Literature Report 7

Synthesis of IAN-type N,N-Ligands *via* Dynamic Kinetic Asymmetric Buchwald-Hartwig Amination

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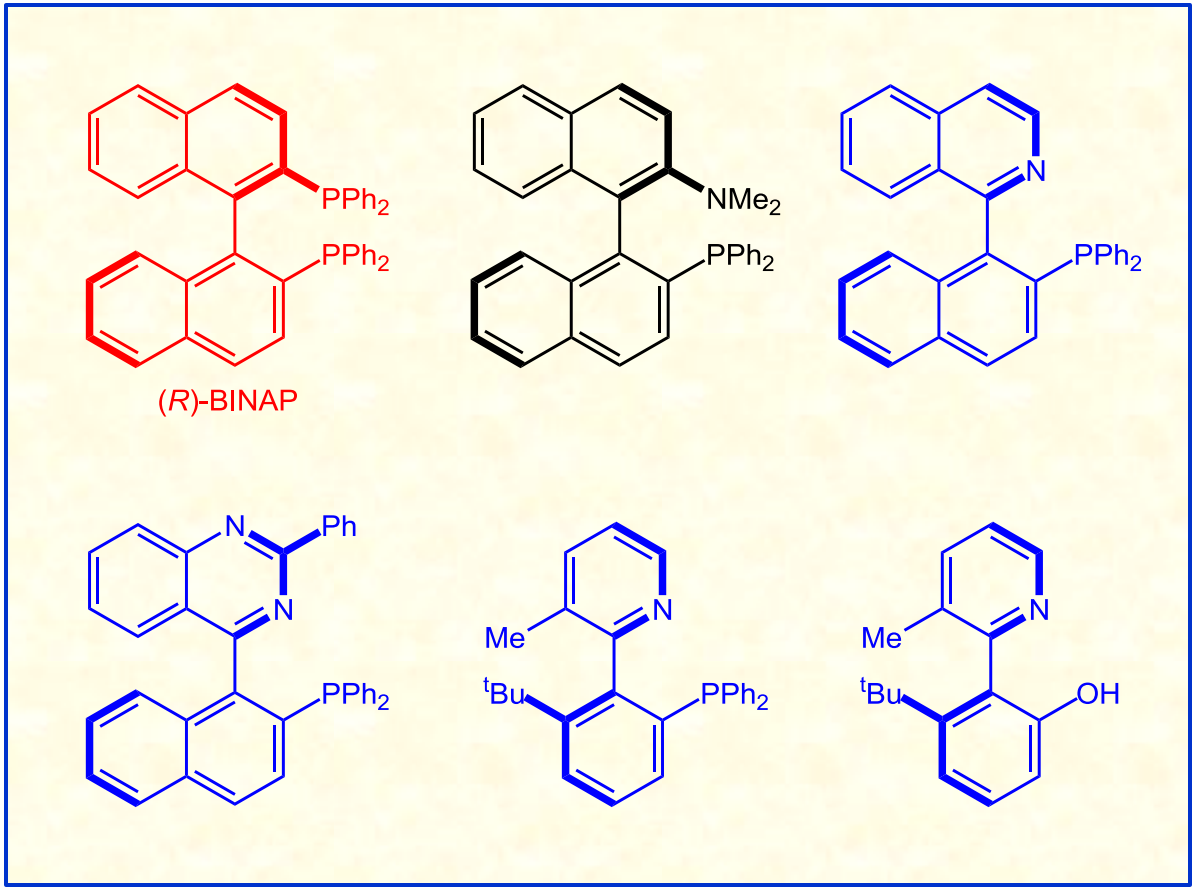
Checker: Lei Shi
Date: 2016-10-17

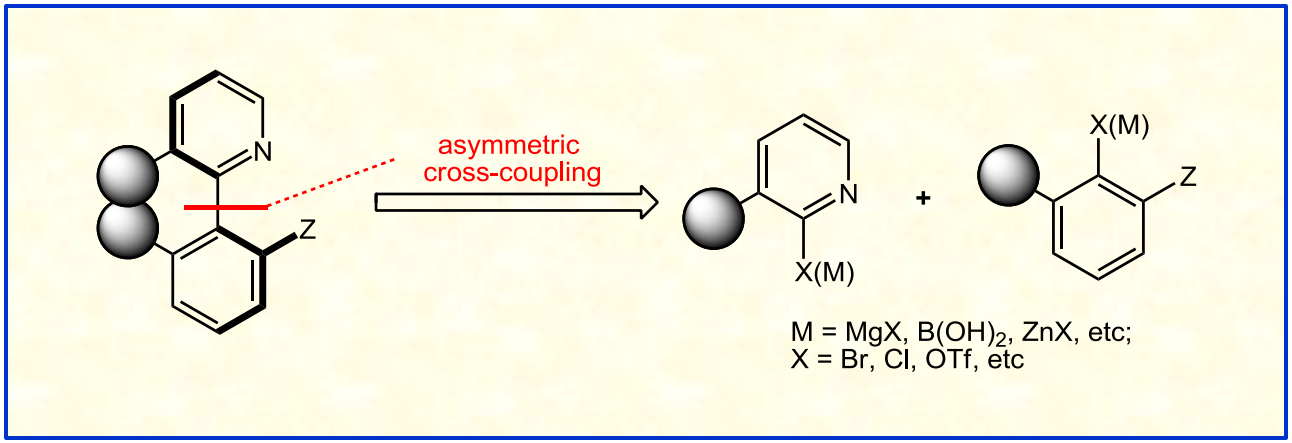
Lassaletta, J. M. et al
J. Am. Chem. Soc. **2016**, *138*, 12053.

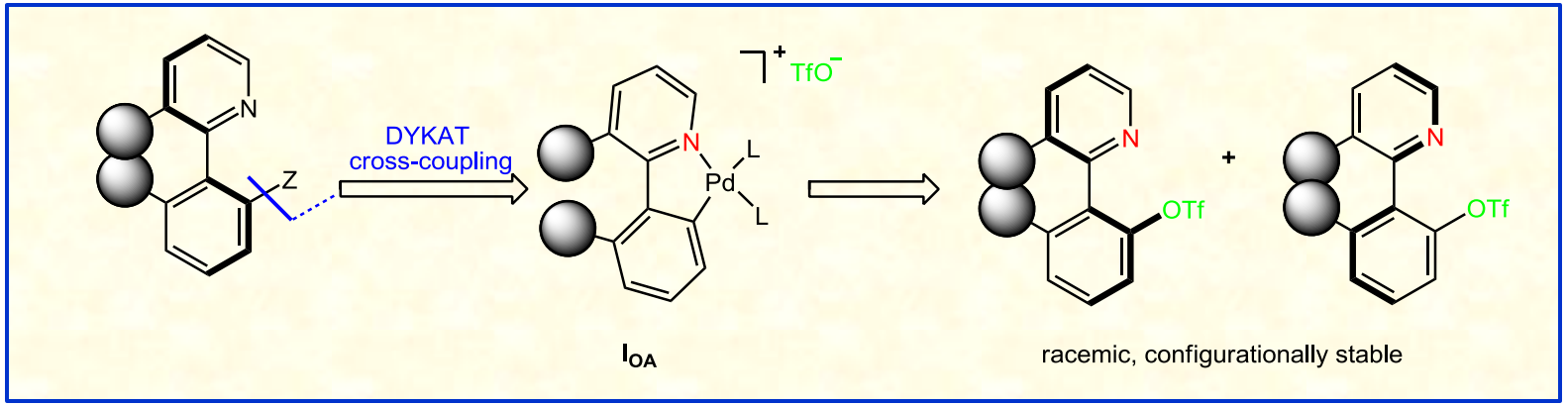
Contents

Introduction



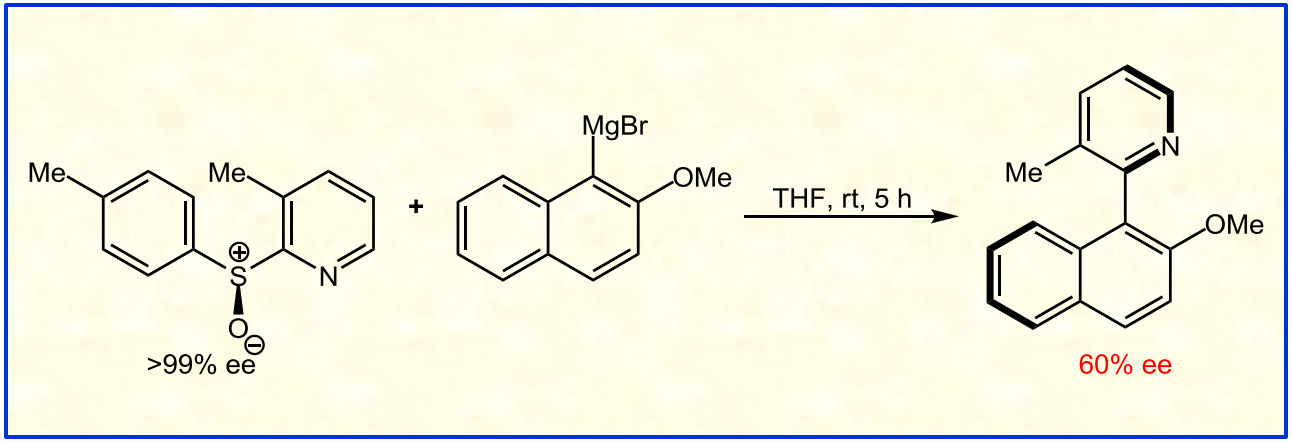
Introduction





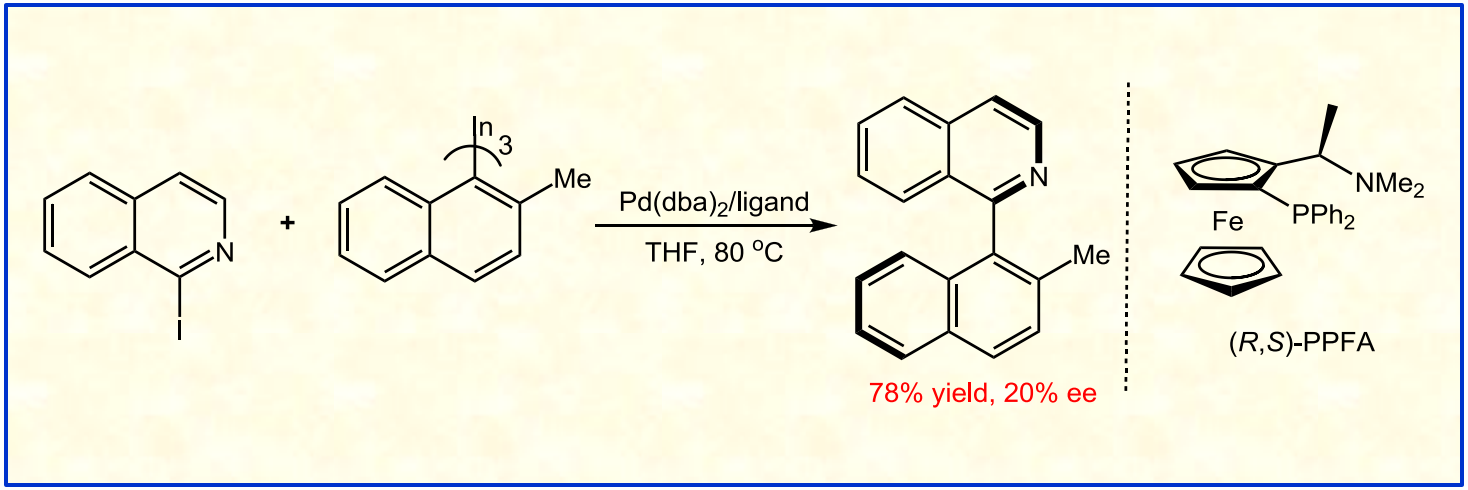
Lassaletta, J. M. et al *J. Am. Chem. Soc*. **2013**, *135*, 15730.

