benzylidenesuccinimide instead of the expected C3-arylated product. This is due to base-induced isomerization of the double bond to generate *N*-phenyl-2-methylenesuccinimide,[109] which is likely to be more reactive than *N*-phenyl-2-methylmalemide in the Heck reaction (Scheme 3.18).



Scheme 3.18 Formation of *N*-cyclohexyl-2-benzylidene-succinimide

3.3.5 Mechanism of Heck arylation of maleimides

The mechanism of the reaction is proposed as follows (Scheme 3.19).

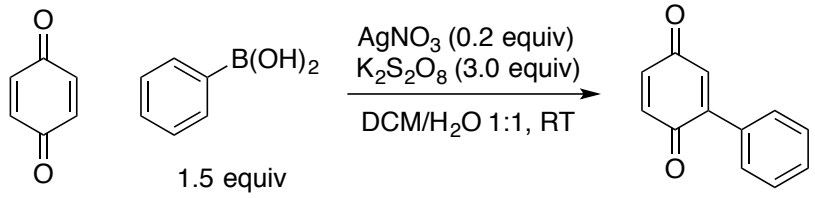


Scheme 3.19 A proposed catalytic cycle of Heck reaction of *N*-cyclohexylmaleimide with iodobenzene

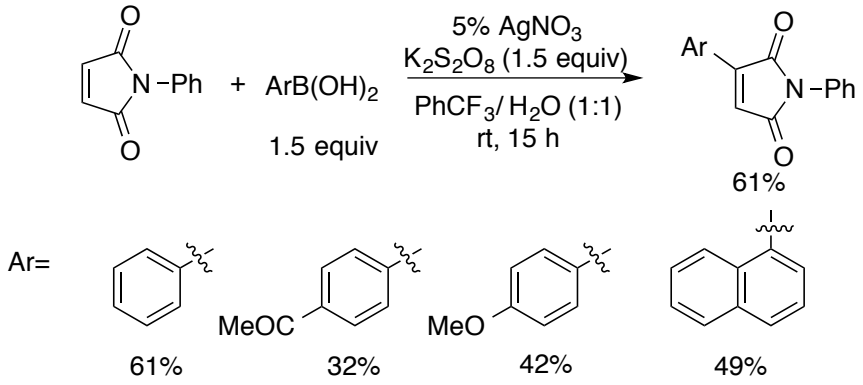
The catalytic cycle is initiated when iodobenzene undergoes oxidative addition onto a palladium(0) center. *N*-cyclohexylmaleimide then binds onto the palladium center, displacing one arm of biphosphine and to allow 1,2-insertion to occur. Since there is no adjacent proton for *β*-hydride elimination, the palladium enolate undergoes isomerization and the palladium center shift to the opposite face, followed by *β*-hydride elimination to give the Heck product. KOAc then removes the hydride from the palladium center and regenerates the active palladium(0) catalyst (Scheme 3.19).

3.4 Other attempt on free-radical arylation of maleimides

On a side note, we also attempted free radical arylation of maleimides by modifying Baran's procedure on silver-catalyzed free radical arylation of quinones (Scheme 3.20).[110,111] To our dismay, only poor to moderate yields of monoarylated products were obtained after extensive condition optimization (Scheme 3.21).

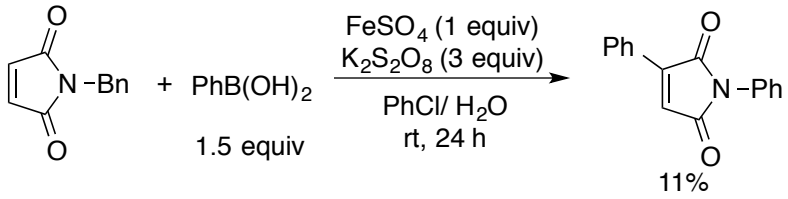


Scheme 3.20 Baran's silver-catalyzed free radical arylation of quinones



Scheme 3.21 Free radical alkylation of *N*-phenylmaleimide with arylboronic acids

Komeyama et al. also reported on a similar free radical arylation of *N*-benzylmaleimide promoted by Fe_2SO_4, but monoarylated product was obtained in only 11% yield (Scheme 3.22).[112] These examples illustrated sensitivity of maleimide rings towards ring opening even under mild conditions.



