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COMMUNICATION

# Transition metal-free ether coupling and hydroamidation enabling the efficient synthesis of congested heterocycles

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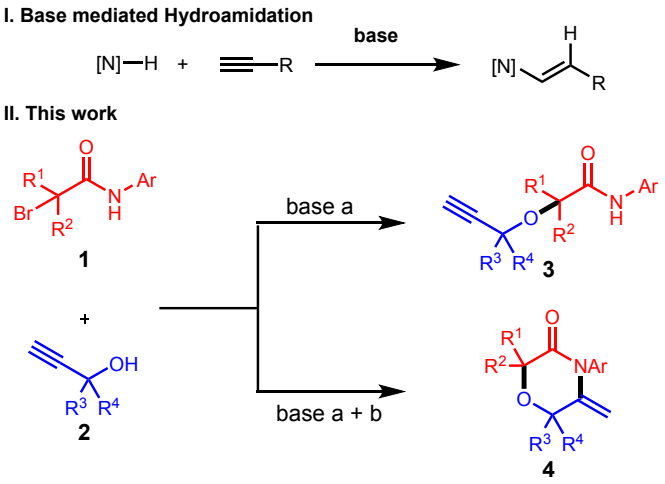
**In this study, we discovered that α-bromocarboxamides react with alkynols containing tertiary alcohol moieties to produce congested ethers or heterocycles. Here, the etherification and hydroamidation reactions can be controlled by a suitable base. Both C-O and C-N bond formations occurred without a transition-metal catalyst. The stereospecific etherification and cyclization of diastereo-enriched α-bromocarboxamide afforded the corresponding diastereo-enriched ether and heterocyclic compound.**

The inter- or intramolecular reactions of heteroatomic nucleophiles and proper electrophiles can produce heterocycles via a cyclization process. Many nitrogen-containing heterocycles have been synthesized by using unique nitrogen reactivities[1]. After the discovery of transition metal-catalyzed intramolecular hydroamidation using amide-based nucleophiles by Larock[2] and Anderson [3], various C–N bond formation reactions, including carboamidations, were developed to synthesize complex nitrogen heterocycles [1,4-6], such as pyrrolidines, indolidines, and isoxazolidines. These heterocycles are often observed in biologically active compounds and natural products [7]. However, traditional transition metal-free hydroamination or -amidation reactions have been used to synthesize various heterocycles. For example, the Shostakovskii and Trofimov group reported the base-mediated hydroamination reaction of indole and acetylene at 220 °C [8]. Knochel reported CsOH-catalyzed hydroamination [9], and some groups developed base-mediated or -catalyzed hydroamination or -amidation reactions with alkynes [10-12] (Scheme 1. I).

We have studied the various radical reactivities of α-bromocarbonyl compounds in the presence of Cu or Fe catalysts [13]. Recently, we reported the stereospecific etherification reaction of α-bromocarboxamides and tert-alkyl alcohols mediated by $Cs_2CO_3$ [14]. Kürti reported the Cu-catalyzed alkoxylation of non-chiral α-bromocarboxamides with a tertiary alkyl source[15]. Moreover, Mizuta reported the Ag-mediated α-alkoxylations of α-bromocarboxamides[6]. During the course of our study, we discovered that α-bromocarboxamides (**1**) react with alkynols (**2**) containing tertiary alcohol moieties to produce ethers (**3**) or heterocycles (**4**) in the absence of a transition metal catalyst. Here, etherification is followed by hydroamidation. Both etherification and hydroamidation can be controlled by adding bases. Herein, we report a transition-metal-free ether coupling and hydroamidation controlled by a base (Scheme 1. II).