Introduction



Totaro, A. et al *Tetrahedron* **2005**, *61*, 3733.

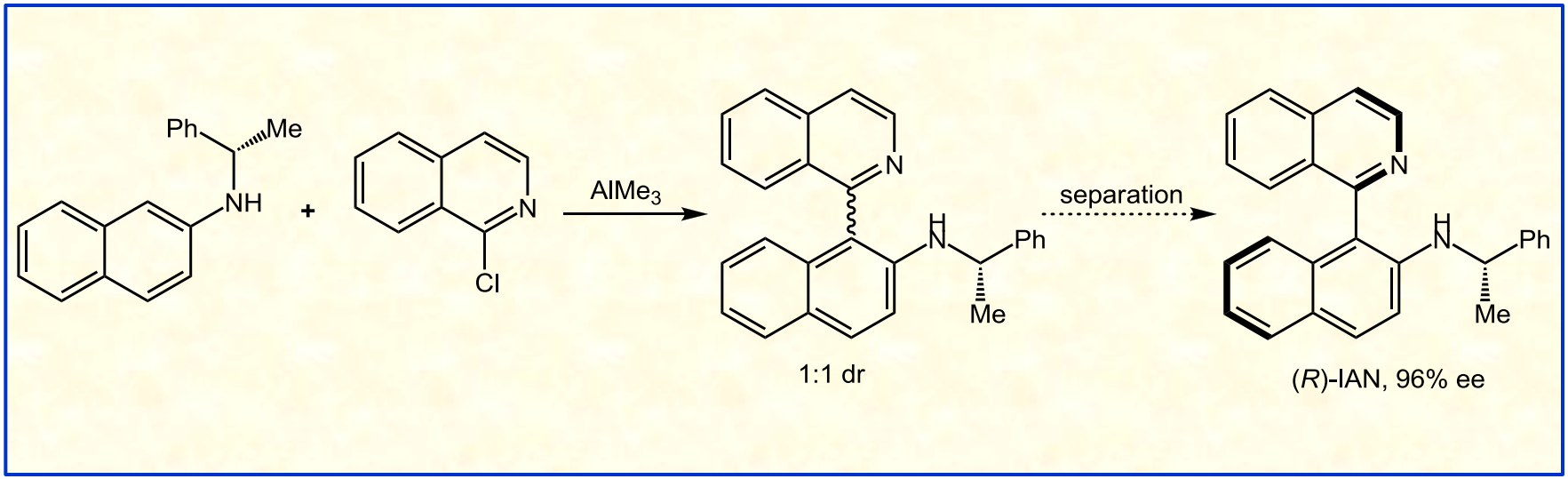
Introduction



Sarandeses, L. A. et al *Eur. J. Org. Chem*. **2013**, 2555.

Introduction

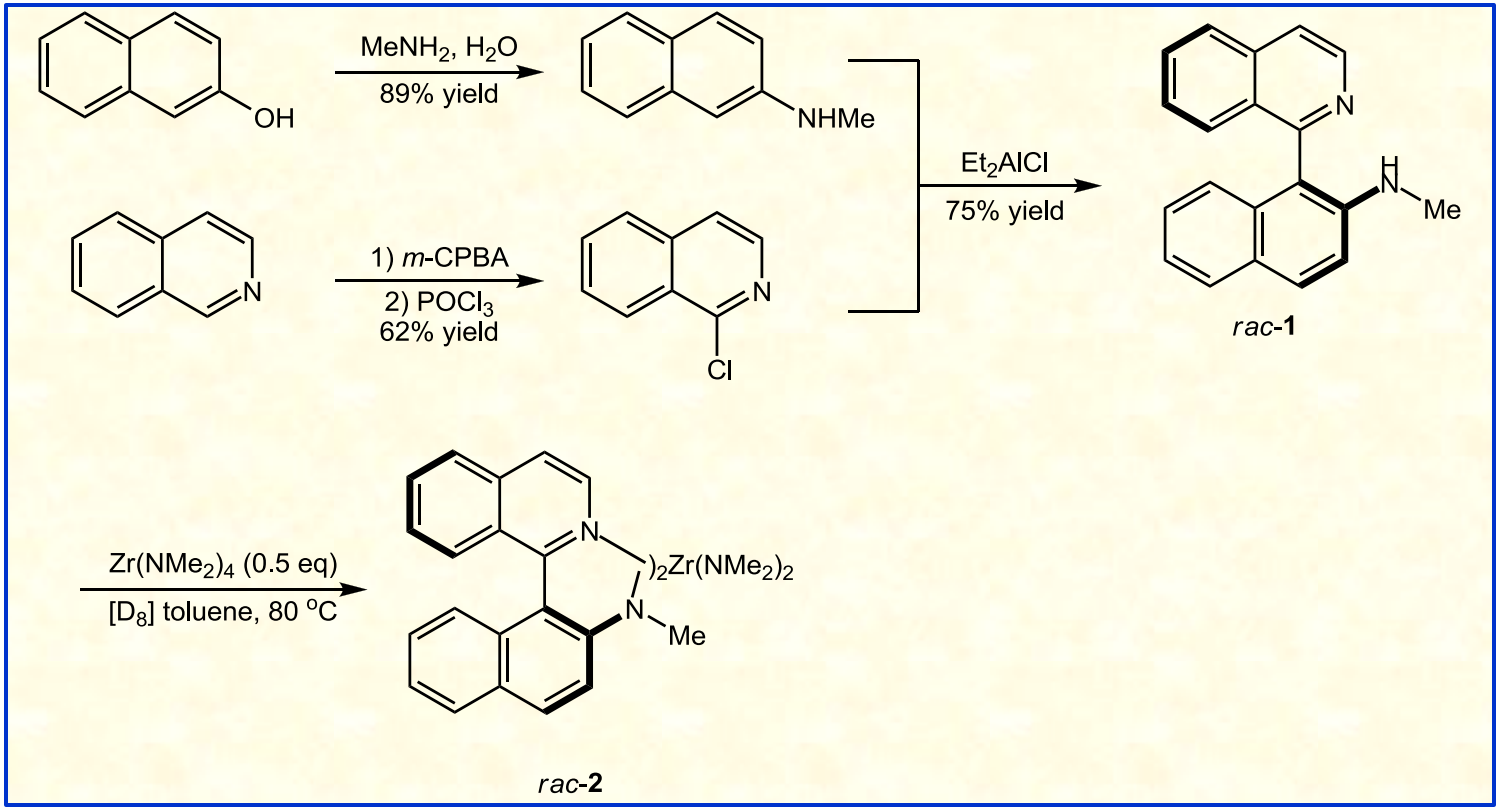
Previous synthesis of isoquinoline-amino naphthalene (IAN)



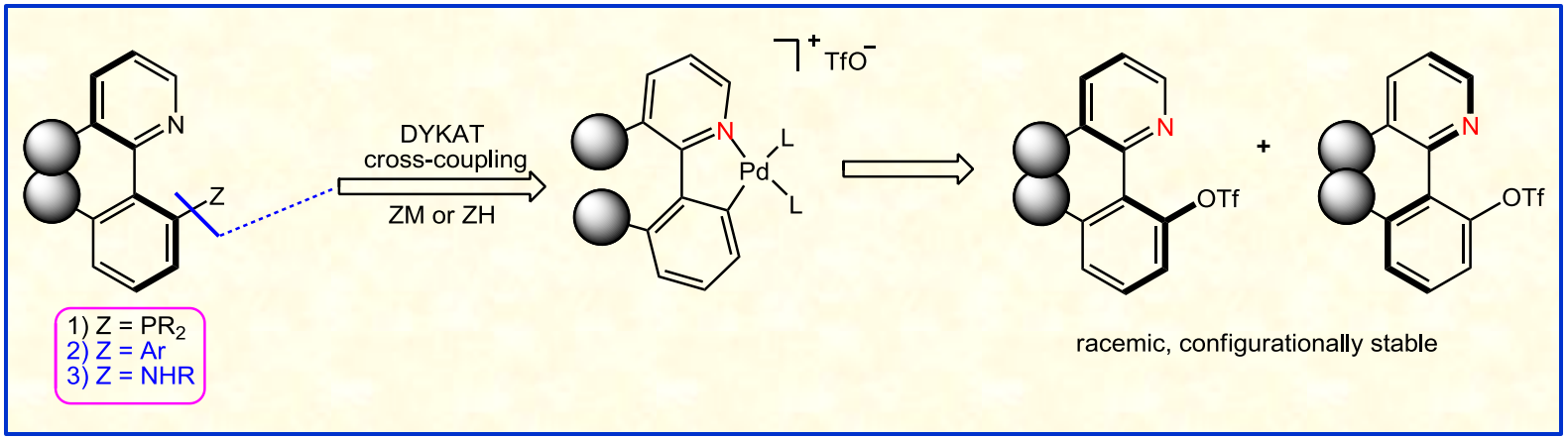
Johnston, J. N. et al *Org. Lett.* **2008**, *10*, 2445.

Introduction

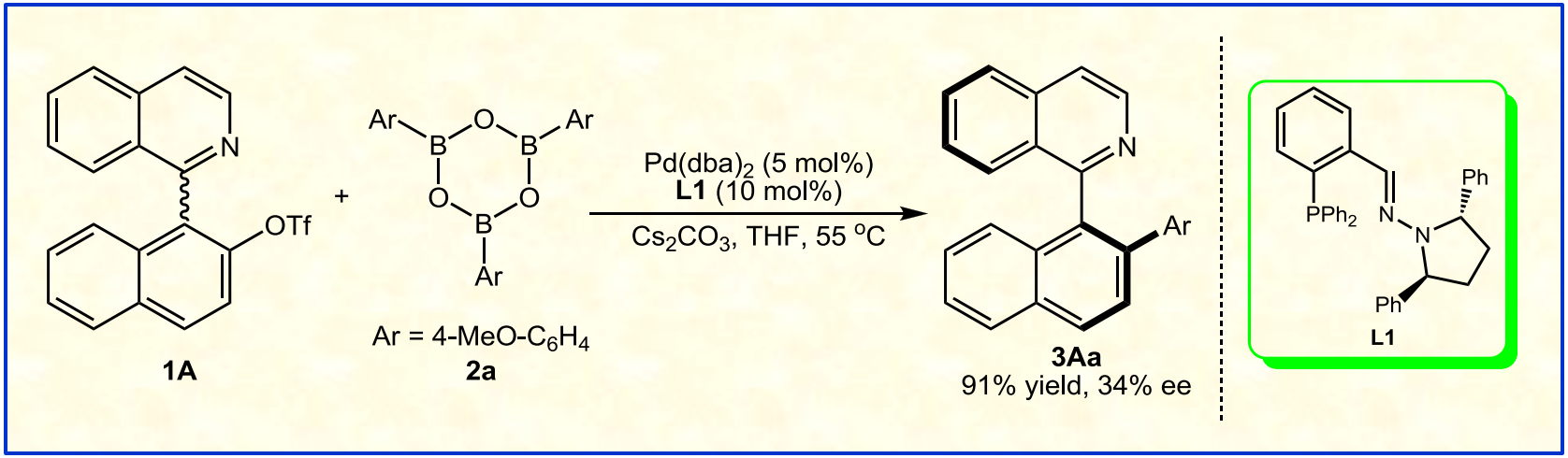
Synthesis of zirconium complexes *rac*-2



Johnston, J. N. et al *Angew. Chem. Int. Ed.* **2002**, *41*, 345.

