Literature Report

Catalytic asymmetric addition of Grignard reagents to alkenyl-substituted aromatic *N*-heterocycles

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Date: 2016-05-17

Harutyunyan, S. R. *et al.*
Science **2016**, *352*, 433.

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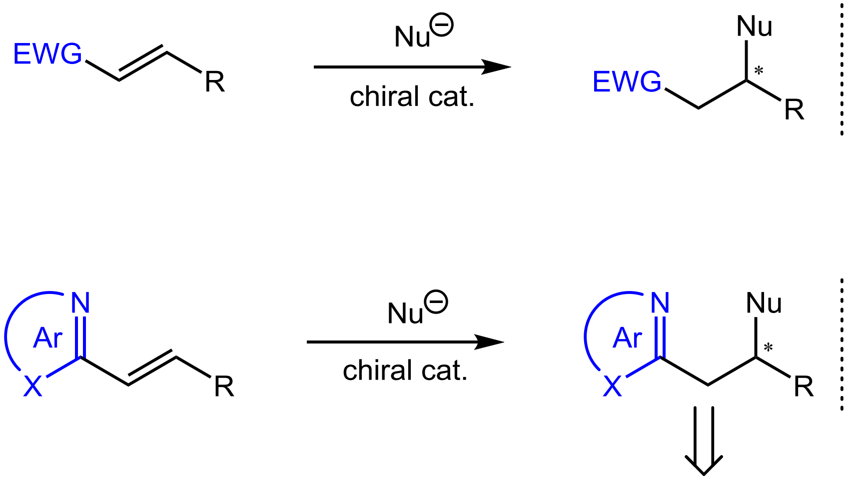
Biography

- Associate professor at Stratingh institute for Chemistry (since 2013) (University of Groningen, Netherlands)
- Assistant professor at Stratingh institute for Chemistry (2010-2013) (University of Groningen, Netherlands)
- Senior scientist in Johnson & Johnson-Tibotec-Janssen Pharmaceutica (2007-2009) (Beerse, Belgium)
- Post doctoral research with Prof. Feringa (2003-2007) (University of Groningen, Netherlands)
- Ph.D. in Organic and organometallic chemistry with Prof. Belokon (2003) (INEOS, Moscow, Russia)
- Medical representative at Hoffmann-La Roche (2000) (Armenia)
- M.Sc. in Pharmacology, Pharmaceutical chemistry with Prof. Saghian (1999) (Yerevan State University, Armenia)

Contents

Introduction

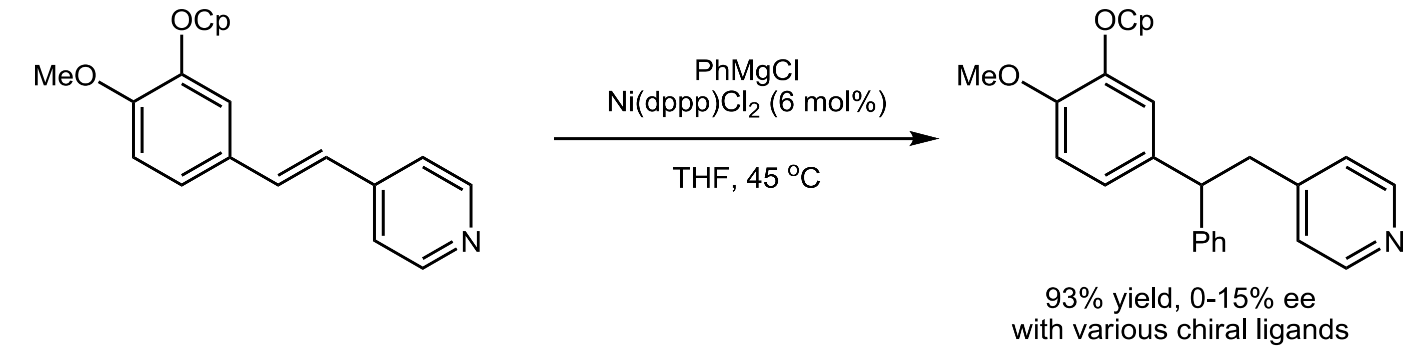


EWG = COR, CN, SO_2R
$PO(OR)_2$, NO_2

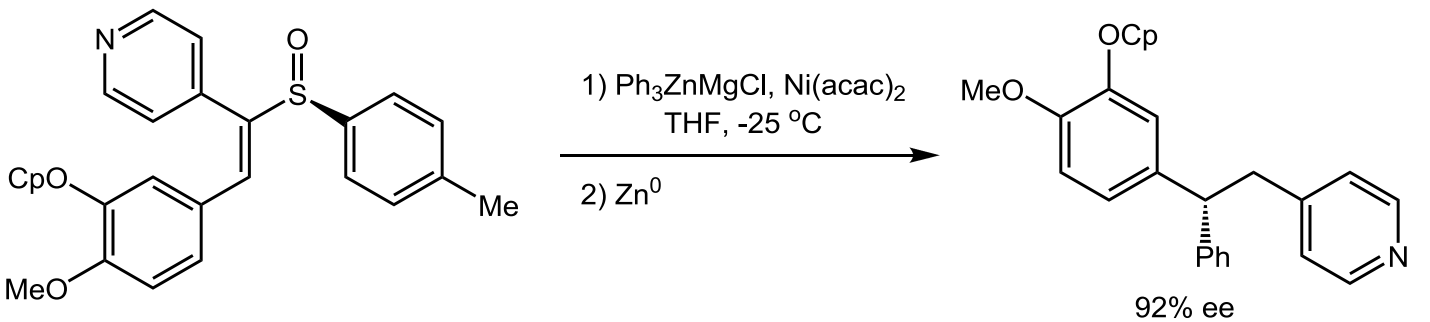
Ar = benzoxazole, thiazole, oxazole
pyrimidine, triazine and quinoline

The majority (88%) of all known active pharmaceutical ingredients contain *N*-containing aromatic heterocycles.

Introduction



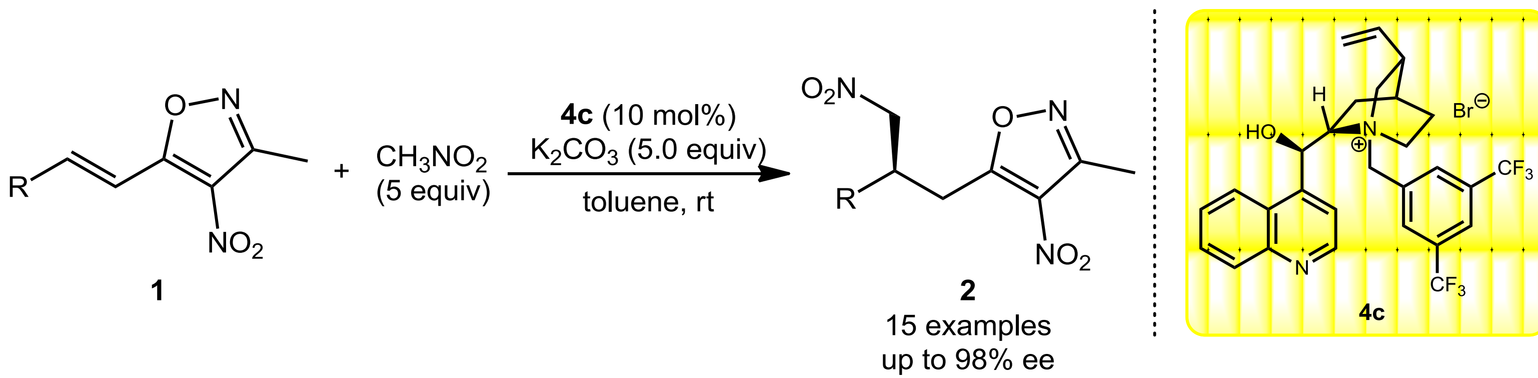
- **Ph-M**: PhMgCl; PhLi; $PhCeCl_2$; $Ph_2CuCNLi_2$; Ph_2CuLi; PhI + Pd^0 + HCO_2^-; PhHgCl + $NaBH_4$
- **Activation of pyridine nitrogen**: $ClCO_2Et$; $PhCH_2Cl$; BH_3·THF; ${}^tBuMe_2SiOTf$
- **Activation of double bond**: sulfoxide functionality



