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Shiwen Liu, Xiaojun Zeng, Bo Xu*

College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China

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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.

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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 B₂pin₂ 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 examples, 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 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.

1. Cu-B formation 2. alkyne/alkene insertion to Cu-B 3. protodemetalation

Scheme 1. Regioselectivity for copper catalyzed borylation.

It is well established that copper catalyzed borylation of alkynes and alkenes using diboron reagents goes through 3 major stages:^{2a1} 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 coworkers^{3v} further imply the regioselectivity is not due to thermodynamic difference between two Cu-B addition intermediates (**A** or **B** in **Scheme 1**). Also theoretical and experimental data obtained by both Arrayas, Carretero⁶ and Lee^{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**).

Scheme 2. Ligand effects in copper catalyzed borylation.

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	NaOtBu	46	82:18
2	CuCl ₂ ·2H ₂ O	-	1,4-dioxane	NaOtBu	68	83:17
3	CuSO ₄ ·5H ₂ O	-	1,4-dioxane	NaOtBu	63	88:12
4	Cu(OAc) ₂	-	1,4-dioxane	NaOtBu	61	91:9
5	Cu(OTf) ₂	-	1,4-dioxane	NaOtBu	75	94:6
6	Cu(OTf) ₂	Lp1	1,4-dioxane	NaOtBu	90	96:4
7	Cu(OTf) ₂	Lp2	1,4-dioxane	NaOtBu	88	95:5
8	Cu(OTf) ₂	Lp3	1,4-dioxane	NaOtBu	73	80:20
9	Cu(OTf) ₂	Lp4	1,4-dioxane	NaOtBu	52	85:15
10	Cu(OTf) ₂	Lp5	1,4-dioxane	NaOtBu	76	95:5
11	Cu(OTf) ₂	Lp6	1,4-dioxane	NaOtBu	76	98:2
12	Cu(OTf) ₂	Lp7	1,4-dioxane	NaOtBu	70	>99:1
13	Cu(OTf) ₂	Lp8	1,4-dioxane	NaOtBu	90	97:3
14	Cu(OTf) ₂	LN1	1,4-dioxane	NaOtBu	80	98:2
15	Cu(OTf) ₂	LN2	1,4-dioxane	NaOtBu	63	>99:1
16	Cu(OTf) ₂	LN3	1,4-dioxane	NaOtBu	30	>99:1
17	Cu(OTf) ₂	LN4	1,4-dioxane	NaOtBu	74	99:1
18	Cu(OTf) ₂	LN5	1,4-dioxane	NaOtBu	88	>99:1
19	Cu(OTf) ₂	LN6	1,4-dioxane	NaOtBu	14	87:13
20	Cu(OTf) ₂	LN7	1,4-dioxane	NaOtBu	82	89:11
21	Cu(OTf) ₂	LN8	1,4-dioxane	NaOtBu	77	>99:1
22	Cu(OTf) ₂	LN5	THF	NaOtBu	77	98:2
23	Cu(OTf) ₂	LN5	toluene	NaOtBu	86	98:2
24	Cu(OTf) ₂	LN5	DMF	NaOtBu	85	98:2
25	Cu(OTf) ₂	LN5	DMSO	NaOtBu	77	>99:1
26	Cu(OTf) ₂	LN5	DCE	NaOtBu	78	93:7
27	Cu(OTf) ₂	LN5	MeOH	NaOtBu	95	95:5
28	Cu(OTf) ₂	LN5	CH ₃ CN	NaOtBu	89	>99:1
29	Cu(OTf) ₂	LN5	CH ₃ CN	KOtBu	87	99:1
30	Cu(OTf) ₂	LN5	CH ₃ CN	LiOtBu	67	98:2
31	Cu(OTf) ₂	LN5	CH ₃ CN	NaOAc	80	85:15
32	Cu(OTf) ₂	LN5	CH ₃ CN	NaOMe	62	83:17
33	Cu(OTf) ₂	LN5	CH ₃ CN	NaOH	81	97:3
34	Cu(OTf) ₂	LN5	CH ₃ CN	Na ₂ CO ₃	71	93:7
35	Cu(OTf) ₂	LN5	CH ₃ CN	Na ₃ PO ₄	69	86:14
36	Cu(OTf) ₂	LN5	CH ₃ CN	Et ₃ N	50	82:17
37	Cu(OTf) ₂	LN5	CH ₃ CN	DBU	55	93:7
38^d	Cu(OTf)₂	LN5	CH₃CN	NaOtBu	99	>99:1
39 ^e	Cu(OTf) ₂	LN5	CH ₃ CN	NaOtBu	66	>99:1
40	Cu(OTf) ₂	-	CH ₃ CN	NaOtBu	78	90:10

^a Reaction conditions: **1a** (0.3 mmol), B₂pin₂ (0.36 mmol), NaOt-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 % **LN5** were used.