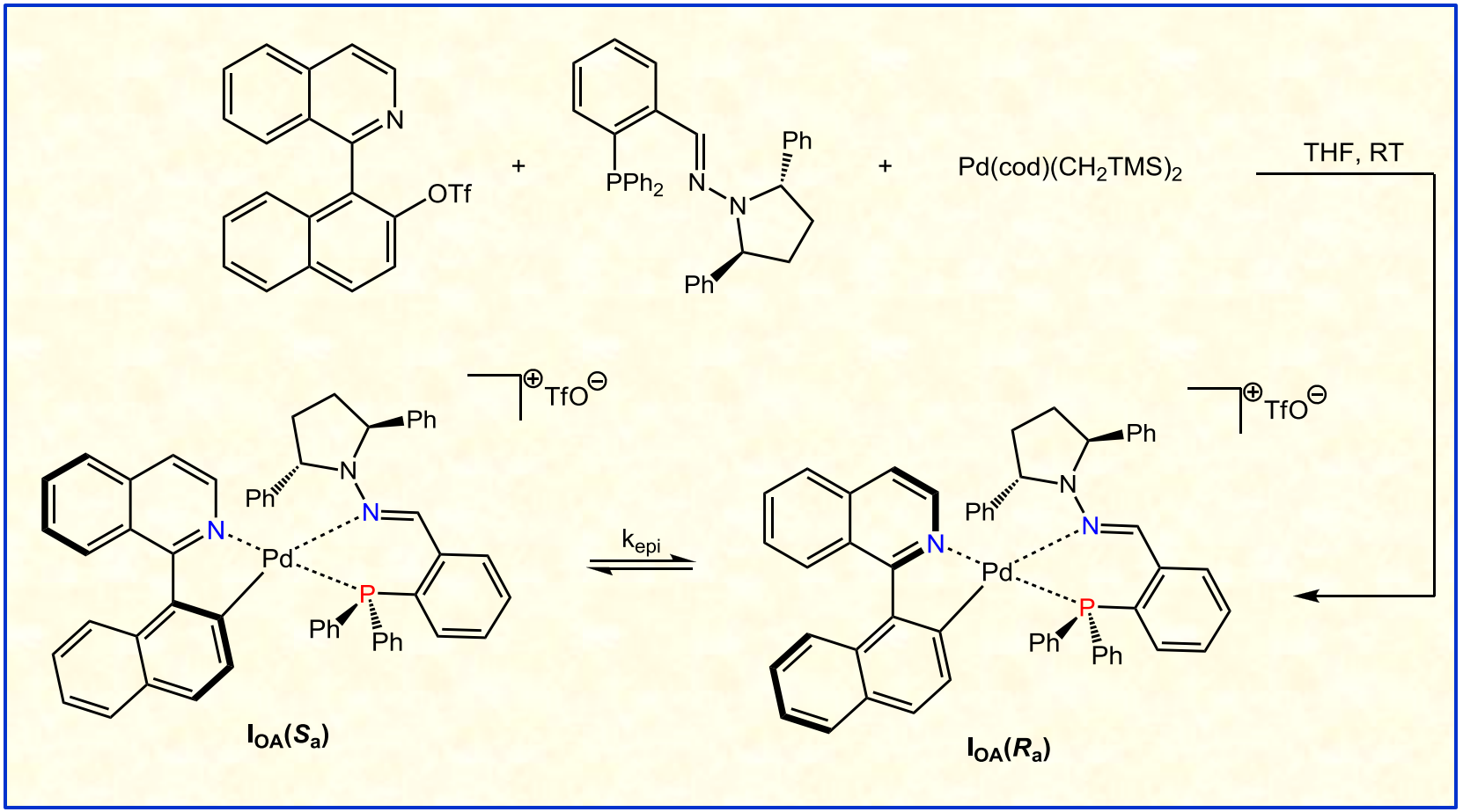

N
Z
DYKAT
cross-coupling
ZM or ZH
N
Pd
L
L
+
TfO−
N
OTf
+
N
OTf
1) Z = PR2
2) Z = Ar
3) Z = NHR
racemic, configurationally stable

Dynamic Kinetic Asymmetric C−C Coupling



Lassaletta, J. M. et al *J. Am. Chem. Soc*. **2013**, *135*, 15730.

Synthesis of the Oxidative Addition Intermediate



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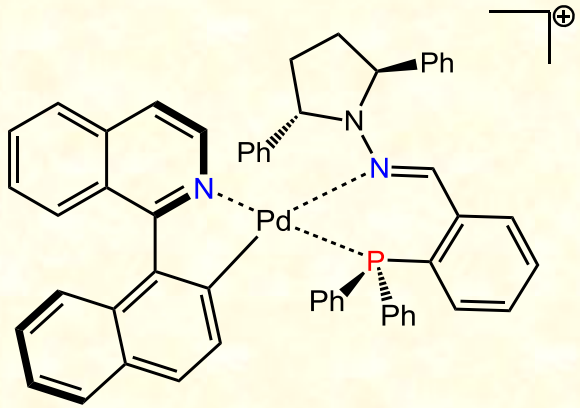
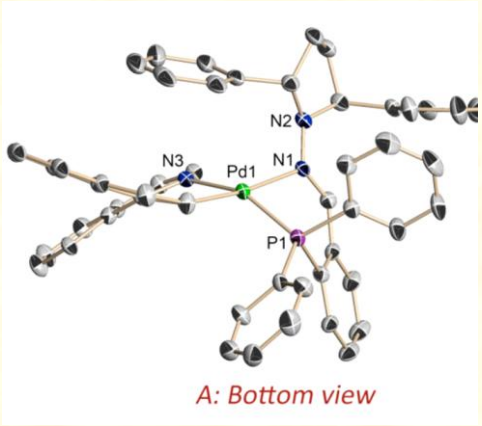
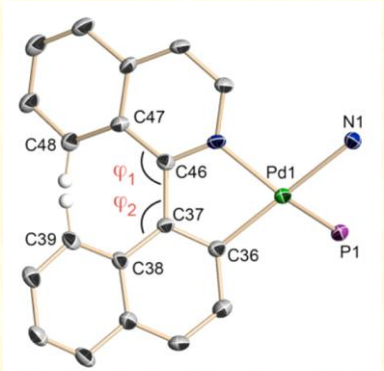
Synthesis of the Oxidative Addition Intermediate

Crystallization from a CH_2Cl_2/THF mixture afforded pure major isomer as yellow-orange X-Ray crystals.

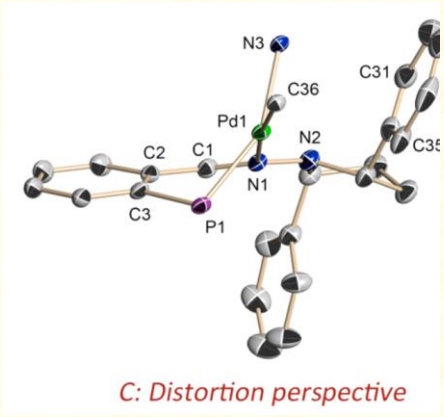




A: Bottom view

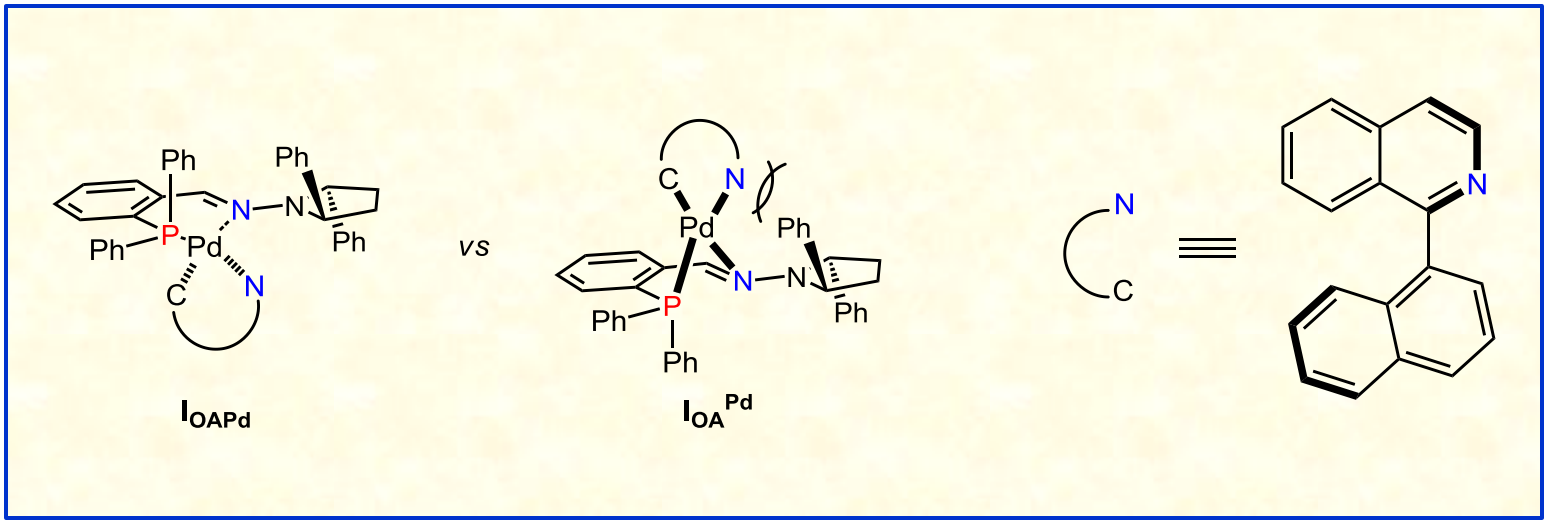


B: Lateral view (ligand omitted)