Houpis, I. N. *et al Tetrahedron* **1998**, *54*, 1185.

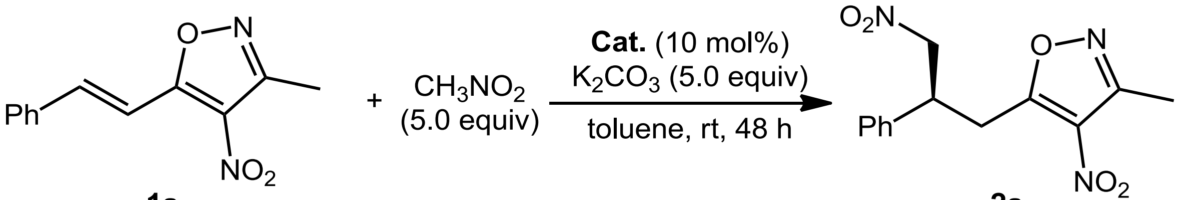
Organocatalytic enantioselective conjugate addition

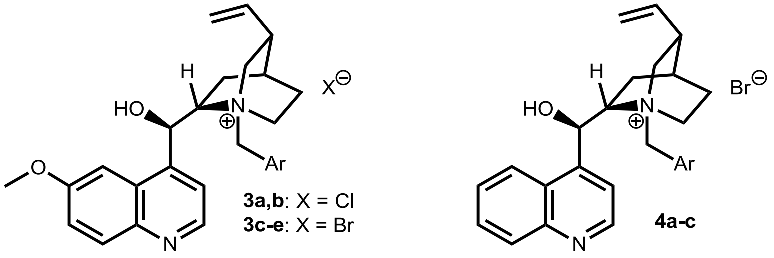
Adamo's work



Adamo, M. F. A. *et al Angew. Chem. Int. Ed.* **2009**, *48*, 9342.

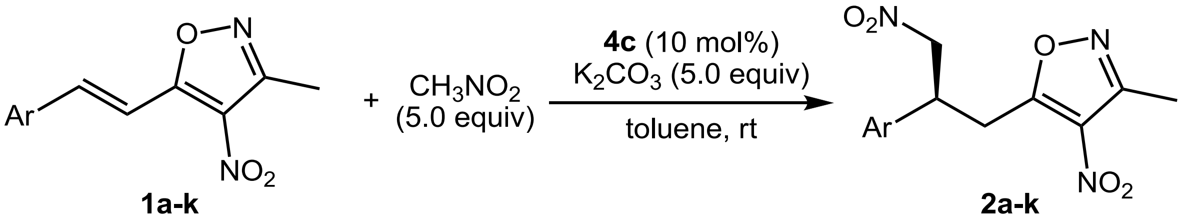
Screening of catalysts





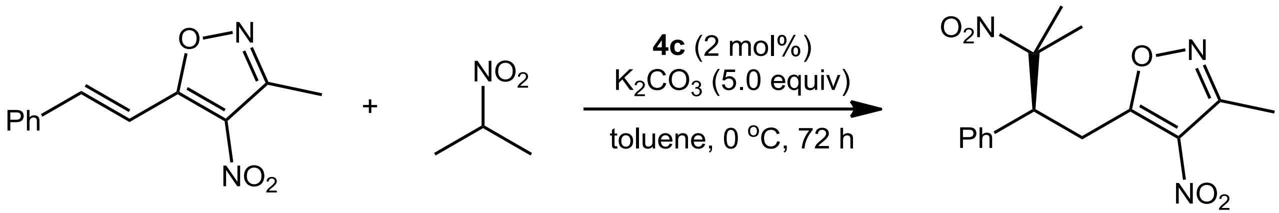
Entry	**Cat.**	Ar	Conv. (%)	ee (%)
1	**3a**	C_6H_5	89	78
2	**3b**	2-MeOC_6H_4	>95	76
3	**3c**	2-FC_6H_4	57	78
4	**3d**	4-MeOC_6H_4	91	69
5	**3e**	4-$CF_3C_6H_4$	78	83
6	**4a**	C_6H_5	>95	90
7	**4b**	4-$CF_3C_6H_4$	>95	93
8	**4c**	3,5-$(CF_3)_2C_6H_3$	>95	97

Substrate scope of the reaction



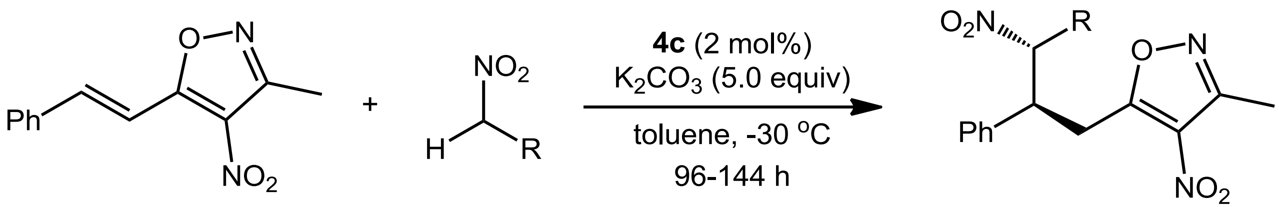
Entry	**1**	Ar	t (h)	yield (%)	ee (%)
1	**1a**	C_6H_5	48	80	97
2	**1b**	$3\text{-}ClC_6H_4$	48	75	94
3	**1c**	$4\text{-}ClC_6H_4$	48	74	91
4	**1d**	$2,6\text{-}Cl_2C_6H_3$	48	50	77
5	**1e**	$3,5\text{-}Cl_2C_6H_3$	48	70	93
6	**1f**	$2,4\text{-}Cl_2C_6H_3$	48	75	87
7	**1g**	$4\text{-}MeOC_6H_4$	48	88	96
8	**1h**	1-pyranyl	160	80	98
9	**1i**	3-indolyl	240	55	88
10	**1j**	2-furyl	120	65	97
11	**1k**	2-pyridyl	48	82	96

