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Improved Process for a Copper-Catalyzed C−N Coupling in the Synthesis of Verubecestat

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Supporting Information

ABSTRACT: Verubecestat is a β-site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitor which was previously evaluated for the treatment of Alzheimer's disease. The synthesis of verubecestat relies on a Cu-catalyzed carbon−nitrogen coupling. During process development, observations of impurity formation led to a more robust understanding of the catalyst. The transformation was discovered to be highly dependent on the ratio of ligand to substrate concentration during the course of the reaction. In-depth studies aimed at attaining mechanistic understanding provided an explanation of experimental findings and ultimately led to the identification of conditions that resulted in a more robust process.

KEYWORDS: *C−N coupling, BACE1 inhibitor, NMR spectroscopy, copper catalysis*

Verubecestat (**1**)[1] is a β-secretase 1 (BACE1) inhibitor that was previously under clinical investigation for the treatment of Alzheimer's disease.[2] We recently disclosed a commercial manufacturing route of the active pharmaceutical ingredient which begins with a Mannich-type addition of sulfonamide **3** to *tert*-butyl sulfinimine **2**. Successive copper-catalyzed coupling with 5-fluoropicolinamide **6** and *p*-methoxybenzyl deprotection provide the central amide present in the active pharmaceutical ingredient (API). Lastly, guanidinylation with cyanogen bromide furnishes verubecestat in 61% overall yield (Scheme 1).[3]

During development, the C−N coupling between **5** and **6** drew interest due to the varying impurity profile generated during experiments exploring process robustness (Scheme 2). The current reaction conditions require combining sulfonamide **5** and 1.15 equiv of picolinamide **6** in a toluene:water (~2.5:1) mixture in the presence of 20 mol % CuI and 25 mol % ligand **L1**.[4] The resulting biphasic mixture is heated at 104 °C under a closed, inert system for 20 h with 7 equiv of K_2CO_3. Upon cooling, the reaction is diluted with EtOAc and washed with ethane-1,2-diamine. Distillation to remove residual water and EtOAc and direct crystallization upon addition of heptane furnishes desired amide **7** in 89−92% isolated yield.

While the reaction typically generates **7** in reproducibly >89% yield and has been demonstrated on >50 kg scale, it suffers from a few notable issues. Specifically, reaction temperatures of >100 °C are required to obtain satisfactory conversion, which results in generation of impurity **10**, a side product from the reaction between the ligand and product **7** (Figure 1). The high temperature also necessitates the use of excess amide **6**. Hydrolysis of **6** to carboxylic acid **11** is a prominent side reaction but has not been problematic as the acid is easily washed away in the aqueous phase and residual **6** can be removed downstream via crystallization if it is present in <5 area%[5] following isolation of product **7**. However, during our extensive Design of Experiments (DoE) studies,[6] variable amounts of residual **6** were present at the end of reaction with upward of 8 area% remaining. While we could reduce the residual amide at the end of the reaction by extending the reaction time or running at higher temperature to promote hydrolysis, these changes would result in an increase of impurity **10**[7] whose presence is greatly increased at temperatures above 100 °C and has limited rejection downstream. These robustness issues compelled us to gain a better understanding of this transformation.

We began by evaluating the root cause of the hydrolysis of amide **6** and whether the catalytic system may be involved in the hydrolysis mechanism (Table 1). We subjected **6** to toluene and water in the presence of K_2CO_3 and heated the mixture at 104 °C. After 5 h, approximately 8% conversion to the carboxylic acid (**11**) was observed. Heating for a total of 10 h produced only 14% of **11**. When the reaction is repeated with 20 mol % of CuI, a significant rate enhancement of hydrolysis ensues, where 19 and 31% of **11** is produced after 5 and 10 h aging, respectively. Notably, introduction of ligand **L1** to mimic the copper coupling reaction retards the rate of the hydrolysis but still significantly outpaces the rate of reaction without copper present. These results indicate that copper plays a significant role in the hydrolysis of **6** and a competition for copper binding between the ligand and amide substrate exists.