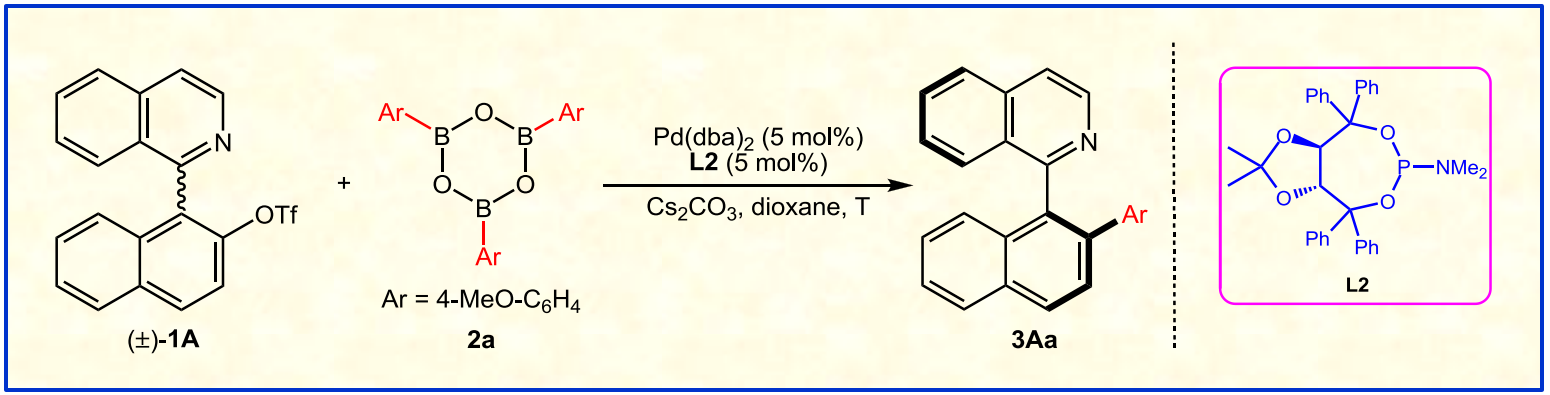
C: Distortion perspective

Synthesis of the Oxidative Addition Intermediate



I_{OAPd} I_{OA}^{Pd}

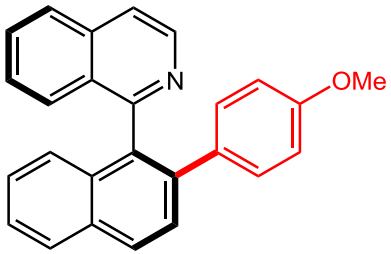
Dynamic Kinetic Suzuki–Miyaura Couplings



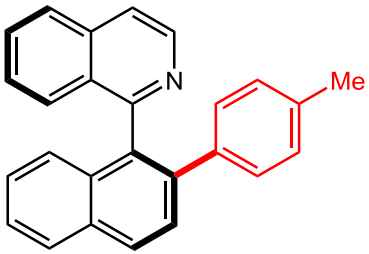
entry[a]	1	2	T (°C)	t (h)	yield (%)[b]	ee[c]
1[d]	**1A**	**2a**	55	24	64	64
2	**1A**	**2a**	55	8	76	84
3[e]	**1A**	**2a'**	55	8	42	38
4[f]	**1A'**	**2a**	55	24	78	40
5	**1A**	**2a**	40	48	87	90

[a] Performed at 0.15 mmol scale. [b] Isolated yield. [c] Determined by HPLC. [d] Performed in THF. [e] Performed with *p*-anisylboronic acid. [f] Performed with 1-(2-bromonaphthalen-1-yl)isoquinoline.

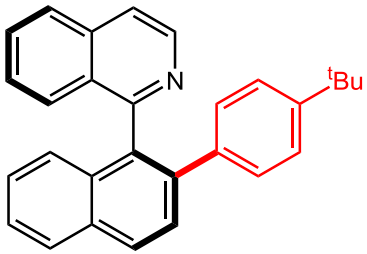
Substrate Scope



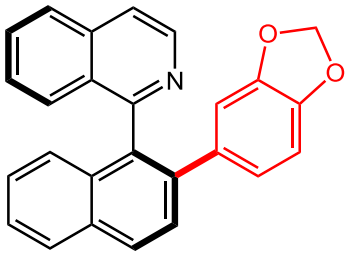
87% yield, 90% ee



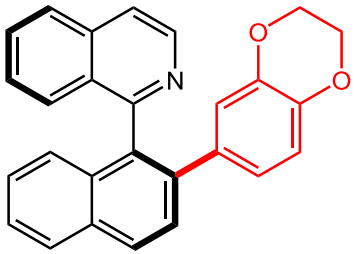
87% yield, 80% ee



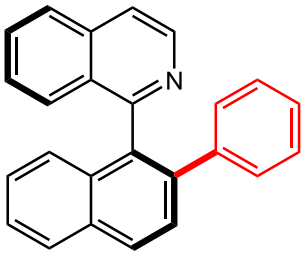
66% yield, 82% ee



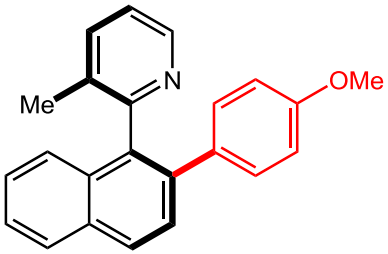
77% yield, 80% ee



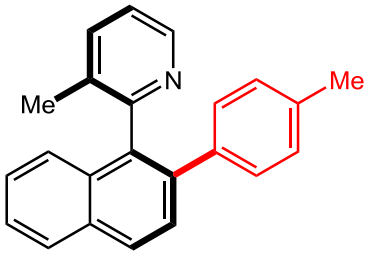
79% yield, 90% ee



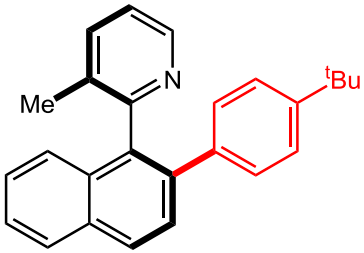
52% yield, 59% ee



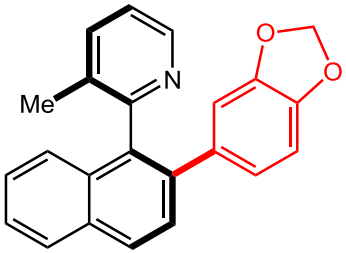
86% yield, 90% ee



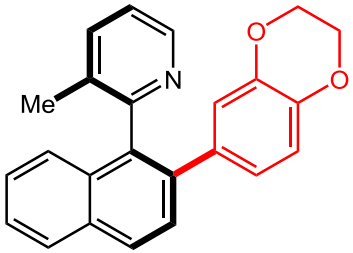
88% yield, 92% ee



82% yield, 84% ee

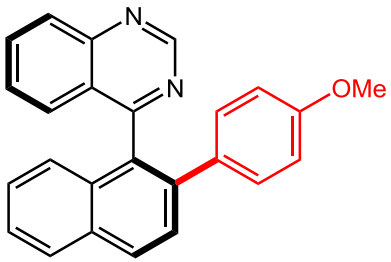


96% yield, 80% ee

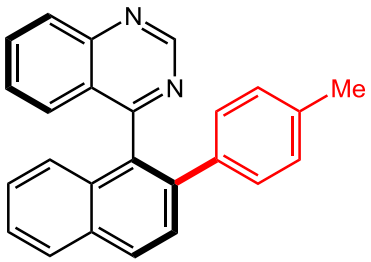


76% yield, 93% ee

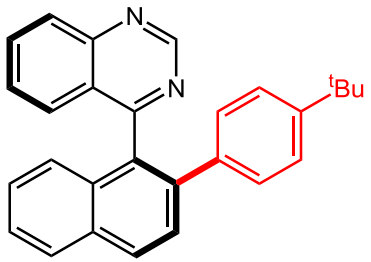
Substrate Scope



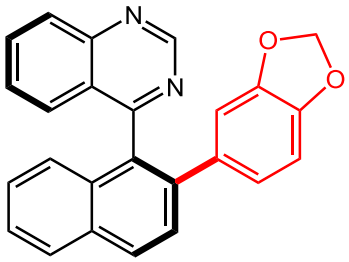
95% yield, 90% ee



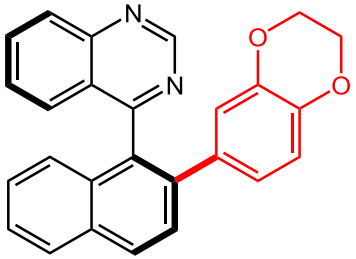
96% yield, 90% ee



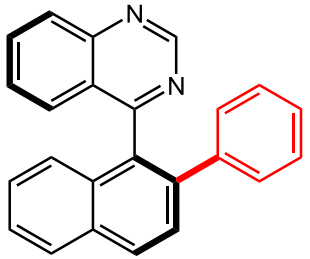
84% yield, 87% ee



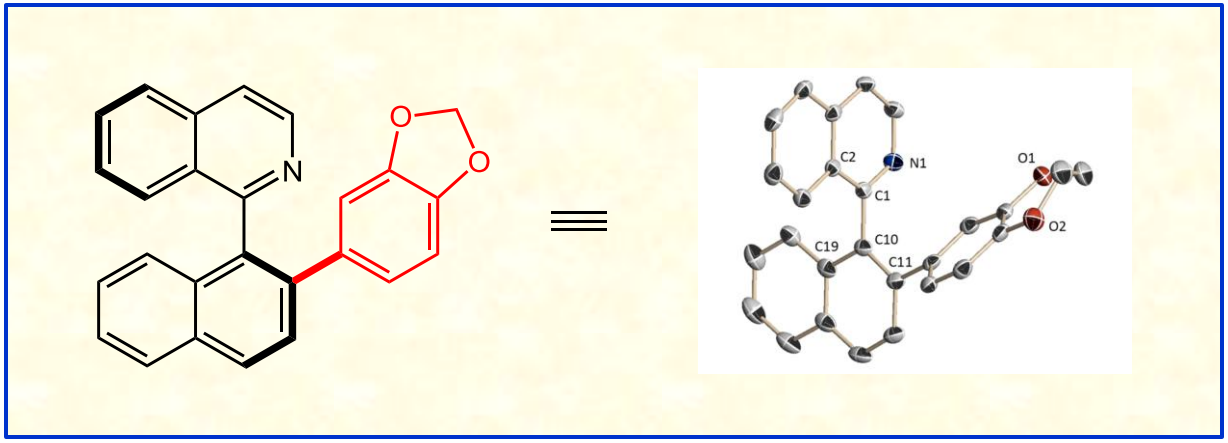
98% yield, 88% ee



97% yield, 86% ee



98% yield, 65% ee



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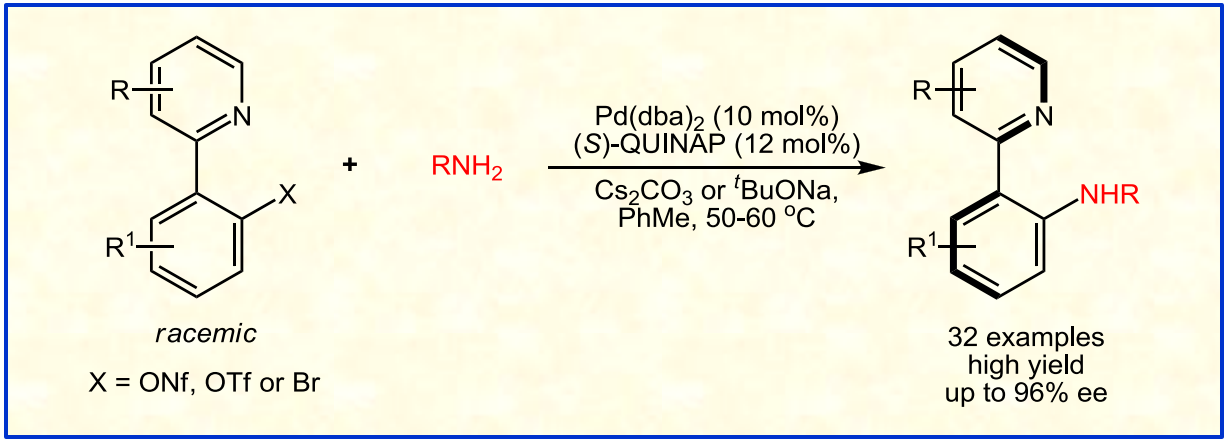
Dynamic Kinetic Asymmetric C−N Coupling



