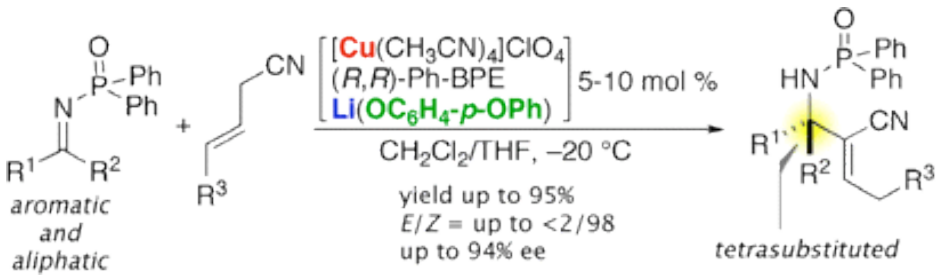
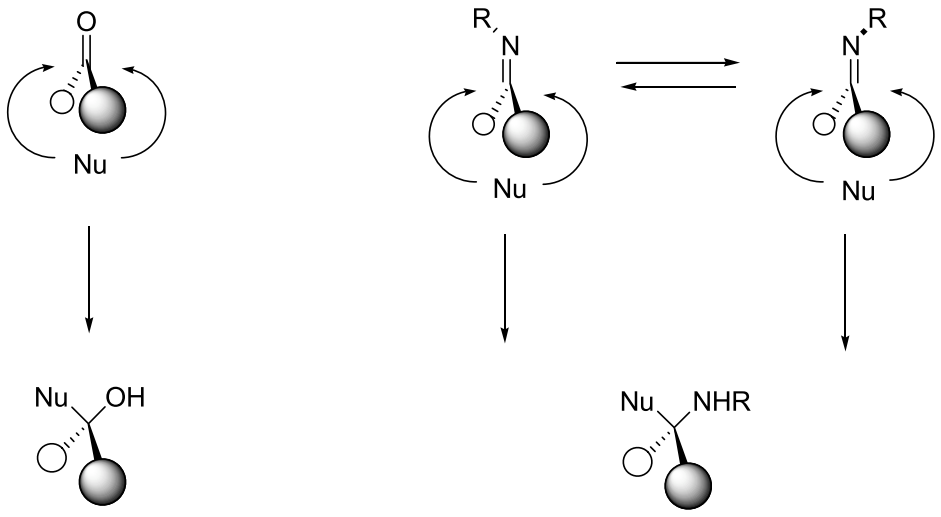
Direct Catalytic Asymmetric Addition of Allylic Cyanides to Ketoimines

Ryo Yazaki, Tatsuya Nitabaru, Naoya Kumagai, Masakatsu Shibasaki



J. Am. Chem. Soc. ASAP

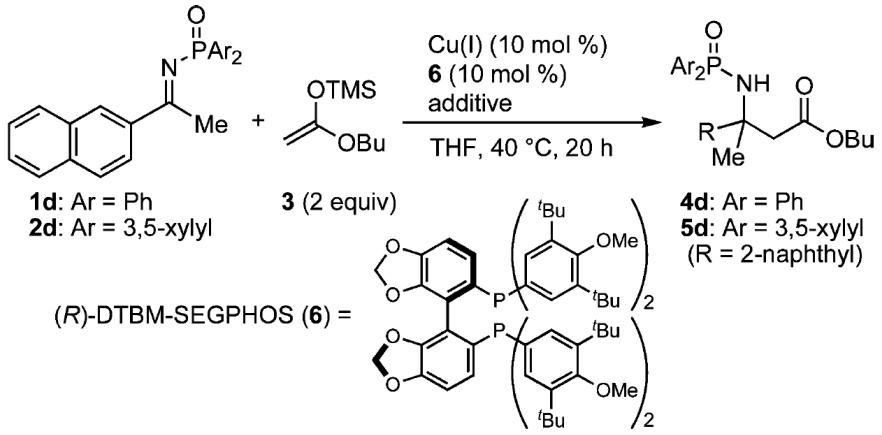
Asymmetric catalysis for the construction of quaternary carbon centers: nucleophilic addition on ketones vs. ketimines



- lower reactivity compared to ketones
- rapid isomerization to an enamine under basic conditions
- difficulty in differentiating the two substituents

J. Am. Chem. Soc. **2007**, *129*, 500.

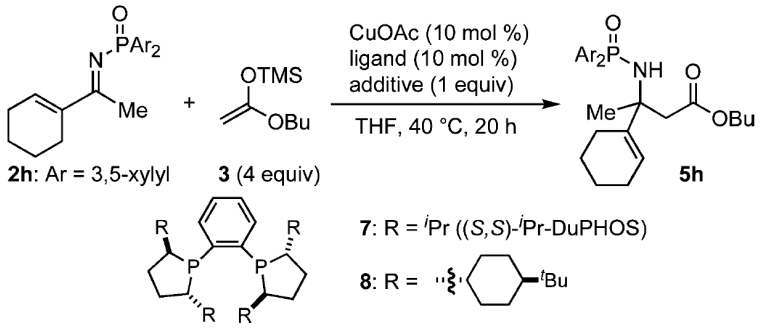
Catalytic Enantioselective Mannich-type Reactions of Ketoimines



entry	ketoimine	Cu source	additive[a]	yield[b] (%)	ee[c] (%)
1	**1d**	CuF[d]	$(EtO)_3SiF + PhBF_3K$	60	60
2	**1d**	CuOAc	$(EtO)_3SiF + PhBF_3K$	58	85
3	**1d**	CuOAc	$(EtO)_3SiF$	54	94
4	**1d**	CuOAc	$(MeO)_2SiF_2$	85	93
5	**1d**	CuOAc	$Me_2Si(OAc)_2$	68	78
6	**1d**	CuOAc	$EtSi(OAc)_3$	60	80
7	**1d**	CuOAc	$(EtO)_2Si(OAc)_2$	82	92
8	**2d**	CuOAc	$(EtO)_2Si(OAc)_2$	74	96

[a] In entries 1 and 2, 1 equiv of $(EtO)_3SiF$ and 10 mol % of $PhBF_3K$ were used. In other entries, 1 equiv of additive was used. [b] Isolated yield. [c] Determined by chiral HPLC. [d] $CuF \cdot 3PPh_3 \cdot 2EtOH$.