Table 2. Scope for borylation of alkynes and alkenes.

Reaction scheme for the synthesis of **2** from **1** and **3** using **5% Cu(OTf)₂ · L_N5 (10%)** in **MeOH (3 equiv)** and **CH₃CN (0.15 M)** at **50 °C, 3 h**.

$$\text{R}-\text{C}\equiv\text{C}-\text{H} \xrightarrow[\text{CH}_3\text{CN (0.15 M), 50 }^\circ\text{C, 3 h}]{\text{5\% Cu(OTf)}_2 \cdot \text{L}_N\text{5 (10\%)}} \text{R}-\text{C}(\text{H})=\text{C}(\text{B(pin)})-\text{H} + (\text{pin})\text{B}-\text{C}(\text{H})=\text{C}(\text{R})-\text{H}$$

1 **2** **3**

Entry	1	2	yield of 2 (%) ^b	2 : 3 ^c	Entry	1	2	yield of 2 (%) ^b	2 : 3 ^c
1			99	>99:1	14			90	92:8
2			90	>99:1	15			55	>99:1
3			86	>99:1	16			83	92:8
4			95	>99:1	17			88	>99:1
5			90	>99:1	18			77	-
6			86	>99:1	19			85	>99:1
7			84	>99:1	20			0	-
8			77 70 ^d	75:25 80:20	21 ^d			98	>99:1
9			99	97:3	22 ^d			99	>99:1
10			99	97:3	23 ^d			99	>99:1
11			38	>99:1	24 ^d			99	>99:1
12			93	>99:1	25 ^d			99	54:45
13			91	>99:1	26 ^d			99	>99:1

^aReaction conditions: **1** (0.3 mmol), B₂pin₂ (0.36 mmol), NaOt-Bu (0.03 mmol), Cu(OTf)₂ (5 mol %), Ligand (10 mol %), MeOH (0.9 mmol), CH₃CN (2 mL), 50°C; ^b isolated yields; ^c determined by GC; ^d L_p**7** was used as ligand.

Our hypothesis is that β -selectivity can be 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 phosphine⁷ and NHC ligands.⁸ In the alkyne insertion process (or boron migration process), B(pin) acts as a nucleophile, so an electron deficient Cu complexed alkyne will have high reactivity. Although nitrogen ligands could be ideal in term of stability and cost, vast majority of ligand reported are phosphine or NHC ligands. Nitrogen ligands have only been used in

reactive acceptor (e.g. ester) substituted alkynes.⁹ This could be due to the fact that nitrogen ligands are usually good σ -donors but not π -acceptors. This leads to copper substituted alkyne/alkenes are not as electron deficient when nitrogen ligands are employed. So when we select nitrogen ligands, we have to somehow limit the σ -donor ability (or electron density) of nitrogen ligands in order to maintain good reactivity (**Scheme 2**).

We used borylation of alkyne **1a** as our model system to investigate the effect of metal and especially the ligands on the regioselectivity (Table 1). First, we explored the ligandless copper salts catalyzed process (Table 1, entries 1-5) for comparison. All the copper salts have certain

reactivity, and Cu^{II} salts especially Cu^{II}(OTf)₂ gave better both chemical yields and regioselectivity (Table 1, entry 5). So we used Cu^{II}(OTf)₂ complex to study the ligand effects. So far, most literature reports on Cu catalyzed borylations are Cu^I based, relatively few Cu^{II} salts have been used.^{3h, ab, 9-10} Because Cu^{II} could be reduced to Cu^I *in situ*, we are not sure about the real catalyst is Cu^{II} or Cu^I yet, but use of oxygen stable Cu^{II} could make our method more robust.

We tested a number of commercially available phosphine ligands to get some general idea on how regioselectivity was affected by steric and electronic factors of ligands. Commonly used PPh₃ and PCy₃ increased the chemical yields but not the regioselectivity compared to the ligandless system (Table 1, entries 6-7 vs entry 5). Using of bulky mono-dentate Buchwald type ligands did not improve the regioselectivity (Table 1, entries 8-9). But to our delight, bidentate phosphine ligands significantly improved the regioselectivity (Table 1, entries 10-13), especially the skeleton rigid bidentate ligand **Lp7** gave exclusive β-adduct (Table 1, entry 12). These data indicates that structurally rigid multi-dentate ligands may be good for β-selectivity, while the electronic factor of ligands is not crucial.

