Catalytic Asymmetric [4+1] Annulation of Sulfur Ylides with Copper−Allenylidene Intermediates

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Checker: Shubo Hu
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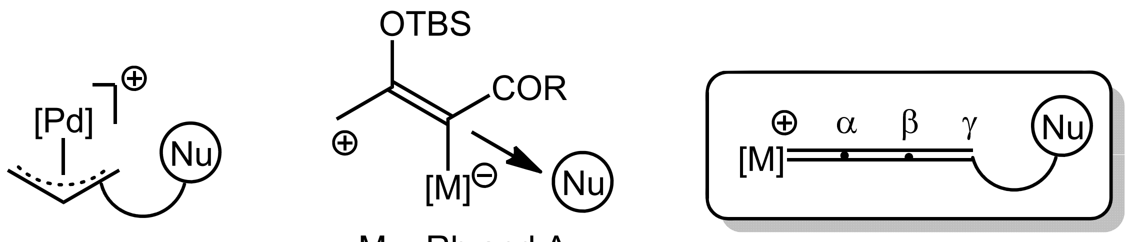
Xiao, W.-J. *et al*. *J. Am. Chem. Soc.* **2016**, *138*, 8360.

Contents

Introduction

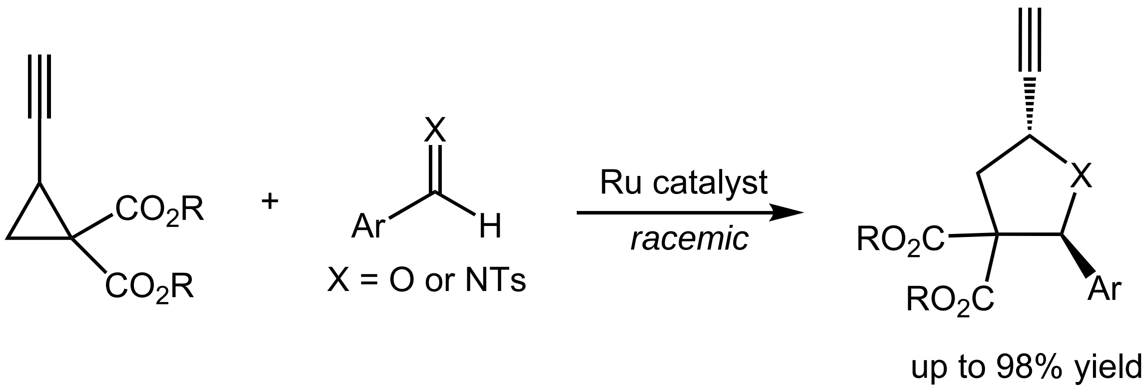
Metal-associated dipolar intermediates



type-I type-II type-III

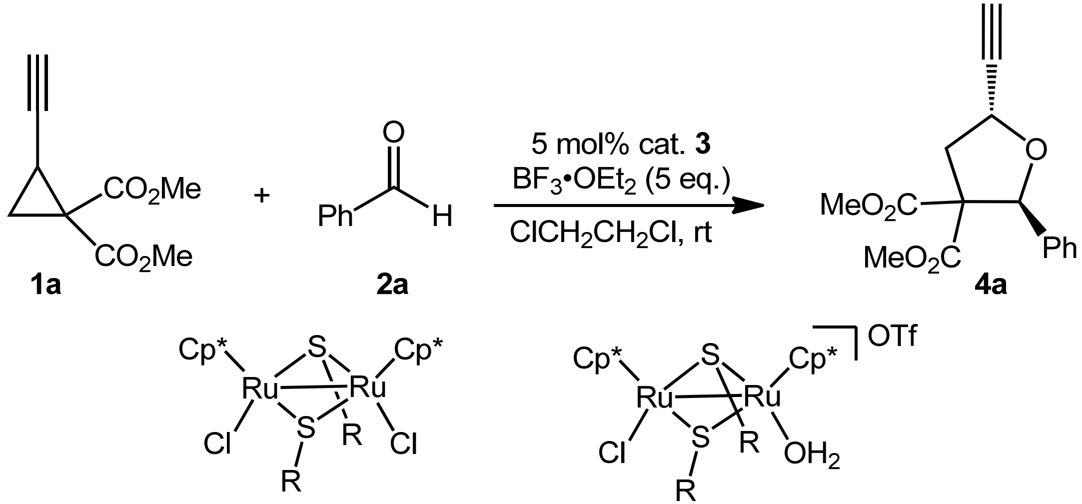
Trost, B. M. *et al. J. Am. Chem. Soc.* **2012**, *134*, 17823.
Doyle, M. P. *et al. J. Am. Chem. Soc.* **2016**, *138*, 44.

Ruthenium Allenylidene



Nishibayashi, Y. *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 1758.

Condition Optimization

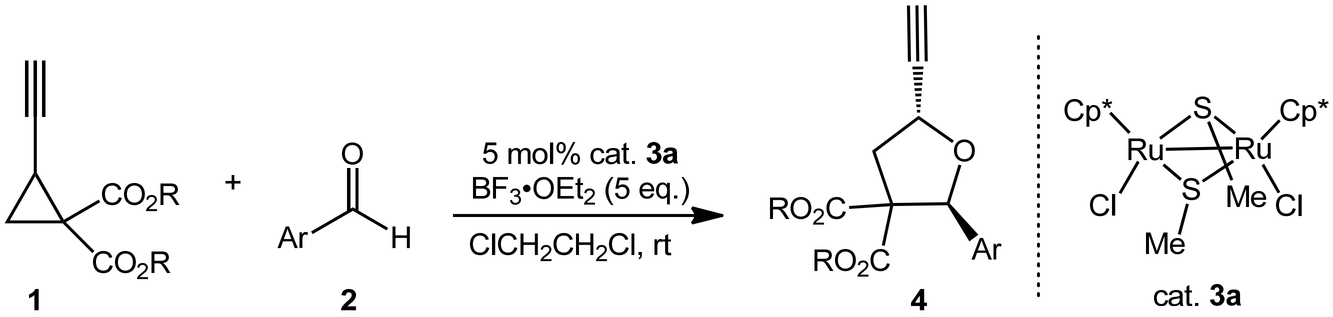


R = Me (**3a**)
R = ^{i}Pr (**3b**)

R = Me (**3c**)

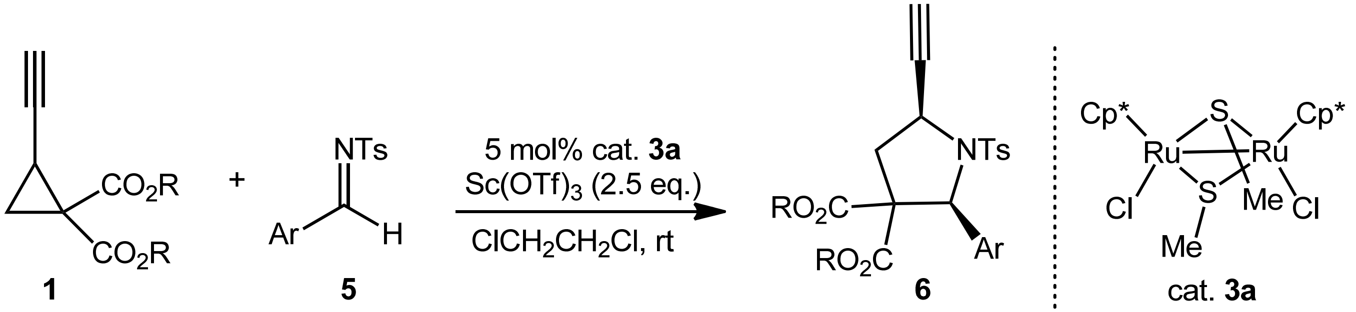
entry	cat. **3**	**2a** (eq.)	**4a** yield (%) (*trans*:*cis*)
1	**3a**	**5**	**88 (2:1)**
2	**3a**	3	67 (2:1)
3	**3b**	5	73 (2:1)
4	**3c**	5	51 (2:1)