Scheme 3.22 Komeyama's attempt on free radical arylation of *N*-benzylmaleimide

3.5 Conclusion

In conclusion, we reported an effective procedure for challenging Heck arylation of *N*-substituted maleimides, which are very prone to basic hydrolysis. The use of weakly basic KOAc in ethylene carbonate solvent is important to minimize ring opening of sensitive maleimides and allows Heck product to be formed in good yields. This work was published in 2014.[113]

3.6 Experimental data

3.6.1 General

^{1}H NMR spectra were acquired on Bruker 400 MHz spectrometers and chemical shifts were recorded relative to tetramethylsilane (δ 0.00) or residual protiated solvent ($CDCl_3$: δ 7.26). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by nH. Coupling constants were reported as a *J* value in Hz. ^{13}C NMR spectra were obtained at 100 MHz on 400 MHz instruments and chemical shifts were recorded relative to solvent resonance ($CDCl_3$: δ 77.16). Proof of purity of new compounds was demonstrated with copies of ^{1}H and ^{13}C NMR spectra.

Glassware was dried in an oven at 120 ^{o}C for at least 2 hours before use. Ethylene carbonate was purchased from Fluka and was used without further purification.

Unless noted otherwise, commercially available chemicals were used without further purification. The GC standard, *n*-tetradecane was degassed with argon bubbling and dried over activated 4 Å molecular sieve beads for a few days in the glove box before use.

Thin-layer chromatography (TLC) was conducted with Merck 60 F254 coated silica gel plate (0.2 mm thickness). Flash chromatography was performed using Merck silica gel 60 (0.040-0.063 mm).

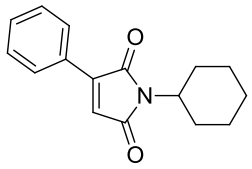
Gas chromatography (GC) analysis was performed on a Shimadzu GC-2010 instrument with Agilent J & W GC column DB-5MS-UI. GC/MS analysis was conducted on a Thermo Scientific DSQ II single quadrupole GC/MS instrument with Agilent J & W GC column DB-5MS-UI. ESI/MS analysis was conducted on a ThermoFinnigan LCQ Fleet MS spectrometer.

3.6.2 Condition optimization of Heck reaction of *N*-substituted maleimides

A typical procedure for isolation of Heck product: In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), dppf (3.3 mg, 0.006 mmol), *N*-cyclohexylmaleimide (21.5 mg, 0.12 mmol), KOAc (29.4 mg, 0.3 mmol), ethylene carbonate (396 mg) and iodobenzene (20.4 mg, 0.1 mmol). The Schlenk tube was capped tightly and the mixture was heated with vigorous stirring in a 60 ^{o}C oil bath. After 12 h, aliquots were taken from the reaction mixture and passed through a short plug of silica gel with ethyl acetate washings. The filtrate was subjected to GC analysis to determine the conversion of *N*-cyclohexylmaleimide and iodobenzene, and the calibrated GC yield of the Heck product.

3.6.3 Isolation of Heck Product

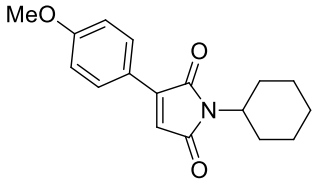
A typical procedure for isolation of Heck product: In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), dppf (16.6 mg, 0.03 mmol), *N*-substituted maleimide (0.6 mmol), KOAc (147.0 mg, 1.5 mmol), ethylene carbonate (1.98 g) and aryl iodide (0.5 mmol). The Schlenk tube was capped tightly and the mixture was heated with vigorous stirring in a 60 ^{o}C oil bath. After the aryl iodide was fully consumed (monitored by GC), the reaction mixture was passed through a pad of silica gel with EA washings to remove the catalyst and inorganic salts. The filtrate was then concentrated on a rotary evaporator and the residue was directly subjected to silica gel flash chromatography.