Table 2. Optimization of Catalytic Enantioselective Mannich Reaction to Aliphatic Ketoimine

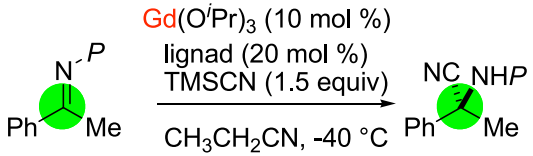


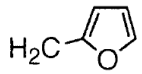
entry	ligand	additive	yield[a] (%)	ee[b] (%)
1	**6**	$(EtO)_2Si(OAc)_2$	29	87
2	**6**	$(EtO)_3SiF$	58	86
3	**7**	$(EtO)_3SiF$	90	75
4	**8**	$(EtO)_3SiF$	99	81

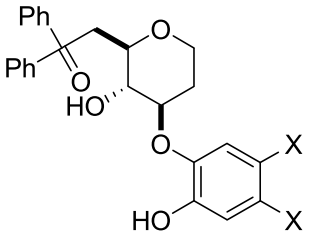
[a] Isolated yield. [b] Determined by chiral HPLC.

J. Am. Chem. Soc. **2007**, *129*, 500.

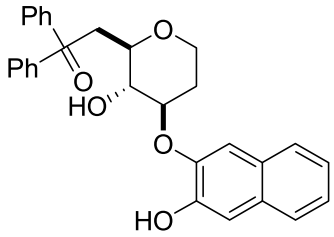
Catalytic Enantioselective Strecker Reaction of Ketoimines



entry	*P*	ligand	time (h)	conversion (%)[a]	ee (%)[b]
1[c,d]	CH_2Ph	**1**	24	95	35
2[c,d]		**1**	88	84	48
3[d]	$P(O)Ph_2$	**1**	16	100	72
4[e]	$P(O)Ph_2$	**1**	14	100	82
5[e]	$P(O)Ph_2$	**2**	8	100	85
6[e]	$P(O)Ph_2$	**3**	6	100	96



1: X = H
3: X = F



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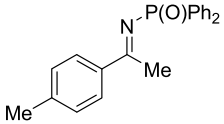
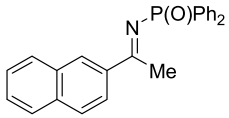
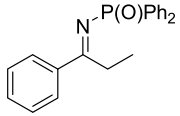


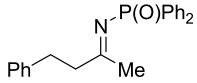
94% (95 % *ee*)



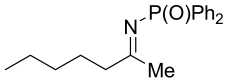
67% (94 % *ee*)



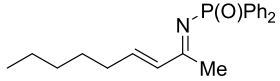
72% (85 % *ee*)



87% (89 % *ee*)



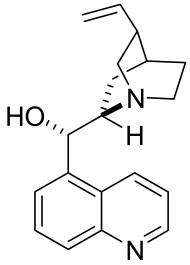
73% (72 % *ee*)



99% (88 % *ee*)

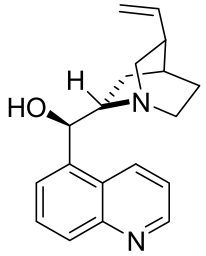
J. Am. Chem. Soc. **2003**, *125*, 5634.

Catalytic Asymmetric Strecker Reaction of Ketoimines: Asymmetric Activation of *tropos* 2,2'-Biphenol with Cinchonine



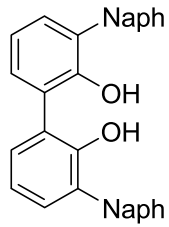
cinhonine

1



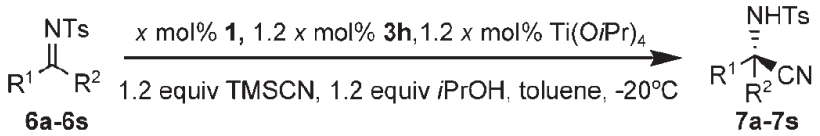
cinhonidine

2

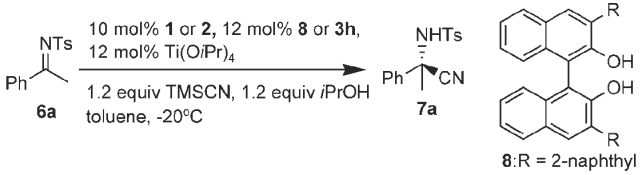


2,2'-biphenol

3



Entry	R^1	R^2	Product	*x*	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	Me	**7a**	5	8	>99	>99 (*S*)
2	4-FC_6H_4	Me	**7b**	5	4	90	98
3	4-ClC_6H_4	Me	**7c**	5	4	>99	>99 (*S*)
4	4-BrC_6H_4	Me	**7d**	5	8	>99	>99 (*S*)
5	4-MeC_6H_4	Me	**7e**	10	4	>99	>99 (*S*)
6	4-$MeOC_6H_4$	Me	**7f**	10	4	99	>99 (*S*)
7	3-ClC_6H_4	Me	**7g**	5	4	>99	>99
8	2-FC_6H_4	Me	**7h**	10	4	>99	90
9	2-naphthyl	Me	**7i**	5	22	90	>99 (*S*)
10	2-furyl	Me	**7j**	5	22	97	99