Substrate Scope



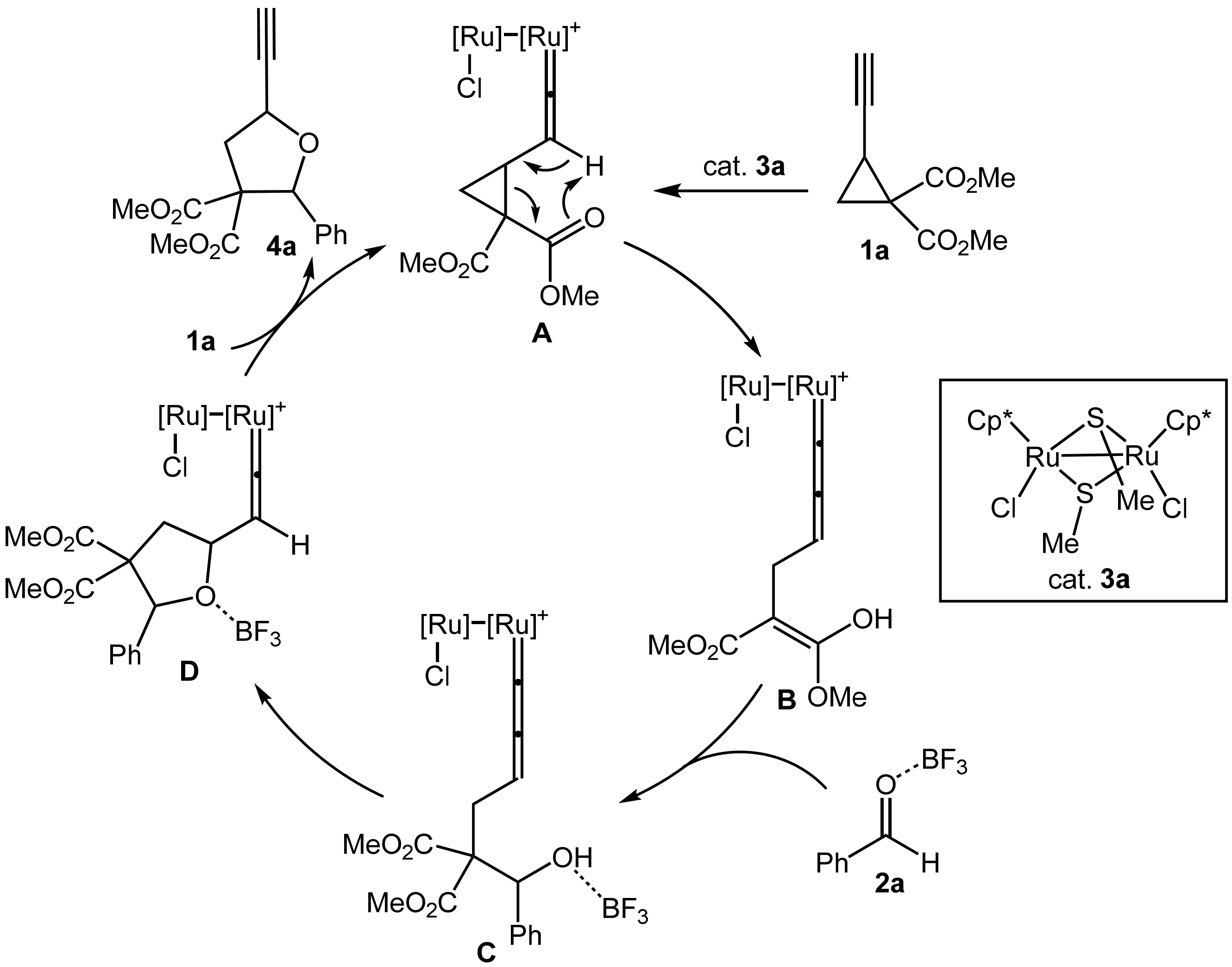
entry	R	Ar	**4** yield (%) (*trans*:*cis*)
1	Me	Ph	88 (2:1)
2	Me	4-$MeOC_6H_4$	87 (2:1)
3	Me	4-MeC_6H_4	81 (2:1)
4	Me	4-FC_6H_4	75 (2:1)
5	Me	3-MeC_6H_4	80 (2:1)
6	Me	2-MeC_6H_4	61 (1:1)
7	Et	Ph	74 (2:1)
8	Et	4-$MeOC_6H_4$	70 (2:1)

Substrate Scope

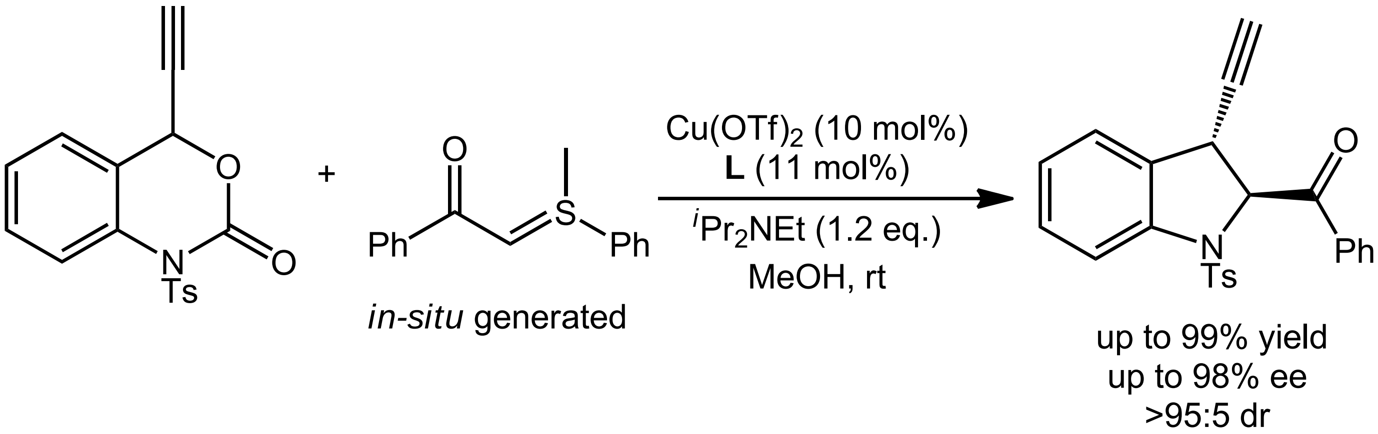


entry	R	Ar	**6** yield (%) (*trans*:*cis*)
1	Me	Ph	88 (1:50)
2	Me	4-MeOC_6H_4	52 (1:8)
3	Me	4-MeC_6H_4	63 (1:20)
4	Me	4-FC_6H_4	86 (1:50)
5	Me	3-MeC_6H_4	80 (1:30)
6	Me	2-naphthyl	76 (1:50)
7	Et	Ph	77 (1:50)
8	Et	4-ClC_6H_4	90 (1:50)

