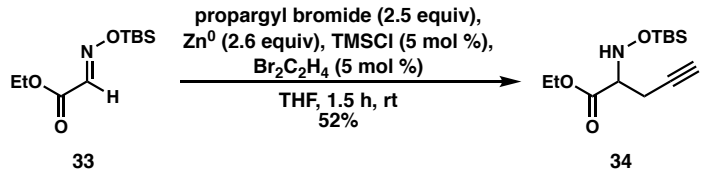
Chapter 2

Efforts in Our Laboratory[‡]

2.1 LEWIS ACID-CATALYZED ASYMMETRIC ADDITION TO OXIME ESTERS

Initial studies (performed by Nicholas Cowper) showed that the racemic propargylation could be carried out using propargyl bromide, and 2.6 equivalents of Zn^0 to achieve 52% yield. Initially the ethyl ester (**33**) was used (Scheme 2.1), but this was replaced by the phenethyl ester (**35**) in order to have a UV-active moiety for ease of detection.

Scheme 2.1. *Racemic propargylation of ethyl glyoxylate oxime.*



33 **34**

An initial ligand screen showed that most ligands gave almost no enantioselectivity in this reaction (Figure 2.1). The yields were reduced from greater than 50% to 6% and lower. The highest ee attained was from ^{t}BuCNBox (**L18**), which gave the desired product in 2% yield and 15% ee (Figure 2.1).

[‡] Work conducted in collaboration with Nicholas Cowper.

Figure 2.1. *Survey of ligands for zinc nucleophile propargylation.*

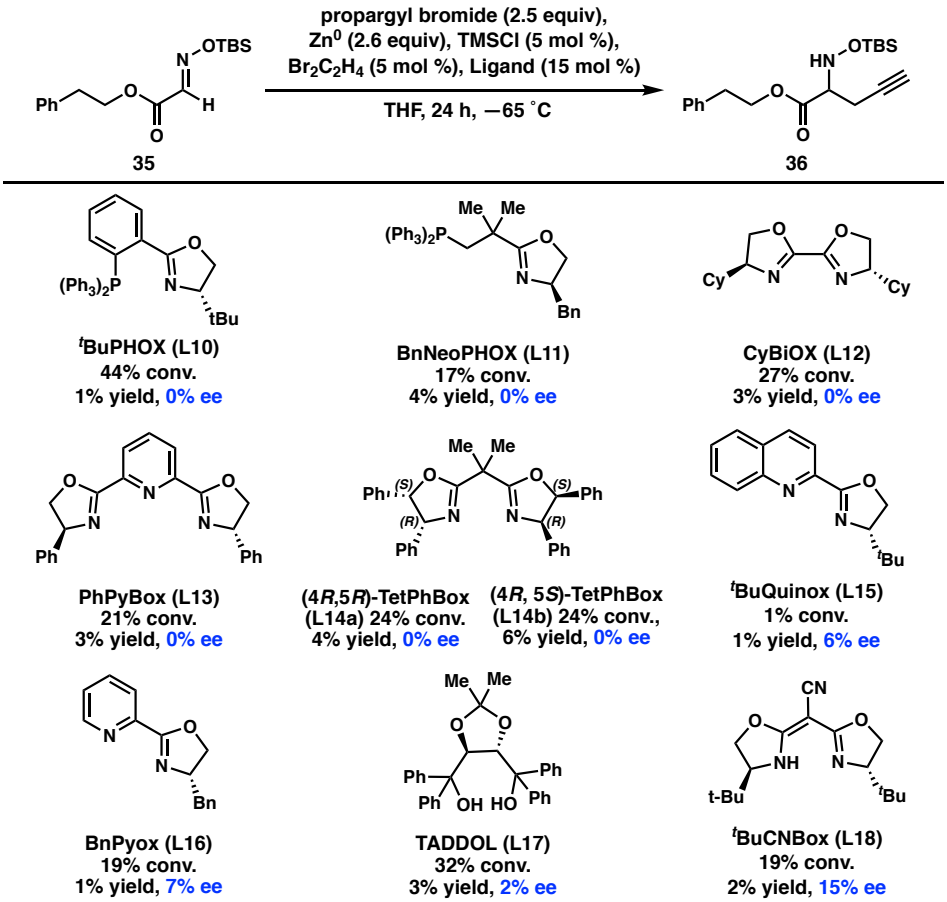
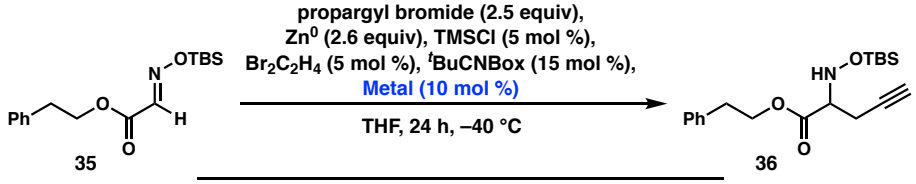


Table 2.1. *Effect of Lewis acids on the nucleophilic addition.*

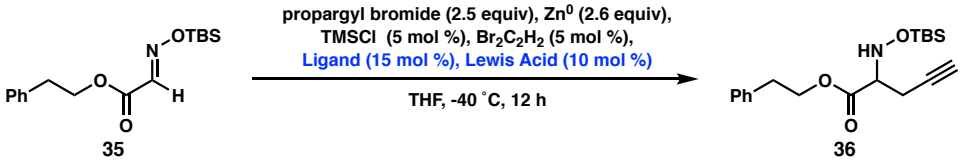


Entry	Metal	Conversion (%)	Yield (%)	ee (%)
1	none	30	10	0
2	$Yb(OTf)_3$	48	40	0
3	$In(OTf)_3$	59	42	1
4	$Sc(OTf)_3$	70	70	0
5	$NiCl_2$·dme	49	47	1
6	$(CuOTf)_2$·PhMe	60	48	0
7	$Cu(OTf)_2$	53	49	2
8	$MgBr_2$	70	57	0

Further investigation using **L18** and various Lewis acids showed that $Sc(OTf)_3$ gave the product (**36**) in 70% yield but with no enantioselectivity (Table 2.1, entry 4). This was also the most efficient reaction as all starting material consumed was converted to product. $In(OTf)_3$, NiCl•dme, and $Cu(OTf)_2$ all gave 1-2% ee but at far lower yields (Table 2.1, entries 3, 5, and 7). All other Lewis acids showed no enantiomeric excess.

