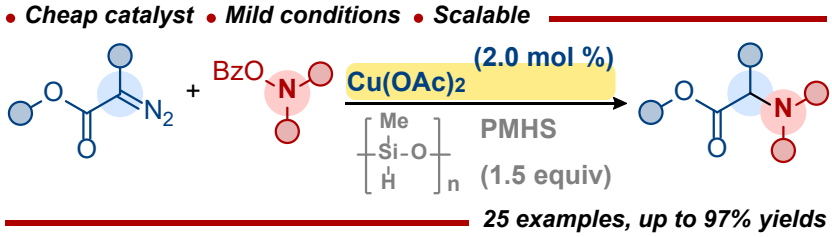
Cu-Catalyzed Cross-Electrophilic Coupling of α-Diazoesters with *O*-Benzoyl Hydroxylamines for the Synthesis of Unnatural *N*-Alkyl α-Amino Acid Derivatives

Yiu-Wai Yeung[1], Chun-Ming Chan[1], Yu-Ting Chen[1], Marco Chan[1], Mingyu Luo[1], Xin Gao[2], Bingnan Du*[2], Wing-Yiu Yu*[1]

[1]State Key Laboratory of Chemical Biology and Drug Discovery, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong

[2]School of Food Science and Pharmaceutical Engineering, Nanjing Normal University, Nanjing, China

*Corresponding Author



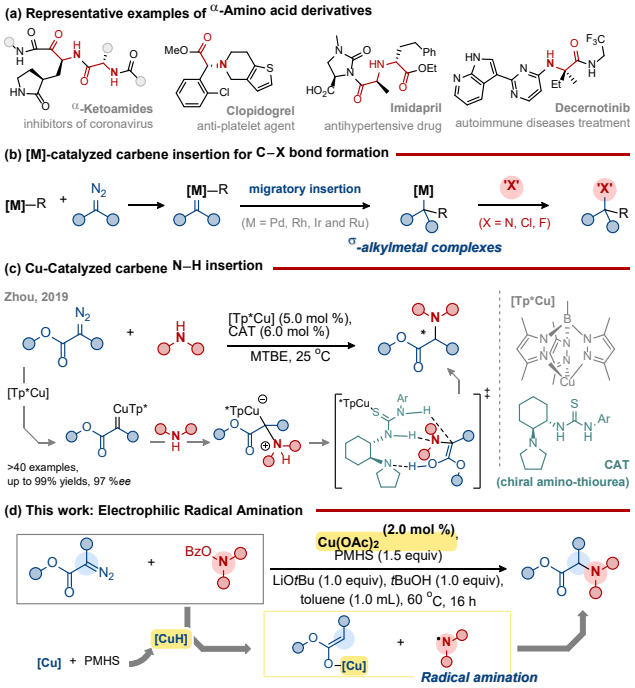
ABSTRACT: We describe a Cu-catalyzed cross-electrophilic coupling reaction for synthesizing α-amino acid derivatives from α-diazoesters with *O*-benzoyl hydroxylamines with $Cu(OAc)_2$ as the catalyst and polymethylhydrosilane (PMHS) as the hydride reagent. Excellent functional group compatibilities were demonstrated. With ethyl 2-diazo-3-oxobutanoate as precursor, a Cu-acetoacetate complex has been characterized by ESI-MS analysis. Results from the radical trap experiments are consistent with the intermediacy of nitrogen-centered radicals. This strategy offers a simple and inexpensive retrosynthetic disconnection for synthesis of α-amino acid derivatives.