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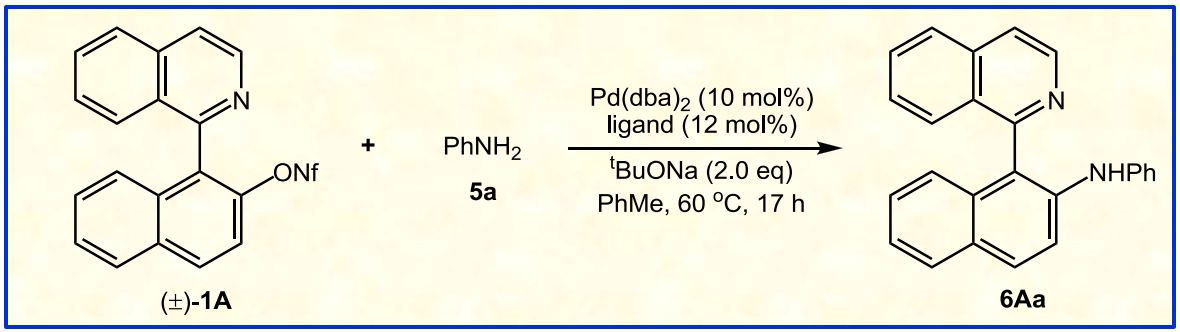
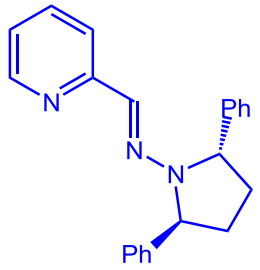
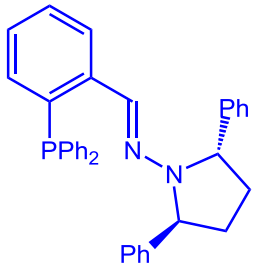
Ligand Screening

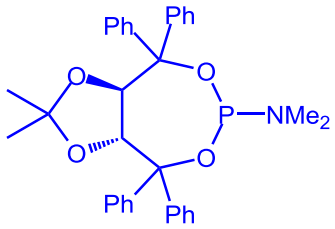




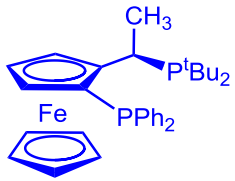
L1: 0%, --



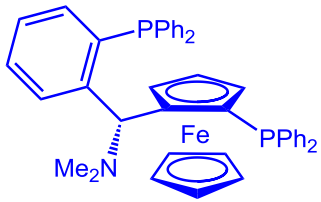
L2: 17%, 72% ee



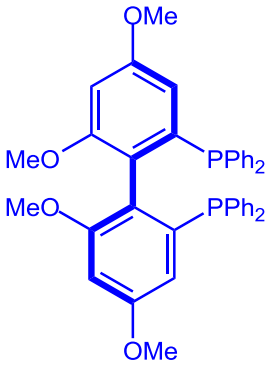
L3: 8%, 8% ee



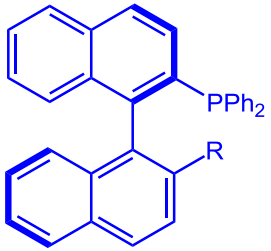
L4: 60%, 67% ee



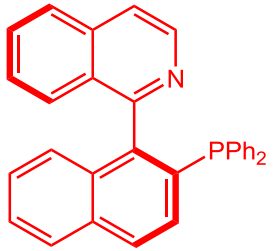
L5: 76%, 44% ee



L6: 44%, 4% ee

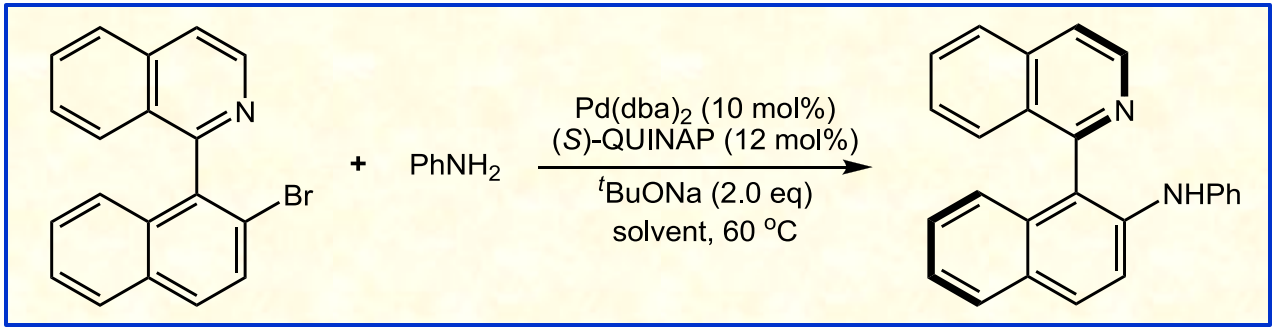


L7: R = PPh_2 61%, 19% ee
L8: R = OMe 18%, 34% ee



L9: 45%, 87% ee

Solvent Screening



entry[a]	solvent	yield(%)	ee (%)[c]
1	PhMe	95	89
2	$PhCF_3$	93	88
3	1,4-Dioxane	59	87
4	DME	62	88
5	THF	78	89
6	^{t}BuOH	38	88
7	DMSO	--	--

[a] Reactions were performed at 60 °C on a 0.1 mmol scale using anhydrous solvents (2 mL/0.1 mmol substrate).[b] Isolated yield. [c] Determined by HPLC.

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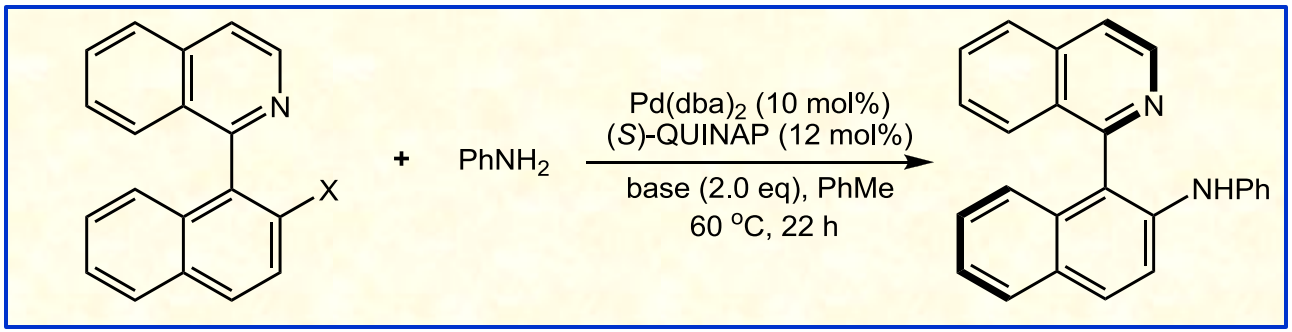
Base Screening



entry[a]	X	base	yield(%)[b]	ee (%)[c]
1	Br	^{t}BuOLi	46	87
2	Br	^{t}BuONa	95	89
3	Br	^{t}BuOK	90	85
4	Br	Cs_2CO_3	82	89
5	NfO	^{t}BuOLi	44	89
6	NfO	^{t}BuONa	59	89
7[d]	NfO	Cs_2CO_3	99	88

[a] Reactions were performed at 60 °C on a 0.1 mmol scale using anhydrous toluene(2 mL/0.1 mmol substrate). [b] Isolated yield. [c] Determined by HPLC. [d] Reaction was stopped and analyzed after 20 h.

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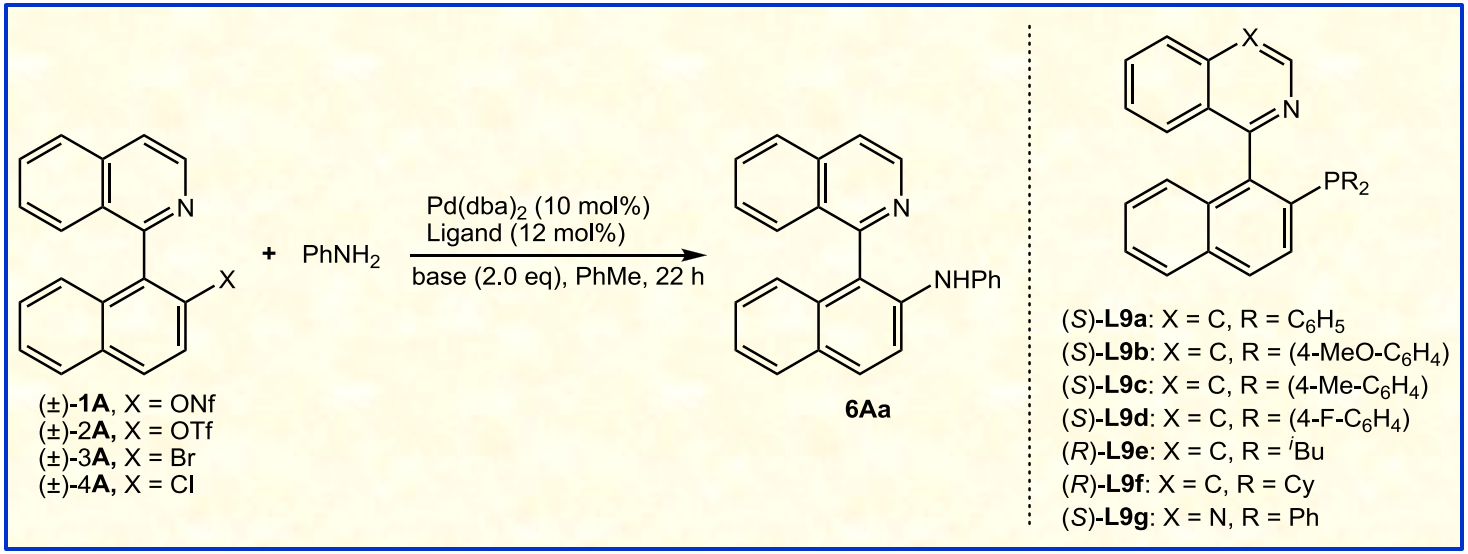
Optimization Reaction Conditions



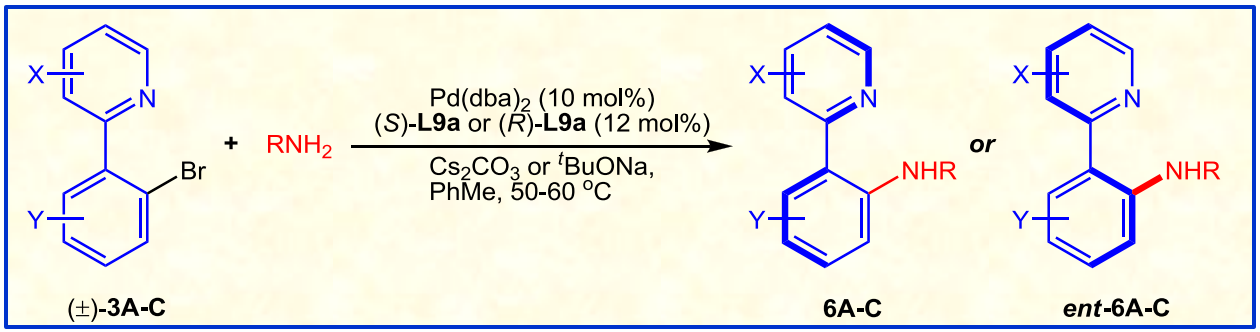
entry[a]	substrate	base	T (°C)	**ligand**	yield (%)	ee[b]
1	(±)-**1A**	Cs_2CO_3	60	(*S*)-**L9a**	99	88
2[c]	(±)-**2A**	Cs_2CO_3	50	(*S*)-**L9a**	81	92
3[d]	(±)-**3A**	^{t}BuONa	60	(*S*)-**L9a**	95	89
4	(±)-**1A**	Cs_2CO_3	50	(*S*)-**L9a**	84	90
5	(±)-**3A**	^{t}BuONa	50	(*S*)-**L9a**	90	91