Based on effect of phosphine ligands on regioselectivity, we tried to find suitable nitrogen ligands. First we tested commercially available bidentate N-ligands like bipyridine and phenanthroline. They did give excellent regioselectivity, and among them bipyridine based system had the highest reactivity (Table 1, entries 14-16). Since bipyridine ligand has good regioselectivity and reasonable reactivity, we tried to keep one pyridine ring and change another pyridine moiety to other less donating nitrogen groups. Mono-pyridine-mono-pyrazole hybrid ligand **Ln4**¹¹ gave good regioselectivity (Table 1, entry 17). To our delight, tridentate mono-pyridine-di-pyrazole hybrid ligand **Ln5** gave exclusive β-selectivity and good reactivity at same time (Table 1, entry 18). Other nitrogen ligands did not behave well. **Ln6**¹² based catalyst has very low reactivity (Table 1, entry 19), this could be explained by the fact that **Ln6** could bond with Cu covalently, which block the formation of Cu-B intermediate. **Ln7** (TMEDA) based catalyst gave poor regioselectivity (Table 1, entry 20), this could be explained by the fact that it is less sterically hindered and less rigid. **Ln8**¹³ based catalyst had good regioselectivity but its reactivity was not as good as **Ln5** (Table 1, entry 21).

Ln5 can easily prepared from 2,6-dichloropyridine and pyrazole in one step.¹⁴ With the best ligand **Ln5** in hand, we screened the effect of solvents, CH₃CN gave best regioselectivity and chemical yields (Table 1, entries 22-28). Also we explored the effect of bases: weaker bases gave less satisfactory regioselectivity (Table 1, entries 29-37). Lastly we increased the temperature to 50°C, we can obtained almost quantitative yields and exclusive β-selectivity (Table 1, entry 38). Reducing loading of copper and ligand led to lower chemical yield, but regioselectivity can be maintained (Table 1, entry 39). To ensure the effect of **Ln5**, we conducted a control experiment without ligand under optimized conditions, the regioselectivity was only 90:10 (Table 1, entry 40).

With the optimized condition in hand, we explored the scope of the borylation reaction (Table 2). For aryl substituted terminal alkynes, excellent yields and exclusive β-regioselectivity can be obtained (Table 2, entries 1-6). Both electron donating groups and electron withdrawing groups do not affect the reaction (Table 2, entries 1-4).

Heteroaromatics like pyridine and thiophene are well tolerated (Table 2, entries 5-6). Simple alkyl group substituted alkynes also gave good chemical yields (Table 2, entries 7-8). For sterically hindered cyclohexyl substituted alkyne (Table 2, entry 7), excellent β-selectivity can be achieved, but for less sterically hindered *n*-hexyl substituted alkyne (Table 2, entry 8), only moderate β-selectivity is obtained. Then we tested more functionalized terminal alkynes like propargylic alcohols and esters (Table 2, entries 9-15), and in all cases, excellent β-selectivity can be achieved. Some propargylic acetates (Table 2, entries 11, 15) only gave moderate isolated yields due to slow reactions (incomplete reactions). Compared to simple *n*-hexyl substituted alkyne (Table 2, entry 8), ester and hydroxyl groups seems enhancing the β-selectivity (Table 2, entries 16-17). For relatively electron deficient internal alkynes, good chemical yields can be obtained (Table 2, entries 18-19). But for electron rich dialkyl internal alkyne, there is no reaction taking place (Table 2, entry 20). In addition to the electronic effect, the much higher reactivity of diphenyl alkyne compared to dialkyl alkyne could due to the subtle interaction of phenyl ring with copper metal in the corresponding structure.^{6,3t} In general, our method works well for terminal alkynes, but it shows low reactivity towards internal alkynes, only diaryl alkynes are suitable starting materials.

We also tested borylation of alkenes (Table 2, entries 21-26), in these cases, the β-selectivity of **Ln5** based catalyst is not excellent (around 20:1), **Lp7** is a better ligand in term of regioselectivity. The regioselectivity follows almost exact pattern as reaction of alkynes. All the alkenes gave excellent β-selectivity except less sterically hindered 1-octene (Table 2, entry 25). Based on the above observations, the steric hindrance of substrates play a crucial role in regioselectivity, almost exclusive β-selectivity can be achieved in all cases except less sterically hindered simple 1-octyne (Table 2, entry 8) and 1-octene (Table 2, entry 25).

In summary, we developed a robust Cu^{II}/multi-dentate N-ligand based regioselective borylation of alkynes and alkenes based on extensive ligands screening. Currently, use of Cu^{II}/**Ln5** in other catalytic process is under investigation in our laboratory.

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