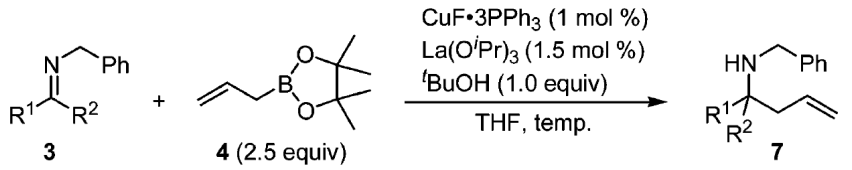


Entry	Activator	Diol	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1**	**3h**	3.5	>99	>99 (*S*)
2	none	(*S*)-**8**	8	–	–
3	**1**	(*S*)-**8**	3.5	>99	>99 (*S*)
4	**1**	(*R*)-**8**	3.5	25	71 (*S*)
5	**2**	(*R*)-**8**	8	95	98 (*R*)
6	**2**	(*S*)-**8**	8	49	68 (*R*)
7	**2**	**3h**	8	87	94 (*R*)

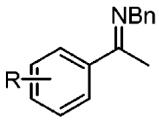
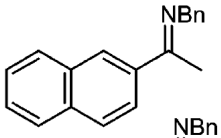
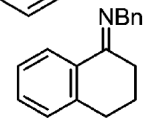
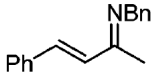
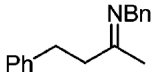
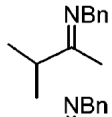
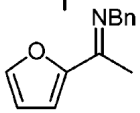
[a] Unless noted otherwise, reactions were carried out with imine (0.1 mmol), TMSCN (0.12 mmol), *i*PrOH (0.12 mmol), and toluene (0.5 mL) at −20°C. [b] Isolated yield. [c] Determined by HPLC.

Angew. Chem. Int. Ed. **2007**, *46*, 8468.

Catalytic Enantioselective Allylation of Ketoimines

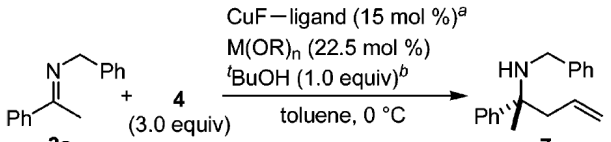


3 **4** (2.5 equiv) **7**

entry	substrate		temp. (°C)	time (h)	yield (%)[a]
1		**3a**: R = H	45	2	94
2		**3b**: R = 3-Me	45	1.5	88
3		**3c**: R = 3-OMe	45	1	94
4		**3d**: R = 3-F	45	1	92
5		**3e**: R = 4-OMe	45	5	93
6		**3f**: R = 4-Cl	45	1.5	96
7		**3g**	45	0.5	98
8[b]		**3h**	45	4	92
9		**3i**	rt	1	85
10		**3j**	rt	1	96
11		**3k**	rt	1	96
12		**3l**	45	1	94

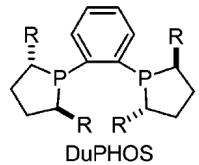
[a] Isolated yield. [b] 5 mol % of CuF•3PPh$_3$ and 7.5 mol % of La(O^{i}Pr)$_3$ were used.

Optimization of Catalytic Enantioselective Allylation of Ketoimine



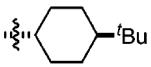
3a + **4** (3.0 equiv) **7a**

entry	ligand	M(OR)$_n$	time (h)	yield (%)[c]	ee (%)[d]
1	**8**	none	24	57	78
2	**8**	La(O^{i}Pr)$_3$	24	63-87[e]	17-80[e]
3	**8**	KO^{t}Bu	14	87	75
4	**8**	Al(O^{t}Bu)$_3$	22	28	43
5	**8**	LiO^{i}Pr	24	99	84
6	**9**	LiO^{i}Pr	2	89	89
7[f]	**9**	LiO^{i}Pr	0.5	92	89
8	**10**	LiO^{i}Pr	14	85	73


DuPHOS

8: (*R*,*R*)-^{i}Pr-DuPHOS (R = ^{i}Pr)

9: R = 

10: R = 

[a] Catalyst was prepared by reducing $CuF_2 \cdot 2H_2O$ with 2 equiv of chiral phosphine to Cu in situ. See Experimental Section for details. [b] ^{t}BuOH was slowly added over 2 h. [c] Isolated yield. [d] Determined by chiral HPLC. [e] Yield and enantioselectivity were not constant in each run. [f] 10 mol % of chiral Cu catalyst and 30 mol % of LiO^{i}Pr were used.

J. Am. Chem. Soc. **2006**, *128*, 7687.

Catalytic Enantioselective Allylation of Ketoimine: Origin of Rate Acceleration by LiO*i*Pr