Unnatural α-amino acids are attractive motifs for designers' peptides with new properties and functions that expand beyond the 20 encoded natural amino acids.[1] For example, peptidomimetic α-ketoamide inhibitors based on unnatural α-amino acids have been recognized as drug candidates for treating COVID-19 (Scheme 1a).[2] Transition metal-catalyzed carbene insertion reactions have emerged as a powerful tool for C–C and C–X bonds formation,[3,4] and enantioselective carbene N–H insertion offers a direct access to enantiopure α-amino acid derivatives.[4a,4c] In general, organometallic intermediates (M = Pd, Rh, Ir and Ru) containing allyl, aryl, alkynyl and amido ligands are known to undergo migratory carbene insertion to afford σ-alkylmetal complexes,[3a-3c] which would further transform to generate organic products with higher structural and functional complexity. For example, we developed the facile Rh-catalyzed arylative cross electrophilic coupling of α-diazoacetates with electrophilic reagents such as *N*-chloroamines,[5] *O*-carboxyl hydroxamic acids[6] and NFSI[7] for $C(sp^3)$–N / $C(sp^3)$–X (X = Cl, F) bond construction (Scheme 1b). Unlike the Pd and Rh-catalysis, the analogous Cu-catalyzed carbene cross coupling reactions exhibit some unique attractive features since the organocopper(I) complexes rarely undergo β-hydride elimination.[8] Indeed, the spontaneous protonation of the organocopper intermediates has been extensively exploited for C–H bond formation.[9] Thus far, few Cu-catalyzed carbene coupling examples concern C–N bond formation in the product turnovers.

While arylamines,[10] amides,[11] hydrazones[12] and carbazoles[13] were effective nitrogen coupling partners for carbene N–H insertion reactions, aliphatic amines remain challenging substrates due to their strong Lewis basicity.[4b] Moreover, aliphatic amines tend to react with the metal-carbenes to form metal-free ylide intermediate, leading to loss of enantiocontrol.[4c,14] Further complication such as β-hydride elimination occurs when α-alkyldiazoacetates are used as substrates.[3,4] Recently Zhou and co-workers have made important advances by the cooperative uses of a [Tp*Cu] complex and chiral amino-thiourea, which would mediate enantioselective protonation of the carbene-derived ylide intermediates (Scheme 1c).[14] This strategy has been extended to enantioselective carbene insertion to ammonia for the direct synthesis of amino acids.[15] Alternative to the conventional carbenoid amine coupling strategy, we herein describe a Cu-catalyzed cross-electrophilic coupling of α-diazoesters with *O*-benzoyl hydroxylamines for synthesizing unnatural α-amino acid derivatives. This reaction

employs $Cu(OAc)_2$ as the catalyst without the need of exogenous ligands under mild conditions (Scheme 1d).

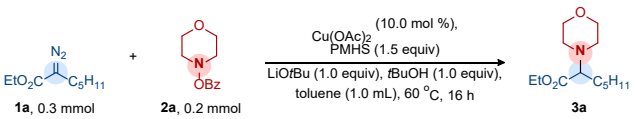
Scheme 1. Strategies for α-Amino Acids Derivatives Synthesis



To begin, we treated ethyl α-diazoheptanoate **1a** (0.3 mmol) and morpholino benzoate **2a** (0.2 mmol), PMHS (1.5 equiv), *t*BuOH (1.0 equiv) and Li*O*t*Bu (1.0 equiv) with $Cu(OAc)_2$ (10 mol %) in toluene at 60 °C for 16 h, and ethyl 2-morpholinoheptanoate **3a** was obtained in 82% yield (Table 1, entry 1). No desired products were formed without the $Cu(OAc)_2$ catalyst (entry 2). Reactions employing $Cu(MeCN)_4PF_6$, and $Cu(OBz)_2$ as catalyst afforded **3a** in moderate yields (entries 3–4). Regarding the use of auxiliary ligands, employing dtbbpy (4,4-di-*tert*-butyl-2,2-dipyridyl; 12 mol %) as ligand resulted **3a** in 72% yield (entry 5). However, the *rac*-BINAP ligand is apparently ineffective for this reaction with full consumption of hydroxylamine **2a** and >90% of diazoester **1a** recovery (entry 6).

Notably, the presence of PMHS is essential for successful amination, **3a** was formed in only 12% yield when the reaction was conducted without PMHS (entry 7). Other common silane reagents such as $HSi(OMe)_3$ and $HSiMe_2Ph$ gave poor results (entries 8–9). Evidently, the presence of the *tert*-butoxide anion is critical for effective coupling, since replacing Li*O*t*Bu / *t*BuOH to LiOAc / MeOH gave poor results (entries 10–13). Apart from toluene, other common organic solvents such as DCE, dioxane, and THF gave moderate (41–69%) results (entries 14–16). Yet, no desired products were obtained when the reaction was performed in DMF solvent (entry 17). To our delight, up to 89% **3a** formation was registered by lowering the catalyst loading to 2.0 mol % (entry 18).