Substrate scope of the reaction



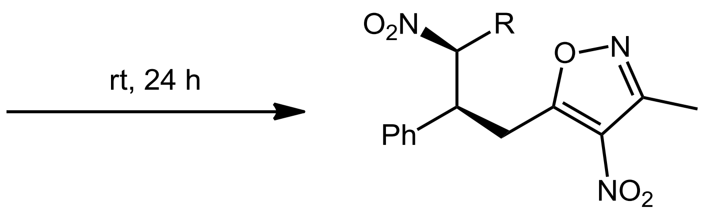
1a

2l: 75% yield, 81% ee



1a

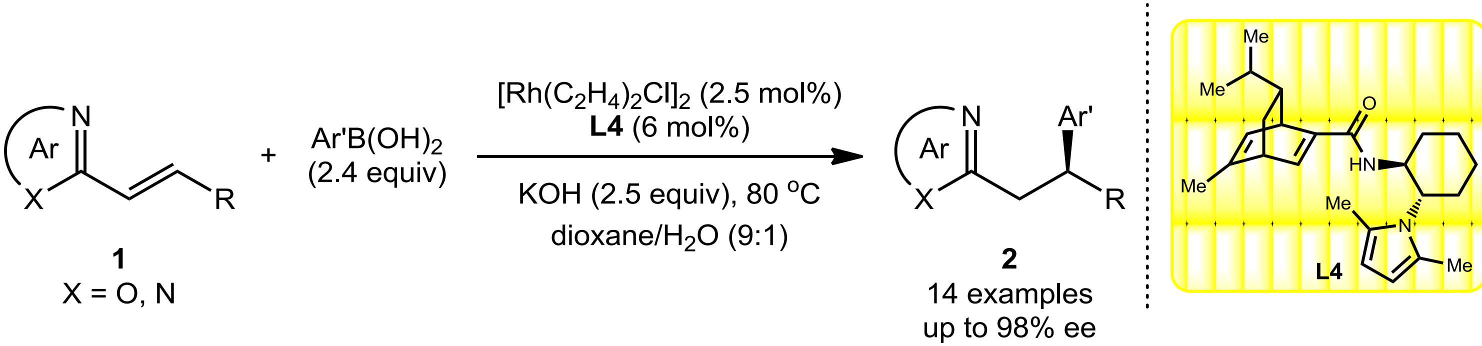
2m: R = Me, 92% yield, 88:12 *anti*/*syn*, 99% ee (*anti*)
2n: R = Et, 85% yield, 91:9 *anti*/*syn*, 99% ee (*anti*)
2o: R = Bn, 75% yield, 91:9 *anti*/*syn*, 97% ee (*anti*)



2m: R = Me, 91% yield, 30:70 *anti*/*syn*, 94% ee (*syn*)
2n: R = Et, 98% yield, 27:73 *anti*/*syn*, 90% ee (*syn*)
2o: R = Bn, 89% yield, 24:76 *anti*/*syn*, 80% ee (*syn*)

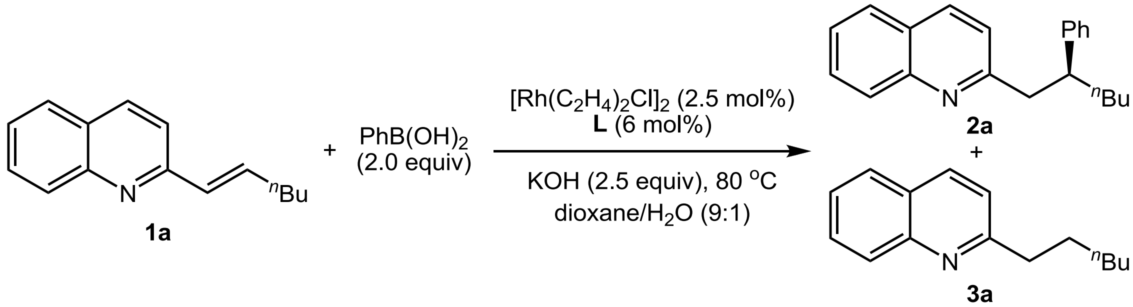
Rh-catalyzed enantioselective conjugate addition

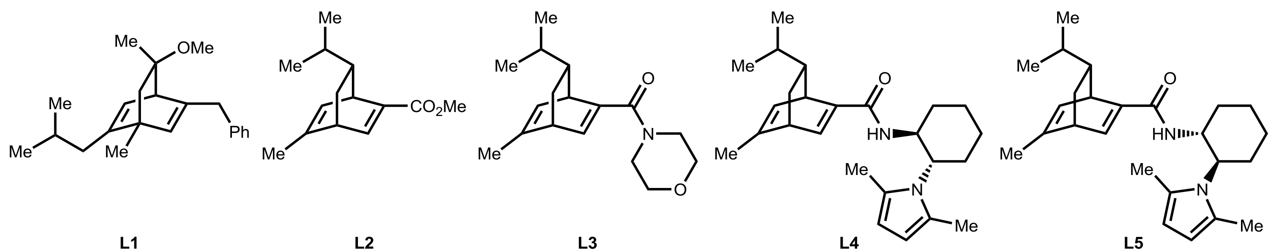
Lam's work



Lam, H. W. *et al J. Am. Chem. Soc.* **2010**, *132*, 14373.

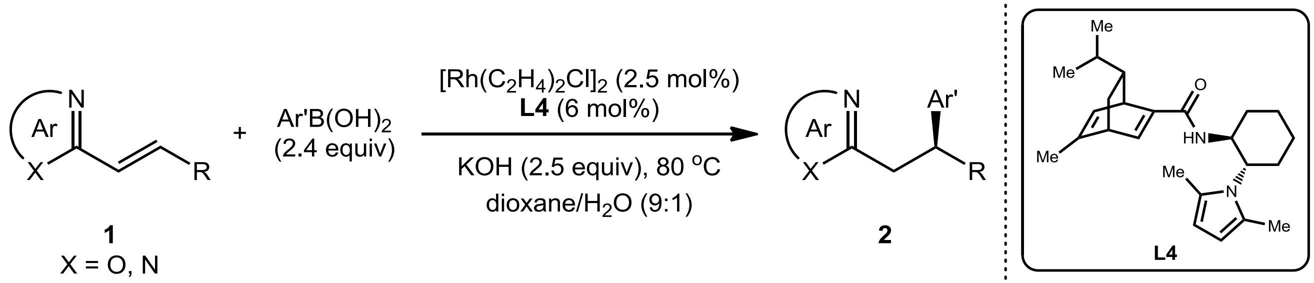
Screening of chiral diene ligands

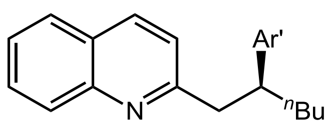




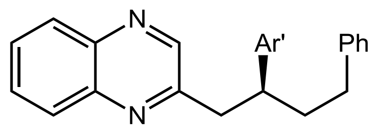
Entry	L	**1a** (%)	**2a** (%)	**3a** (%)
1	**L1**	0	89 (79% ee)	11
2	**L2**	60	33 (78% ee)	7
3	**L3**	75	19 (53% ee)	6
4	**L4**	26	68 (93% ee)	6
5	**L5**	65	31 (81% ee)	4