Proposed Mechanism



Copper Allenylidene



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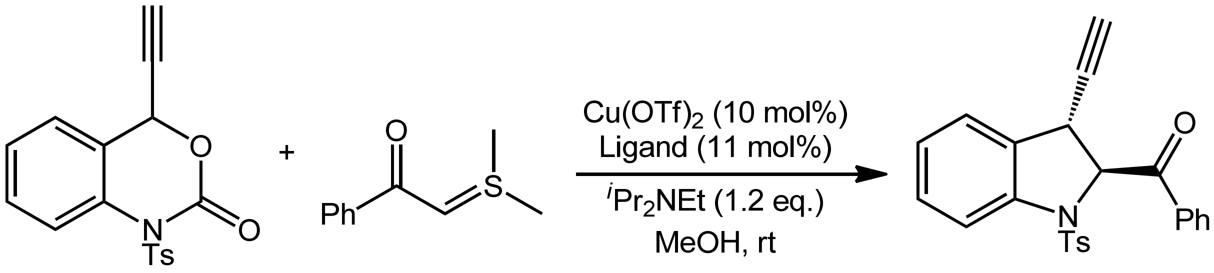
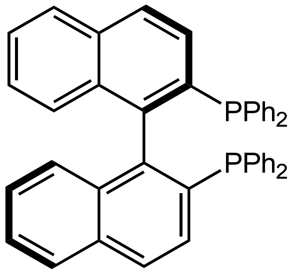
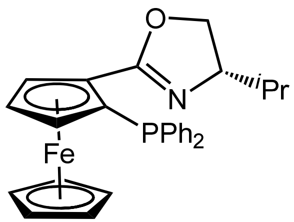
Ligand effects



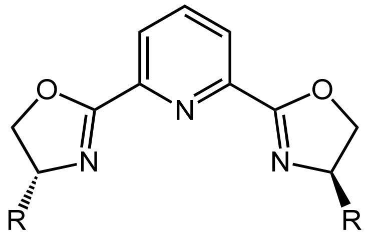
1a **2a** **3aa**: >95:5 dr



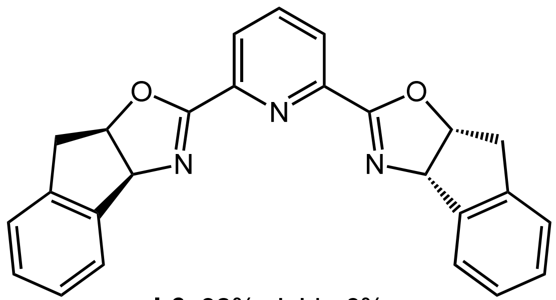
L1: 88% yield, 8% ee



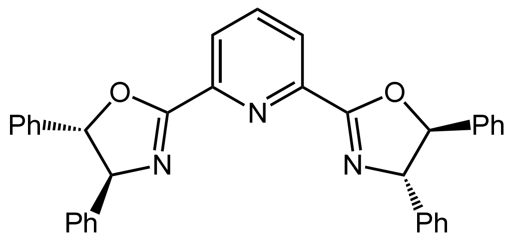
L2: 36% yield, 36% ee



L3: R = ^{i}Pr 53% yield, 50% ee
L4: R = Ph 66% yield, 50% ee
L5: R = Bn 56% yield, 44% ee