***N*-Cyclohexyl-3-phenylmaleimide [16213-23-3].** In an argon-filled glove box, a dry 10-mL Schlenk tube containing a magnetic stir bar was charged with $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), dppf (16.6 mg, 0.03 mmol), *N*-cyclohexylmaleimide (107.4 mg, 0.6 mmol), KOAc (147.0 mg, 1.5 mmol), ethylene carbonate (1.98 g) and iodobenzene (102 mg, 0.5 mmol). The Schlenk tube was capped tightly and the mixture was heated with vigorous stirring in a 60 ^{o}C oil bath for 8 h. The product was directly purified by flash chromatography (EA/hexanes 1: 20) as pale yellow solid (110 mg, 86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.89 (m, 2H), 7.46-7.44 (m, 3H), 6.66 (s, 1H), 3.98 (tt, *J* = 12.1, 3.8 Hz, 1H), 2.12 (qd, *J* = 12.4, 2.7 Hz, 2H), 1.87-1.84 (m, 2H), 1.73-1.67 (m, 3H), 1.40-1.22 (m, 3H).

GCMS (EI): Calcd for $C_{16}H_{17}NO_2$: 255.3. Found: 255.1.

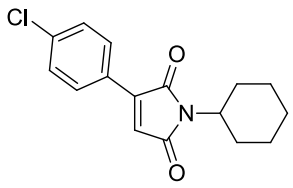


***N*-Cyclohexyl-3-(4-methoxyphenyl)maleimide.** The reaction was stirred at 60 ^{o}C in an oil bath for 6 h. The product was purified by flash chromatography (EA/hexanes 1: 20) as bright yellow solid (115 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-7.90 (m, 2H), 6.97-6.95 (m, 2H), 6.53(s, 1H), 3.96 (tt, *J* = 12.3, 3.8 Hz, 1H), 3.86 (s, 3H), 2.11 (qd, *J* = 12.5, 3.2 Hz, 2H), 1.86-1.83 (m, 2H), 1.71-1.66 (m, 3H), 1.40-1.18 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 171.0, 162.0, 142.9, 130.5, 121.8, 121.3, 114.6, 55.6, 50.9, 30.2, 26.2, 25.3.

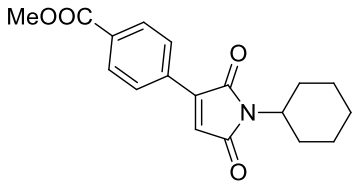
GCMS (EI): Calcd for $C_{17}H_{19}NO_3$: 285.3. Found: 285.1.



***N*-Cyclohexyl-3-(4-chlorophenyl)maleimide [311328-77-5].** The reaction was stirred at 60 ^{o}C in an oil bath for 7 h. The product was purified by flash chromatography (EA/hexanes 1: 20) as white solid (115 mg, 79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.85 (m, 2H), 7.43-7.42 (m, 2H), 6.66 (s, 1H), 3.97 (tt, *J* = 12.4, 3.9 Hz, 1H), 2.20 (qd, *J* = 12.6, 3.1 Hz, 2H), 1.87-184 (m, 2H), 1.72-1.68 (m, 3H), 1.40-1.19 (m, 3H).

GCMS (EI): Calcd for $C_{16}H_{16}ClNO_2$: 289.8. Found: 289.1.