At this point, we began investigating the effects of different ligands and Lewis acids on the reaction (Table 2.2). Three ligands (PhBOX, **L19**; ^{i}PrPyOx, **L20**; and ^{i}PrQuinox, **L21**; see Appendix 2) were investigated. PhBOX gave no enantioselectivity with any of the metals observed (Table 2.2, entries 1-7), although $MgBr_2$ did increase the yield to 77% (entry 5). **L20** showed lower yields and a similar lack of enantioselectivity (Table 2.2, entries 8-14). Although $Cu(OTf)_2$ gave 2% ee, the yield in this case was only 16% (entry 11). **L21** also showed considerably lower yields than the original reaction or the reaction with PhBOX, but all reactions had 1-3% ee (Table 2.2, entries 15-21).

Table 2.2. *Effects of Lewis Acids in conjunction with different ligands on the propargylation.*



	PhBox (L19)				^{i}PrPyOx (L20)				^{i}PrQuinox (L21)			
Metal	**Entry**	**Conv. (%)**	**Yield (%)**	**ee (%)**	**Entry**	**Conv (%)**	**Yield (%)**	**ee (%)**	**Entry**	**Conv (%)**	**Yield (%)**	**ee (%)**
$Yb(OTf)_3$	1	72	64	0	8	59	53	0	15	51	29	2
$In(OTf)_3$	2	47	47	0	9	53	33	0	16	89	6	1
$Sc(OTf)_3$	3	74	71	0	10	69	33	0	17	56	37	3
$Cu(OTf)_2$	4	73	72	0	11	84	16	2	18	53	33	1
$MgBr_2$	5	77	77	0	12	71	45	0	19	55	36	1
$NiCl_2$•dme	6	50	49	0	13	44	22	0	20	65	9	2
$(CuOTf)_2$•PhMe	7	74	18	0	14	62	34	0	21	46	46	1

A broad screen of 40 phosphoramidite and bis-phosphine ligands in conjunction with $(CuOTf)_2$•PhMe was carried out resulting in 0-3% ee. A second screen of eight N/O bidentate ligands with $Sc(OTf)_3$ resulted in 0-8% ee.

2.2 COPPER-CATALYZED ASYMMETRIC ADDITION TO OXIME ESTERS

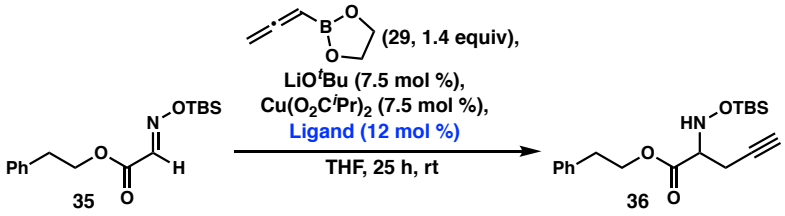
Due to the lack of improvement in the reaction, in particular the low enantioselectivity, we began searching for other reaction conditions. Inspired by Schaus' work on the enantionselective propargylation of ketones using 1,3-dioxaborolanes[21-22] and Fandrick's copper-catalyzed enantioselective propargylations of ketones[23-24], we began investigating 2-allenyl-1,3,2-dioxaborolane (**29**) as a nucleophile and subsequently copper as a catalyst.

We first attempted to replicate Schaus' microwave conditions (without copper) using neat **29** and a selection of diol catalysts, with and without alcohol additives. Yields were extremely low for all catalysts. Although 66% ee could be achieved using 15 mol % 3,3'-Br-BINOL and 3.3 equiv ^{t}BuOH, the yield was only 3%. Similarly, 3,3'-Br_2-BINOL and 4.5 equiv ^{i}PrOH gave 5% yield and 22% ee.

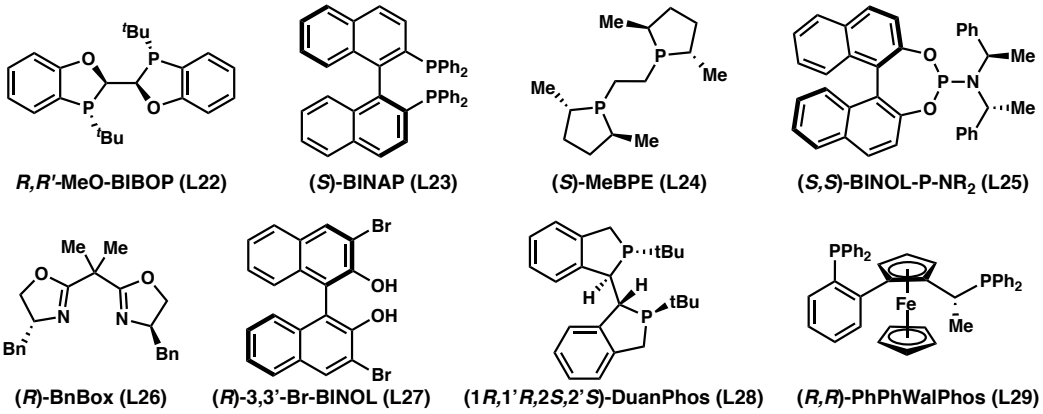
From there, we began to explore copper catalysis. We maintained use of Schaus' allenyl dioxaborolane (**29**) and began investigating Fandrick's conditions with lithium *tert*-butoxide and copper isobutyrate. An initial ligand screen under these conditions showed that Fandrick's optimal ligand,[23] MeO-BIBOP (**L22**) gave no product with our system (Table 2.3, entry 1). Fandrick's later optimal ligand, BINAP (**L23**) gave a 2% yield and 63% ee (entry 2). Further investigation showed MeBPE (**L24**) gave 40% yield but only 3% ee (entry 3). Aside from **L27**, which only gave trace yield, phosphoramidite

L25 gave the next highest ee (26%) to **L23** and 12% yield. Other ligands investigated gave low yields and enantioselectivities.