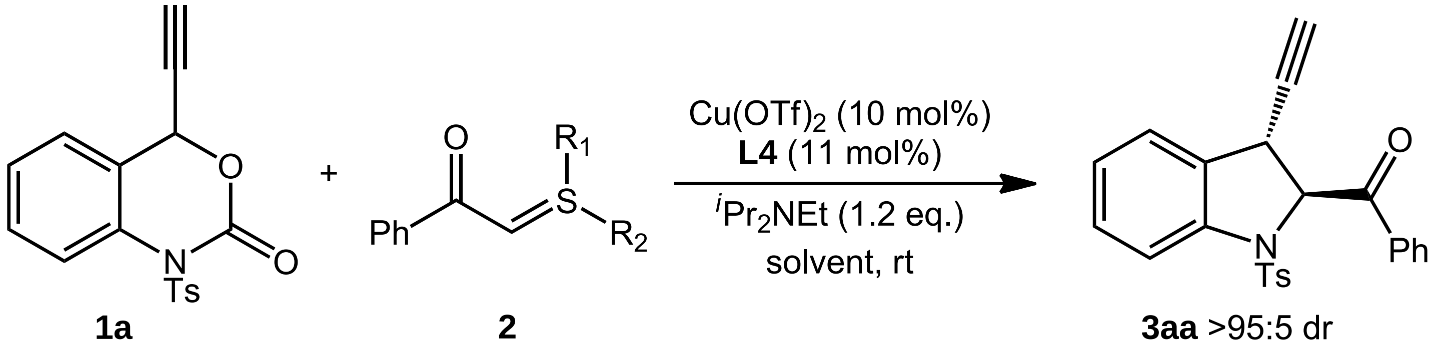


L6: 32% yield, -6% ee



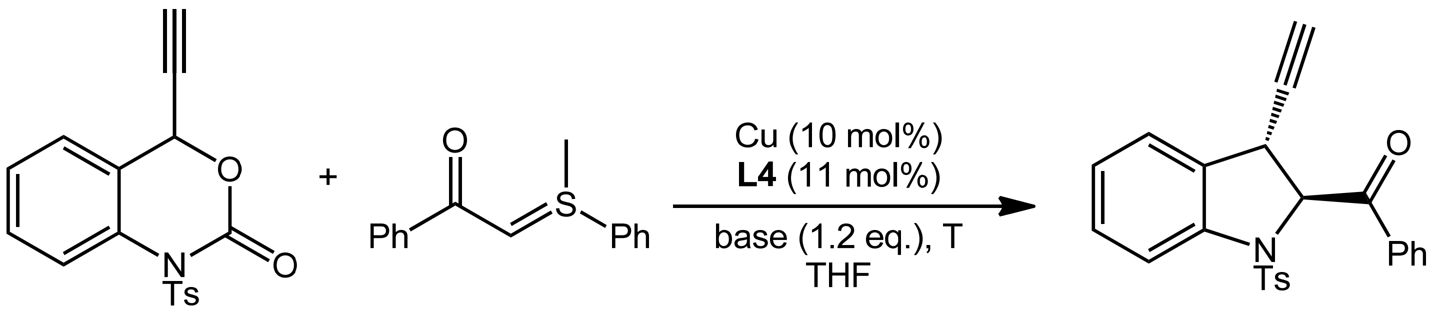
L7: 35% yield, -38% ee

Condition Optimization



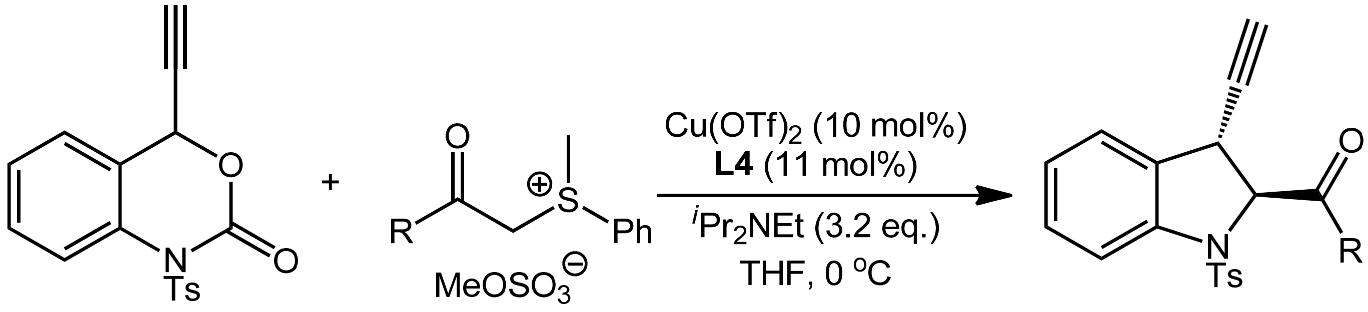
entry	solvent	**2** (R_1/R_2)	yield (%)	ee (%)
1	MeOH	CH_3/CH_3	66	50
2	THF	CH_3/CH_3	97	53
3	Dioxane	CH_3/CH_3	95	34
4	CH_3CN	CH_3/CH_3	96	46
5	Toluene	CH_3/CH_3	83	37
6	CH_2Cl_2	CH_3/CH_3	95	26
7	**THF**	**CH_3/Ph**	**99**	**88**
8	THF	$-(CH_2)_4-$	89	28

Condition Optimization



entry	base	T (°C)	Cu	yield (%)	ee (%)
1	^{i}Pr$_2$NEt	rt	Cu(OTf)$_2$	99	88
2	-	rt	Cu(OTf)$_2$	92	87
3	DABCO	rt	Cu(OTf)$_2$	79	8
4	^{i}Pr$_2$NEt	0	Cu(OTf)$_2$	99	92
5	^{i}Pr$_2$NEt	-10	Cu(OTf)$_2$	90	90
6	^{i}Pr$_2$NEt	0	Cu(CH$_3$CN)$_4$BF$_4$	99	88
7	^{i}Pr$_2$NEt	0	CuI	99	57
8	^{i}Pr$_2$NEt	0	Cu(OTf)$_2$	94	95

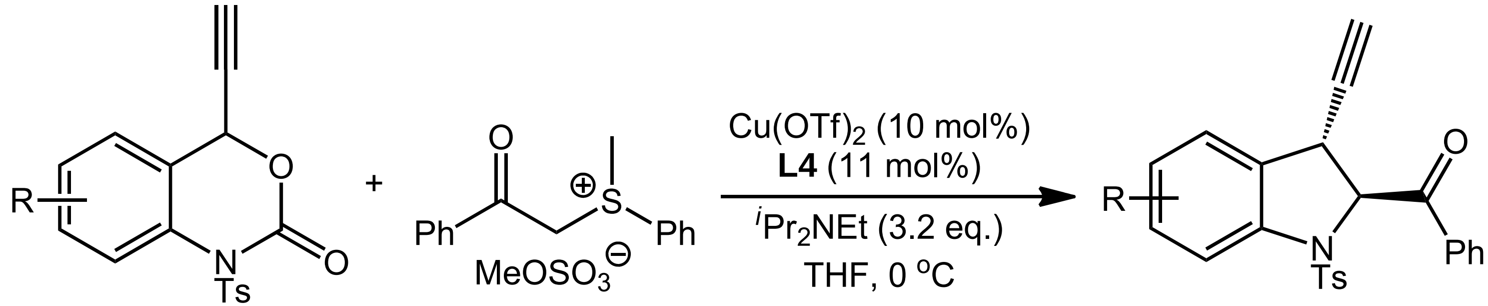
Substrate Scope



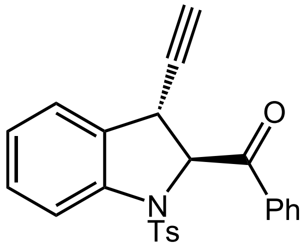
1a **4a** **3:** >95:5 dr

entry	R	yield (%)	ee (%)
1	**C_6H_5**	**94**	**95**
2	4-$NO_2C_6H_4$	98	96
3	4-FC_6H_4	99	94
4	4-MeC_6H_4	96	90
5	3-BrC_6H_4	97	94
6	2-FC_6H_4	99	90
7	2-benzofuryl	90	94
8	methyl	95	91
9	cyclohexyl	90	95