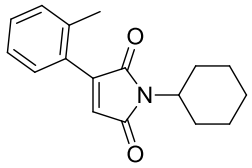


Methyl 4-(1-cyclohexyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)benzoate. The reaction was stirred at 60 ^{o}C in an oil bath for 20 h. The product was purified by flash chromatography (EA/hexanes 1: 20) as white solid (106 mg, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.09 (m, 2H), 7.99-7.97 (m, 2H), 6.77 (s, 1H), 3.99 (tt, *J* = 12.4, 3.8 Hz, 1H), 3.95 (s, 3H), 2.11 (qd, *J* = 12.5, 3.3 Hz, 2H), 1.88-1.84 (m, 2H), 1.73-1.67 (m, 3H), 1.41-1.19 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 170.1, 166.5, 142.3, 133.1, 132.1, 130.1, 128.7, 126.0, 52.5, 51.2, 30.1, 26.1, 25.2.

GCMS (EI): Calcd for $C_{18}H_{19}NO_4$: 313.4. Found: 313.1.

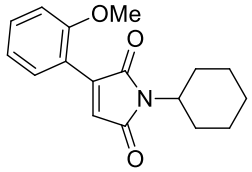


***N*-Cyclohexyl-3-(*o*-tolyl)maleimide.** The reaction was stirred at 60 ^{o}C in an oil bath for 21 h. The product was purified by flash chromatography (EA/hexanes 1: 30) as colourless oil (117 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.46 (m, 1H), 7.36-7.26 (m, 3H), 6.52 (s, 1H), 3.99 (tt, *J* = 12.3, 3.8 Hz, 1H), 2.38 (s, 3H), 2.12 (qd, *J* = 12.5, 3.2 Hz, 2H), 1.87-1.84 (m, 2H), 1.75-1.67 (m, 3H), 1.39-1.22 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 144.9, 137.4, 131.1, 130.4, 130.2, 128.4, 128.2, 126.0, 51.2, 30.1, 26.1, 25.2, 21.1.

GCMS (EI): Calcd for $C_{17}H_{19}NO_2$: 269.3. Found: 269.1.



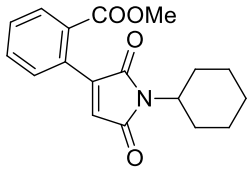
***N*-Cyclohexyl-3-(2-methoxyphenyl)maleimide.** The reaction was stirred at 60 ^{o}C in an oil bath for 21 h. The product was purified by flash chromatography (EA/hexanes 1: 20) as yellow oil (137 mg, 96%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (dd, *J* = 17.8, 1.6 Hz, 1H), 7.40 (pseudo td, *J* = 7.8, 1.6 Hz, 1H), 7.06 (d, *J* = 8 Hz, 1H) 7.02 (s, 1H), 6.97 (d, *J* = 8.4 Hz, 1H), 3.98 (tt, *J* = 12.3, 3.9 Hz, 1H),

3.91 (s, 3H), 2.12 (qd, *J* = 12.5, 3.2 Hz, 2H), 1.86-1.83 (m, 2H), 1.71-1.66 (m, 3H), 1.39-1.22 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 171.7, 159.5, 138.5, 131.8, 131.5, 127.8, 120.8, 118.1, 111.1, 55.6, 50.9, 30.1, 26.2, 25.3.

GCMS (EI): Calcd for $C_{17}H_{19}NO_3$: 285.3. Found: 285.1.

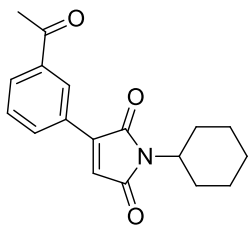


Methyl 2-(1-cyclohexyl-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)benzoate. The reaction was stirred at 60 ^{o}C in an oil bath for 22 h. The product was purified by flash chromatography (EA/hexanes 1: 10) as colourless oil (116 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.60 (pseudo td, *J* = 7.4, 1.6 Hz, 1H), 7.54 (pseudo td, *J* = 7.6, 1.6 Hz, 1H), 7.36 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.50 (s, 1H), 3.96 (tt, *J* = 12.3, 3.9 Hz, 1H), 3.82 (s, 3H), 2.10 (qd, *J* = 12.5, 3.0 Hz, 2H), 1.86-1.83 (m, 2H), 1.74-1.65 (m, 3H), 1.38-1.21 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 170.1, 167.2,148.2, 132.4, 131.0, 130.6, 130.5, 130.3, 130.1, 125.2, 52.5, 51.2, 30.1, 26.1, 25.2.