Table 1. Reaction Optimization[a-d]

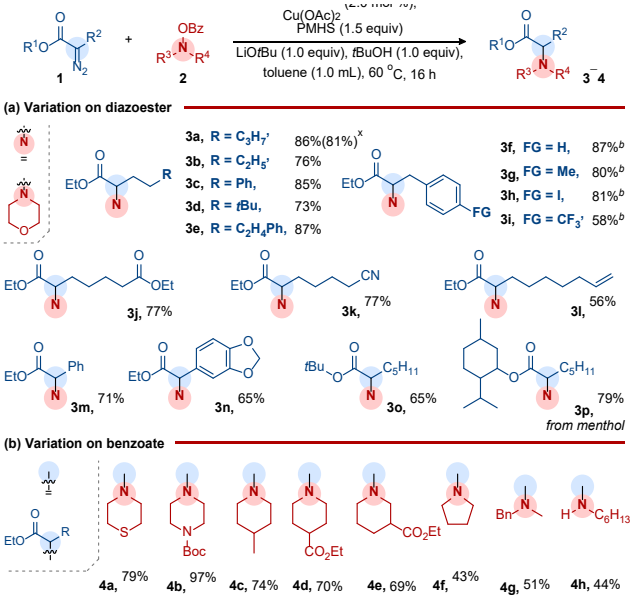


entry	variation from initial conditions	**3a** (%)
1	none	82
2	without $Cu(OAc)_2$	nd
3	$Cu(MeCN)_4PF_6$ instead of $Cu(OAc)_2$	60
4	$Cu(OBz)_2$ instead of $Cu(OAc)_2$	80
5	12 mol % dtbbpy as ligand	72
6	12 mol % *rac*-BINAP as ligand	nd
7	without PMHS	12
8	$HSi(OMe)_3$ instead of PMHS	13
9	$HSiMe_2Ph$ instead of PMHS	27
10	without Li*O*t*Bu	26[c]
11	without *t*BuOH	nd
12	LiOAc instead of Li*O*t*Bu	29[c]
13	MeOH instead of *t*BuOH	60
14	DCE instead of toluene	69
15	dioxane instead of toluene	41
16	THF instead of toluene	64
17	DMF instead of toluene	nd
18	**2.0 mol % of $Cu(OAc)_2$**	**89(86)**[d]

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol), $Cu(OAc)_2$ (10 mol %), PMHS (0.3 mmol), Li*O*t*Bu (0.2 mmol), *t*BuOH (0.2 mmol), PhMe (1 mL), 60 °C, 16 h; nd = not detected. [b]NMR yield (CH_2Br_2 as internal standard). [c]benzoylated product was observed as major product (>50%). [d]Isolated yield shown in parentheses.

With the optimized conditions in hand, we first examined the scope of diazoesters with **2a** as the model substrate (Scheme 2a). A series of alkyl-substituted diazoesters is effective coupling partners, and the corresponding amino esters **3a–3e** were obtained in 76–87% yields. A gram-scale reaction has been performed with 1.97 g of **3a** being obtained in 81% yield. Benzyl diazoesters with different substituents on the *para*-position of the aryl group (FG = H, Me, and I) were converted to their corresponding amines **3f–3h** in 80–87% yields. The results became less satisfactory when FG = CF_3. Diazoesters bearing other functional groups such as esters and cyanide reacted with **2a** to afford **3j** and **3k** in 77% yield respectively. Notably, diazoester with reactive C=C bonds is also compatible with this reaction, furnishing **3m** in 56% yield. α-Aryldiazoesters react with **2a** effectively to afford amino esters **3n** (71%) and **3k** (65%). The analogous reaction of alkyl-substituted diazoester furnished **3o** in 65% yield. The menthol-derived diazoester was also an effective substrate to furnish **3p** in 79% yield.