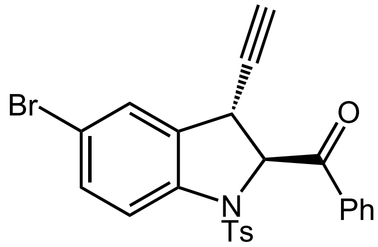
Substrate Scope



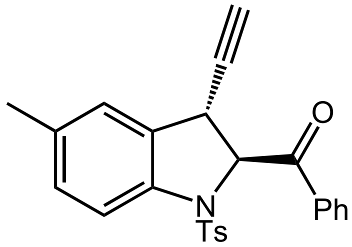
1a-h **4a** **3:** >95:5 dr



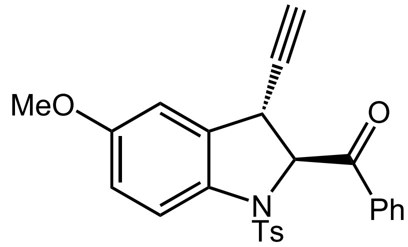
3aa: 94% yield, 95% ee



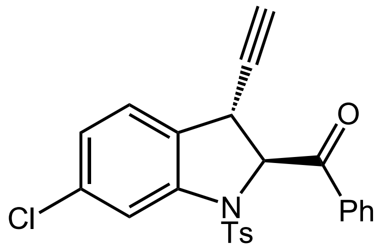
3ba: 97% yield, 90% ee



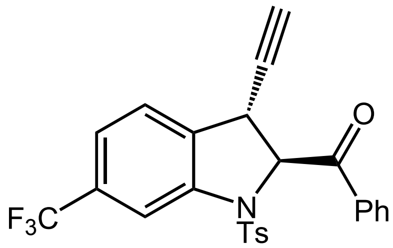
3ca: 99% yield, 91% ee



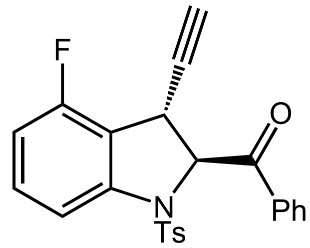
3da: 95% yield, 81% ee



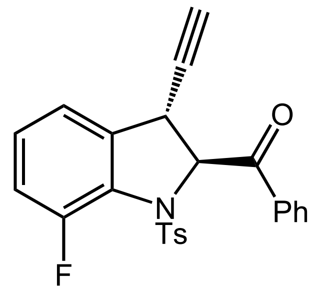
3ea: 99% yield, 95% ee



3fa: 96% yield, 94% ee

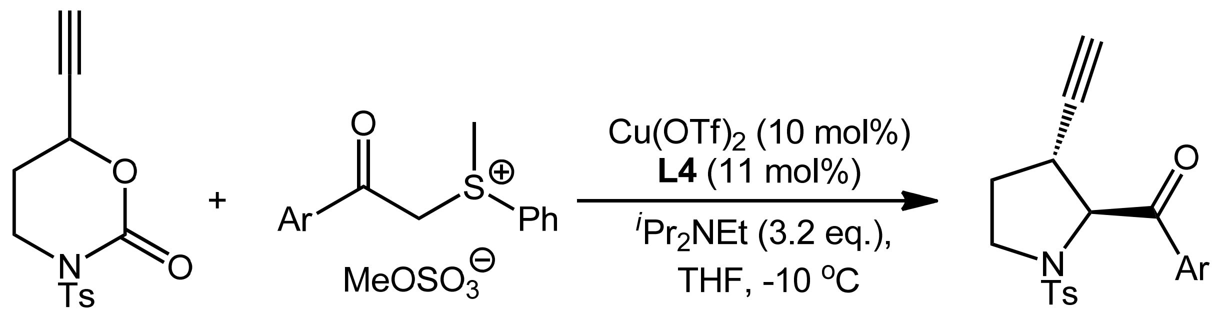


3ga: 93% yield, 80% ee



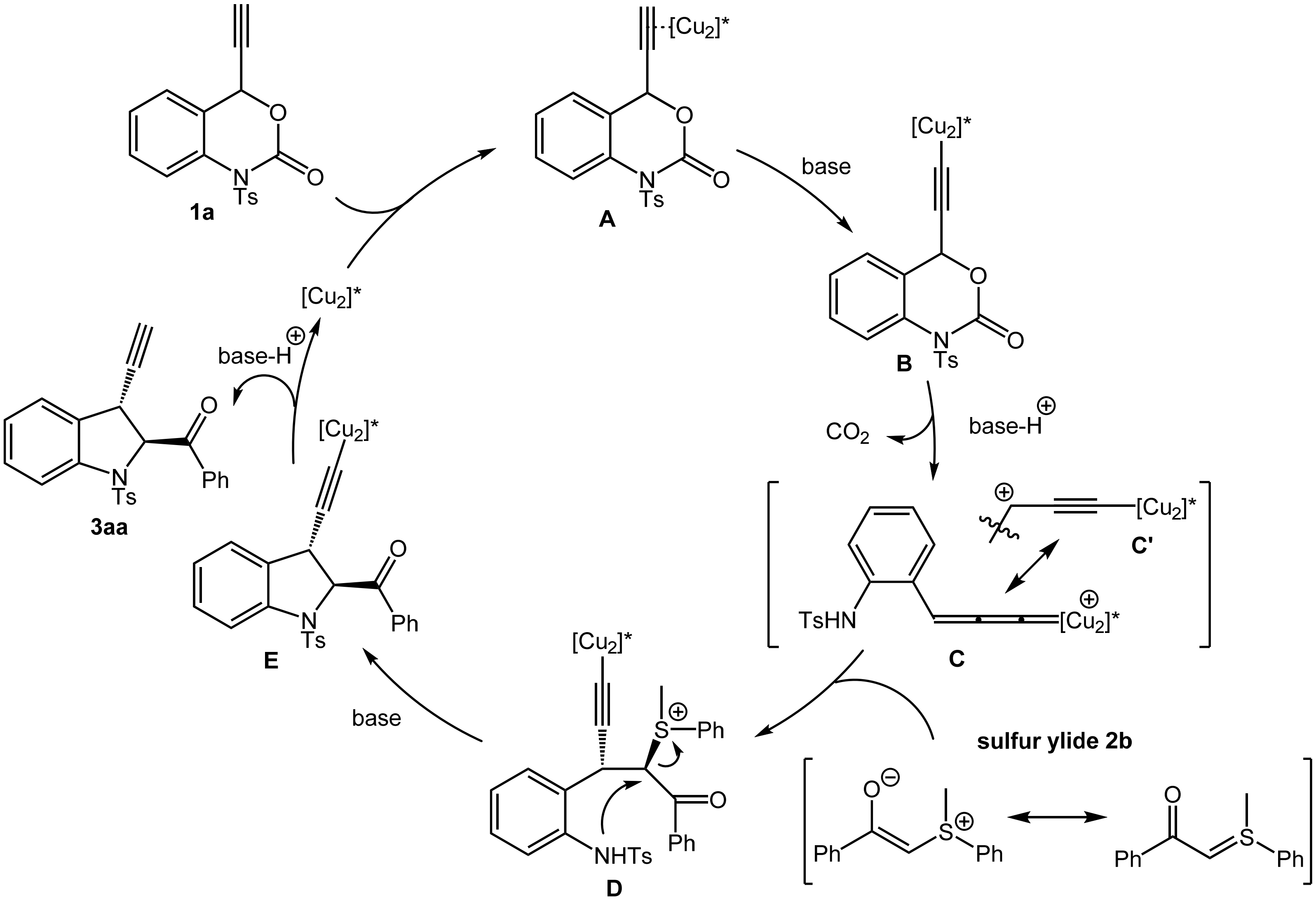
3ha: 82% yield, 88% ee

Substrate Scope



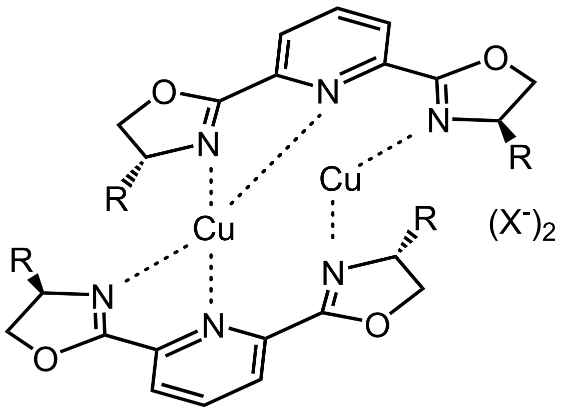
Ar = C_6H_5, 80% yield, 84% ee, >95:5 dr
Ar = 4-BrC_6H_4, 85% yield, 85% ee, >95:5 dr