NMR Studies of Copper Interactions. Given our data showing the impact of copper on hydrolysis coupled to the observation that the ligand inhibits conversion to the carboxylic acid, we hypothesized that the ligand and amide compete for the metal center. We utilized NMR spectroscopy to investigate this hypothesis, where initial experiments included recording ^1H and ^{13}C NMR spectra of ligand **L1** in toluene-*d*[8] in the presence of 0, 0.5, 1, 2, and 5 equiv of CuI (Figure 2). Observable shifts in ^1H and ^{13}C resonances of **L1**

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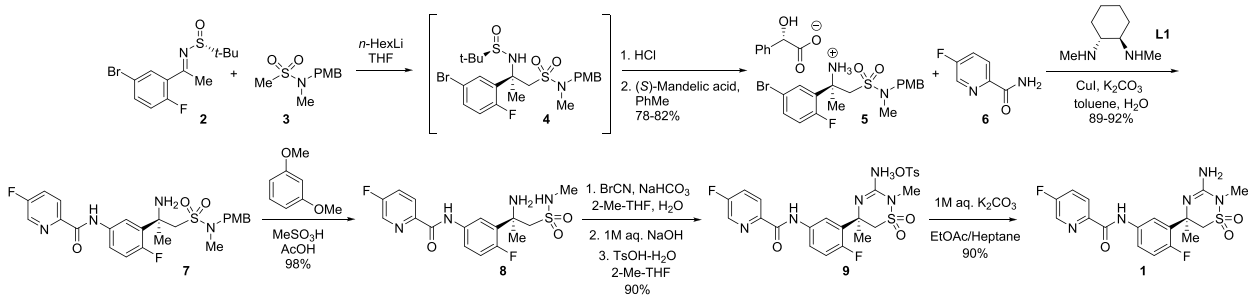
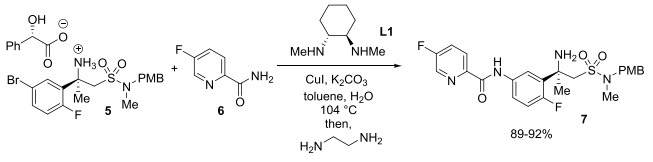
Scheme 1. Synthesis of Verubecestat



Scheme 2. Cu-Catalyzed C−N Coupling



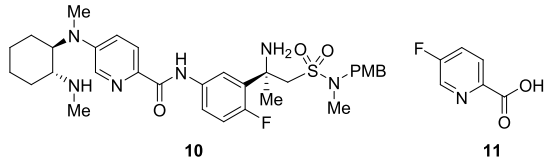
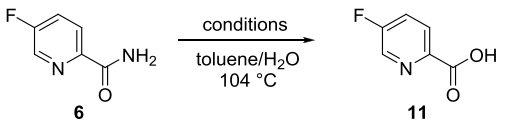


Figure 1. Impurities generated during C−N coupling reaction.

Table 1. Hydrolysis Study



entry	conditions	conversion (5 h, %)	conversion (10 h, %)
1	K_2CO_3	8	14
2	K_2CO_3/CuI (20 mol %)	19	31
3	K_2CO_3/CuI, **L1** (20 mol %)	11	25

were observed when going from 0 to 0.5 to 1 equiv of CuI, but adding more than 1 equiv provided no changes (Figure 2, spectra A−C). These results suggest a formation of **L1**−Cu complex with 1:1 stoichiometry. Another important observation is that the interaction occurs in a fast exchange regime on the NMR time scale, where apparent chemical shifts are a weighted average between the free and bound states, resulting in apparent shifts of **L1** resonances. The upfield shift upon binding Cu(I) and downfield shift upon decomplexation is consistent with that previously reported in the literature.[8]