**Scheme 1**. Hydroamidations

Optimization studies were performed by combining α-bromocarboxamide (**1a)** (1 equiv), an alkynol (**2a)** containing a tertiary alkyl alcohol moiety (3 equiv), and a base (2 equiv) in a solvent at room temperature (Table 1). Initially, we screened various bases, including $Cs_2CO_3$, $K_3PO_4$, NaOH, and *i*-$Pr_2EtN$, to obtain the hydroamidation product (**4a),** which contained a tertiary carbon attached to oxygen (entries 1-4). $Cs_2CO_3$ afforded 77% yield of sterically congested ether **3a;** however, **4a** was not produced here. Generally, the Williamson-type

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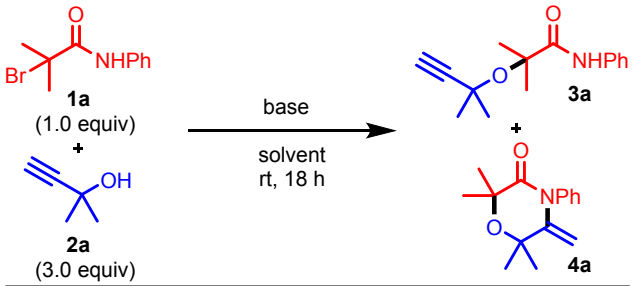
etherification reaction of tert-alkyl alcohols and tert-alkyl halides is difficult to perform due to the low nucleophilicity of tert-alkyl alcohols and steric bulkiness of tert-carbons in alkyl halides. Although a few studies have reported on the synthesis of sterically congested ethers[17-21] or cyclic ethers[22], the general methodology to prepare sec- or tert-alkyl ethers has not yet been established. This suggests an important hint to synthesize sterically bulky ethers. Moreover, **4a** was produced on changing the solvent of the reaction. When the reaction was carried out in cyclopentyl methyl ether (CPME), 2% of **4a** was obtained (entry 5). This encouraged us to further optimize the reaction. $CH_2Cl_2$ and AcOEt improved the yield of **4a**, while acetone was found to be more effective (entries 6-8). We also carried out the reaction in DMSO, NMP, DMA, MeOH, and water, but the reactions were sluggish. To obtain **4a** as the sole product, we tested combinations of two different bases in this reaction. Consequently, the combination of $Cs_2CO_3$ and $K_3PO_4$ afforded **4a** selectively (entries 9 and 10). We screened various amounts of and various types of bases and solvents (entries 11-16) for this reaction. However, the conditions used in run 14 ($Cs_2CO_3$ and $K_3PO_4$ in MeCN/Hexane) were found to be optimal. We also tested various temperatures, but not effective due to the decomposition of **1a** to methacrylamide.

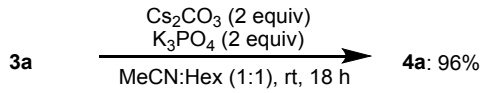
**Table 1.** Optimization of reaction conditions [a]




| entry | base (equiv) | solvent | yield (**3a**) | yield (**4a**) |
|---|---|---|---|---|
| 1 | $Cs_2CO_3$ (2) | THF | 49%(77%[b]) | 0% |
| 2 | $K_3PO_4$ (2) | THF | 17% | 0% |
| 3 | NaOH (2) | THF | 22% | 0% |
| 4 | *i*-$Pr_2EtN$ (2) | THF | 0% | 0% |
| 5 | $Cs_2CO_3$ (2) | CPME | 75% | 2% |
| 6 | $Cs_2CO_3$ (2) | $CH_2Cl_2$ | 54% | 17% |
| 7 | $Cs_2CO_3$ (2) | AcOEt | 73% | 15% |
| 8 | $Cs_2CO_3$ (2) | Acetone | 7% | 47% |
| 9 | $Cs_2CO_3$ (2)/$K_3PO_4$ (2) | Acetone | 0% | 67% |
| 10 | $Cs_2CO_3$ (2)/$K_3PO_4$ (2) | MeCN | 0% | 62% |
| 11 | $Cs_2CO_3$ (2)/$K_3PO_4$ (1) | MeCN | 17% | 50% |
| 12 | $Cs_2CO_3$ (2)/$K_3PO_4$ (2) | THF | 9% | 46% |
| 13 | $Cs_2CO_3$ (2)/$K_3PO_4$ (2) | Hexane | 0% | 64% |
| 14 | $Cs_2CO_3$ (2)/$K_3PO_4$ (2) | MeCN/Hexane[c] | 0% | 74% |
| 15 | $Cs_2CO_3$ (2)/$Na_2CO_3$ (2) | MeCN | 44% | 14% |
| 16 | $Cs_2CO_3$ (2)/NaOH (2) | MeCN | 0% | 44% |

[a]A mixture of **1a** (0.50 mmol), **2a** (1.5 mmol), and base (2 equiv), was stirred at room temperature for 18 h under $N_2$. [b]The reaction time was 24 h. [c]The reaction was carried out in MeCN/Hexane (1/1).