Scheme 2. Substrate Scope Study[a-c]

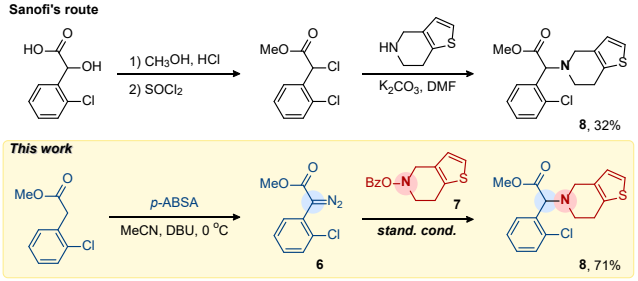


[a]Reaction conditions: **1** (0.3 mmol), **2** (0.2 mmol), $Cu(OAc)_2$ (2 mol %), PMHS (0.3 mmol), LiO*t*Bu (0.2 mmol), *t*BuOH (0.2 mmol), PhMe (1 mL), 60 °C, 16 h. Isolated yield. [b]3.0 equiv of diazoester **1** was used. [c]Gram-scale: (81%, 1.97 g).

The synthetic versatility of this reaction is further explored with the scope of benzoates (Scheme 2b). With ethyl 2-diazoheptanoate **1a** as the substrate, we examine the reactivity of several *O*-benzoyl hydroxylamines. The reaction of **1a** with thiomorpholino benzoate gave **4a** in 79% yield. In this work, *N*-Boc-piperizino benzoate was also transformed to **4b** in 97% yield. The substituted piperidino benzoates bearing 4-methyl, 4-carboxyl and 3-carboxylpiperidino groups were converted to the corresponding amino esters **4c** (74%), **4d** (70%) and **4e** (69%) effectively. The analogous reaction with pyrrolidino benzoate produced **4f** in moderate yield (43%). Similarly, acyclic secondary amino benzoate such as *N*-methylbenzylamino was converted to **4g** in 51% yield. Yet, primary *n*-hexylamino benzoate gave a less satisfactory result with only 44% yield registered for the **4h** formation. The less satisfactory results of product **4f**–**4h** were probably due to rapid consumption of the aminating reagent **2** by CuH species.[16]

In this study, (±)-Clopidogrel was chosen to be our synthetic target for applying our Cu-catalyzed cross-electrophile C–N bond coupling reaction. Clopidogrel was developed by Sanofi, and it is a top-selling antithrombic drug for primary and secondary stroke prevention. Scheme 3 outlined the Sanofi's route of racemic Clopidogrel synthesis, producing the compound in 32% overall yield (over 3 steps).[17,18] In this work, starting from methyl 2-chlorophenylacetate, facile diazo transfer with pABSA furnished the corresponding α-aryldiazoacetate **6** in quantitative yield. Treating the aryldiazoacetate with *O*-benzoyl hydroxylamine derivative **7** under the Cu-catalyzed conditions afforded (±)-Clopidogrel in 71% overall yield (over 2 steps).

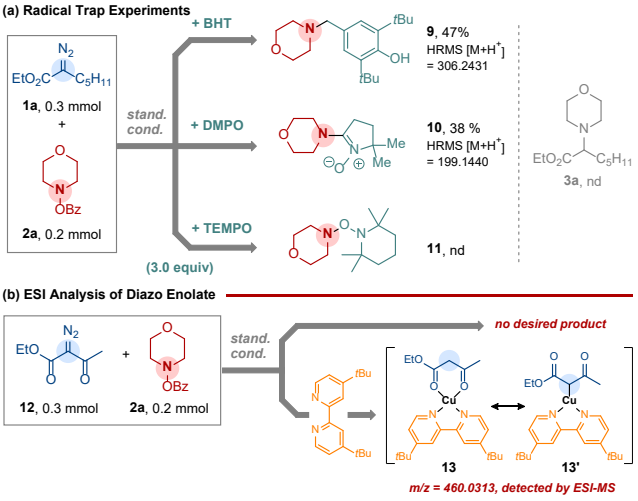
Scheme 3. Synthesis of (±)-Clopidogrel[a]



[a]Standard conditions: **6** (0.2 mmol), **7** (0.2 mmol), $Cu(OAc)_2$ (2 mol %), PMHS (0.3 mmol), LiO*t*Bu (0.2 mmol), *t*BuOH (0.2 mmol), DCE (1 mL), 60 °C, 40 h. Isolated yield.