Substrate scope of the reaction

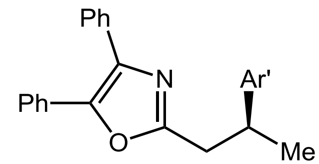




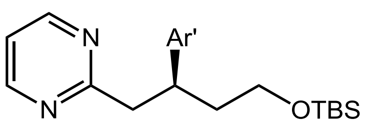
Ar' = Ph, 56% yield, 95% ee
Ar' = 4-MeC_6H_4, 67% yield, 92% ee
Ar' = 3-MeC_6H_4, 71% yield, 95% ee



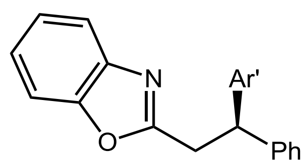
Ar' = Ph, 80% yield, 90% ee
Ar' = 2-MeC_6H_4, 72% yield, 97% ee
Ar' = 4-ClC_6H_4, 75% yield, 90% ee
Ar' = 4-FC_6H_4, 91% yield, 91% ee
Ar' = 4-MeOC_6H_4, 90% yield, 93% ee



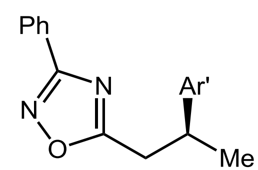
Ar' = 4-MeC_6H_4, 69% yield, 89% ee



Ar' = Ph, 72% yield, 98% ee
Ar' = 4-FC_6H_4, 65% yield, 97% ee

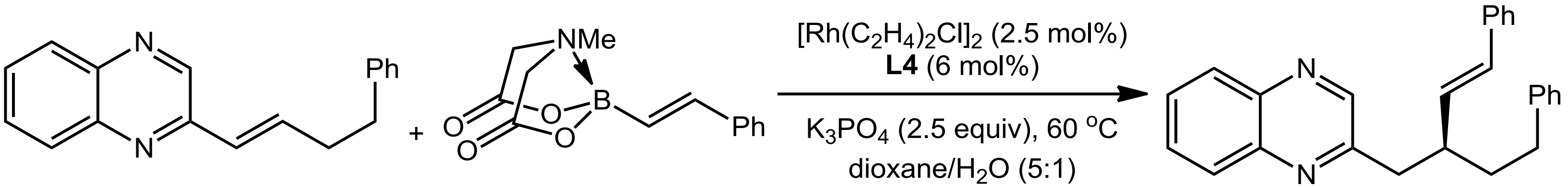


Ar' = 2-naphthyl, 78% yield, 93% ee
Ar' = 3-Cl-4-*i*PrOC_6H_3, 65% yield, 97% ee



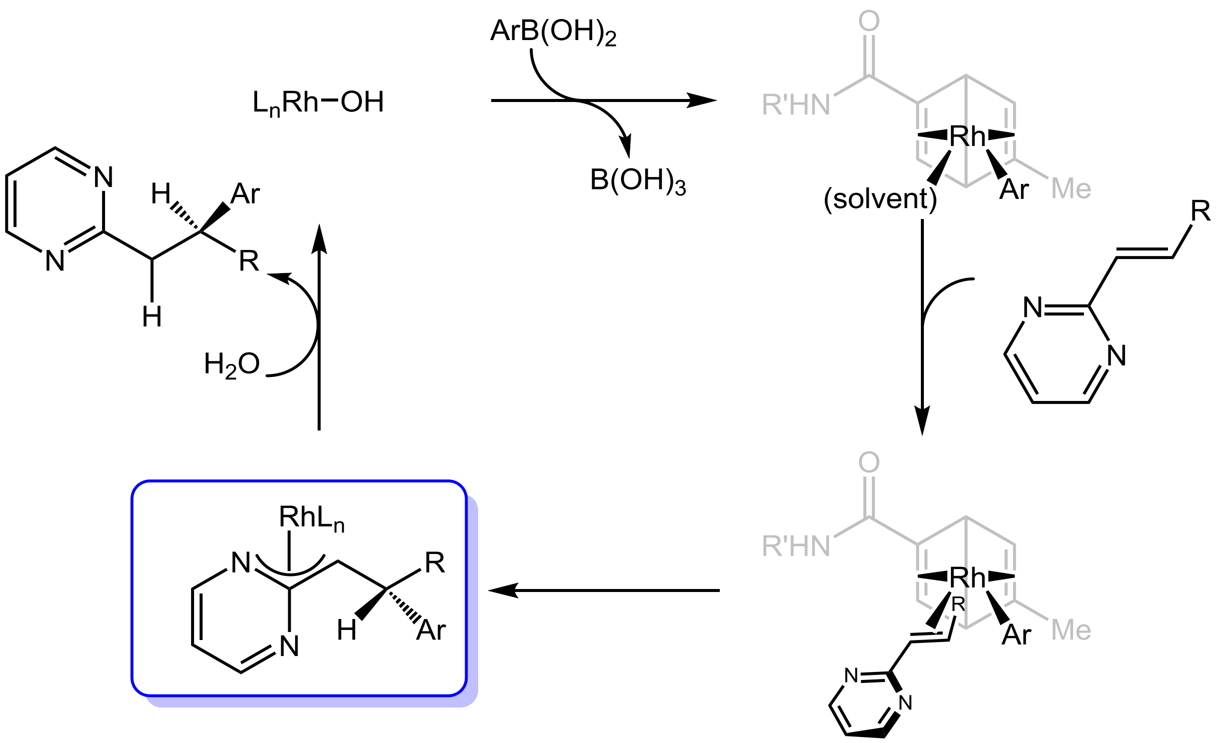
Ar' = 3-MeC_6H_4, 64% yield, 94% ee

Substrate scope of the reaction



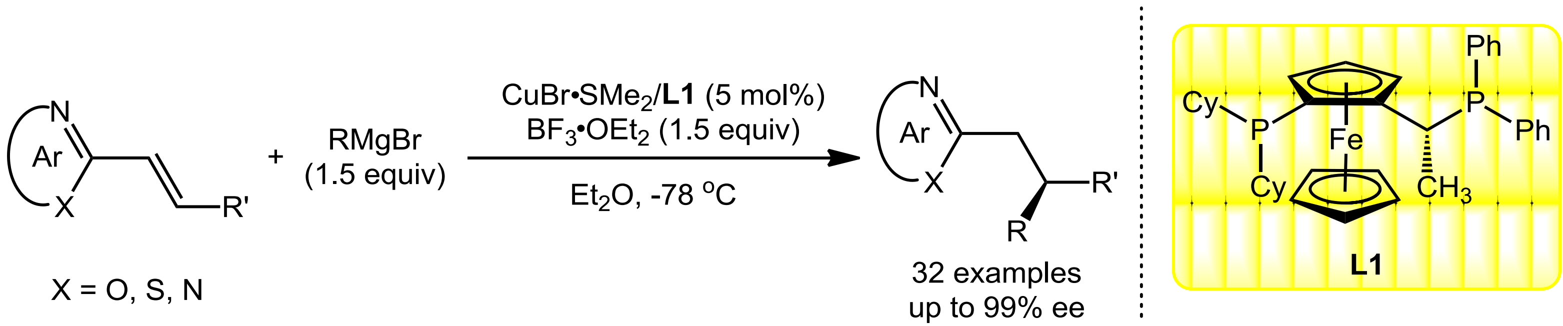
1b (1.2 equiv) **2b** 58% yield, 61% ee

Possible catalytic cycle



Cu-catalyzed enantioselective conjugate addition

Harutyunyan's work



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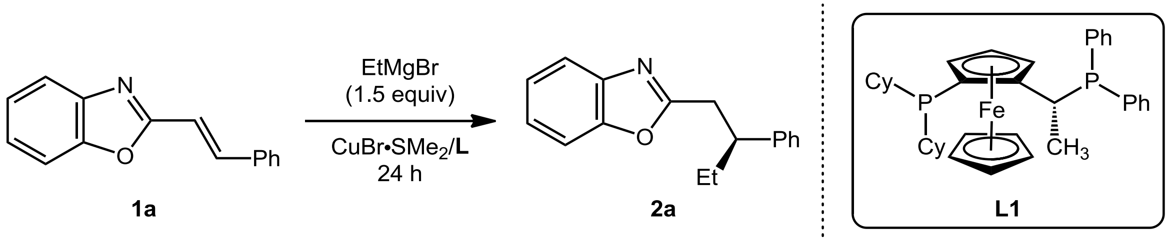
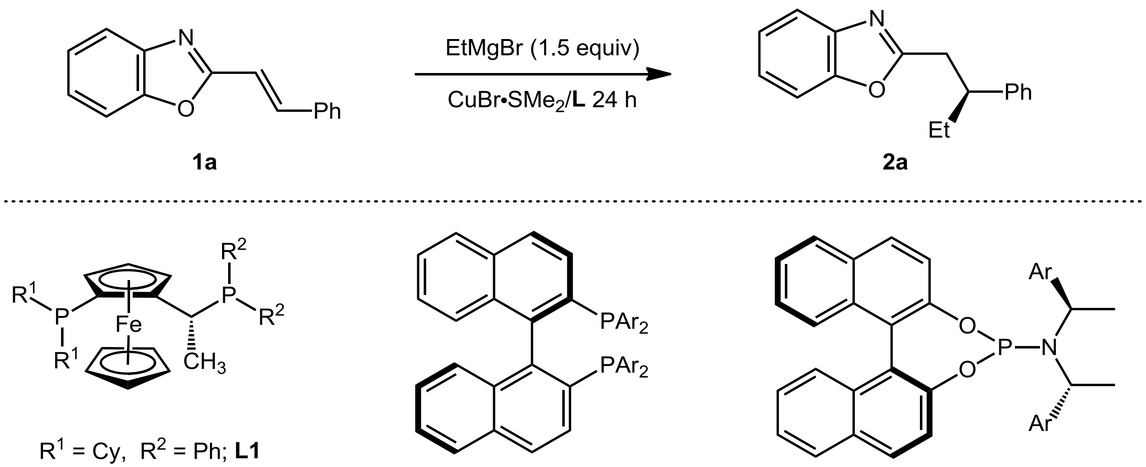
Screening of conditions