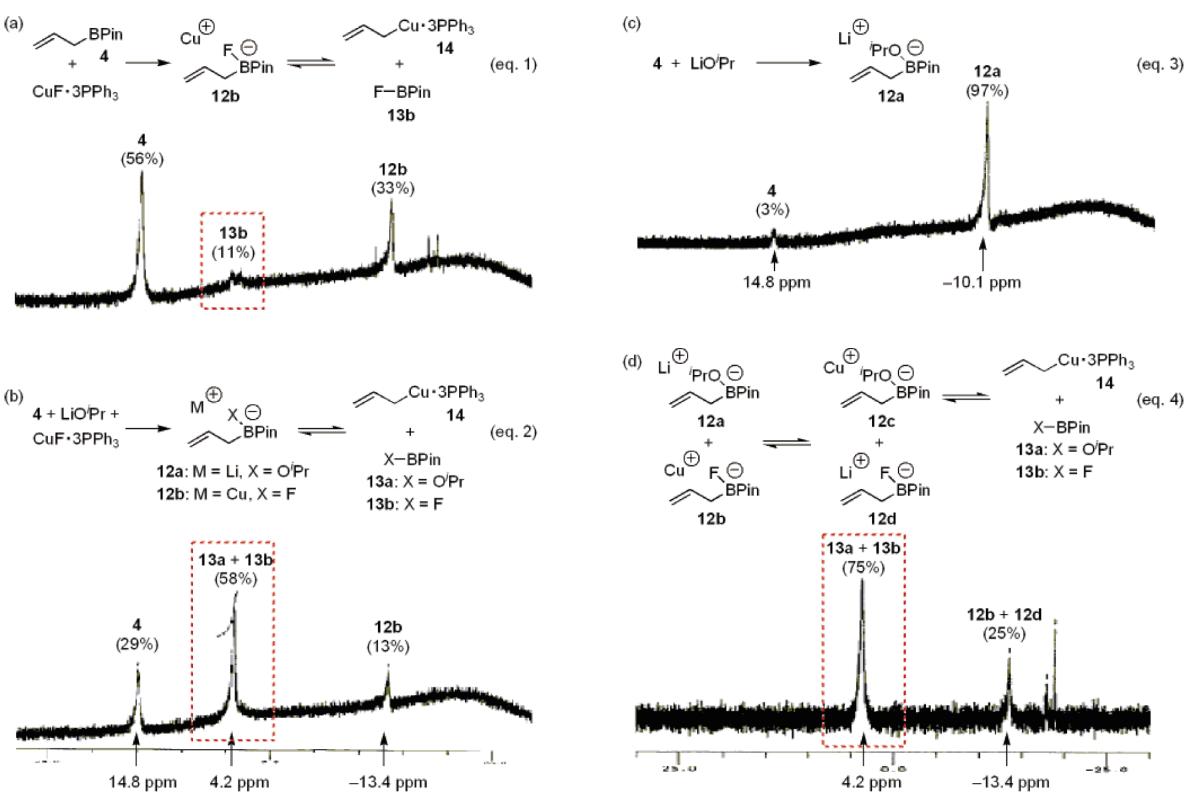
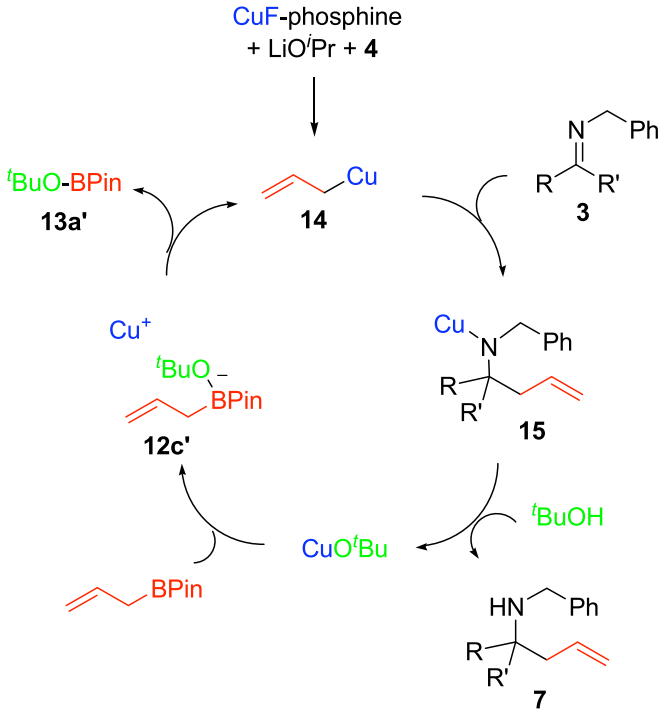


Figure 1. ^{11}B NMR studies for the rate acceleration mechanism of LiO^{i}Pr. (a) CuF·3PPh$_3$ + allylboronate **4** (1:3). (b) CuF·3PPh$_3$ + **4** + LiO^{i}Pr (1:3:1.5). (c) LiO^{i}Pr + **4** (1:1). (d) {LiO^{i}Pr + **4** (1:1)} + {CuF·3PPh$_3$ + **4** (1:1)} (1:1). The intensity of **13a** and **13b** (the peak in dashed squares) corresponds to the concentration of the active allylcopper.



J. Am. Chem. Soc. **2006**, *128*, 7687.

Catalytic Asymmetric Alkylations of Ketoimines

Abstract Full: HTML / PDF (940K) Supporting Info

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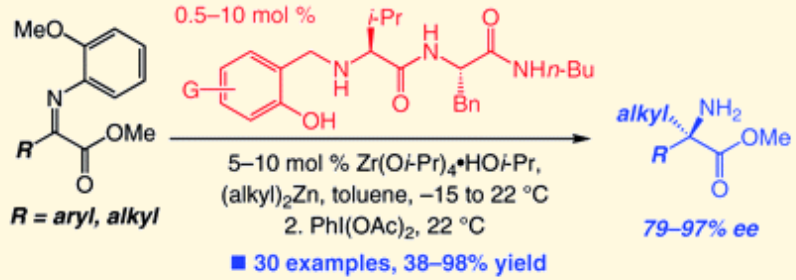
Catalytic Asymmetric Alkylations of Ketoimines. Enantioselective Synthesis of *N*-Substituted Quaternary Carbon Stereogenic Centers by Zr-Catalyzed Additions of Dialkylzinc Reagents to Aryl-, Alkyl-, and Trifluoroalkyl-Substituted Ketoimines