Table 2.3. *Effects of ligands on the copper(II) isobutyrate-catalyzed propargylation.*

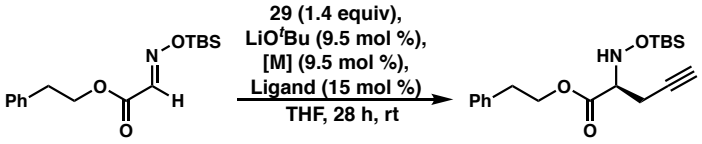


Entry	Ligand	Conversion (%)	Yield (%)	ee (%)
1	MeO-BIBOP	<10	—	—
2	BINAP	13	2	63
3	MeBPE	74	40	3
4	BINOL-P-NR$_2$	53	12	26
5	BnBox	46	26	7
6	3,3'-Br$_2$-BINOL	37	trace	32
7	DuanPhos	37	5	4
8	PhPhWalPhos	27	4	6

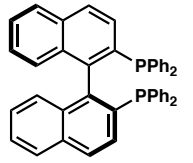


From there, copper sources were screened with both **L23** and **L25** (Table 2.4). It was determined that [Cu(MeCN)$_4$]BF$_4$ gave a low yield and high ee with **L23** as a ligand (Table 2.4, entry 5) and moderate yield and low-moderate ee with **L25** (entry 6). Cu(acac)$_2$ provided slightly higher yield with **L23** and similar results as [Cu(MeCN)$_4$]BF$_4$ with **L25** (entries 11-12).

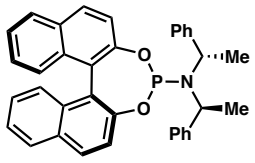
Table 2.4. *Survey of copper sources for the asymmetric propargylation.*[‡]



Entry	[M]	Ligand	Conversion (%)	Yield (%)	ee (%)
1	$(CuOTf)_2$·PhMe	A	23	6	70
2	$(CuOTf)_2$·PhMe	B	65	40	34
3	CuBr·DMS	A	35	9	0
4	CuBr·DMS	B	50	11	28
5	$[Cu(MeCN)_4]BF_4$	A	41	12	72
6	$[Cu(MeCN)_4]BF_4$	B	80	51	30
7	$[Cu(MeCN)_4]PF_6$	A	43	7	65
8	$[Cu(MeCN)_4]PF_6$	B	66	39	30
9	$[Cu(MeCN)_4]ClO_4$	A	47	11	70
10	$[Cu(MeCN)_4]ClO_4$	B	89	47	30
11	$Cu(acac)_2$	A	51	28	66
12	$Cu(acac)_2$	B	92	47	31



A: (*S*)-BINAP (L23)



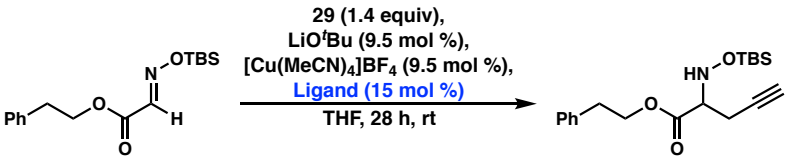
B: (*S,S*)-BINOL-P-N(CH(Me)Ph)$_2$ (L25)

With $[Cu(MeCN)_4]BF_4$ in hand as a copper source, a broad ligand screen was carried out across several classes of ligands. Based on availability in our ligand library, a total of 50 ligands were screened (8 BINAP ligands, 29 phosphoramidites, and 13 biaryl bisphosphines). Among BINAP ligands, (*R*)-DM-BINAP gave a low yield (8%) but moderate enantioselectivity (76% ee) (Table 2.5, entry 1), whereas (*S*)-QUINAP gave the highest yield (72%) with low enantioselectivity (30% ee) (entry 2). Standout phosphoramidite ligands included TADDOL-P-NMe_2 (entry 3, 70% yield, 34% ee), **L33** (entry 4, 25% yield, 41% ee), and **L34** (entry 5, 38% yield, 50% ee). Finally, biaryl bisphosphines included (*R*)-DiFluoroPhos (entry 6, 11% yield, 80% ee), (*R*)-P-Phos (entry 7, 12% yield, 80% ee), and (*R*)-BTFM-GarPhos (**L37**, entry 8, 24% yield, 82%

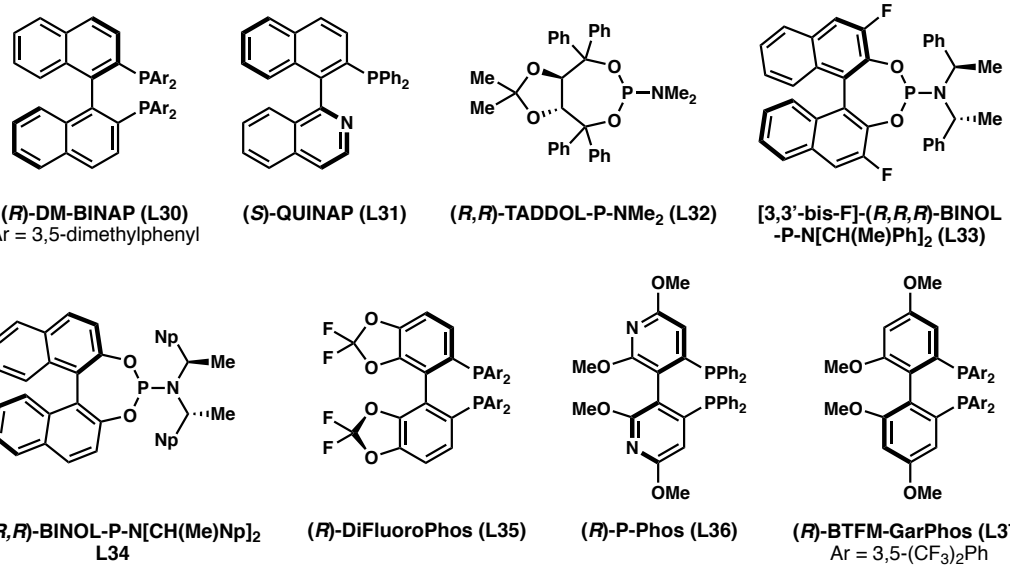
[‡] See Appendix 2.

ee). Of the three ligands with the highest ee, BTFM-GarPhos was chosen for subsequent reaction optimization due to its comparably high yield.