Entry	L	Solvent	Additive	T (°C)	Yield (%)	ee (%)
1	-	*t*BuOMe	-	-25	Complex mix.	-
2	**L1**	*t*BuOMe	-	-25	Complex mix.	-
3	-	Toluene	$BF_3 \cdot OEt_2$	-78	0	-
4	**L1**	Toluene	$BF_3 \cdot OEt_2$	-78	59	87
5	**L1**	*t*BuOMe	$BF_3 \cdot OEt_2$	-78	55	93
6	**L1**	CH_2Cl_2	$BF_3 \cdot OEt_2$	-78	67	94
7	**L1**	THF	$BF_3 \cdot OEt_2$	-78	57	50
8	**L1**	Et_2O	$BF_3 \cdot OEt_2$	-78	94	96

Reactions were conducted on 0.2 mmol scale using 5 mol% of $CuBr \cdot SMe_2$/**L**, and 1.5 equiv of $BF_3 \cdot OEt_2$, 24 h. Reported yields are for isolated **2a**.

Screening of conditions



R[1] = Cy, R[2] = Ph; **L1**
R[1] = *t*Bu, R[2] = Ph; **L2**
R[1] = Ph, R[2] = Cy; **L3**

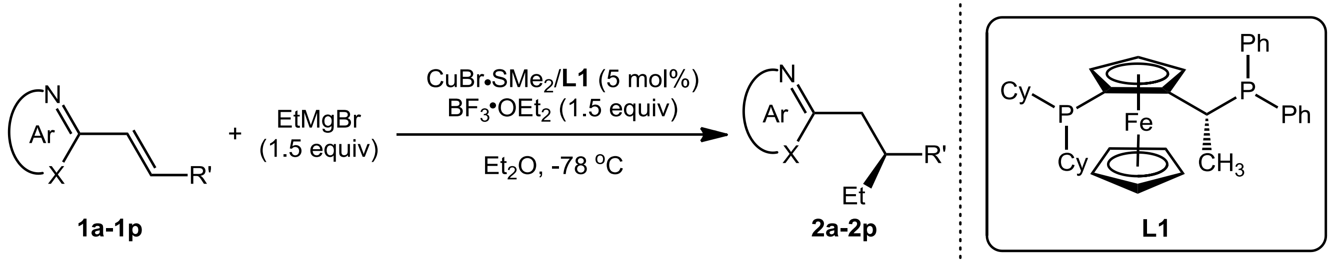
Ar = Ph; **L4**
Ar = 4-MeC$_6$H$_4$; **L5**

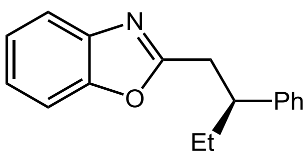
Ar = Ph; **L6**
Ar = 2-MeOC$_6$H$_4$; **L7**

Entry	L	Solvent	Yield (%)	ee (%)
1	**L1**	Et_2O	94	96
2	**L2,L6,L7**	Et_2O	0	-
3	**L3**	Et_2O	35	53
4	**L4**	Toluene	36	91
5	**L5**	Toluene	45	92

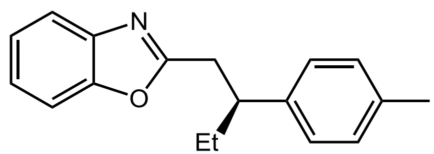
Reactions were conducted on 0.2 mmol scale using 5 mol% of CuBr·SMe$_2$/**L**, and 1.5 equiv of BF_3·OEt_2, 24 h. Reported yields are for isolated **2a**.

