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Cu^{II}-catalyzed regioselective borylation of alkynes and alkenes

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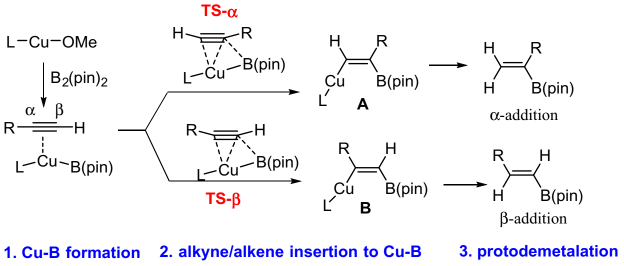
ABSTRACT

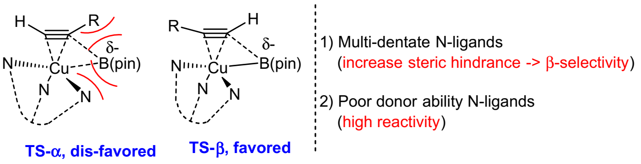
We developed a regioselective borylation of alkynes and alkenes protocol based on air-stable Cu^{II}/multi-dentate ligand system. Our catalytic system gives exclusive β-borylation products for most substrates in excellent chemical yields. We propose that multi-dentate electron poor nitrogen ligands can effectively discourage the formation of α-addition product through the steric hindrance and at same time maintain good reactivity.

Alkenylboron and alkylboron reagents have been widely used in carbon–carbon or carbon-heteroatom bond formation reactions like Suzuki crossing coupling.[1] Borylation of alkynes and alkenes is one of the most straightforward methods to synthesize them. The formal hydroborylation of alkynes and alkenes via diboron reagents like B_2pin_2 has been studied extensively,[2,3] but there are still unmet challenges for this reaction. One of the greatest challenges associated with borylation of alkynes and alkenes is the control of regioselectivity. For example, in the case of terminal alkynes, β-borylation product usually is the major isomer except for few examples.[3v] Although moderate to good regioselectivity for β-borylation (e.g., 90:10) often can be obtained, considering the two isomers are difficult to separate, so even a 90:10 selectivity still can be problematic in real synthetic applications. Another challenge is use of relatively expensive and oxygen sensitive ligands (phosphine or NHC ligands) and metals (e.g., Cu^{I}) in vast majority of reports. Also in many reports, the outcome of regioselectivity cannot be easily predicted by the structure of starting alkynes/alkenes, the substitution pattern has subtle influence on the regioselectivity.

In transition metal catalysis, the selectivity often can be fine-tuned by choice of metal and ligand.[3v] We have reported a systematic study on ligand design in cationic gold catalysis.[4] Along this line, our focus is finding a selective yet robust catalyst system via rational choice of ligand. Herein we are glad to report a robust borylation of alkynes and alkenes based on air-stable, readily available nitrogen ligands and Cu^{II} salts. What is more, the outcome of regioselectivity is predictable.



Scheme 1. Regioselectivity for copper catalyzed borylation.



Scheme 2. Ligand effects in copper catalyzed borylation.

It is well established that copper catalyzed borylation of alkynes and alkenes using diboron reagents goes through 3 major stages:[2a] (1) Cu-B intermediate formation; (2) alkyne/alkene insertion to Cu-B; (3) protodemetalation (Scheme 1). Theoretical investigations indicate that the rate- and regioselectivity-determining step might be alkyne/alkene insertion to Cu–B bond.[5] And crossover experiments conducted by Hoveyda and co-workers[3v] further imply the regioselectivity is not due to thermodynamic

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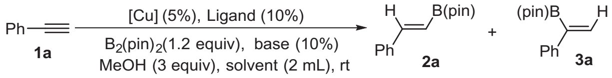
Table 1
Effect of ligands on borylation of alkyne **1a**[a]