Proposed Mechanism

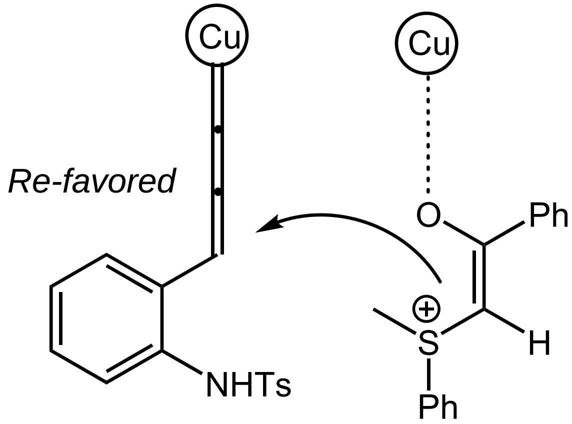


Possible Mode

Two Copper: Cooperative Catalysis



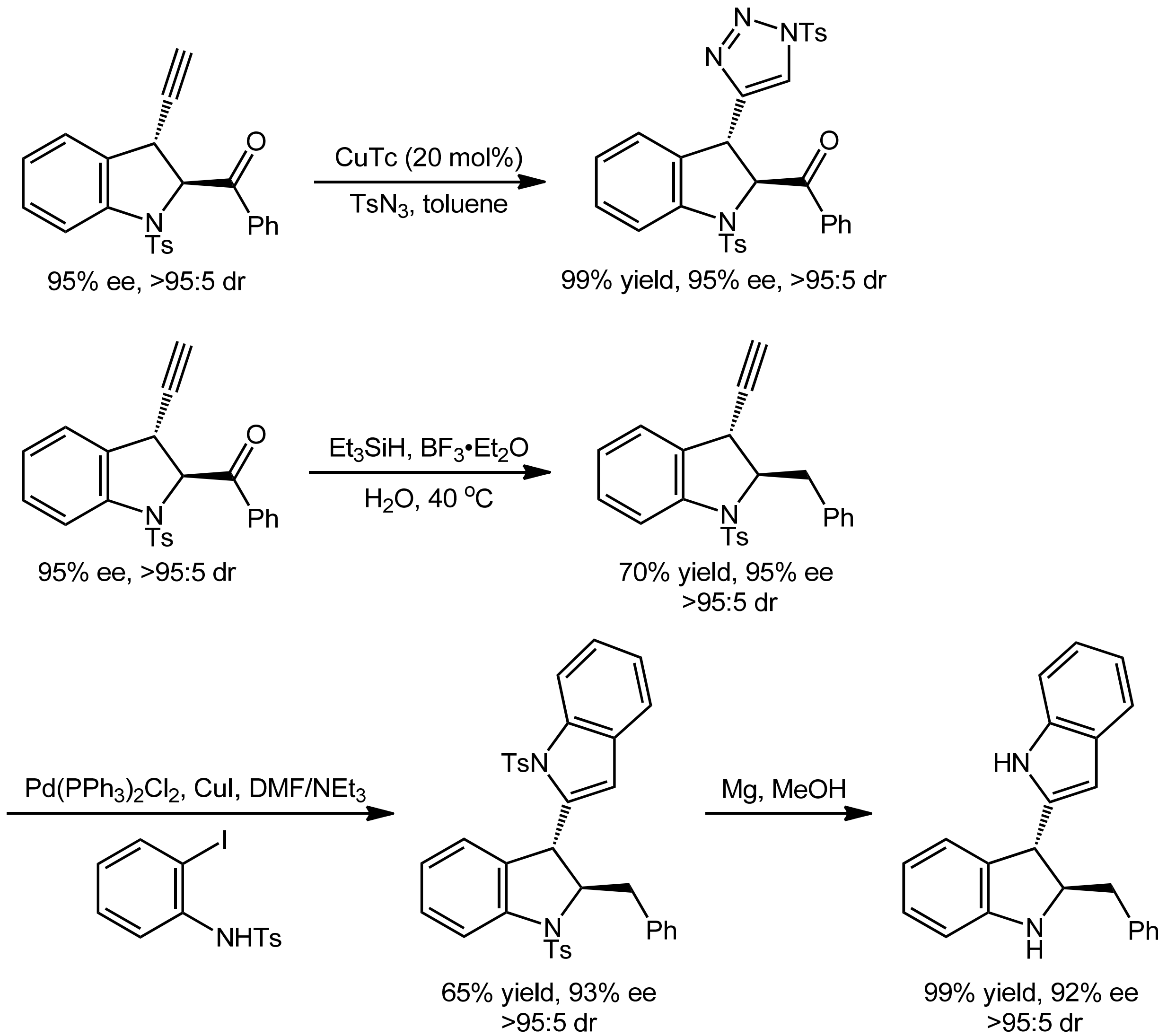
X = OTf or PF_6
results of Gamasa and Nishibayashi



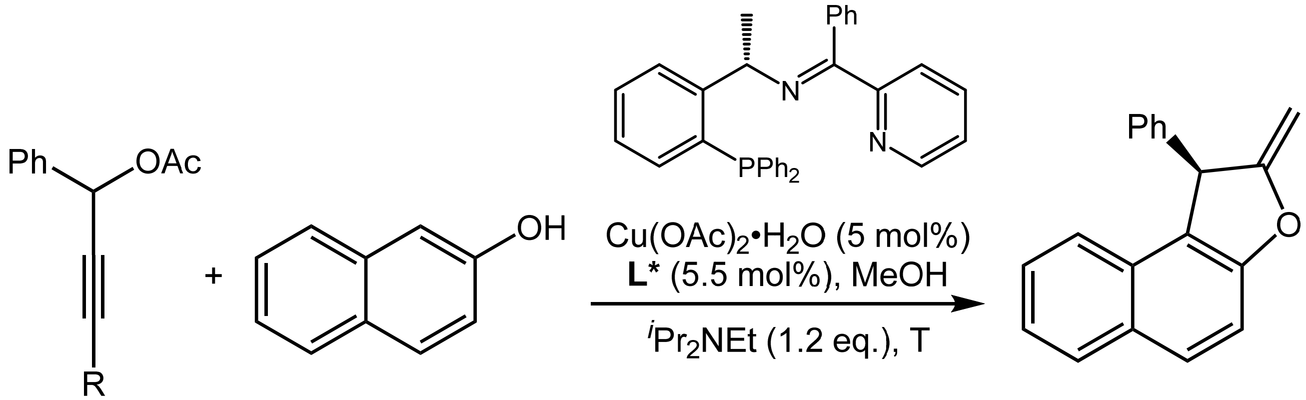
Maarseveen' model

Y. Nishibayashi *et al. J. Am. Chem. Soc.* **2015**, *137*, 2472.

Synthetic Transformation



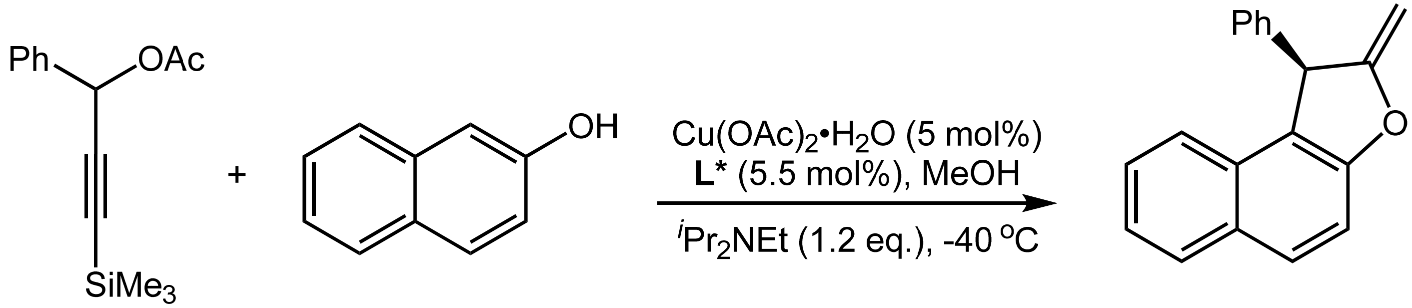
Copper Allenylidene

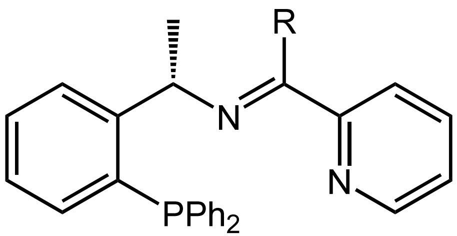


entry	R	T	yield (%)	ee (%)
1	H	RT	32	42
2	$SiMe_3$	RT	98	76
3	$SiEt_3$	RT	74	78
4	Si^tBuMe_2	RT	-	-
5	**$SiMe_3$**	**-40**	**86**	**90**