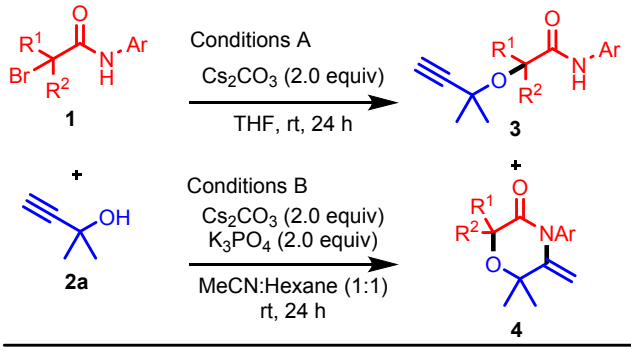
We confirmed that the combination of $Cs_2CO_3$ and $K_3PO_4$ is most effective in obtaining **4a** from **3a** (Scheme 2). When **3a** was mixed with $Cs_2CO_3$ and $K_3PO_4$, the intramolecular hydroamidation of **3a** occurred to produce **4a** in excellent yield. In this reaction, one of each bases were required. This result indicates that **4a** is generated via tandem etherification followed by hydroamidation.




**Scheme 2**. Control experiment

The reactivities of various α-bromocarboxamides (**1**) were examined under the optimized or slightly modified reaction conditions (Table 2). α-Bromocarboxamides possessing various functionalized aryl groups on *N* (**1b-1i**) afforded the corresponding congested ethers (**3b**-**3i**) or hydroamidation products (**4b**-**4i**) in moderate to good yields with perfect selectivities under the optimized or modified conditions (entries 1-8). For example, sterically hindered 2-An (anisyl) substituted **1b**

**Table 2.** Substrate scope of **1**[a]



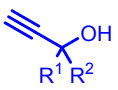

| entry | Substrates **1** | Conditions A yield (**3**) | Conditions B yield (**4**) |
|---|---|---|---|
| | Ar | | |
| 1 | **1b**: 2-An | **3b**: 85% | **4b**: 76%[b,c] |
| 2 | **1c**: 3-An | **3c**: 72%[d,e] | **4c**: 71% |
| 3 | **1d**: 4-An | **3d**: 68%[e] | **4d**: 66% |
| 4 | **1e**: 4-$BrC_6H_4$ | **3e**: 68%[e] | **4e**: 70% |
| 5 | **1f**: 4-$(EtO_2C)C_6H_4$ | **3f**: 45% | **4f**: 34% |
| 6 | **1g**: 3-$(EtO_2CCH{=}CH)C_6H_4$ | **3g**: 64% | **4g**: 69% |
| 7 | **1h**: 3-(phenylethynyl)$C_6H_4$ | **3h**: 81%[e] | **4h**: 70% |
| 8 | **1i**: 4-$(CN(CH_2)_3O)C_6H_4$ | **3i**: 69%[e] | **4i**: 68%[c] |
| | $R^1$ $R^2$ | | |
| 9 | **1j**: Et Et | **3j**: 74% | **4j**: 64% |
| 10 | **1k**: *n*-Pr *n*-Pr | **3k**: 76% | **4k**: 73%[c] |
| 11 | **1l**: *n*-Bu Et | **3l**: 80%[e] | **4l**: 76% |
| 12 | **1m** | **3m**: 79% | **4m**: 75% |

[a]A mixture of **1** (0.50 mmol), **2a** (1.5 mmol) was stirred under conditions A or B at room temperature for 18 h under $N_2$. Conditions A: $Cs_2CO_3$ (2 equiv) in THF. Conditions B: $Cs_2CO_3$ (2 equiv) and $K_3PO_4$ (2 equiv) in MeCN/Hexane (1/1). [b]5 equiv of $Cs_2CO_3$ and $K_3PO_4$ were used. [c]The reaction was 72 h. [d]The reaction time was 48 h. [b]1.5 equiv of $Cs_2CO_3$ was used.