Having investigated the copper−ligand complex by NMR spectroscopy, we explored how another major reaction component, amide **6**, would affect its equilibrium. If **6** disrupts the interaction between **L1** and copper, the resonances of **L1** were expected to shift back toward the free state. We designed a competition experiment by charging increasing amounts of **6** to the 1:1 mixture of **L1** and CuI. While addition of 10 mol % of **6** yielded minimal changes, increasing the amount to as high as 50 mol % resulted in expected shifts in **L1** ^{1}H resonances, indicating that the fraction of the ligand is becoming unbound. The shifts were even more pronounced when the amount of **6** was increased to 1 equiv, consistent with the hypothesis of a competition for copper between the ligand and the reactant (Figure 2, spectra D−F). Notably, product **7** did not show competitive binding observed for amide **6** as supported by a similar experiment where increasing loading of **7** did not change chemical shifts of 1:1 Cu−ligand complex (see the Supporting Information). The final NMR experiment run was to simulate reaction conditions in which 1.15 equiv of **6** was charged to 0.2 equiv of CuI and 0.25 equiv of **L1**. ^{1}H chemical shifts of **L1** resonances are very similar to those in an earlier experiment with copper−ligand ratio of 0.5 (Figure 2, spectra B and G). These results indicate that under the reaction concentrations, approximately half of all copper was bound to the ligand **L1** with the other half being sequestered by binding the reactant **6**. Our NMR data demonstrate that **6** binds copper efficiently and competitively with **L1** with large excesses of **6** inhibiting the binding of **L1** to the metal. This observation is underscored by a recent disclosure by McGowan and coworkers where they found picolinamides can be effective Cu−ligands for C−O coupling reactions.[9] On the basis of these experiments, we hypothesized that minimizing the concentration of amide **6** during the course of the reaction may allow us to obtain better catalyst performance and minimize side reactions such as hydrolysis and S_NAr chemistry between the ligand and product that lead to the formation of **10** and **11**.

Proposed Reaction Pathway. On the basis of our observations from the NMR studies combined with previous work out of the Buchwald laboratory, we proposed a possible reaction pathway for the formation of **7** (Figure 3).[10] Coordination and subsequent deprotonation of the amide to the Cu−ligand (Cu−**L1**) complex forms catalyst complex **B**. Reaction with aryl bromide **5** allows the process to proceed toward a productive pathway. However, when the amide is present in high concentration, a second equivalent of amide can displace **L1**, resulting in the generation of **C**, which could also exist in equilibrium with complex **D**, leading to hydrolysis of the amide starting material and is a nonproductive pathway. As first proposed by Bacon and Karim[11] and later supported by the group of Hartwig,[12] the optimal nucleophile to Cu ratio is <1, which should prevent or minimize the concentration of **C** in the reaction. This problem is potentially exacerbated by having an additional Lewis basic site present on the amide. Buchwald postulates that under these conditions, the reaction is first order in **L1** and inversely related to the concentration of amide **6**.[7] Thus, the desired copper coupling reaction rate should be suppressed by having a high concentration of amide in solution. A possible solution to improving the impurity profile would be to maintain a low concentration of **6** throughout the course of the reaction. The change in protocol