GCMS (EI): Calcd for $C_{18}H_{19}NO_4$: 313.4. Found: 313.1.

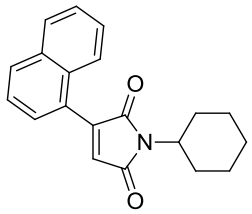


***N*-Cyclohexyl-3-(3-acetylphenyl)maleimide.** The reaction was stirred at 60 ^{o}C in an oil bath for 8 h. The product was purified by flash chromatography (EA/hexanes 1: 8) as white solid (114 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (t, *J* = 1.6 Hz, 1H), 8.08 (td, *J* = 8.0, 1.6 Hz, 1H), 8.03 (td, *J* = 8.0, 1.3 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 6.76 (s, 1H), 3.98 (tt, *J* = 12.3, 3.9 Hz, 1H), 2.64 (s, 3H), 2.11 (qd, *J* = 12.4, 3.0 Hz, 2H), 1.87-1.83 (m, 2H), 1.73-1.66 (m, 3H), 1.39-1.18 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 170.6, 170.2, 142.4, 137.8, 132.9, 130.5, 129.5, 129.4, 128.6, 125.2, 51.2, 30.1, 26.8, 26.1, 25.2.

GCMS (EI): Calcd for $C_{18}H_{19}NO_3$: 297.4. Found: 297.1.

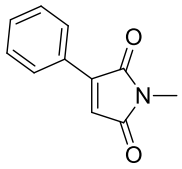


***N*-Cyclohexyl-3-(1-naphthyl)maleimide.** DPEPhos (16.1 mg, 6 mol%) was used as the ligand instead of DPPF. The reaction was stirred at 60 ^{o}C in an oil bath for 15 h. The product was purified by flash chromatography (EA/hexanes 1: 10) as yellow oil (151 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-7.90 (m, 3H), 7.68 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.57-7.53 (m, 3H), 6.77 (s, 1H), 4.06 (tt, *J* = 12.3, 3.9 Hz, 1H), 2.17 (qd, *J* = 12.5, 3.3 Hz, 2H), 1.90-1.68 (m, 5H), 1.43-1.24 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 143.8, 134.0, 131.3, 130.9, 129.1, 129.0, 128.9, 127.3, 126.5, 126.3, 125.2, 124.7, 51.4, 30.3, 26.2, 25.3.

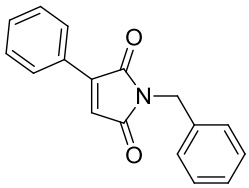
GCMS (EI): Calcd for $C_{20}H_{19}NO_2$: 305.4. Found: 305.1.



***N*-Methyl-3-phenylmaleimide [54433-49-7].** DPEPhos (16.1 mg, 6 mol%) was used as the ligand instead of DPPF. The reaction was stirred at 60 ^{o}C in an oil bath for 2 h. The product was purified by flash chromatography (EA/hexanes 1: 8) as pale yellow solid (81.2 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.90 (m, 2H), 7.48-7.44 (m, 3H), 6.73 (s, 1H), 3.08 (s, 3H).

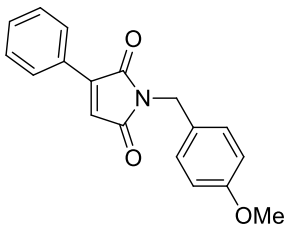
GCMS (EI): Calcd for $C_{17}H_{13}NO_2$: 187.2. Found: 187.1.



***N*-Benzyl-3-phenylmaleimide [15093-83-1].** The reaction was stirred at 60 ^{o}C in an oil bath for 4 h. The product was purified by flash chromatography (EA/hexanes 1: 20) as white solid (121.2 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.90 (m, 2H), 7.47-7.39 (m, 5H), 7.35-7.27 (m, 3H), 6.74 (s, 1H), 4.74 (s, 2H).