required 5 equivalent bases and a longer reaction time to produce **4b** in 76% yield (entry 1). The reaction exhibited good functional group compatibilities; however, they required longer times or high equivalents of bases to obtain good yields (Runs 2-8). The reaction of 4-ethylbenzoate substituted alkyl bromide (**1f**) and **2a** produced **3f** and **4f** in moderate yield (entry 5). The acidity of the N-H proton could play an important role in this reaction; however, its actual contribution in this reaction was unclear. When the yield was low, HBr and methacryl amide (**1**) were generated. Sterically hindered bromides (**1j**-**1m**) afforded good yields of **3j**-**3m** and **4j**-**4m** (entries 9-12). For example, **1l** possessing long alkyl chains at the α-position of carbonyl group produced 76% of **3k** and 73% of **4k** (entry 10). In all other cases, the substrates exhibited good selectivities, and good yields were obtained under standard or modified conditions.

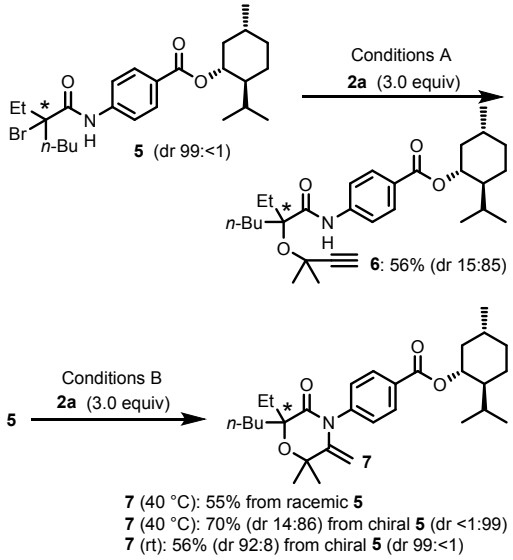
Next, we performed the reaction using different alkynol substrates (**2**) with acyclic- and cyclic alkyl chains (Table 3). Simple dialkyl substituted alkynols (**2b**-**2e**) afforded **3n**-**3q** or **4n**-**4q** in moderate to good yields (entries 1-4). Alkyl, aryl, or styryl substituted alkynols (**2f**-**2j**) also produced the corresponding products with good selectivities (entries 5-8). In the case of hydroamidation reactions, longer reaction time or high equivalents of bases were required to obtain good yields of **4.** This probably occurred due to the steric bulkiness of **2**. Sterically congested alcohols are generally less reactive toward such substitution reactions. However, these reactions occurred smoothly under optimized or modified conditions. Overall, the sterically congested alkynols **2** exhibited moderate to good reactivities.

**Table 3.** Substrate scope of 2[a]

| entry | Substrates **2** | | | Conditions A yield (**3**) | Conditions B yield (**4**) |
|---|---|---|---|---|---|
| | | $R^1$ | $R^2$ | | |
| 1 |  | **2b**: Et | Et | **3n**: 62% | **4n**: 68%[b,c] |
| 2 | | **2c**: *n*-Pr | *n*-Pr | **3o**: 57% | **4o**: 71%[b,d] |
| 3 | | **2d**: | -$(CH_2)_4$- | **3p**: 63% | **4p**: 73%[b] |
| 4 | | **2e**: | -$(CH_2)_5$- | **3q**: 76% | **4q**: 89%[d] |
| 5 | | **2f**: Me | Ph | **3r**: 63% | **4r**: 60%[d] |
| 6 | | **2g**: Et | Ph | **3s**: 74%[f] | **4s**: 71%[d,e] |
| 7 | | **2h**: *n*-Pr | Ph | **3t**: 68%[f] | **4t**: 68%[d,e] |
| 8 | | **2i**: Me | 4-Br$C_6H_4$ | **3u**: 63% | **4u**: 69%[d] |
| 9 | | **2j**: Me | styryl | **3v**: 50% | **4v**: 55%[d] |

[a]A mixture of **1a** (0.50 mmol), **2** (1.5 mmol) was stirred under conditions A or B at room temperature for 18 h under $N_2$. Condition A: $Cs_2CO_3$ (2 equiv) in THF. Condition B: $Cs_2CO_3$ (2 equiv) and $K_3PO_4$ (2 equiv) in MeCN/Hexane (1/1). [b]Run at 50 °C. [c]The reaction was 24 h. [d]The reaction time was 72 h. [e]5 equiv of $Cs_2CO_3$ and $K_3PO_4$ were used. [f]The reaction time was 48 h.