Table 2.5. *Standout ligands for [Cu(MeCN)$_4$]BF$_4$-catalyzed propargylation.*[‡]



Entry	Ligand	Conversion (%)	Yield (%)	ee (%)
1	(*R*)-DM-BINAP	45	8	76
2	(*S*)-QUINAP	85	72	30
3	TADDOL-P-NMe$_2$	97	70	34
4	[3,3'-bis-F]-(*R,R,R*)-BINOL-P-N[CH(Me)Ph]$_2$	69	25	41
5	(*R,R,R*)-BINOL-P-N[CH(Me)Np]$_2$	77	38	50
6	(*R*)-DiFluoroPhos	32	11	80
7	(*R*)-P-Phos	34	12	80
8	(*R*)-BTFM-GarPhos	60	24	82



(*R*)-DM-BINAP (L30)
Ar = 3,5-dimethylphenyl

(*S*)-QUINAP (L31)

(*R,R*)-TADDOL-P-NMe$_2$ (L32)

[3,3'-bis-F]-(*R,R,R*)-BINOL-P-N[CH(Me)Ph]$_2$ (L33)

(*R,R,R*)-BINOL-P-N[CH(Me)Np]$_2$ L34

(*R*)-DiFluoroPhos (L35)

(*R*)-P-Phos (L36)

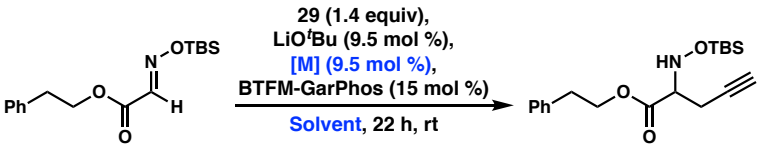
(*R*)-BTFM-GarPhos (L37)
Ar = 3,5-(CF$_3$)$_2$Ph

Using BTFM-GarPhos (**L37**), we then investigated the effects of solvent and copper source on the reaction. The reaction was screened with Cu(acac)$_2$ and [Cu(MeCN)$_4$]BF$_4$ in various solvents. The highest enantioselectivities were observed with [Cu(MeCN)$_4$]BF$_4$ with yields ranging from 16% to 33% (Table 2.6, entries 2, 4, 6,

[‡] See Appendix 2.

and 8). $Cu(acac)_2$ gave lower ee's (54-73%) with yields at times lower than the other metal (entries 1, 3) and occasionally higher (entries 5, 7). The highest yields observed with $[Cu(MeCN)_4]BF_4$ were 31% with THF (entry 2) and 33% with 2-MeTHF (entry 4). THF was chosen because it is more readily available.

Table 2.6. *Effects of solvents and comparison of copper sources on the Cu-catalyzed propargylation.*



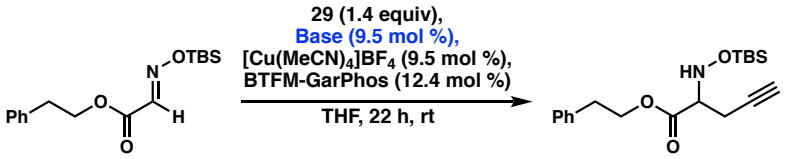
Entry	Solvent	Metal[a]	Conversion (%)	Yield (%)	ee (%)
1	THF	A	50	25	54
2	THF	B	51	31	94
3	2-MeTHF	A	45	22	58
4	2-MeTHF	B	63	33	>95
5	Et_2O	A	80	50	71
6	Et_2O	B	39	17	>95
7	Hexane	A	76	41	73
8	Hexane	B	59	16	>95

[a] A = $Cu(acac)_2$, B = $[Cu(MeCN)_4]BF_4$

At this point, we examined the base used. The previously used base, lithium *tert*-butoxide gave 33% yield and 80% ee (Table 2.7, entry 2). It was found that Cs_2CO_3 and no base gave similar yields to LiO^{t}Bu with higher enantioselectivity (Table 2.7, entries 1 and 7). It was therefore decided to examine new reactions under conditions of both Cs_2CO_3 and no base until the optimal conditions were achieved. (Some reactions later in this paper were carried out with LiO^{t}Bu simply due to being carried out at nearly the same time as the base screen.)

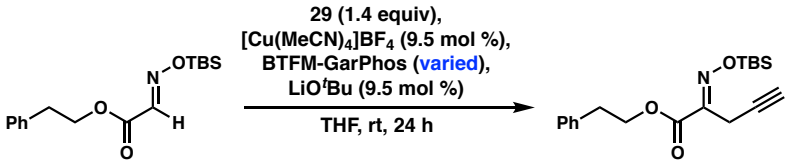
The effect of the stoichiometry of the metal and ligand was examined by varying the equivalence of BTFM-GarPhos. The highest enantioselectivity and yield were found using a 1:1.3 ratio of $[Cu(MeCN)_4]BF_4$ to BTFM-GarPhos (Table 2.8, entry 2).

