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Ligand-Controlled Copper-Catalyzed Regiodivergent Carbonylative Synthesis of α -Amino Ketones and α -Boryl Amides from Imines and Alkyl Iodides

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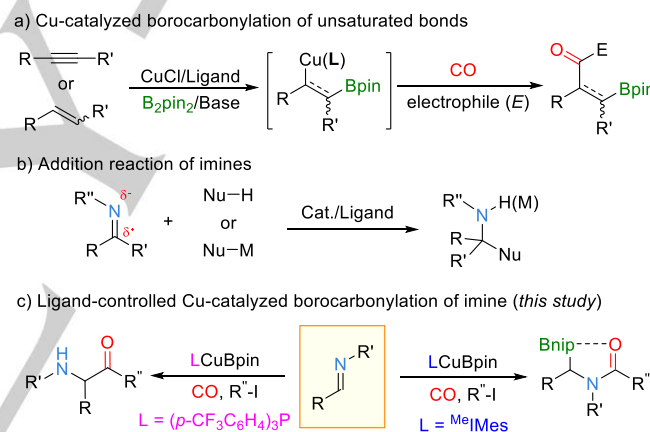
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Abstract: Regioselective transformation is among the long-standing challenges in organic synthesis. In this communication, a copper-catalyzed selectivity controlled regiodivergent borocarbonylation of imines with alkyl iodides has been developed. Various α -amino ketones and α -boryl amides were produced in moderate to good yields from the same substrates. The choosing of the appropriate ligand is the key for the regioselectivity control: α -amino ketones were produced selectively in good yields with $(p\text{-CF}_3\text{C}_6\text{H}_4)_3\text{P}$ as the ligand; while the corresponding α -boryl amides were obtained in high regioselectivity with $^{\text{Me}}\text{IMes}$ as the ligand.

Over the past few decades, carbonylation reactions have experienced significant progresses with CO as an attractive C1 source for the preparation of various carbonyl-containing compounds and extending the carbon chain at the same time.^[1] Among the numerous transformations, transition-metal catalyzed borocarbonylation represents a novel strategy for converting CO/boron(ester) into complexed carbonyl-boryl-compounds. Some borocarbonylation reactions of alkynes and alkenes have been achieved by using Cu^[2] or Cu/Pd^[3] catalyst systems. The key step in these reactions is the addition of LCu-Bpin to unsaturated bonds to generate an active alkenyl- or alky-CuL intermediate, which can subsequently react with CO and electrophiles to deliver the final products (Scheme 1a). Thus, as an inexpensive and abundant metal, copper is crucial and unique in borocarbonylation reactions.^[4]

On the other hand, achieving regioselective transformation of unsaturated chemical bonds is among the long-standing challenges in organic synthesis.^[5] Based on the continues efforts from organic chemists, great successes have been made during the past decades. In particular, transition-metal catalysts such as copper,^[6] palladium,^[7] and rhodium^[8] have been extensively studied in this topic. Furthermore, ligands design provides more opportunities for regioselective transformations, which can affect the metallic complex's structural and electronic properties by the electronic and steric properties of the ligands. Although the regioselective carbonylative reaction is even more challenge as CO coordinates to the metal and decrease its electron density, a variety of ligand-controlled regiodivergent carbonylation have been developed recently. For example, Liu et al. reported a regioselective alkoxy carbonylation of allenes in 2015,^[9] and Alper and co-workers develop an elegant palladium-catalyzed regioselective aminocarbonylation of styrenes.^[10] Additionally, several other original regioselective transformations on carbonylation have been established in recent years as well.^[11] Despite these achievements, regiodivergent carbonylative conversion of C=N double has rarely been reported.^[12] This is due to the polarized imine (C=N) groups place a part of positive charge at the carbon atom, making the carbon positive (electrophilic)-attracted by negatively charged nucleophiles

(Scheme 1b).^[13] Therefore, inverting the inherent polarity of the imines is the key to reach regiodivergent transformation.^[14] Additionally, borocarbonylation reaction of C=N double bonds offers an ideal option for the synthesis of α -amino ketones^[15] or α -boryl amides^[16] if the regioselectivity of the C=N double bond could be altered, which represent important building blocks in organic synthesis as well as with potent biomedical applications. Herein, we developed a ligand-controlled copper-catalyzed highly regioselective borocarbonylation of imines with Bpin₂ and alkyl iodides to give diverse α -amino ketones and α -boryl amides (Scheme 1c).



Scheme 1. Strategies for regiodivergent borocarbonylation of imines.