Entry	[Cu]	Ligand	Solvent	Base	Yield[b] (%)	**2a:2b**[c]
1	CuBr	–	1,4-Dioxane	NaO*t*Bu	46	82:18
2	$CuCl_22H_2O$	–	1,4-Dioxane	NaO*t*Bu	68	83:17
3	$CuSO_45H_2O$	–	1,4-Dioxane	NaO*t*Bu	63	88:12
4	$Cu(OAc)_2$	–	1,4-Dioxane	NaO*t*Bu	61	91:9
5	$Cu(OTf)_2$	–	1,4-Dioxane	NaO*t*Bu	75	94:6
6	$Cu(OTf)_2$	$\mathbf{L_P1}$	1,4-Dioxane	NaO*t*Bu	90	96:4
7	$Cu(OTf)_2$	$\mathbf{L_P2}$	1,4-Dioxane	NaO*t*Bu	88	95:5
8	$Cu(OTf)_2$	$\mathbf{L_P3}$	1,4-Dioxane	NaO*t*Bu	73	80:20
9	$Cu(OTf)_2$	$\mathbf{L_P4}$	1,4-Dioxane	NaO*t*Bu	52	85:15
10	$Cu(OTf)_2$	$\mathbf{L_P5}$	1,4-Dioxane	NaO*t*Bu	76	95:5
11	$Cu(OTf)_2$	$\mathbf{L_P6}$	1,4-Dioxane	NaO*t*Bu	76	98:2
12	$Cu(OTf)_2$	$\mathbf{L_P7}$	1,4-Dioxane	NaO*t*Bu	70	>99:1
13	$Cu(OTf)_2$	$\mathbf{L_P8}$	1,4-Dioxane	NaO*t*Bu	90	97:3
14	$Cu(OTf)_2$	$\mathbf{L_N1}$	1,4-Dioxane	NaO*t*Bu	80	98:2
15	$Cu(OTf)_2$	$\mathbf{L_N2}$	1,4-Dioxane	NaO*t*Bu	63	>99:1
16	$Cu(OTf)_2$	$\mathbf{L_N3}$	1,4-Dioxane	NaO*t*Bu	30	>99:1
17	$Cu(OTf)_2$	$\mathbf{L_N4}$	1,4-Dioxane	NaO*t*Bu	74	99:1
18	$Cu(OTf)_2$	$\mathbf{L_N5}$	1,4-Dioxane	NaO*t*Bu	88	>99:1
19	$Cu(OTf)_2$	$\mathbf{L_N6}$	1,4-Dioxane	NaO*t*Bu	14	87:13
20	$Cu(OTf)_2$	$\mathbf{L_N7}$	1,4-Dioxane	NaO*t*Bu	82	89:11
21	$Cu(OTf)_2$	$\mathbf{L_N8}$	1,4-Dioxane	NaO*t*Bu	77	>99:1
22	$Cu(OTf)_2$	$\mathbf{L_N5}$	THF	NaO*t*Bu	77	98:2
23	$Cu(OTf)_2$	$\mathbf{L_N5}$	Toluene	NaO*t*Bu	86	98:2
24	$Cu(OTf)_2$	$\mathbf{L_N5}$	DMF	NaO*t*Bu	85	98:2
25	$Cu(OTf)_2$	$\mathbf{L_N5}$	DMSO	NaO*t*Bu	77	>99:1
26	$Cu(OTf)_2$	$\mathbf{L_N5}$	DCE	NaO*t*Bu	78	93:7
27	$Cu(OTf)_2$	$\mathbf{L_N5}$	MeOH	NaO*t*Bu	95	95:5
28	$Cu(OTf)_2$	$\mathbf{L_N5}$	CH_3CN	NaO*t*Bu	89	>99:1
29	$Cu(OTf)_2$	$\mathbf{L_N5}$	CH_3CN	KO*t*Bu	87	99:1
30	$Cu(OTf)_2$	$\mathbf{L_N5}$	CH_3CN	LiO*t*Bu	67	98:2
31	$Cu(OTf)_2$	$\mathbf{L_N5}$	CH_3CN	NaOAc	80	85:15
32	$Cu(OTf)_2$	$\mathbf{L_N5}$	CH_3CN	NaOMe	62	83:17
33	$Cu(OTf)_2$	$\mathbf{L_N5}$	CH_3CN	NaOH	81	97:3
34	$Cu(OTf)_2$	$\mathbf{L_N5}$	CH_3CN	Na_2CO_3	71	93:7
35	$Cu(OTf)_2$	$\mathbf{L_N5}$	CH_3CN	Na_3PO_4	69	86:14
36	$Cu(OTf)_2$	$\mathbf{L_N5}$	CH_3CN	Et_3N	50	82:17
37	$Cu(OTf)_2$	$\mathbf{L_N5}$	CH_3CN	DBU	55	93:7
38[d]	$\mathbf{Cu(OTf)_2}$	$\mathbf{L_N5}$	$\mathbf{CH_3CN}$	**NaO*t*Bu**	**99**	**>99:1**
39[e]	$Cu(OTf)_2$	$\mathbf{L_N5}$	CH_3CN	NaO*t*Bu	66	>99:1
40	$Cu(OTf)_2$	-	CH_3CN	NaO*t*Bu	78	90:10