Peng Fu, Marc L. Snapper, and Amir H. Hoveyda

pp 5530 - 5541; **(Article)** DOI: 10.1021/ja8001343



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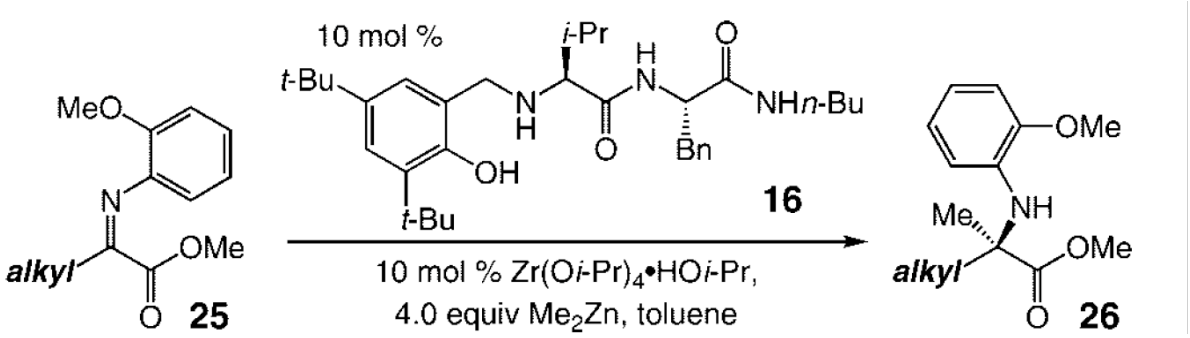
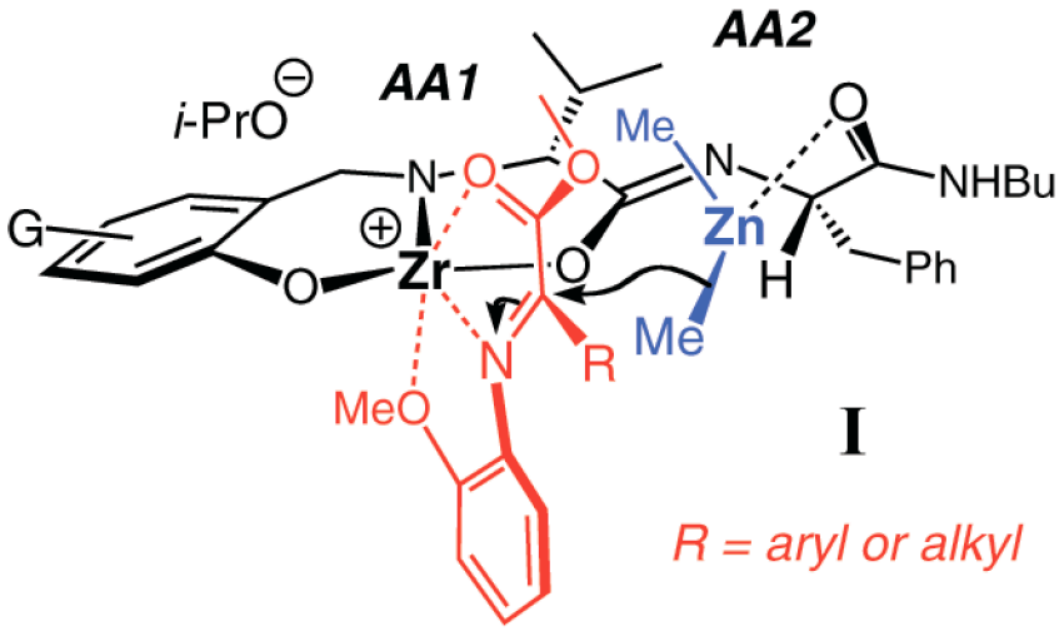
Henk H. Dam, Hans Beijleveld, David N. Reinhoudt, and Willem Verboom

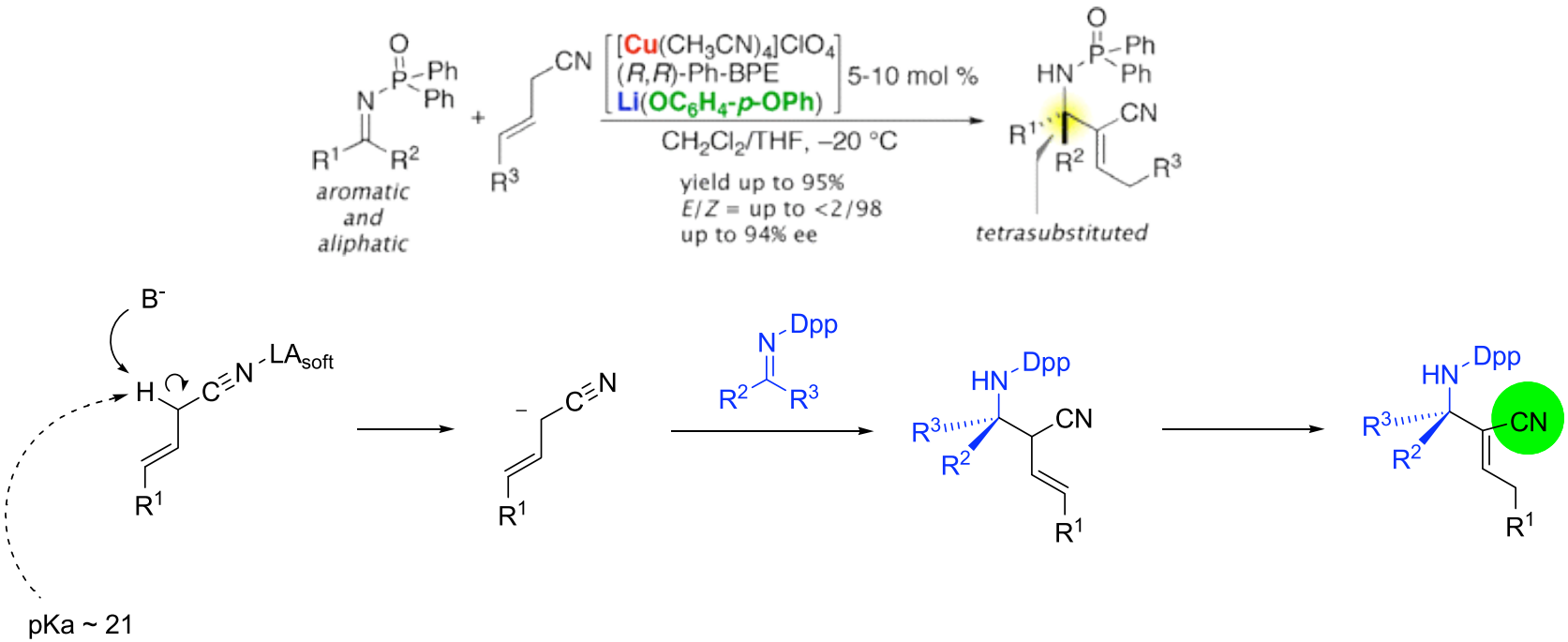
Catalytic Asymmetric Alkylations of Ketoimines