Table 2.7. *Optimization of base in the Cu-catalyzed propargylation.*



Entry	Base	Conversion (%)	Yield (%)	ee (%)
1	none	73	30	95
2	LiO^{t}Bu	36	33	80
3	KOH	72	29	95
4	NaO^{t}Bu	58	26	90
5	KO^{t}Bu	40	11	68
6	Li_2CO_3	80	18	94
7	Cs_2CO_3	65	30	96
8	K_3PO_4	48	28	84
9	DBU	32	11	42
10	Et_3N	27	7	88

Table 2.8. *Metal-ligand stoichiometry.*

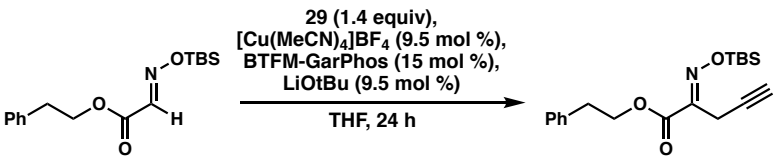


Entry	Metal:Ligand (Ligand mol %)	Conversion (%)	Yield (%)	ee(%)
1	1:2 (19 mol %)	78	16	90
2	1:1.3 (12.4 mol %)	80	26	94
3	1:1 (9.5 mol %)	63	11	74
4	1:0.8 (7.6 mol %)	78	16	90
5	1:0.67 (6.4 mol %)	74	13	88
6	1:0.5 (4.8 mol %)	62	8	72

The effects of temperature on the reaction were examined by testing the reaction at -20, 0, 20, 40, and 60 ˚C (Table 2.9, entries 1-5). However, this screen was determined to be contaminated as the reactions – including the control at room temperature – gave abnormally low yields (6-14%). The reaction was later tested with optimized conditions at room temperature and 40 ˚C (Table 2.9, entries 6-7). Increasing the temperature was found to improve the yield to 37%, compared to a control of 33%, and the

enantioselectivities were comparable. Since the increase in yield was minor, it was therefore decided to proceed at room temperature for ease of set-up.

Table 2.9. *Effects of temperature on the Cu-catalyzed propargylation.*

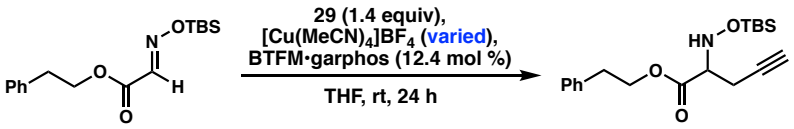


Entry	Temperature	Conversion (%)	Yield (%)	ee (%)
1	−20 ˚C	80	6	94
2	0 ˚C	67	9	88
3	r.t.	72	8	82
4	40 ˚C	87	14	88
5	60 ˚C	89	13	26
6[a]	r.t.	63	33	95
7[a]	40 ˚C	75	37	94

[a] Second screen; 12.4 mol % BTFM-GarPhos.

At this point, we investigated the effects of the equivalence of copper used in the reaction (Table 2.10). We also re-examined the effects of base on the reaction. This experiment was run in two series (with and without 0.095 equiv of Cs_2CO_3) of increasing $[Cu(MeCN)_4]BF_4$, from 0.095 equiv to 1.0 equiv, while maintaining the GarPhos ligand at 0.124 equiv. It was found that when the reaction included Cs_2CO_3 and 0.4 equiv copper, the yield was 24% and the ee was 95% (Table 2.10, entry 3). However, this was determined to be anomalous as later repetition of this experiment gave 14% yield and 68% ee. Using no base and 0.2 equiv copper gave a considerable increase in yield (37%) with a decrease in ee to 88% (Table 2.10, entry 6). The control experiment in this case (0.095 equiv copper, without base) showed 19% yield but 94% ee (Table 2.10, entry 5). It was determined that since the ee was greater in this case than with 0.2 equiv copper, and higher yield had been observed under these conditions, the optimal copper stoichiometry was 0.095 equiv and the best reaction conditions were without base.

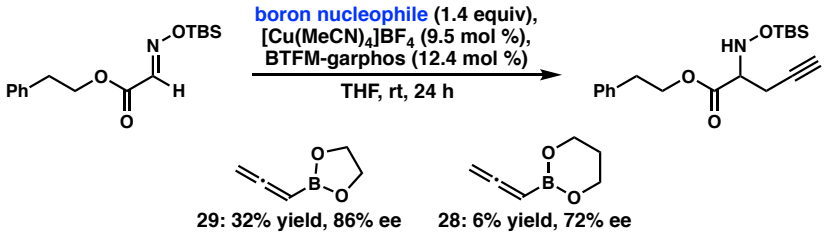
Table 2.10. *Effects of copper stoichiometry with and without base on the propargylation reaction.*



Entry	Conditions	Conversion (%)	Yield (%)	ee (%)
1	$[Cu(MeCN)_4]BF_4$ (0.095 equiv) Cs_2CO_3 (0.095 equiv)	71	21	90
2	$[Cu(MeCN)_4]BF_4$ (0.2 equiv) Cs_2CO_3 (0.095 equiv)	67	18	90
3	$[Cu(MeCN)_4]BF_4$ (0.4 equiv) Cs_2CO_3 (0.095 equiv)	73	24	95
4	$[Cu(MeCN)_4]BF_4$ (1 equiv) Cs_2CO_3 (0.095 equiv)	59	11	40
5	$[Cu(MeCN)_4]BF_4$ (0.095 equiv)	78	19	94
6	$[Cu(MeCN)_4]BF_4$ (0.2 equiv)	53	37	88
7	$[Cu(MeCN)_4]BF_4$ (0.4 equiv)	65	10	50
8	$[Cu(MeCN)_4]BF_4$ (1 equiv)	62	1	26

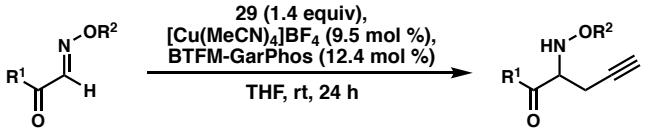
Schaus notes that the greater ring strain in the five-membered ring of borolane **29** is thought to cause it to exchange better with their BINOL-based catalyst.[22] It is also possible that a softer nucleophile with less ring strain such as borinane **28** could be more compatible with the oxime in our case. In order to test this with our own system, we synthesized **28** using 1,3-propanediol and a similar procedure as **29**. We discovered that our reactivity followed a similar pattern to Schaus', in that yield was greatly decreased from 32% in the control to 6% with the 6-membered boronate (Figure 2.2).