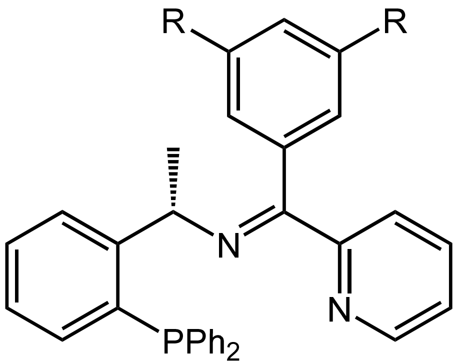
Hu, X.-P. *et al. Angew. Chem. Int. Ed*. **2016**, *55*, 5014.

Condition Optimization



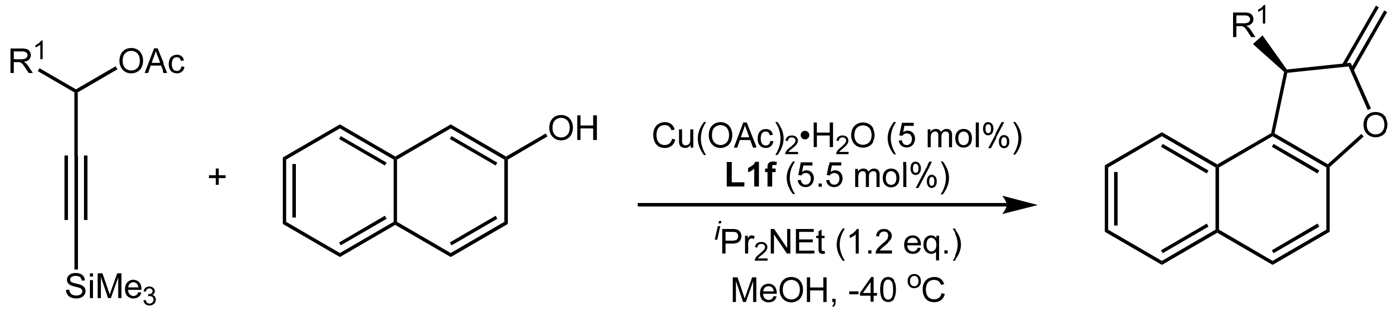


L1a: R = Ph 86% yield, 90% ee
L1b: R = H 77% yield, 74% ee
L1c: R = 1-naphthyl 71% yield, 89% ee



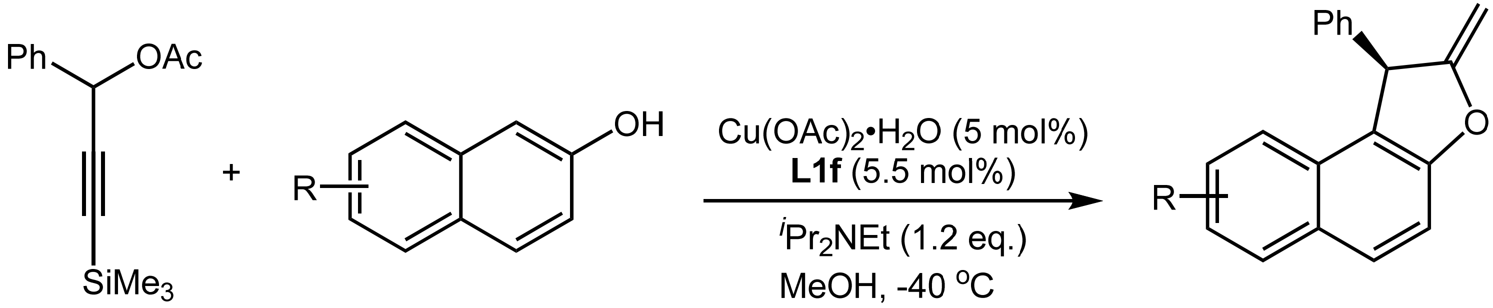
L1d: R = Me 87% yield, 89% ee
L1e: R = OMe 83% yield, 87% ee
L1f: R = CF_3 92% yield, 93% ee

Substrate Scope



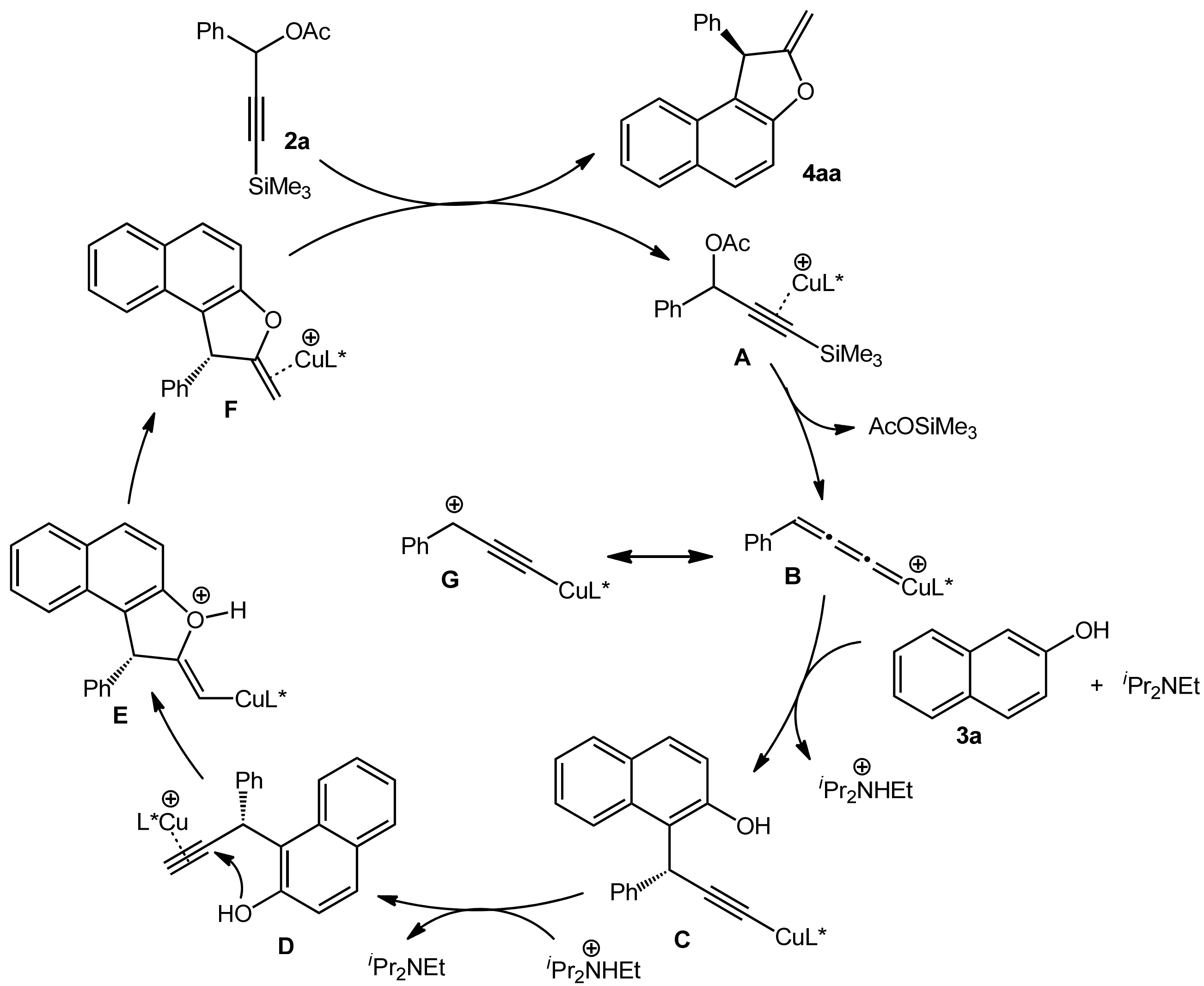
entry	R^1	yield (%)	ee (%)
1	Ph	92	93
2	4-MeOC_6H_4	88	93
3	4-MeC_6H_4	90	93
4	4-FC_6H_4	86	91
5	3-ClC_6H_4	89	94
6	2-ClC_6H_4	76	73
7	2-Furyl	98	92
8	Et	52	91
9	cyclohexyl	48	88