J. Am. Chem. Soc. **2008**, *130*, 5530.

Title Paper: Catalytic Asymmetric Addition of Allylic Cyanides to Ketoimines



- nitriles are readily available and stable enough
- unique topology poses minimal steric bias
- nitriles can be viewed as a masked carboxylic acids or amine

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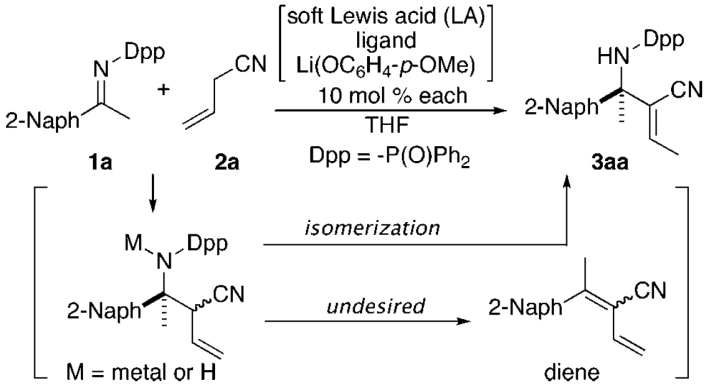
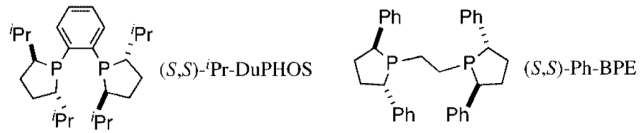
Title Paper: Initial Screening



entry	LA	ligand	temp. (°C)	time (h)	yield[b] (%)	ee (%)
1	CuOAc	(*S*,*S*)-^{i}Pr-DuPHOS	0	16	59[c]	33
2	$[Cu(CH_3CN)_4]PF_6$	(*S*,*S*)-^{i}Pr-DuPHOS	0	16	83[c]	37
3	$[Pd(CH_3CN)_4](BF_4)_2$	(*S*,*S*)-^{i}Pr-DuPHOS	0-rt	24	<5	—
4	$[Ag(CH_3CN)_4]BF_4$	(*S*,*S*)-^{i}Pr-DuPHOS	0-rt	24	0	—
5	$[Cu(CH_3CN)_4]PF_6$	(*S*,*S*)-^{i}Pr-DuPHOS	–20	16	67	65
6[d]	$[Cu(CH_3CN)_4]ClO_4$	(*S*,*S*)-^{i}Pr-DuPHOS	–20	16	95	53
7[d]	$[Cu(CH_3CN)_4]ClO_4$	(*S*,*S*)-Ph-BPE	–20	16	95	86
8[d,e]	$[Cu(CH_3CN)_4]ClO_4$	(*S*,*S*)-Ph-BPE	–20	12	50	73
9[d,f]	$[Cu(CH_3CN)_4]ClO_4$	(*S*,*S*)-Ph-BPE	–20	12	<5	84



[a] **1a/2a** = 0.2 mmol/2.0 mmol. [b] Determined by ^{1}H NMR analysis with Bn_2O as an internal standard. [c] The formation of diene was observed. [d] Solvent was CH_2Cl_2/THF = 2/1. [e] $Na(OC_6H_4$-*p*-OMe) was used instead of $Li(OC_6H_4$-*p*-OMe). [f] $K(OC_6H_4$-*p*-OMe) was used instead of $Li(OC_6H_4$-*p*-OMe).