Figure 2.2. *Comparison of 5- and 6-member boron nucleophiles with the Cu-catalyzed propargylation.*



We also wondered what effect changing the parameters of the starting material would have on the reaction. We found that using a TIPS protecting group on the oxime rather than a TBS group effectively eliminated product formation, with or without added LiO^{t}Bu (Table 2.11, entries 1-2). A benzyl ester starting material showed similar results to the phenethyl (entry 3). Finally, using a benzyl amide instead of an ester decreased reactivity to 5% yield (entry 4).

Table 2.11. *Screen of different starting materials with the Cu-catalyzed propargylation.*

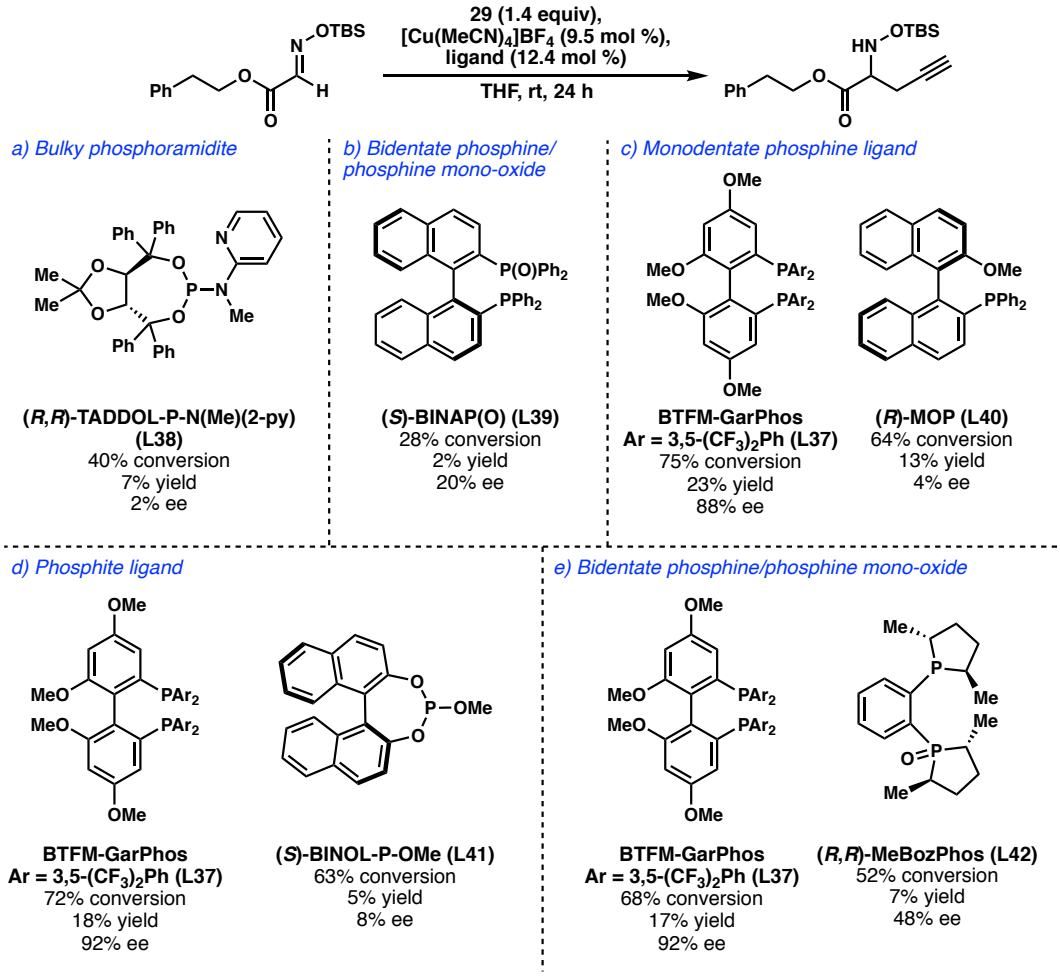


Entry	R^1	R^2	Conversion (%)	Yield (%)	ee (%)
1	OCH_2CH_2Ph	OTIPS	39	1	—
2[a]	OCH_2CH_2Ph	OTIPS	42	0	—
3	OCH_2Ph	OTBS	70	32	84
4	NCH_2Ph	OTBS	55	5	17

[a] LiO^{t}Bu (9.5 mol %) added.

We investigated whether different ligands, in particular those with different electronic configurations, could improve results on our propargylation. A bulky TADDOL-based phosphoramidite, **L38**, decreased yield to 7% and ee to 2% (Figure 2.3, a). BINAP ligands had previously shown low yield but promising ee, so we tried BINAP mono-oxide, hoping that the oxidation would be sufficient to improve our yield. However the yield was 2% and ee only 20% (Figure 2.3, b). We subsequently tried MOP (**L40**, a monodentate phosphine ligand), a BINOL-based phosphite (**L41**), and MeBozPhos (**L42**, a bidentate phosphine/phosphine mono-oxide with different bite angle), all of which showed severely decreased yield and enantioselectivity compared to the control, BTFM-GarPhos (Figure 2.3, c-e).

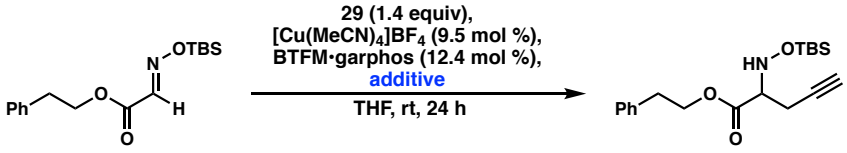
Figure 2.3. *Ligand screens for the Cu-catalyzed propargylation.*



Inspired by a surprising success by a colleague in our lab,[25] we screened 2,6-dibromophenol as a proton source in our reaction (Table 2.12). However, concentration of 2,6-dibromophenol was found to have an inverse effect on the yield of our reaction. At 0.4 equiv 2,6-dibromophenol, the reaction yield was only 15%, and the ee dropped to 88% (Table 2.12, entry 1). At 1.0 equiv, the yield was reduced to 2%, and the ee could not be measured (entry 2). *Tert*-butanol showed similar effects on reactivity. At 0.7 equiv ^{t}BuOH, the reaction yield decreased to 11% (Table 2.12, entry 8). At higher equivalences, no product was observed, although some starting material was consumed (entries 9-10).