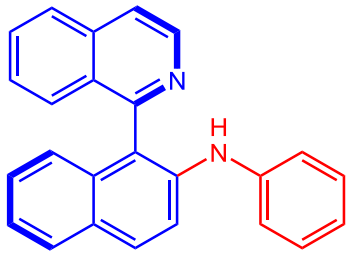
Optimization Reaction Conditions

entry	substrate	base	T (^{o}C)	**ligand**	yield (%)	ee[b]
6	(±)-4**A**	^{t}BuONa	50	(*S*)-**L9a**	92	89
7	(±)-**3A**	^{t}BuONa	60	(*S*)-**L9b**[e]	99	84
8	(±)-**3A**	^{t}BuONa	60	(*S*)-**L9c**[f]	98	77
9	(±)-**3A**	^{t}BuONa	60	(*S*)-**L9d**	98	61
10	(±)-**3A**	^{t}BuONa	60	(*R*)-**L9e**	26	50
11	(±)-**3A**	^{t}BuONa	60	(*R*)-**L9f**	77	68
12	(±)-**3A**	^{t}BuONa	60	(*S*)-**L9g**[g]	78	20

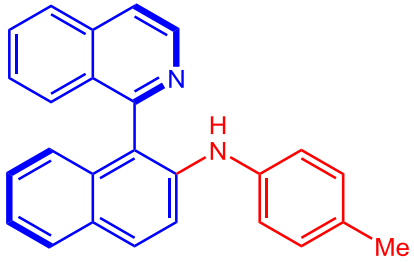
[a] Reactions conditions: 0.1 mmol scale in toluene (2 mL), 2 equiv of **5a**, 2 equiv of base. [b] Determined by chiral HPLC analysis. [c] t = 48 h. [d] t = 17 h. [e] 98% ee. [f] 96% ee. [g] 99% ee.