Substrate scope of the reaction

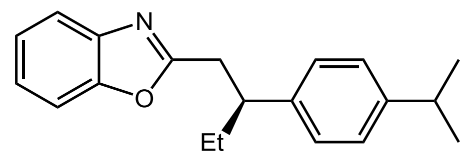




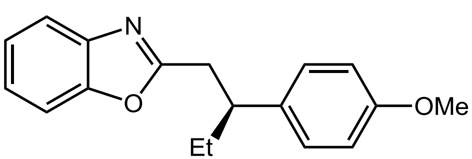
2a, 94% yield, 96% ee



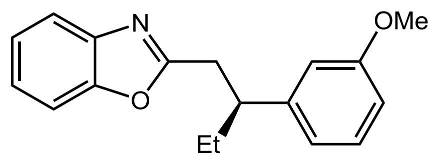
2b, 78% yield, 95% ee



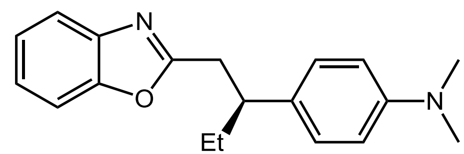
2c, 46% yield, 96% ee



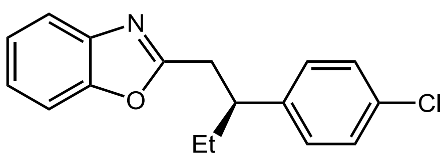
2d, 67% yield, 95% ee



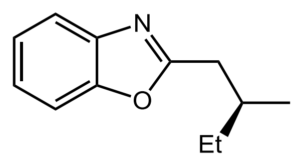
2e, 89% yield, 97% ee



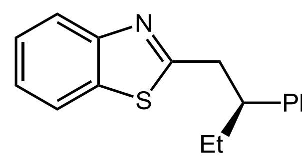
2f, 54% yield, 95% ee



2g, 53% yield, 95% ee

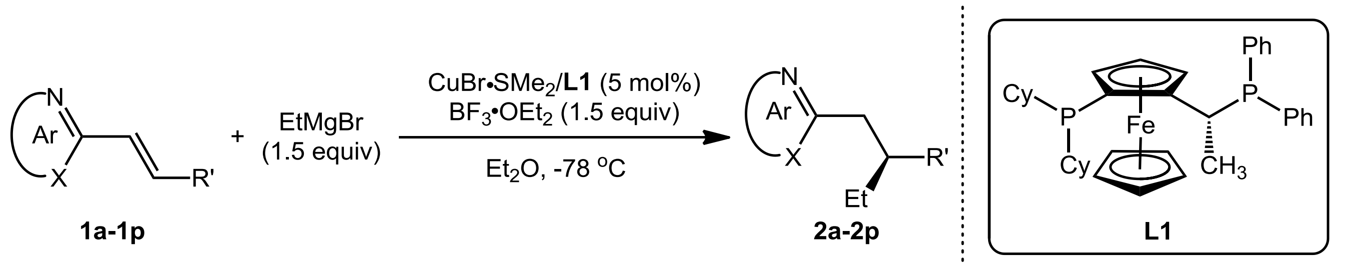


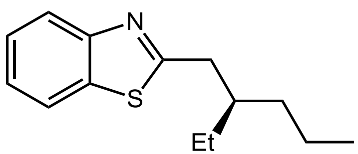
2h, 71% yield, 87% ee



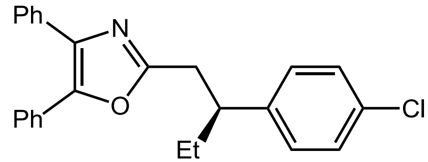
2i, 88% yield, 86% ee

Substrate scope of the reaction

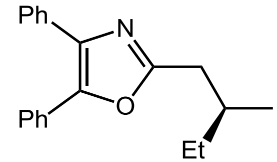




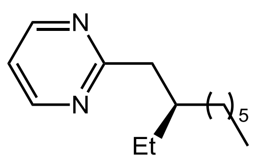
2j, 85% yield, 88% ee



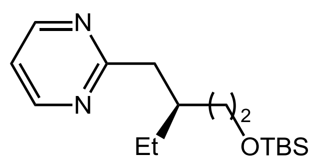
2k, 69% yield, 91% ee



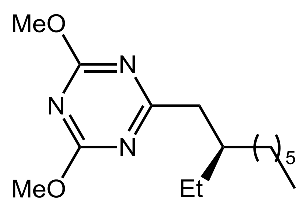
2l, 75% yield, 98% ee



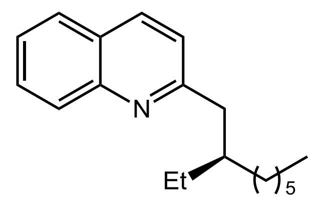
2m, 93% yield, 99% ee



2n, 95% yield, 97% ee

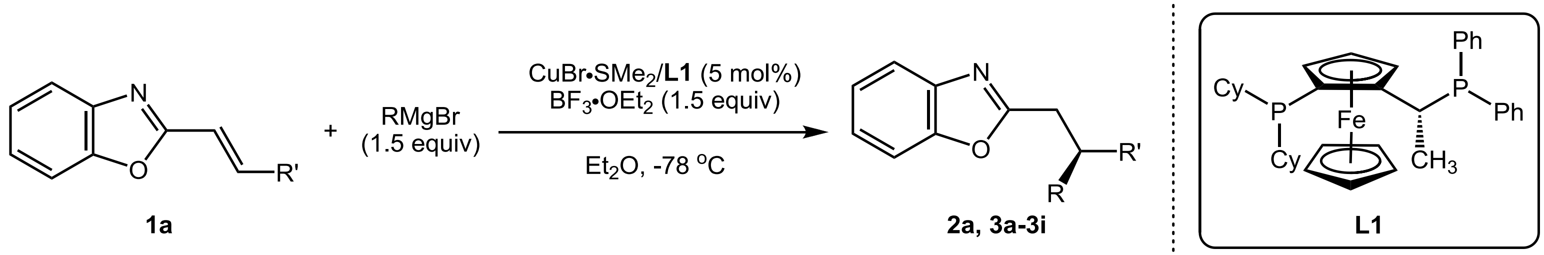


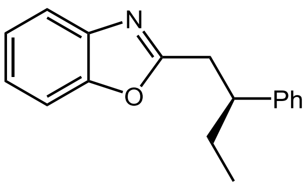
2o, 90% yield, 91% ee



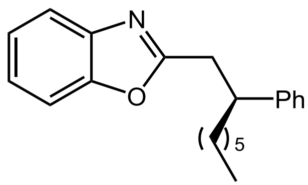
2p, 84% yield, 99% ee

Substrate scope of the reaction

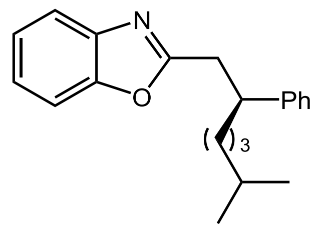




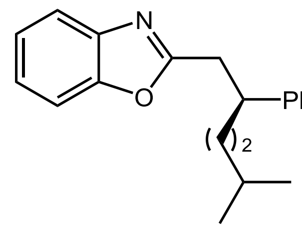
2a, 94% yield, 96% ee



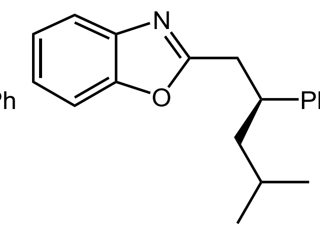