Substrate Scope

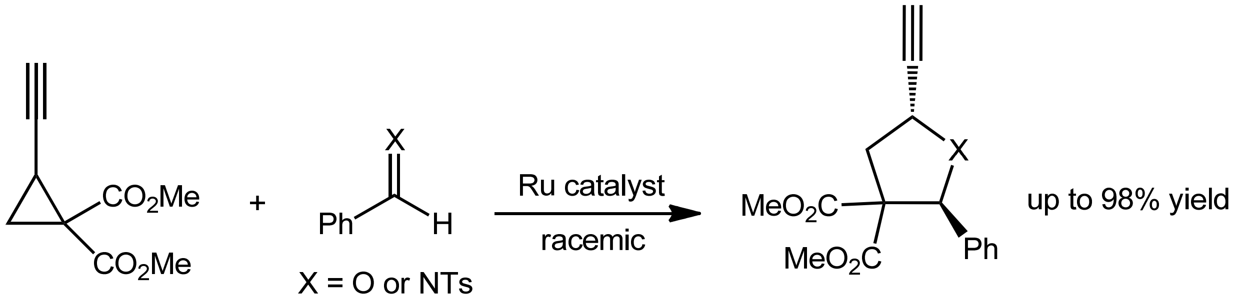


entry	R	yield (%)	ee (%)
1	H	92	93
2	3-OMe	91	92
3	6-OMe	82	93
4	7-OMe	83	96
5	7-Br	82	95
6	6-Br	83	93
7	3-OH	83	91
8	3-CONHPh	87	95
9	7-OH	85	88

Proposed Mechanism



Summary



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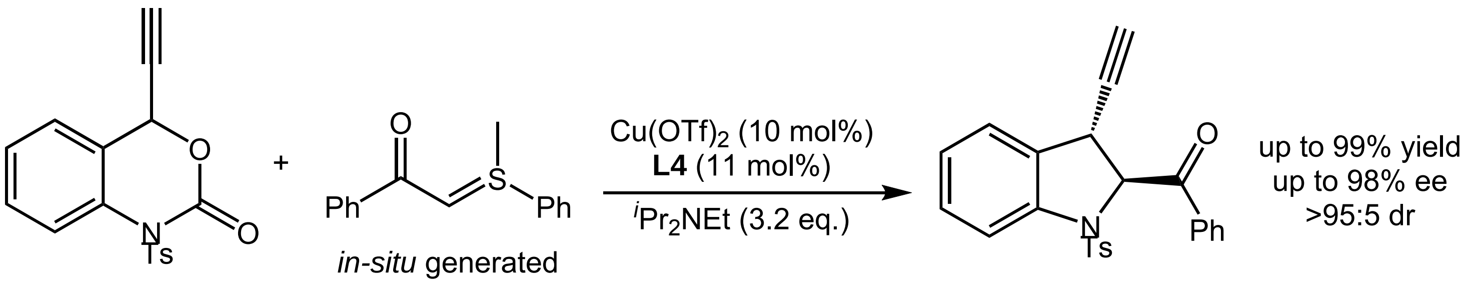

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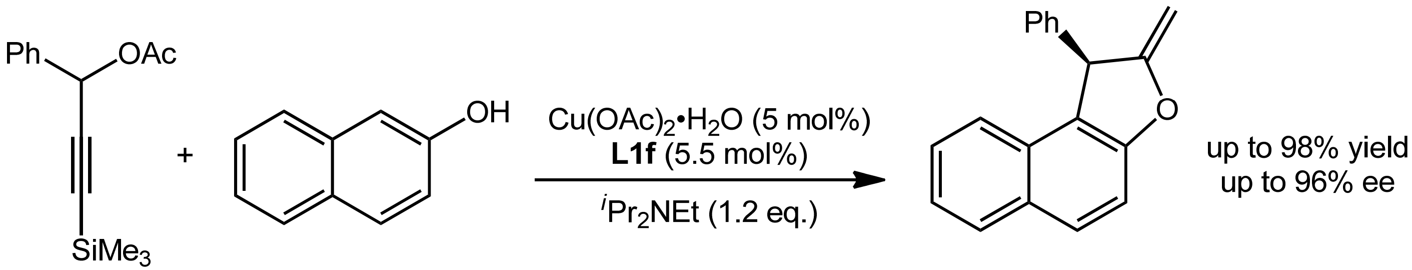

Hu, X.-P. *et al. Angew. Chem. Int. Ed*. **2016**, *55*, 5014.

Transition-metal-catalyzed cycloaddition reactions have been the focus of extensive study because of their fundamental importance in organic, medicinal, and materials chemistry. Many reactions proceed *via* metal-associated dipolar intermediates, which involve two independent reaction centers: one acts as an electrophile, and the other acts as a nucleophile. For example, various nucleophile-containing π-allyl−Pd complexes and metallo-enolcarbenes have been widely applied in transition-metalcatalyzed cycloadditions. To expand this cycloaddition chemistry, we applied asymmetric catalysis by earth abundant metals to achieve the first example of formal [4+1] cycloaddition of copper−allenylidene dipolar intermediates with high reaction yields and enantio- and diastereoselectivities.

In conclusion, we developed a copper catalyzed asymmetric formal [4+1] cycloaddition for the first time by trapping copper−allenylidene dipolar intermediates with sulfur ylides. Thus, a new approach to chiral indoline products and related cycloadducts with high reaction yields and stereoselectivities was explored. Mechanistic studies suggest that this reaction is a sequence process that involves decarboxylative propargylation/S_N2 reactions promoted by dinuclear copper complexes. Further studies with this type of metal-associated dipolar intermediate are currently in progress.