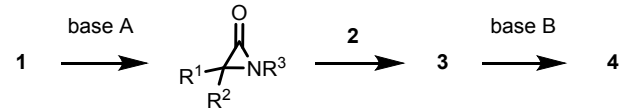
Diastereo-enriched tert-alkyl bromide **5** containing an (*l*)-menthol moiety was also tested under optimized conditions (Scheme 3). Intriguingly, the reaction of **2a** and **5** (dr 99:<1) under condition A resulted in 56% yield of **6** with dr 15:85. We expected that the ether product **6** could be racemic, but **6** exhibited a high diastereomer ratio. Under the hydroamidation




**Scheme 3.** Reaction with diastereo-enriched substrate

conditions (B), a higher dr was obtained for **7** with 56% yield. Elevated temperature effectively improved the chemical yield of **7** but decreased its selectivity. We were unable to determine the absolute configurations of products **6** and **7** because they were obtained in the form of liquids. We attempted to crystalize the derivatives of **6** and **7**, but they were also obtained in the liquid form, probably due to the presence of long alkyl chains at the α-position of the carbonyl group. A high dr is rarely observed in the reactions of chiral tert-alkyl halides and tert-alkyl alcohols.

Although an accurate mechanism is not yet available, 3 could generates via an aziridinone intermediate[23], which could be generated via proton abstraction by a base **1**. Subsequently, **4** is obtained via amidate attack to the alkyne.

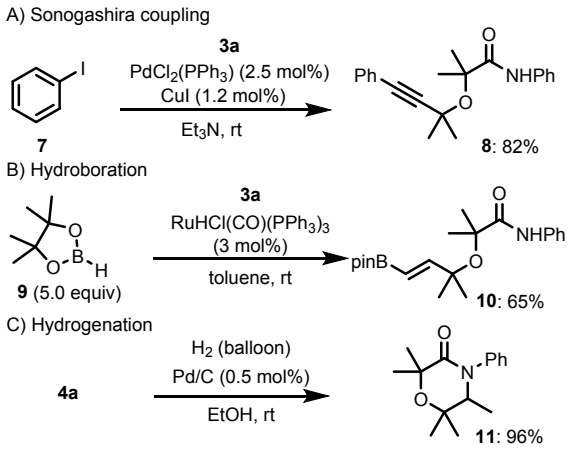



**Scheme 4.** Proposed mechanism

The synthesized products, including ether **3** and hydroamidation product **4** can be transformed into various functionalized products via C-C coupling, hydroboration, and reduction (Scheme 4). The Sonogashira reaction of **3a** with **7** produced **8** in 82% yield (Scheme 4A). Hydroboration of the alkyne moiety in **3a** afforded the 1-alkenyl boron compound **9** in the presence of a ruthenium catalyst (Scheme 4B). The methylene moiety in **4a** can be reduced by Pd/C-catalyzed hydrogenation reaction to produce the saturated heterocycle **11** (Scheme 4C).

## Conclusions

In conclusion, we established the ether coupling and hydroamidation reactions of α-bromocarboxamides and alkynols. Each reaction can be controlled by adding suitable bases. Reactions in the presence of $Cs_2CO_3$ underwent etherification reaction, while a combination of $Cs_2CO_3$ and $K_3PO_4$ produced heterocycles via etherification, followed by hydroamidation. Under our conditions, the reaction of amides (-NH) and alkynes enabled facile C–N bond formation without a transition metal catalyst. Furthermore, chiral α-bromocarboxamides underwent stereospecific reactions to produce chiral acyclic or acyclic products in good yields and selectivities.




**Scheme 5.** Transformations of **3a** and **4a**

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