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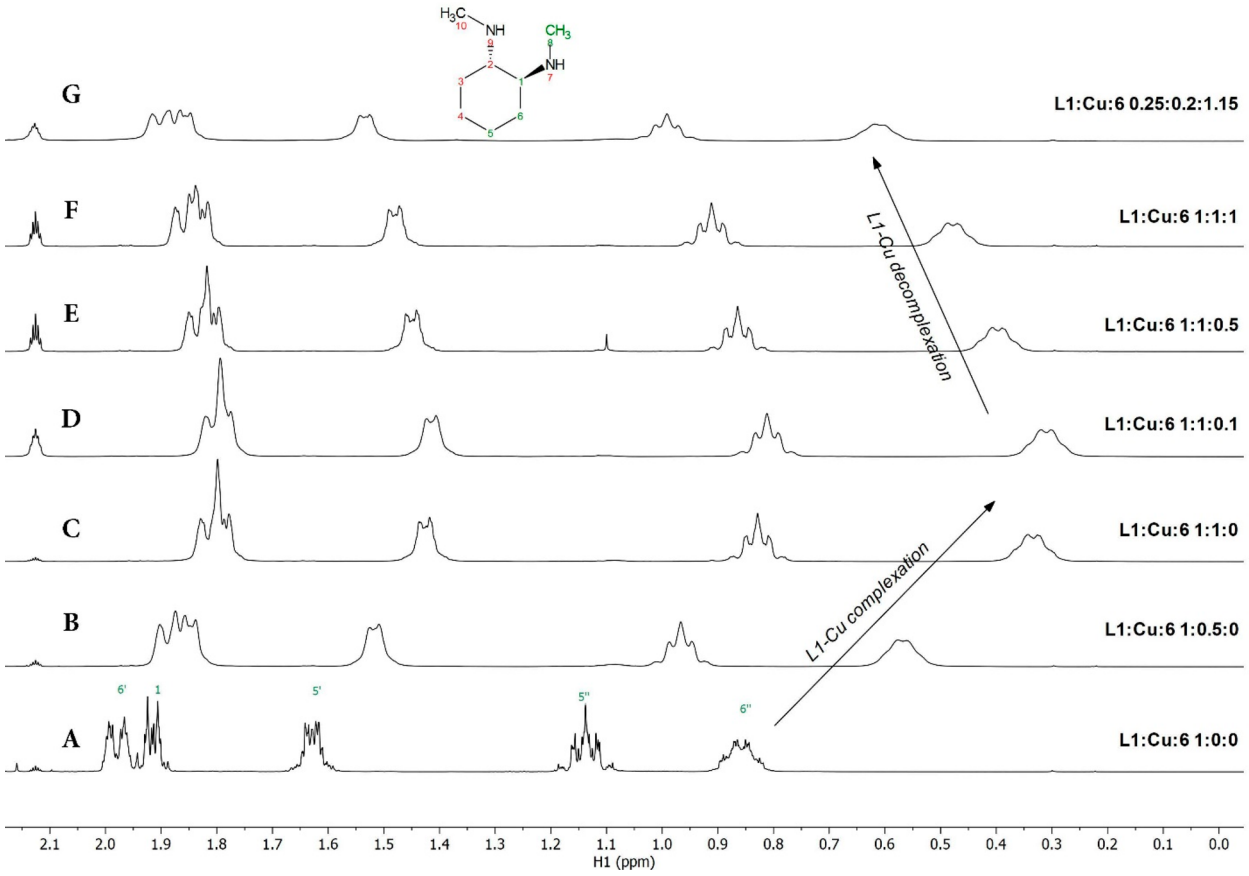

Figure 2. [1]H NMR study of competitive Cu binding between the ligand **L1** and reactant **6**. A: 1 equiv of **L1**, no copper or **6**; B: 1 equiv of **L1** and 0.5 equiv of CuI; C: 1 equiv of **L1** and CuI each; D: 1 equiv of **L1** and CuI each and 0.1 equiv of **6**; E: 1 equiv of **L1** and CuI each and 0.5 equiv of **6**; F: 1 equiv of **L1**, CuI and **6** each; G: 1.15 equiv of **6**, 20 mol % of CuI, and 25 mol % of **L1**. All experiments were performed in toluene-*d*8, D_2O, and K_2CO_3.

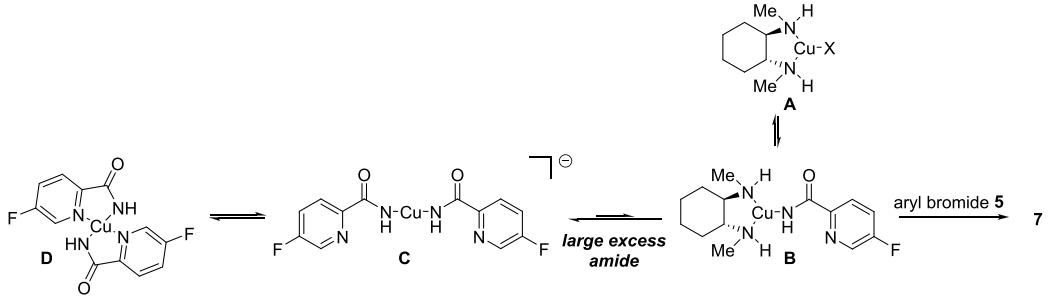

Figure 3. Proposed reaction pathway.

could possibly allow us to perform the reaction at lower temperatures and lower the charging of amide **6** due to decreased rates of hydrolysis.