We commenced our studies with *N*,1-diphenylmethanimine (**1a**), 1-iodobutane (**2a**) and Bpin₂. Ancillary ligands were thought to be the crucial factor for the reaction, thus we screened ligands under our conditions (For details of the optimization process, see supporting information). As shown in Figure 1, both bipyridine (**L1**) as nitrogen ligand and BuPAD₂ (**L2**) as bulky and electron-rich ligand failed to produce the desired product α -amino ketones **3a** or α -boryl amides **4a**. To our surprise, by using the classic ligand triphenylphosphine (**L3**), we been able to obtain 53% yield of **3a** with high selectivity (>20:1), and the major byproduct was *N*-(1-phenylpentyl)aniline. Then this type of ligand with different electronic properties were examined, phosphine ligands with electron-withdrawing group (**L4-L6**) improved the reaction efficiency. On the other side, electron-donating ligands (**L7, L8**) decreased the reaction efficiency and steric hindrance (**L8**) reduced the reaction selectivity meanwhile. Bisphosphine ligands such as DCyPE (**L9**), DCyPP (**L10**), DCyPB (**L11**) and Cy-Xantphos (**L12**) delivered the wished **3a** in low yields and with poor selectivity. In the absence of ligand, **3a** could be formed in 61% yield and without **4a** formation. Impressively, only α -boryl amides **4a** (10% yield, **3a:4a** <1:20 selectivity) was obtained by switching to NHC

ligands IMes (**L14**). The starting material **1a** was completely converted and the main byproduct was *N*-(phenyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)aniline due to the complete consumption of **2a**. Finally, the desired product **4a** can be generated preferentially (62% yield, <20:1) by careful fine-tuning the loading of **2a** and other reaction parameters. Among the other analyzed NHC ligands (**L15-L18**), ^{Me}IMes ligand (**L15**) with enhanced donating-electron property improved the yield of

4a to 71% with high selectivity (<20:1). These results imply that the regioselective addition of LCuBpin to C=N double bonds is mainly dictated by the electronic properties of the ligands applied. Specifically, phosphine ligands with electron-withdrawing group mainly produce α -amino ketones **3a**, while ligands with strong coordination property tend to give α -boryl amides **4a**.