- copper acetate promoted α-addition sluggishly and isomerization occurred rapidly with good geometric control
- cationic Pd(II) and Ag(I) complex failed
- cationic Cu(I) complex enhances catalytic activity ($[Cu(CH_3CN)_4]ClO_4$ is the best Cu source)
- the use of Ph-BPE and DCM/THF solvent improves enantioselectivity
- the use of Na or K aryloxide results in inferior conversion (bimetallic system stability)

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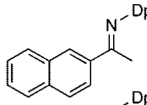
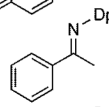
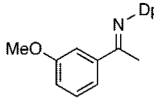
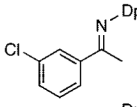
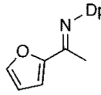
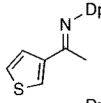
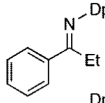
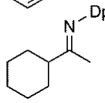
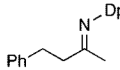
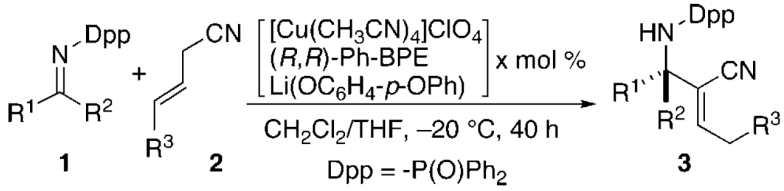
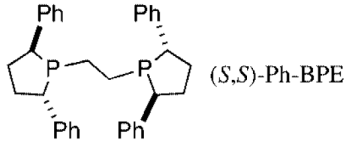
Title Paper: Scope of the Reaction

entry	ketoimine	allylic cyanide	x	product	yield[b] (%)	*E*/*Z*[c]	ee (%)
1[d]	 **1a**	 **2a**	10	**3aa**	91	7/93	90[i]
2	 **1b**	**2a**	10	**3ba**	74	9/91	91
3	 **1c**	**2a**	10	**3ca**	95	11/89	89
4	**1c**	**2a**	5	**3ca**	88	12/88	83
5[e]	**1c**	**2a**	10	**3ca**	71	10/90	94
6[d]	 **1d**	**2a**	10	**3da**	84	5/95	77[i]
7	 **1e**	**2a**	10	**3ea**	78	6/94	90
8	 **1f**	**2a**	10	**3fa**	83	3/97	88
9	 **1g**	**2a**	10	**3ga**	63	8/92	71
10[f]	 **1h**	**2a**	10	**3ha**	76	<2/98	92
11[f]	 **1i**	**2a**	10	**3ia**	80	4/96	89
12[g]	**1c**	 **2b**	10	**3cb**	62[h]	<2/98	90





[a] **1/2** = 0.2 mmol/2.0 mmol, CH_2Cl_2/THF = 2/1. [b] Isolated yield of *E* and *Z* geometrical isomers. [c] Determined by ^1H NMR analysis of the crude mixture. [d] (*S*,*S*)-Ph-BPE was used. [e] 3 equiv (0.6 mmol) of **2a** were used. [f] The reaction was conducted at 0.5 M in THF. $Li(OC_6H_4$-*p*-OMe) was used instead of $Li(OC_6H_4$-*p*-OPh). [g] Reaction time was 60 h. [h] Isolated yield after two steps (α-addition/isomerization by DBU). [i] Opposite absolute configuration.

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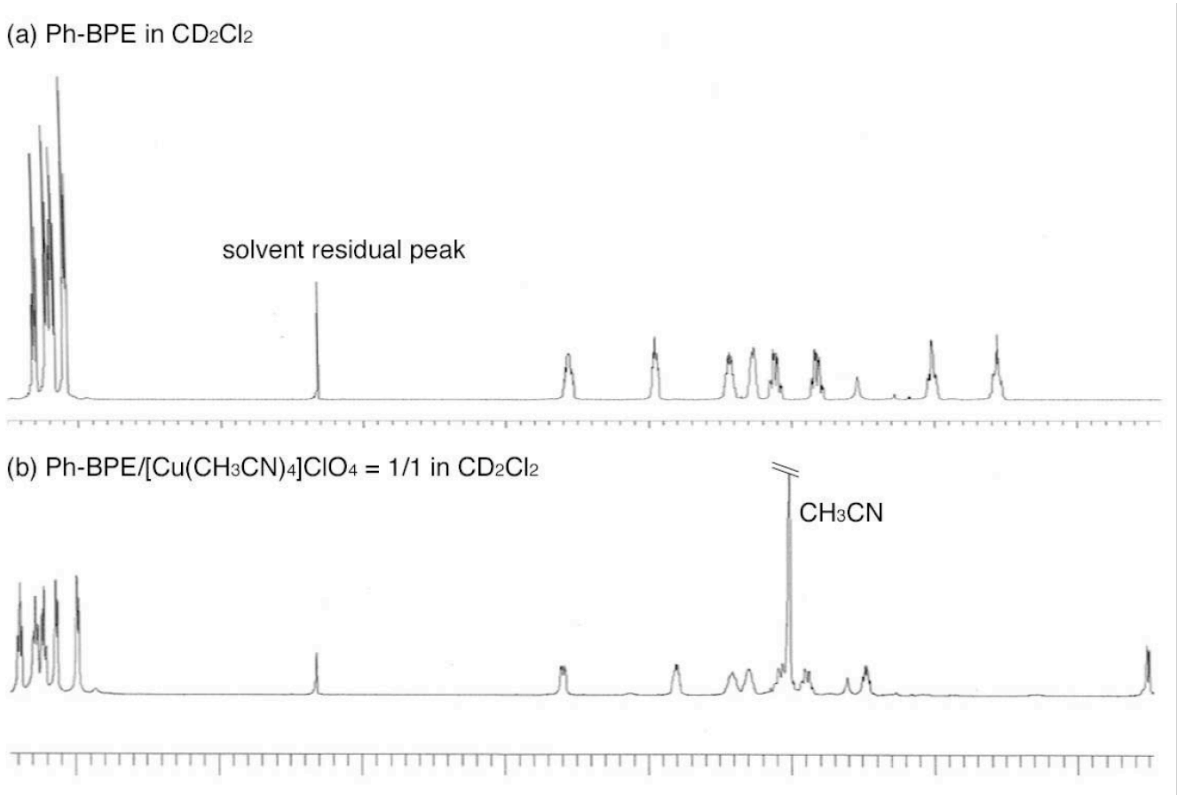
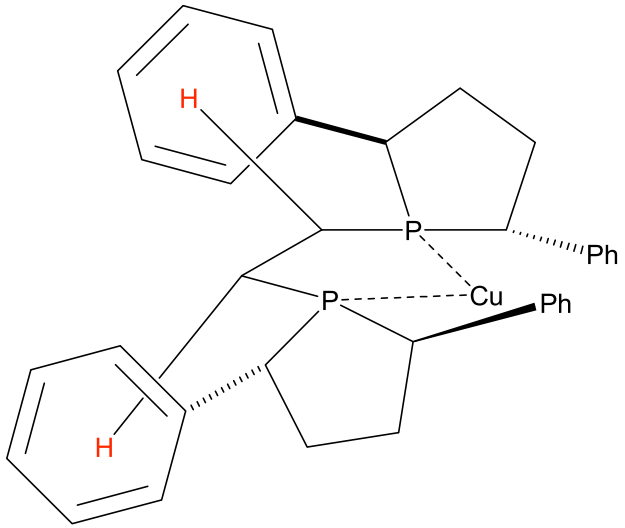
Title Paper: Control Experiments