Water was also investigated as a proton source. It was found that at low concentrations it neither hindered nor improved reactivity (Table 2.12, entries 3, 6), as yield stayed approximately the same as had been observed in previous reactions. However, the enantioselectivity was reduced to 82-84%. At higher concentrations, the yield decreased considerably (Table 2.12, entries 4-5, 7). This trend was the same for the reaction with and without 0.095 equiv Cs_2CO_3.

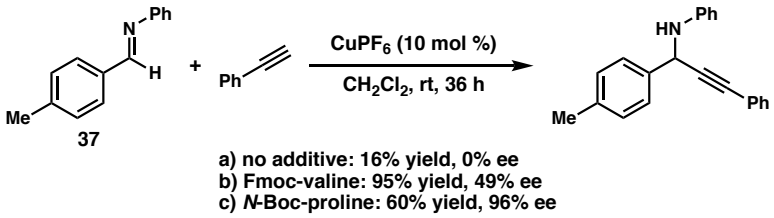
Table 2.12. *Effects of proton-bearing additives on the Cu-catalyzed propargylation.*



Entry	Additive	Conversion (%)	Yield (%)	ee (%)
1	2,6-dibromophenol (0.4 equiv)	75	15	88
2	2,6-dibromophenol (1.0 equiv)	64	2	—
3	H_2O (0.1 equiv)	45	27	84
4	H_2O (0.4 equiv)	47	13	78
5	H_2O (1.0 equiv)	9	6	52
6	H_2O (0.1 equiv) Cs_2CO_3 (0.095 equiv)	72	29	82
7	H_2O (1.0 equiv) Cs_2CO_3 (0.095 equiv)	76	1	20
8	^{t}BuOH (0.7 equiv)	45	11	81
9	^{t}BuOH (1.4 equiv)	31	0	—
10	^{t}BuOH (2.8 equiv)	27	0	—

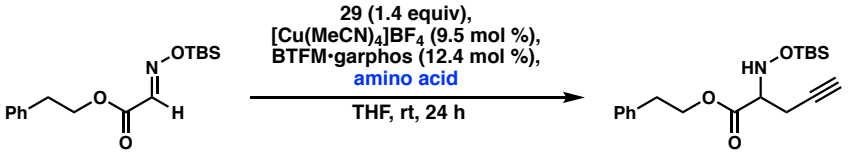
Arndtsen *et al.* demonstrated that amino acids could be used as a highly tunable additive to increase the enantioinduction of a reaction, in their case copper-catalyzed alkyne-imine coupling (Scheme 2.2).[26] They showed that their initial reaction, the coupling of imine **37** to phenylacetylene using $CuPF_6$, could be raised from 16% yield and 0% ee to 95% yield and 49% ee using Fmoc-valine. A quick screen determined *N*-Boc-proline could be used to raise the ee to 96% with a yield of 60%.

Scheme 2.2. *Use of amino acids to increase enantioenduction of copper-catalyzed alkyne-imine coupling.*[26]



Based on this, we hoped it might be possible to use amino acids as a tunable hydrogen bond donor in our reaction. We investigated both L-Boc-proline and D-Boc-proline in case of possible additive effects on enantioselectivity; however, both amino acids caused a decrease in reactivity – no product was observed and there was an additional decrease in consumption of starting material (Table 2.13, entries 2-3). It should be noted that the control (entry 1) showed an unusually low yield in this screen, but the complete lack of product with the addition of amino acids in the reaction was clear.

Table 2.13. *Amino acid additives in the Cu-catalyzed propargylation.*

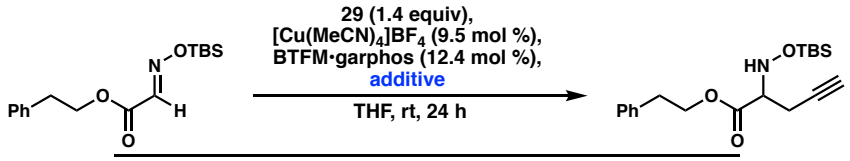


Entry	Amino acid	Conversion (%)	Yield (%)	ee (%)
1	none	87	7	90
2	Boc-L-proline (0.19 equiv)	59	0	—
3	Boc-D-proline (0.19 equiv)	63	0	—

Shibasaki *et al.* found they could use La(O^{i}Pr)$_3$ as a cocatalyst to greatly accelerate the copper-catalyzed enantioselective allylation of ketones and imines.[27-28] They also found it greatly improved their yield. We therefore hoped to be able to use the same effect to our advantage and screened La(O^{i}Pr)$_3$ in the same stoichiometry (1.5 times the amount of copper catalyst) as Shibasaki. We also revisited Sc(OTf)$_3$ to see if it would

give a higher yield with our new conditions. We found that both compounds greatly decreased the yield, to 12% and 11% respectively (Table 2.14, entries 1-2). The enantioselectivity was also considerably reduced.

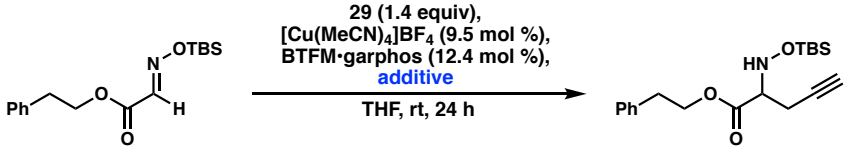
Table 2.14. *Lewis acid additives in the Cu-catalyzed propargylation.*



Entry	Additive	Conversion (%)	Yield (%)	ee (%)
1	$La(O^iPr)_3$ (14.3 mol %)	40	12	65
2	$Sc(OTf)_3$ (9.5 mol %)	54	11	40