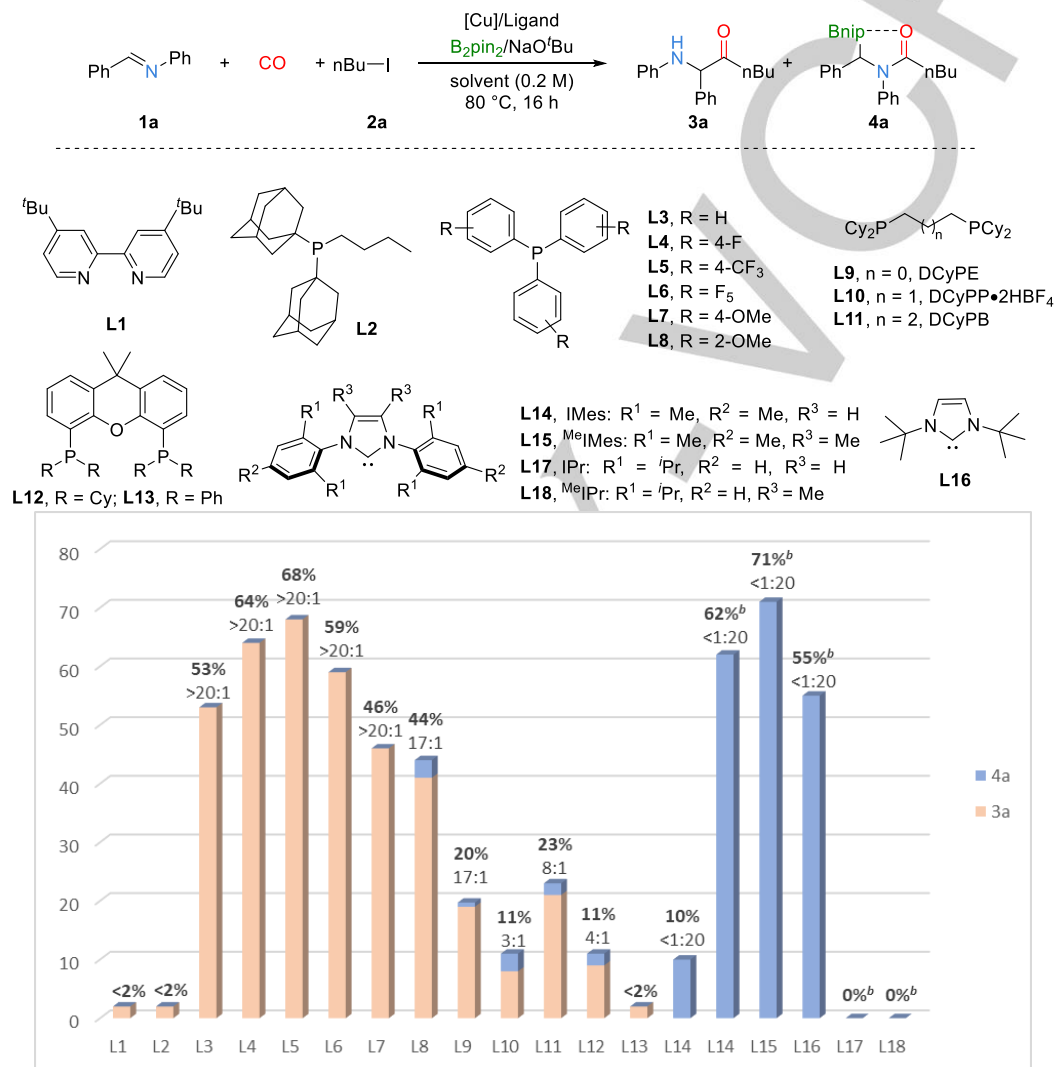


Figure 1. Cu-catalyzed borocarbonylation of imine: Influence of ligands. [a] Reaction conditions: **1a** (0.2 mmol), **2a** (2.4 equiv.), CuCl (10 mol%), ligand (**L1** and **L9-L13**: 10 mol%; **L2-L8**: 20 mol%), B₂pin₂ (3.0 equiv.), NaO^tBu (3.0 equiv.), CO (10 bar), THF/toluene (4:1, 0.2 M), 80 °C, 16 h; in the case of carbene ligand, NHC-CuCl complex was used. [b] **2a** (3 equiv.), NHC-CuCl complex (10 mol%), B₂pin₂ (1.5 equiv.), NaO^tBu (1.5 equiv.), toluene (0.2 M).

With the two sets of optimized reaction conditions in hand, we examined the scope of this regioselective copper-catalyzed carbonylation of imines with alkyl iodides for the synthesis of α -amino ketones. As shown in the Table 1, alkyl iodides with different chain length (**3a-3e**) showed good reactivity, delivered the corresponding products in moderate yields. Substrates containing ether or thiophene produced the desired products in moderate yields as well. However, the reaction failed in the case of secondary iodoalkane (**3i**). Subsequently, we evaluated a series of imines. Imines derived from benzaldehyde and anilines bearing electron-withdrawing groups such as F, Cl, and Br

showed excellent reactivity, afforded the corresponding α -amino ketones in moderate to excellent yields (**3j**, **3n**, **3p** and **3q**). Amide, morpholine, methoxyl-containing imines were also compatible with the reaction conditions to produce the target products in slightly decreased yields (**3k**, **3l**, **3m** and **3o**). The results reveal that electronic properties of imines are consistent with electronic effects from the ligand. Moreover, *ortho*-ether or thioether substituted imines were also tolerated well (**3r** and **3s**). Finally, imines derived from anilines and electron-poor or electron-rich benzaldehyde were tested; the corresponding products were successfully prepared in moderated yields (**3t-3cc**).

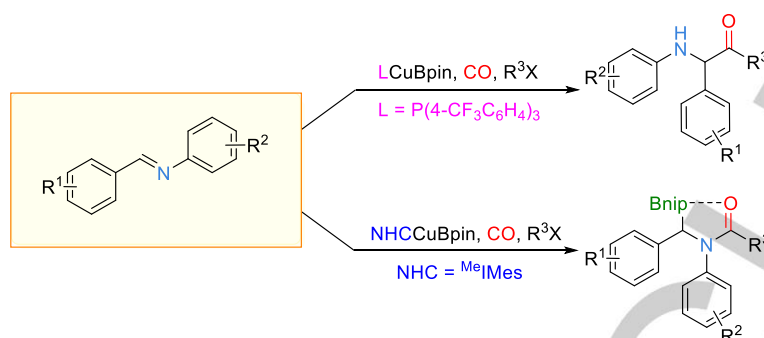
In summary, a novel ligand-controlled copper-catalyzed borocarbonylation for the selective synthesis of α -amino ketones and α -boryl amides from imines and alkyl iodides has been developed. In this catalyst system, the choosing of the appropriate ligand is the key for the regioselectivity control: α -amino ketones were produced selectively in good yields with (*p*-CF₃C₆H₄)₃P as the ligand; while the corresponding α -boryl amides were obtained in high regioselectivity with MeIMes as the ligand.

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Keywords: regioselective • carbonylation • α -amino ketones • α -boryl amides • iodoalkane

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