Substrate Scope

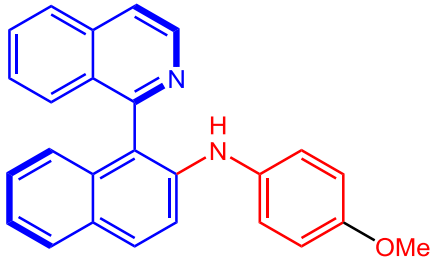




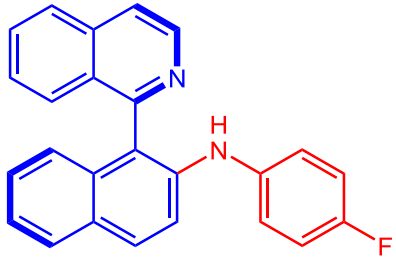
90% yield, 91% ee



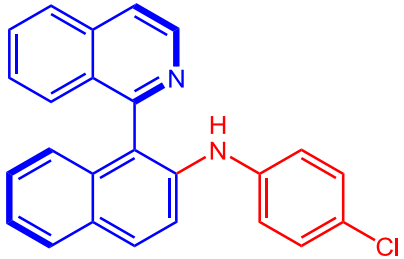
89% yield, 96% ee



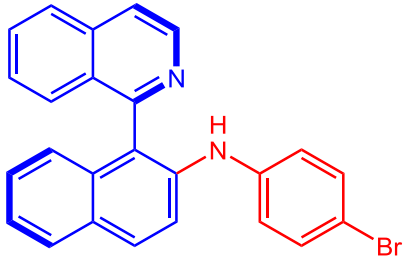
92% yield, 92% ee



99% yield, 92% ee

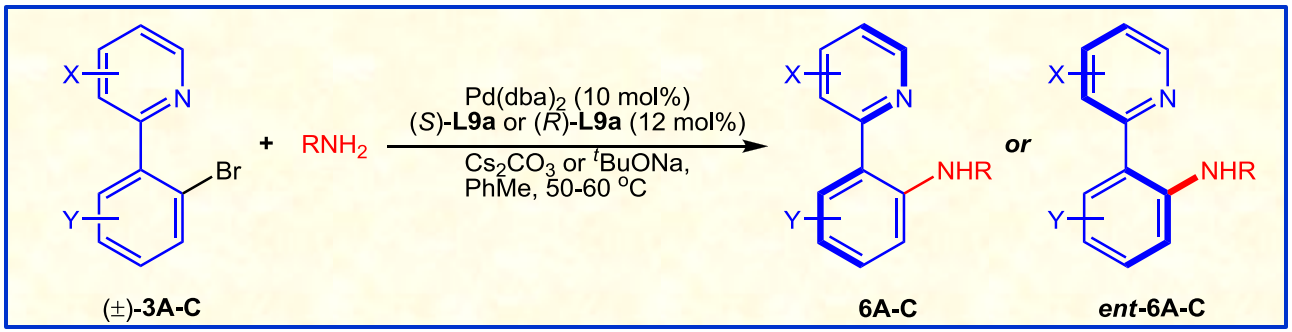


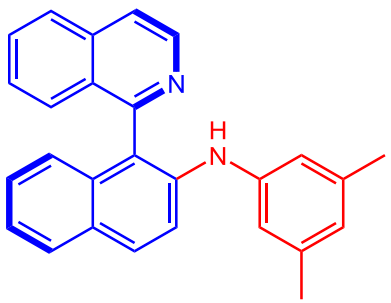
74% yield, 90% ee



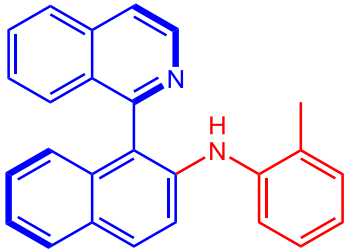
64% yield, 91% ee

Substrate Scope

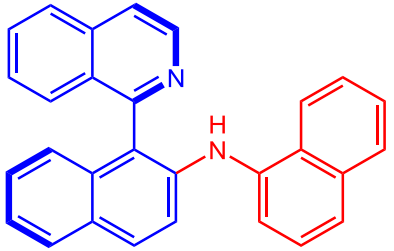




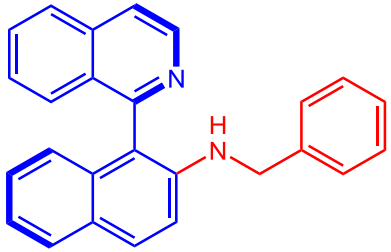
88% yield, 90% ee



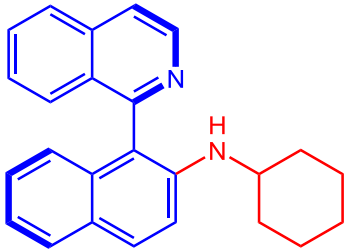
97% yield, 92% ee



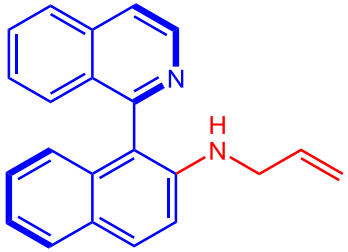
91% yield, 93% ee



86% yield, 86% ee

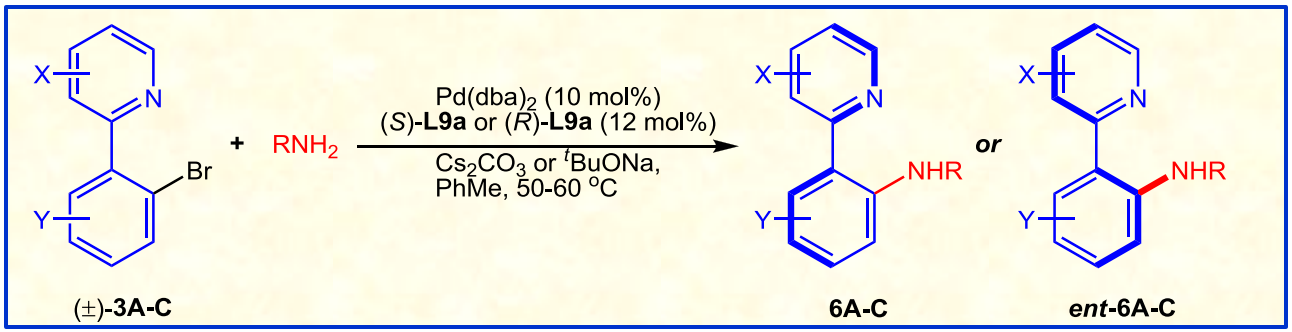


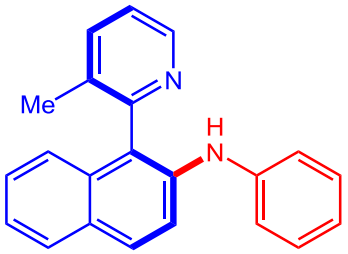
63% yield, 91% ee



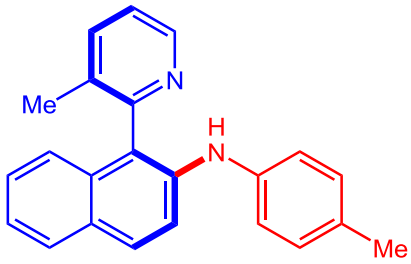
61% yield, 88% ee

Substrate Scope

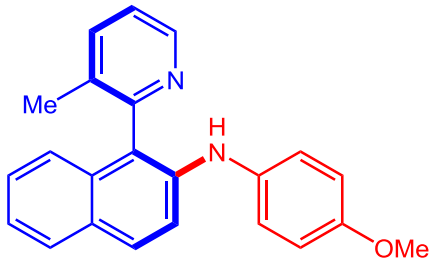




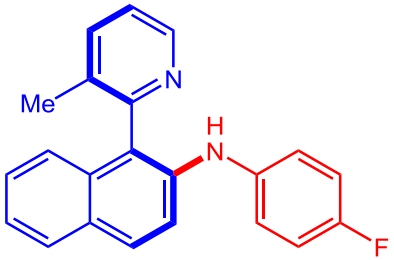
84% yield, 89% ee



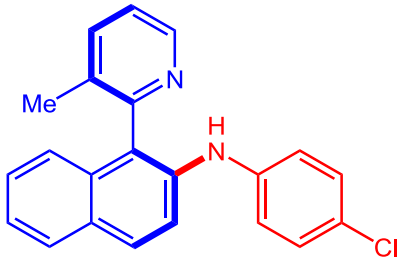
98% yield, 90% ee



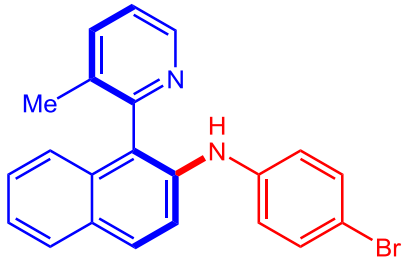
78% yield, 91% ee



89% yield, 92% ee

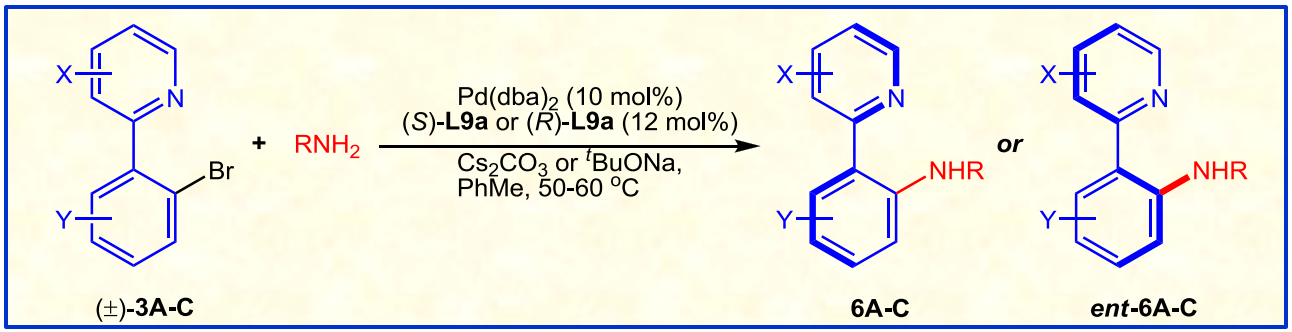


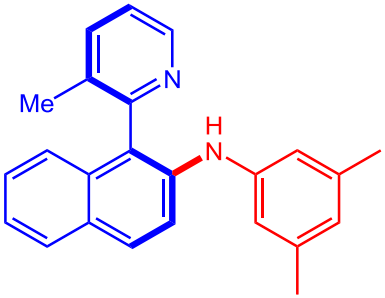
83% yield, 93% ee



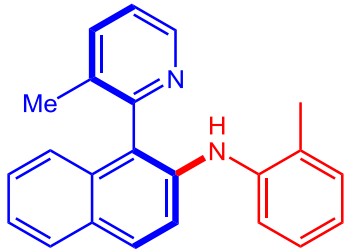
67% yield, 89% ee

Substrate Scope

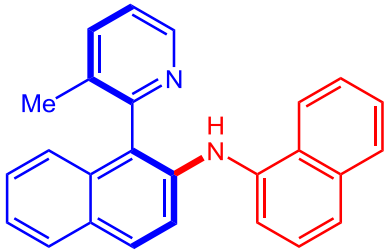




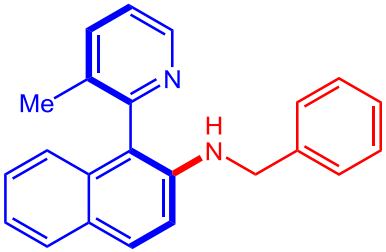
97% yield, 88% ee



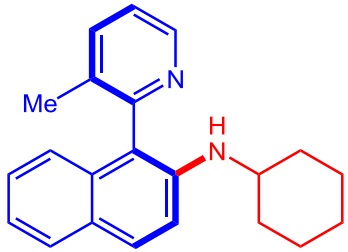
94% yield, 90% ee



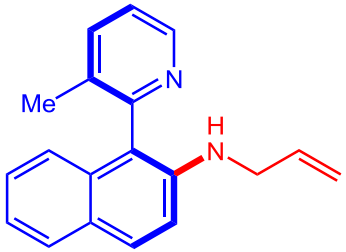
94% yield, 92% ee



94% yield, 93% ee

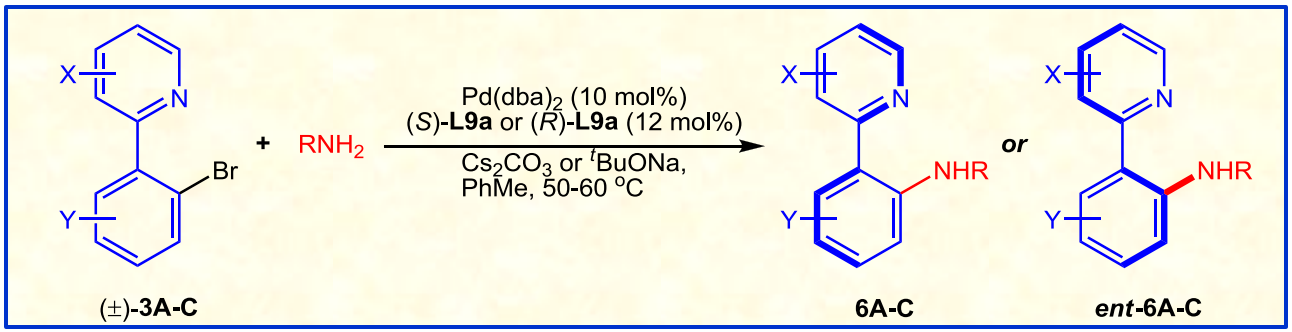


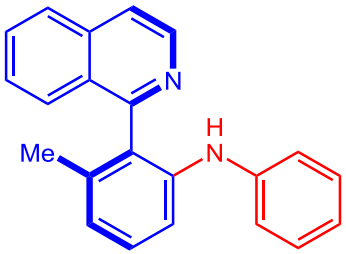
60% yield, 91% ee



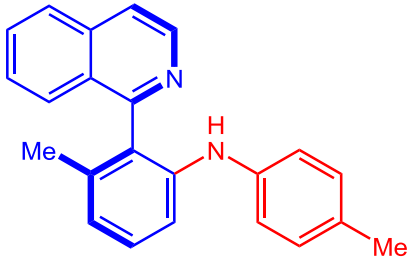
59% yield, 92% ee

Substrate Scope

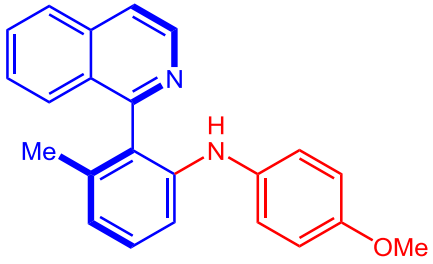




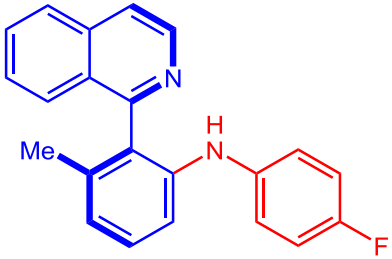
93% yield, 90% ee



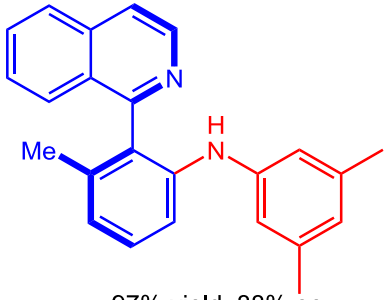
98% yield, 90% ee



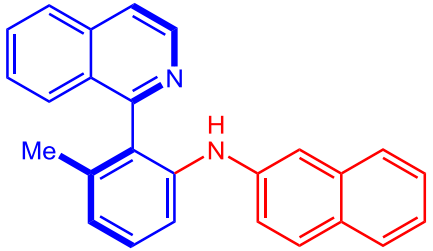
94% yield, 91% ee



95% yield, 91% ee

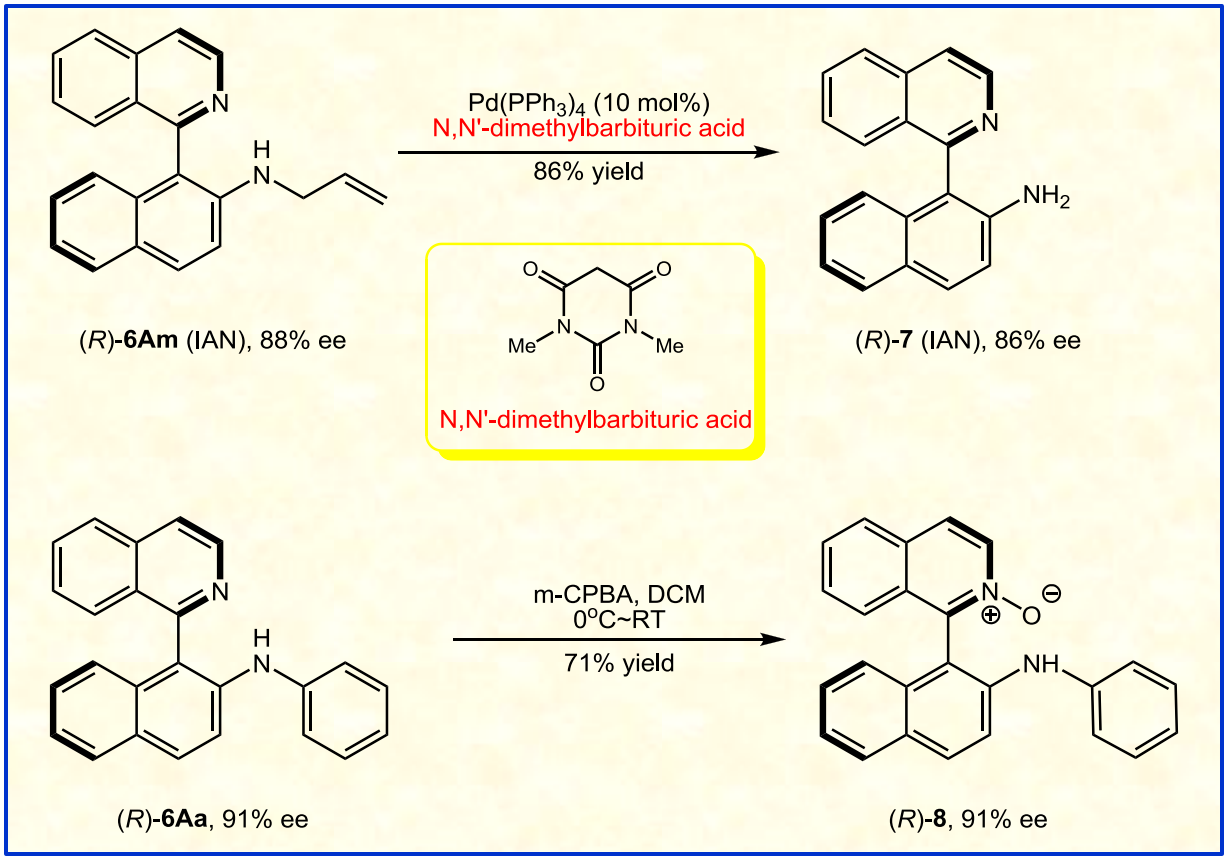


97% yield, 88% ee

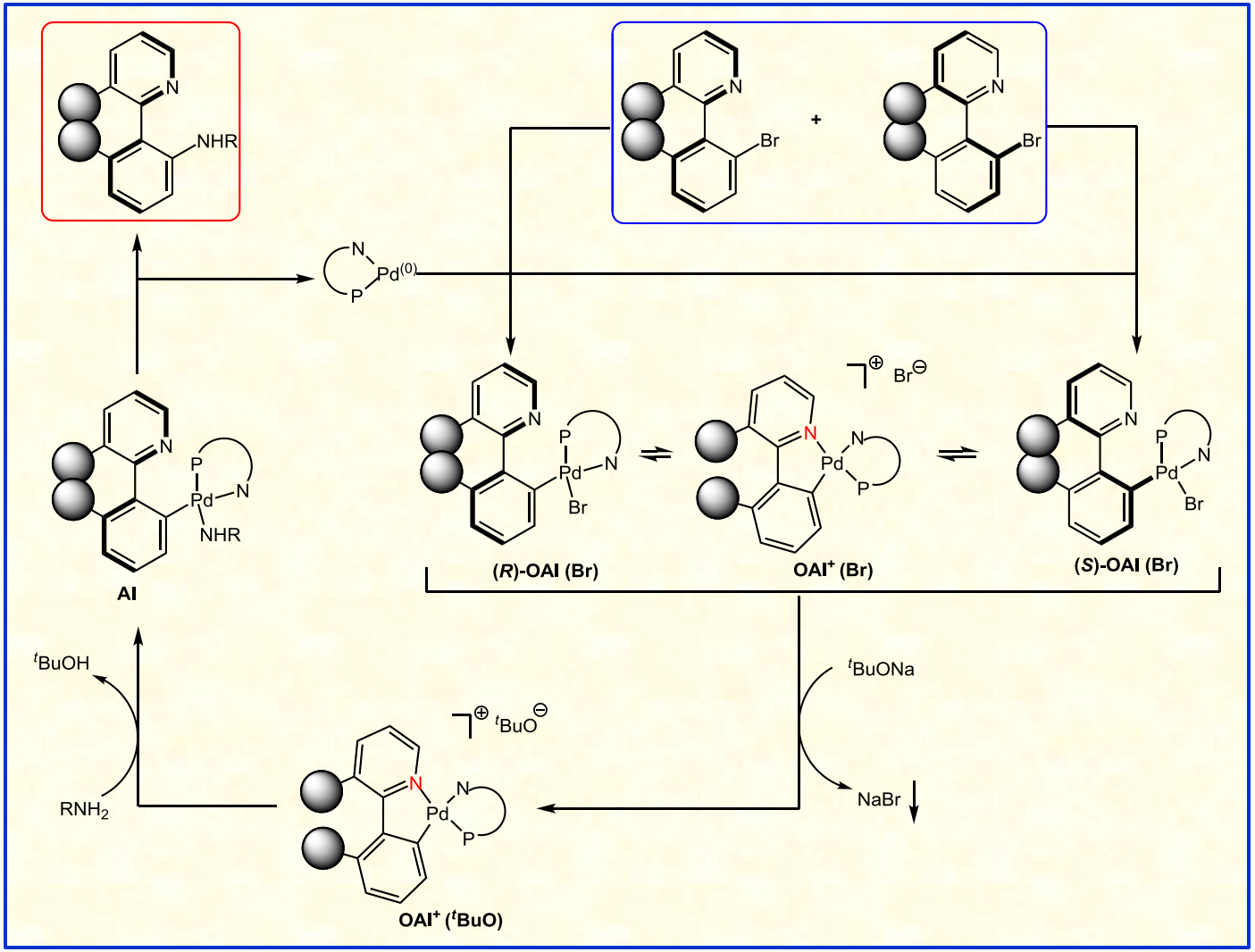


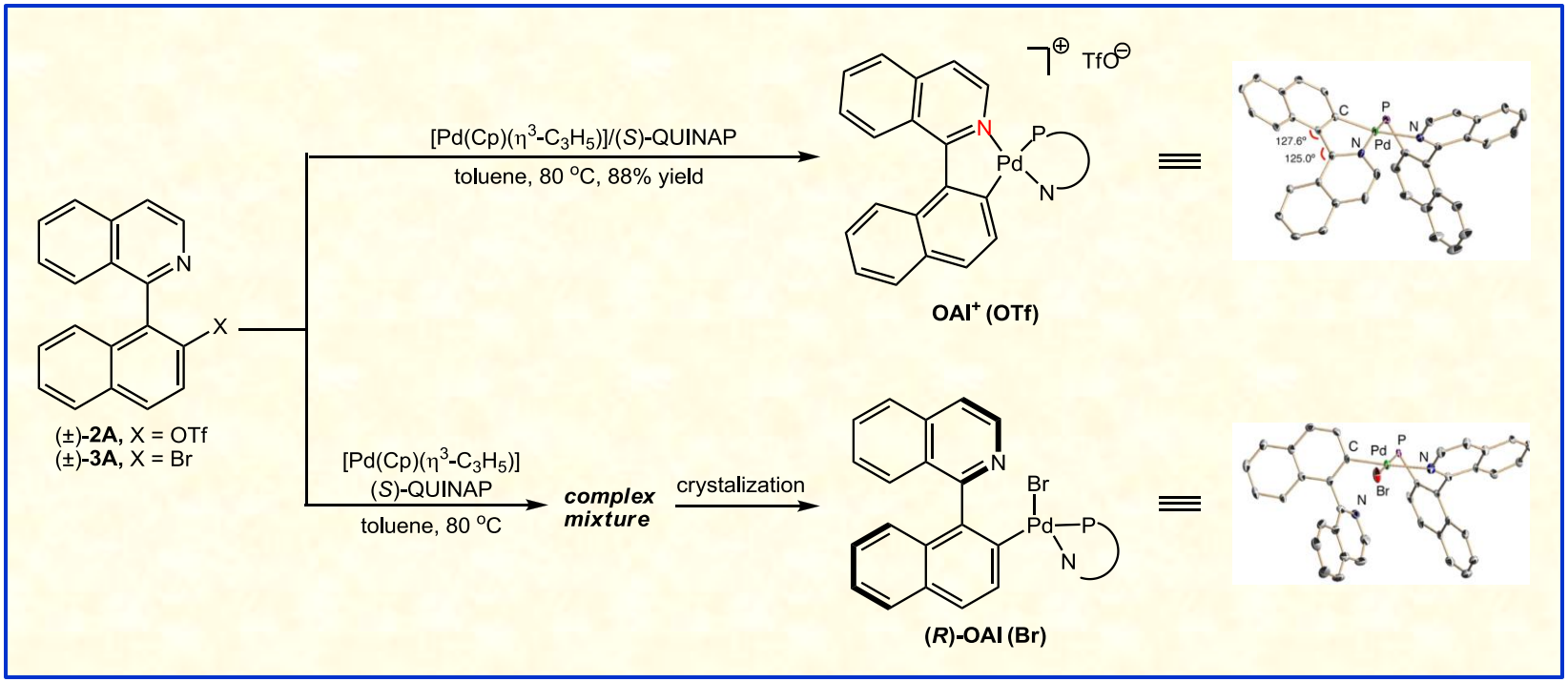
72% yield, 91% ee

Representative Transformations

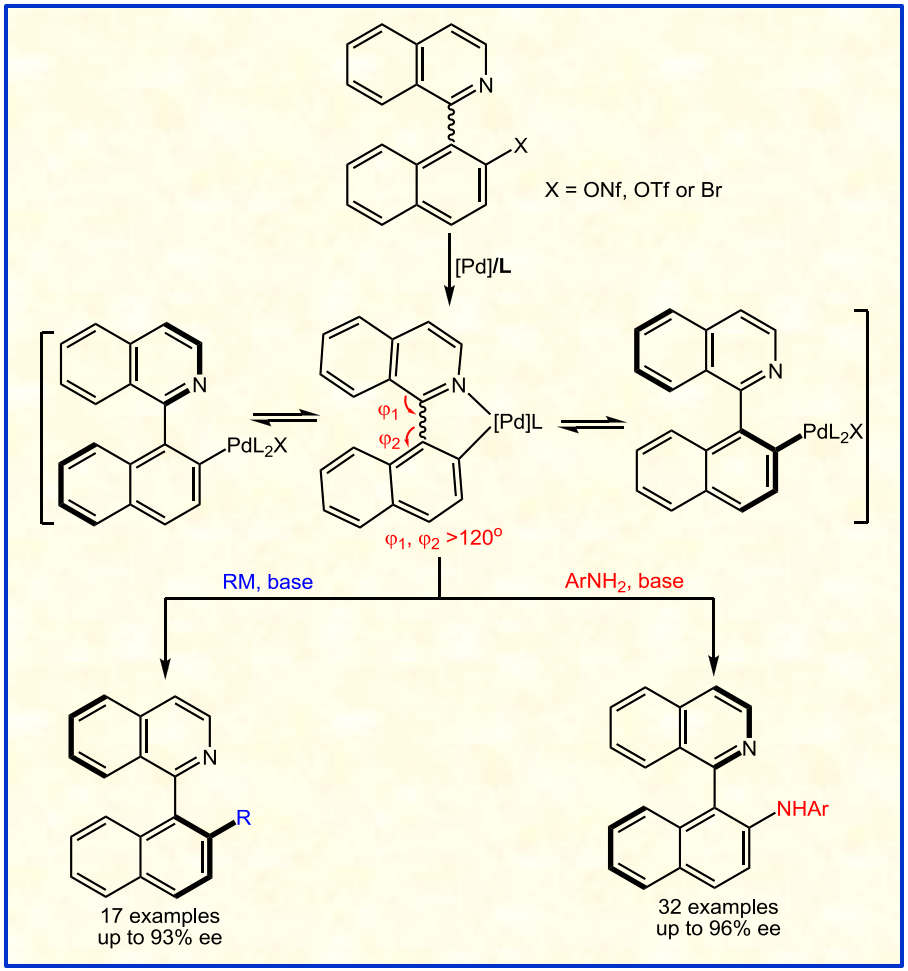


Proposed Amination Mechanism




(±)-2A, X = OTf
(±)-3A, X = Br