Best condition is highlighted in bold.

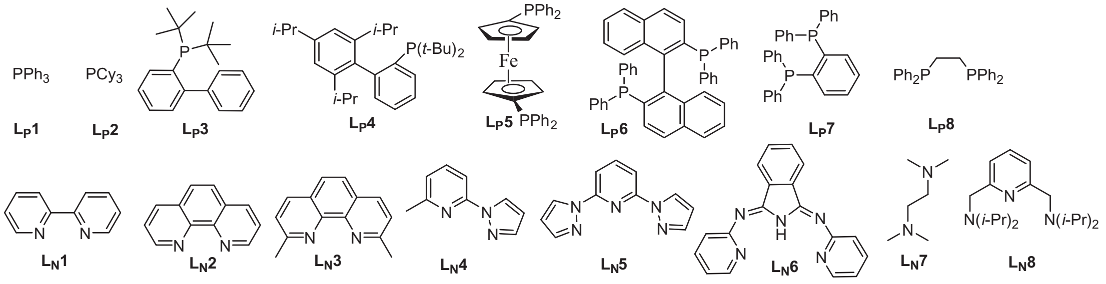
[a] Reaction conditions: **1a** (0.3 mmol), B_2pin_2 (0.36 mmol), NaO*t*-Bu (0.03 mmol), $Cu(OTf)_2$ (5 mol %), ligand (10 mol %), MeOH (0.9 mmol), solvent (2 mL), rt.

[b] Isolated yields.

[c] Determined by GC–MS.

[d] The reaction was conducted at 50 °C.

[e] 2.5% $Cu(OTf)_2$ and 5% $\mathbf{L_N5}$ were used.



difference between two Cu-B addition intermediates (**A** or **B** in Scheme 1). Also theoretical and experimental data obtained by both Arrayas, Carretero and co-workers[6] and Lee and co-workers[3t] indicate steric hindrance of substitution on the alkynes as long as subtle orbital interaction in the transition state are important in regioselectivity. The regioselectivity may be determined by kinetic formation **A** and **B** (Scheme 1).

Our hypothesis is that β-selectivity can enhanced by increasing the steric hindrance of ligands, especially by multi-dentate ligands (Scheme 2). Multi-dentate ligands will effectively increase the size of copper metal complex and discourage the formation of **TS-α** through the steric hindrance interaction among the ligand, B(pin) and R group. Also we want to use nitrogen ligands to replace generally more expensive and oxygen sensitive phosphine[7] and NHC

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