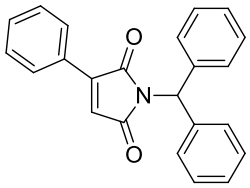
GCMS (EI): Calcd for $C_{17}H_{13}NO_2$: 263.3. Found: 263.1.



***N*-(4-Methoxybenzyl)-3-phenylmaleimide [935689-24-0].** The reaction was stirred at 60 ^{o}C in an oil bath for 7 h. The product was purified by flash chromatography (EA/hexanes 1: 20) as white solid (135 mg, 92%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-7.89 (m, 2H), 7.46-7.44 (m, 3H), 7.36-7.34 (m, 2H), 6.86-6.84 (m, 2H), 6.72 (s, 1H), 4.68 (s, 2H), 3.78 (s, 3H).

GCMS (EI): Calcd for $C_{18}H_{15}NO_3$: 293.3. Found: 293.1.

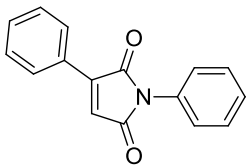


***N*-(1-Benzhydryl)-3-phenylmaleimide.** The reaction was stirred at 60 ^{o}C in an oil bath for 7 h. The product was purified by flash chromatography (EA/hexanes 1: 20) as white solid (149 mg, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.90 (m, 2H), 7.45-7.44 (m, 3H), 7.35-7.30 (m, 10H), 6.76 (s, 1H), 6.59 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 170.1, 143.8, 138.4, 131.4, 129.1, 128.9, 128.82, 128.79, 128.6, 127.9, 124.2, 57.9.

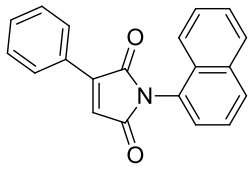
GCMS (EI): Calcd for $C_{17}H_{19}NO_3$: 339.4. Found: 339.1.



***N*-Phenyl-3-phenylmaleimide [75066-70-5].** DPEPhos (16.1 mg, 6 mol%) was used as the ligand instead of DPPF. The reaction was stirred at 60 ^{o}C in an oil bath for 6 h. The product was purified by flash chromatography (EA/hexanes 1: 20) as bright yellow solid (99 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00-7.97 (m, 2H), 7.51-7.48 (m, 5H), 7.42-7.37 (m, 3H), 6.89 (m, 1H).

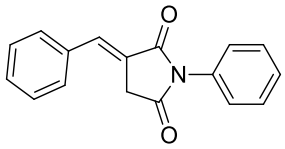
GCMS (EI): Calcd for $C_{16}H_{11}NO_2$: 249.3. Found: 249.1.



***N*-(1-Naphthyl)-3-phenylmaleimide [1082665-73-3].** DPEPhos (16.1 mg, 6 mol%) was used as the ligand instead of DPPF. The reaction was stirred at 60 ^{o}C in an oil bath for 7 h. The product was purified by flash chromatography (EA/hexanes 1:8) as white solid (139 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06-8.04 (m, 2H), 7.99-7.93 (m, 2H), 7.65-7.50 (m, 7H), 7.44 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.01 (s, 1H).

GCMS (EI): Calcd for $C_{20}H_{13}NO_2$: 299.3. Found: 299.1.



3-Methylene-1,4-diphenylpyrrolidine-2,5-dione [838846-38-1]. DPEPhos (16.1 mg, 6 mol%) was used as the ligand instead of DPPF. The reaction was stirred at 60 ^{o}C in an oil bath for 6 h. The product was purified by flash chromatography (EA/hexanes 1: 8) as white solid (92 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (t, *J* = 2.2 Hz, 1H), 7.56-7.38 (m, 10H), 3.78 (d, *J* = 2.4 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 170.2, 135.6, 134.3, 132.2, 130.5, 130.4, 129.4, 129.3, 128.8, 126.6, 123.2, 34.5.

GCMS (EI): Calcd for $C_{17}H_{13}NO_2$: 263.3. Found: 263.0.

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