Modified Procedure. To keep the concentration of amide low during the course of the reaction, we decided to charge **6** in aliquots over the course of 8−10 h to the reaction solution. This change should allow for roughly equal concentrations of **6** and **L1** throughout the reaction timeline. Our previous studies indicated that we could remove up to 5 area% of **6** downstream, so we limited the total charging of the amide (**6**) to 1.05 equiv. Due to the limited solubility of **6** in toluene at room temperature, we decided to charge amide to the reaction as a solid, and because of this constraint, we performed the reactions inside an oxygen-free glovebox.[13] We started by adjusting the initial loading of amide **6** to only 0.25 equiv, which matched the charging of ligand **L1**. The internal temperature of the reaction was brought to 80 °C, and the remaining amount of amide was charged in 5 aliquots over the extended time. After mixing for 20 h, only 91% conversion and 89% assay yield had been achieved (Table 2, entry 1). We attributed this incomplete conversion to the lower temperature at which the reaction was performed. Increasing the temperature to a range of 94−100 °C allowed for 99% conversion of the starting material and 97% assay yield (entry 2). Increasing the scale to 5 g allowed for a better control of the temperature while affording a similar high conversion and assay yield.

Lastly, we increased the scale to 75 g (entry 4). This size of reaction allows us to mimic pilot scale conditions with the use of overhead mixing assauging our concerns about the scalability of our process. Maintaining an inert atmosphere

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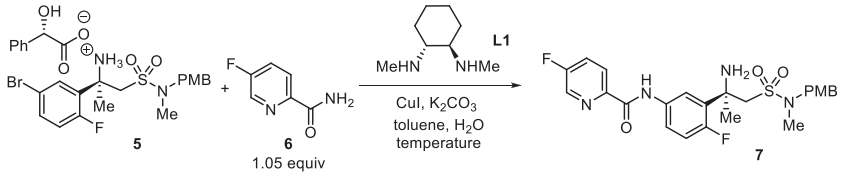
Table 2. Controlled Addition Study[a]



entry	scale (g)[b]	temperature (°C)	equiv of **6**	charges of **6**	conversion (%)[c]	assay yield (%)[c]	area % **10**[c]	area % **6**[c]
1	5	80	1.05	5	91	89	n/d	3.4
2	1	94–100[d]	1.05	4	99	97	0.19	1.7
3	5	96	1.05	5	98	95	0.17	3.3
4[e]	75	94	1.05	8	98	94	0.16	1.2
5[f]	45	104	1.00		95	90	0.32	0.08
6[f]	45	92–96	1.15		95	88	0.08	8.0

[a]Reactions performed by initially charging 0.25 equiv of **6** and bringing the mixture to the desired reaction temperature. The remaining 0.8 equiv of **6** charged over 8 h with total reaction time being 20 h. [b]Amount of parent amine following salt break. [c]Determined by reverse phase HPLC. [d]Reaction was aged on a hot plate, rendering temperature control difficult. [e]Amide **6** was charged as a slurry. [f]The entire charge of **6** was performed at the beginning of the reaction.

while charging **6** was challenging and impractical on scale. To render the procedure amenable to pilot plant scale, we opted to charge the amide as a suspended slurry mixture and run the reaction open with a reflux condenser as opposed to the closed, pressurized system on small scale. This modification forced us to begin the Cu-catalyzed reaction at a slightly higher concentration as the volume would increase over time. We began by running the reaction in ∼4 mL of toluene per gram of aryl bromide **5**. Amide **6** was slurried in 1 mL/g of toluene with respect to **5**. Nonetheless, the increase in scale and modified reaction procedure provided nearly identical results to the smaller scale runs, where high conversion and assay yields were obtained. Importantly, in all four of these runs, the impurity **10** was maintained below 0.2 area% in the reaction stream, and amide **6** was consistently below 5 area%. The portion-wise addition of amide **6** resulted in improved reaction performance compared to the initial procedure. Using only 1.0 equiv of amide **6** charged upfront and maintaining the reaction at 104 °C afforded only 95% conversion, lower assay yield, and increased amide hydrolysis (entry 5). We also performed the conventional batch mixing procedure between 92 and 96 °C while keeping the amide loading at 1.15 equiv. Again, the reaction failed to exceed 95% conversion.