[Pd(Cp)(η3-C3H5)]/(S)-QUINAP
toluene, 80 °C, 88% yield
OAI+ (OTf)
[Pd(Cp)(η3-C3H5)]
(S)-QUINAP
toluene, 80 °C
complex mixture
crystalization
(R)-OAI (Br)

Summary



Lassaletta, J. M. et al *J. Am. Chem. Soc*. **2013**, *135*, 15730.

Lassaletta, J. M. et al *J. Am. Chem. Soc*. **2016**, *138*, 12053.

In recent years, significant advances have been achieved in the field of asymmetric cross-coupling, in particular for the synthesis of axially chiral biaryls. In sharp contrast, the direct asymmetric heteroaryl-aryl cross-coupling remains as an unmet challenge, limiting the access to functionalized heterobiaryls with appealing structures for their use as ligands in asymmetric catalysis. As a remarkable example, the use isoquinoline-amino naphthalene (IAN) and related derivatives, which can be seen as N(sp^2), N(sp^3) analogues of QUINAP, have been scarcely investigated. A plausible explanation is the poor availability: There are no commercially available representatives, and their synthesis still requires chromatographic separation of diastereomeric mixtures, while the lack of a general and practical method of synthesis has also limited the structural diversity of known ligands of this type. Recently, we have reported a novel strategy for the synthesis of functionalized heterobiaryls

based on dynamic kinetic asymmetric C−C and C−P bond formations starting from heterobiaryl triflates to ensure the formations of cationic oxidative addition intermediates. Stimulated by the growing potential of related axially chiral heterobidentate ligands, we decided to focus on the development of dynamic kinetic Buchwald−Hartwig (DYKAT: dynamic kinetic asymmetric transformation) amination of heterobiaryl electrophiles for the asymmetric synthesis of axially chiral IAN-type diamines.

In summary, we have developed a new and efficient procedure for the asymmetric synthesis of IAN-type N,N-ligands based on a dynamic kinetic asymmetric Buchwald−Hartwig amination of racemic heterobiaryl electrophiles. The use of QUINAP as the ligand allowed the isolation of the products in high yields and good to excellent enantioselectivities. The isolation of cationic and neutral oxidative addition intermediates supports a mechanism based in the labilization of the stereogenic axis in the former.