3a, 78% yield, 96% ee



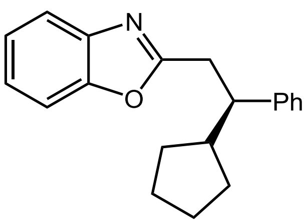
3b, 80% yield, 95% ee



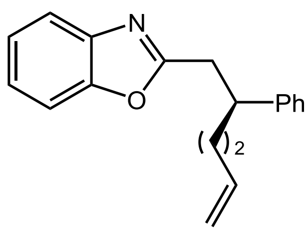
3c, 70% yield, 95% ee



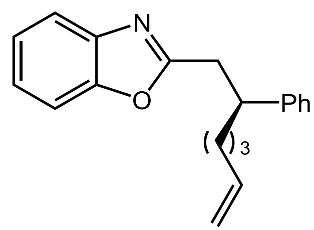
3d, 65% yield, 91% ee



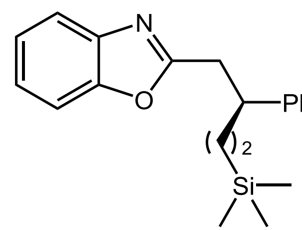
3e, 58% yield, 90% ee



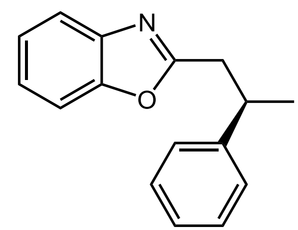
3f, 44% yield, 89% ee



3g, 57% yield, 93% ee

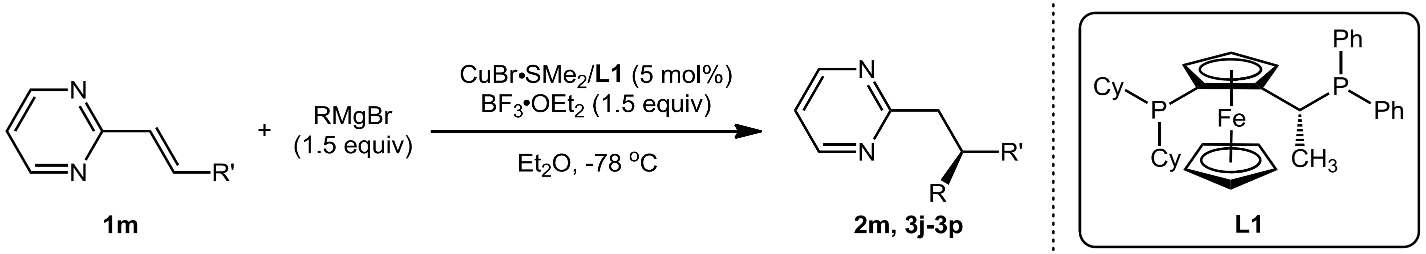


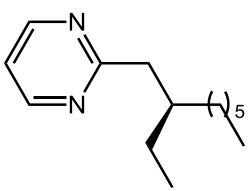
3h, 74% yield, 95% ee



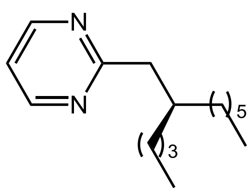
3i, 55% yield, 92% ee

Substrate scope of the reaction

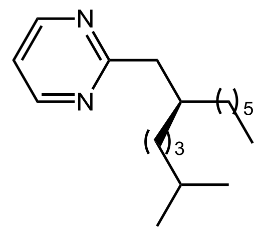




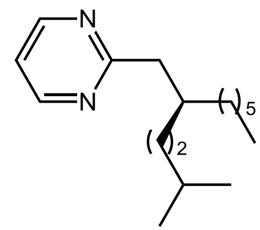
2m, 93% yield, 99% ee



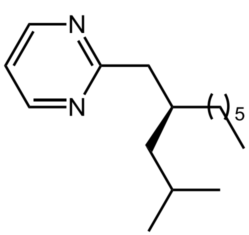
3j, 94% yield, 99% ee



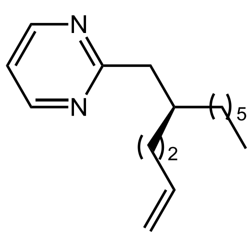
3k, 89% yield, 99% ee



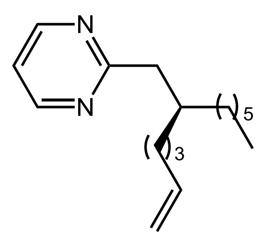
3l, 91% yield, 99% ee



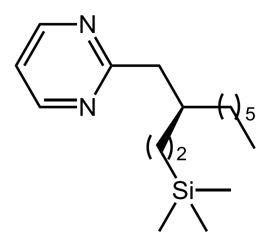
3m, 78% yield, 98% ee



3n, 90% yield, 99% ee



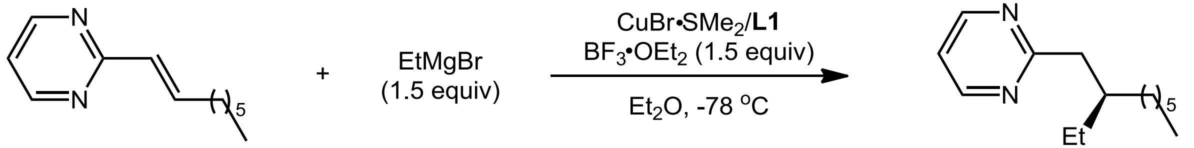
3o, 51% yield, 99% ee



3p, 78% yield, 97% ee

Scale-up and mechanistic considerations

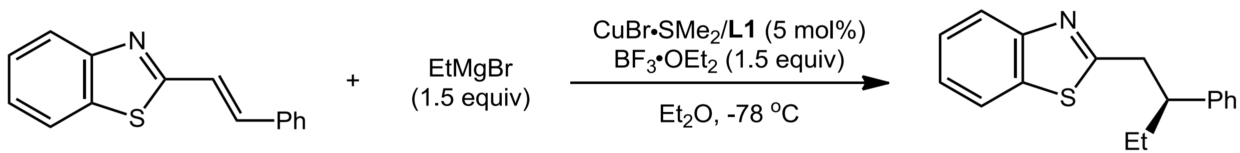
A



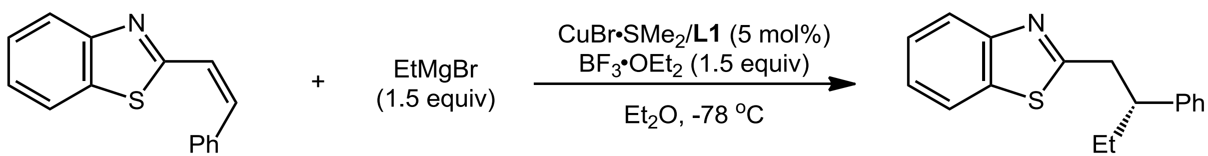
1m **2m**

1) with 1 mol% of $CuBr{\cdot}SMe_2$/**L1** 90% yield, 99% ee;
2) on preparative scale (1 mmol) 84% yield, 99% ee;
3) with recovered $CuBr{\cdot}SMe_2$/**L1** 87% yield, 99% ee;