In summary, we demonstrated that there is a competition between the ligand (**L1**) and the amide substrate (**6**) with the copper catalyst used in the formation of **7**. This critical attribute of the reaction requires the process to be run at high temperatures, increasing the risk of impurity generation and inconsistent reaction profiles. We used NMR spectroscopy to interrogate the catalyst system and used that data to develop a revised procedure where the concentration of the amide substrate is kept roughly equal to the concentration of the ligand during the course of the reaction. This change improves catalyst performance and allows the process to be run at lower temperatures. This process improvement alleviates the risk that critical impurity levels could increase and allows us to decrease stoichiometry of the expensive reagent (i.e., amide **6**). We anticipate that these findings could be impactful to other Cu-mediated C−N bond-forming transformations which are ubiquitous in academic and industrial applications.

Procedure. *Stage 1.* To a 2-L cylindrical reactor equipped with an overhead stirrer and thermocouple was charged (*R*)-2-(5-bromo-2-fluorophenyl)-1-(*N*-(4-methoxybenzyl)-*N*-methylsulfamoyl)propan-2-aminium (*S*)-2-hydroxy-2-phenylacetate (**5**, 100 g, 167 mmol). Toluene (500 mL) and H_2O (420 mL) were added, and the internal temperature was adjusted to 50 °C. After mixing for 2 h, the mixture was cooled to 35 °C, and the phases were settled and separated.

Stage 2. The organic layer was charged to a 1-L cylindrical reactor equipped overhead stirrer, reflux condenser, N_2 inlet, and thermocouple containing 5-fluoropicolinamide (4.25 g, 30 mmol), CuI (5.91 g, 30 mmol), and K_2CO_3 (147 g, 1.06 mol). H_2O (182 mL) and **L1** (5.48 g, 38 mmol) were charged. The reactor was closed and sparged with N_2 for approximately 1 h. The reaction was then heated to refluxing temperature (94 °C). A separate round-bottom flask equipped with magnetic stirring bar was charged with 5-fluoropicolinamide (20.3 g, 145 mmol) and toluene (75 mL). The flask was sealed with a rubber septum and sparged with N_2 for 30 min. The picolinamide (**6**) solution was charged portion-wise every hour for 8 h via cannula transfer. The reaction was aged for a total of 20 h at 94 °C and then cooled to 30 °C. Ethane-1,2-diamine (30.4 mL, 455 mmol) was added followed by EtOAc (75 mL). Contents were aged for 30 min. Phases were settled and separated. Organics were washed with water (2 × 300 mL) and 10 wt % NaCl (300 mL). The organic layer was separated and distilled to ∼200 mL. The batch was heated to an internal temperature of ∼60 °C to dissolve any remaining solids. 2-Propanol (15 mL) and *n*-heptane (80 mL) were added. The batch was cooled to 50 °C and seeded with **7** (400 mg). The mixture was aged for 2 h, and *n*-heptane (270 mL) was added over 8 h. The mixture was cooled to 30 °C, and an additional 400 mL of *n*-heptane was added over 3 h. The mixture was aged overnight and then filtered. The solids were washed with a 2:3 mixture of toluene to *n*-heptane (200 mL) and once with *n*-heptane to provide **7** as a white solid (69 g, 90% yield).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00192.

General experimental methods for the hydrolysis study, NMR spectroscopy study, modified C−N coupling procedure, previous C−N coupling procedure, DoE data, and characterization data for product **7** and impurity **10** (PDF)

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Notes

The authors declare no competing financial interest.

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(5) Area% refers to area under the curve as determined by reverse phase HPLC.

(6) DoE data are included in the Supporting Information.

(7) Generation of **10** in greater than 0.8 area% was difficult to remove through crystallization and DoE data suggested this impurity was a risk for successful process validation.

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(13) Oxygen is detrimental to the reaction and has been shown to limit conversion.

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