As we noted previously (Table 2.12), water can slow or nearly halt the reaction. In order to test if trace water was holding back the reaction, we screened molecular sieves. However, these reduced the yield from 34% to 21% as well as decreasing the ee (Table 2.15, entry 2). Subsequently, we wondered if adding a fluoride source could improve catalyst turnover by taking up excess boronate. However, CsF reduced the yield to 13-18% (Table 2.15, entries 3-5). We screened pyridine, 2,6-lutidine, and proton

Table 2.15. *Additives in the Cu-catalyzed propargylation.*



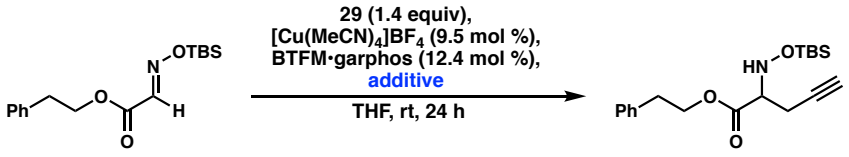
Entry	Additive	Conversion (%)	Yield (%)	ee (%)
1	none	71	34	92
2	mol sieves	74	21	84
3	CsF (0.095 equiv)	64	13	94
4	CsF (0.19 equiv)	70	18	93
5	CsF (1.0 equiv)	69	14	90
6	pyridine (0.095 equiv)	95	19	90
7	2,6-lutidine (0.95 equiv)	59	24	92
8	proton sponge[a] (0.095 equiv)	66	12	92
9	DMS (0.095 equiv)	74	13	94

[a] 1,8-Bis(dimethylamino)naphthalene

sponge to see if excess protons were stopping catalyst turnover; however, all three gave reduced yields (entries 6-8). Finally, we examined DMS to see if a reducing agent could improve catalyst turnover; this too reduced yield to 13% (entry 9).

We also wondered if copper-ligand electron transfer was playing a role in preventing catalyst turnover. We therefore screened electron scavengers such as nitrobenzene and metallic copper. Nitrobenzene showed little change in reactivity compared to control (Table 2.16, entry 2), but the copper reduced both yield and ee (entry 3). Finally, in order to see if the initial ligand on the copper had any effect, we screened both 0.095 and 1.0 equiv acetonitrile. The lower concentration had little effect (Table 2.16, entry 4) but the higher concentration (entry 5) raised the yield 6 percentage points compared to the control (entry 1).

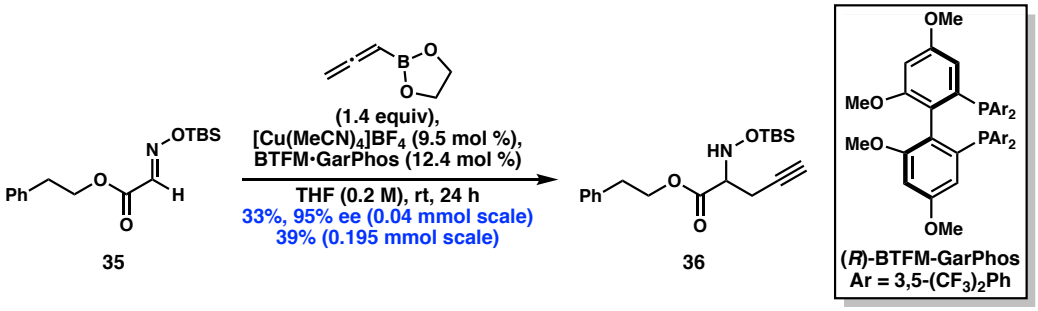
Table 2.16. *Electron scavengers and acetonitrile in the Cu-catalyzed propargylation.*



Entry	Additive	Conversion (%)	Yield (%)	ee (%)
1	none	79	19	93
2	nitrobenzene (0.095 equiv)	77	20	94
3	copper bead	82	15	88
4	acetonitrile (0.095 equiv)	95	21	95
5	acetonitrile (1.0 equiv)	79	25	92

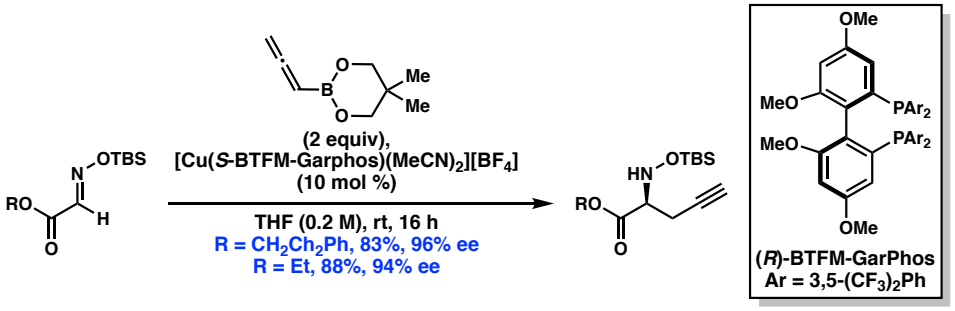
The highest yield of the propargylation reaction was found to be 39% upon scaleup (0.060 mg starting material). Enantiomeric excess found during screening was as high as 95%. The best conditions are shown in Scheme 2.3.

Scheme 2.3. *Optimized reaction conditions for the copper-catalyzed asymmetric propargylation.*



Later efforts by Nicholas Cowper and Matthew Hesse showed that by using 2 equivalences of 5,5-dimethyl-2-(allenyl)-1,3,2-dioxaborinane and a copper-BTFM-GarPhos complex the nucleophilic addition could be achieved in 83% yield and 96% ee for the phenethyl oxime ester, and 88% yield and 94% ee for the ethyl ester (Scheme 2.4).

Scheme 2.4. *Best conditions for the catalytic asymmetric propargylation of oxime esters.*



2.3 CONCLUDING REMARKS

In conclusion, a copper catalyzed asymmetric addition to oxime esters has been developed. The $[Cu(MeCN)_4]BF_4$–BTFM-GarPhos system gives the propargylated

hydroxylamine product with high enantioselectivity. Later work was able to raise the yield considerably. The product is potentially useful in total synthesis or in various biochemical or medical applications. Further work is needed to expand the reaction scope, at which point the reaction could be a useful tool in organic synthesis.