B



(*E*)-**1i**, 100% pure (*S*)-**2i**, 86% ee



(*Z*)-**1i**, 90% pure (*R*)-**2i**, 40% ee

Scale-up and mechanistic considerations

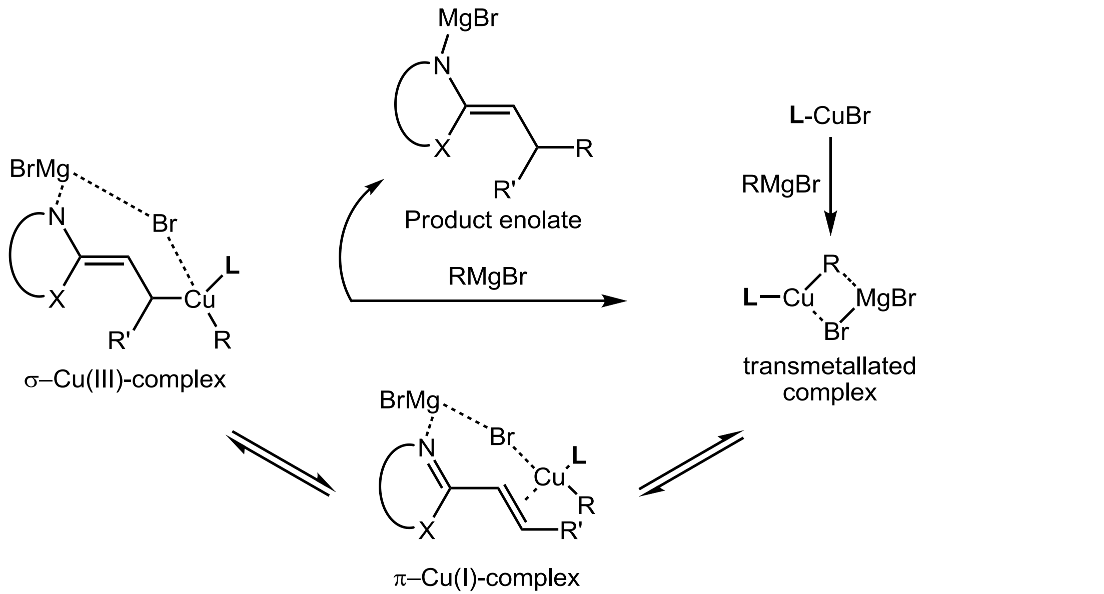
C

(*Z*)-**1i** —reagents, Et_2O, -78 °C→

(*Z*):(*E*) = 90:10

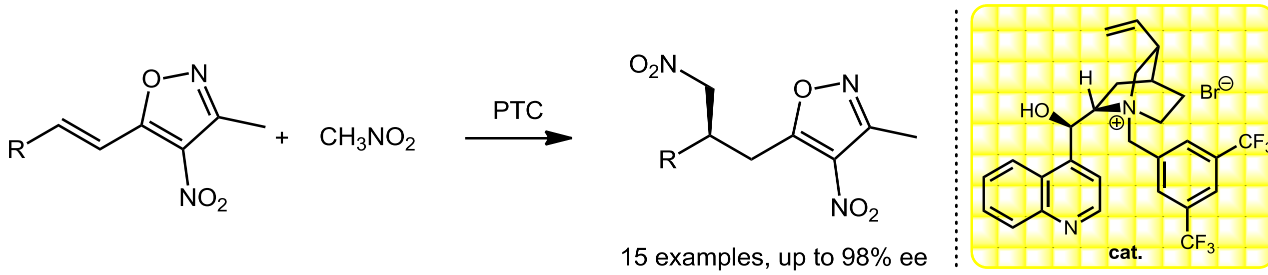
(*Z*):(*E*)	reagents
90:10	with BF_3•OEt_2
90:10	with MeMgBr
90:10	with BF_3•OEt_2 + MeMgBr
38:62	with BF_3•OEt_2 + MeMgBr + CuBr•SMe_2/**L1**

D

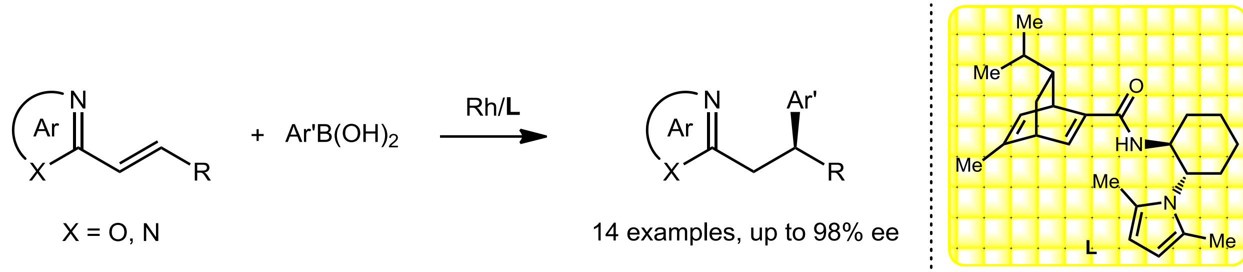


Summary

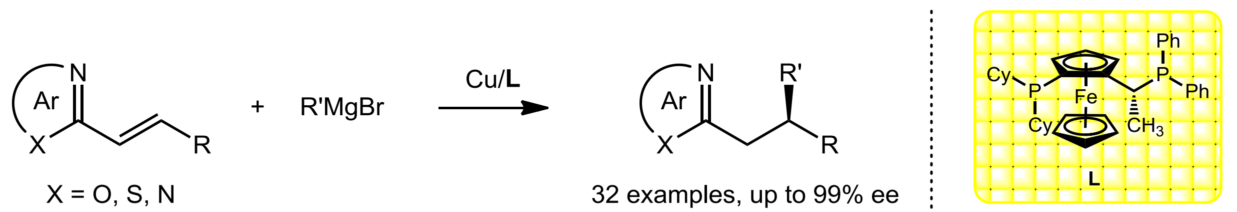
Organocatalytic enantioselective conjugate addition by Adamo



Rh-catalyzed enantioselective conjugate addition by Lam



Cu-catalyzed enantioselective conjugate addition by Harutyunyan



The majority (88%) of all known active pharmaceutical ingredients (APIs) contain functionalized heterocyclic aromatic rings with a preponderance of *N*-containing aromatic heterocycles. Furthermore, approximately half of all APIs are chiral. Because the two enantiomers of a chiral drug can exhibit markedly different bioactivity, any new chiral API must be produced as a single enantiomer. Catalytic asymmetric carbon-carbon (C-C) bond formation represents the most straightforward and atom efficient strategy for the construction of organic chiral molecules. Organometallic reagents are used in a substantial fraction of the C-C bond–forming reactions used to construct API molecules. The conjugate addition of organometallic reagents to electron-deficient substrates (Michael acceptors) has proven to be a powerful method for creating new C-C bonds in a catalytic asymmetric manner for more than 20 years.

In this context, the catalytic asymmetric addition of organometallics to conjugated alkenyl-heteroaromatic compounds represents an attractive strategy to access valuable chiral heterocyclic aromatic compounds in enantiopure form. Addition of carbon nucleophiles to conjugated vinyl-substituted heteroaromatic compounds, leading mainly to achiral molecules, is well known. In contrast, there are only a handful of reports of nucleophilic additions to β-substituted analogs, in particular when organometallics are considered.

The precise mechanism of this reaction remains under investigation, as the role of the LA additive is not clear. It seemed plausible for the LA to activate the heteroaromatic substrate toward the addition reaction. However, preliminary nuclear magnetic resonance (NMR) spectroscopic studies have revealed that new species are formed upon addition of $BF_3 \cdot OEt_2$ to each of the components of the reaction individually, indicating that the LA can modulate the reactivity of Grignard reagents and can also be involved in the structure of the catalytically active species.