- 1:1 complex of Ph-BPE/$[Cu(CH_3CN)_4]ClO_4$ is formed
- upon the addition of LiOAr, 1:1 complex Ph-BPE/CuOAr and $LiClO_4$ are formed

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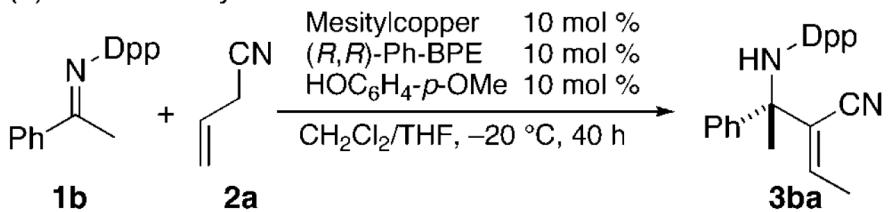
Title Paper: Control Experiments

(a) Li-free catalyst



1b **2a** **3ba**

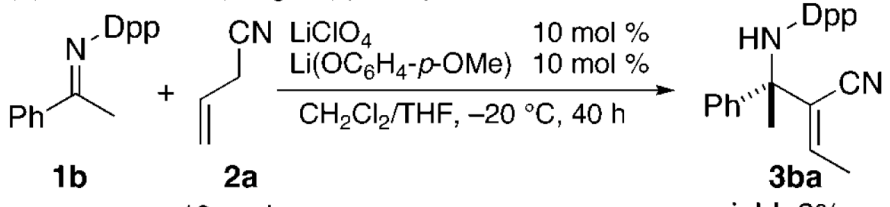
10 equiv. yield: <5%, 88% ee

(b) Li-free catalyst + $LiClO_4$

1b **2a** **3ba**

10 equiv. yield: 78%, 83% ee

(c) Without $[Cu(CH_3CN)_4]ClO_4$



1b **2a** **3ba**

10 equiv. yield: 8%

- Li-free conditions provided trace amounts of product
- *in situ* generated $LiClO_4$ is essential to drive the reaction
- Lack of $[Cu(CH_3CN)_4]ClO_4$ provided small amount of product: soft Cu was required to promote the reaction

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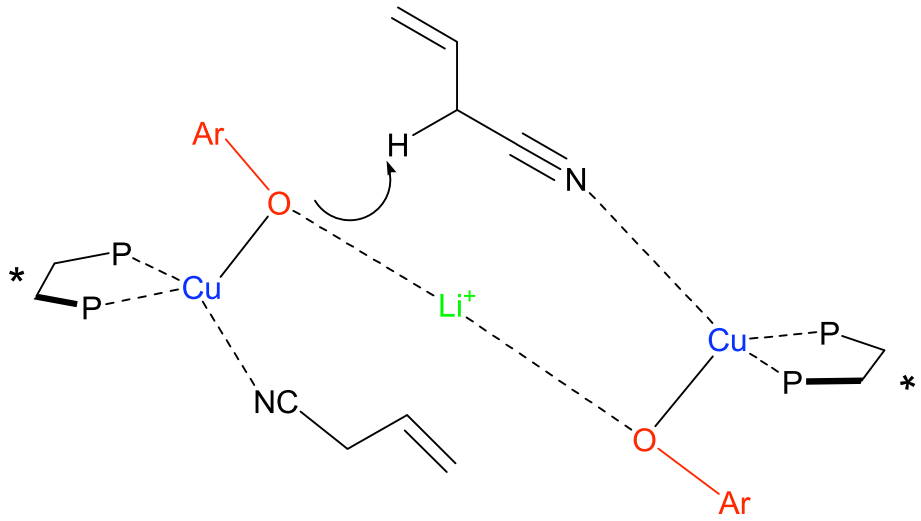
Title Paper: Mechanistic Proposal



- 2 Ph-BPE/CuOAr could work together to deprotonate allyl nitrile
- Li^+ could be beneficial for the association of two Ph-BPE/CuOAr complexes via a hard-hard Li-O interaction
- more reactive N-Dpp aldimine in the absence of $LiClO_4$ provided only 10% yield of the product, so $LiClO_4$ was important in deprotonation step

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Conclusions

- Direct catalytic asymmetric addition of allylic nitriles to ketoimines was developed
- In this reaction, CuOAr/Ph-BPE work cooperatively with $LiClO_4$
- This methodology enables the formation of α,β-unsaturated nitriles with a stereogenic tetrasubstituted carbon atom
- The reaction conditions tolerate both aryl-alkyl and alkyl-alkyl ketoimines with no loss in *E/Z* and enantioselectivity
- More detailed mechanistic studies are ongoing