To probe the mechanism, adding 3.0 equivalent radical trapping agents such as BHT, DMPO or TEMPO was found to suppress the **3a** formation (Scheme 4a). Morpholine adducts **9**–**10** were obtained when BHT or DMPO was used as the radical trap. Yet, the expected TEMPO-morpholine adduct **11** was not obtained probably due to thermodynamic instability. The suppressed **3a** formation due to TEMPO and the morpholine adduct formation imply that the reaction involves morpholine nitrogen radical as the intermediate. During the substrate scope study, the reactions of the acceptor-acceptor diazoesters failed to give the desired amination products. For example, no amination product was obtained from **2a** with acceptor-acceptor diazo **12** under the standard conditions. Notably, both **12** and **2a** remained unconsumed (>90% recovery) in the reaction. We surmised that the coupling reaction might have been interrupted by some stable intermediates, thereby shutting down the amination reaction. Repeating the reaction of "**2a** + **12**" with the addition of dtbbpy as ligand shows a set of ion cluster peaks with m/z = 460.0313 signal in ESI-MS analysis. Based on isotope distribution patterns and mass values, the molecular ion species can be assigned as the copper-enolate complex (**13** or **13′**). Plausibly, the copper-enolate complex is generated by the migratory carbene insertion to the CuH complex.

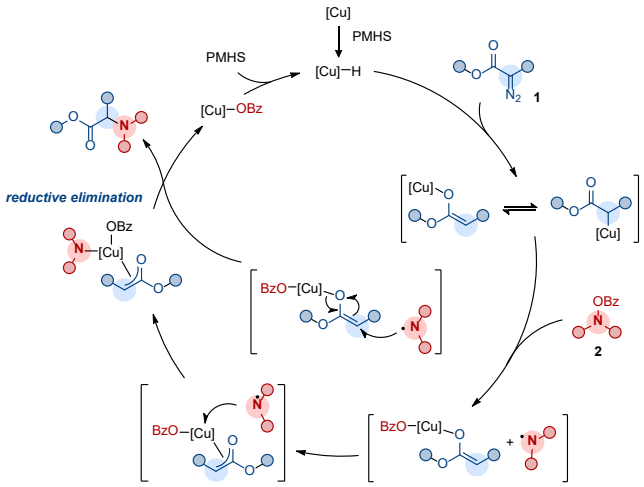
Scheme 4. Radical Trap Experiments and ESI Characterization of the Cu-Enolate Intermediate



According to our findings, a plausible mechanism is proposed in Scheme 5. The copper-catalyzed amination reaction was initiated by the formation of CuH from transmetalation of Cu complex with PMHS. A carbene insertion to CuH should then afford the canonical structure (Cu-alkyl or Cu-

enolate) species. Single electron transfer from the Cu(I) complex to **2a** give a nitrogen radical and the Cu(II) complex. The nitrogen radical could undergo radical rebound, followed by reductive elimination (path a). Alternatively, direct substitution (path b) should furnish **3a** and regenerate the Cu(I) complex for transmetalation with the silane.

Scheme 5. Proposed Mechanism



In conclusion, we have developed a hydroamination of diazoesters using *O*-benzoyl hydroxylamines as aminating reagents. The hydroamination reaction delivers the unnatural α-amino acid derivatives in good yields and functional group tolerance (including cyano, alkene and esters). The Cu-catalyzed protocol operates under mild conditions and is applicable to several classes of diazoesters and amino benzoates affording the desired amino acids. Mechanistic experiments revealed the intermediacy of a nitrogen radical, suggesting that radical amination of the Cu(II) enolate complex generated by the hydrocupration of the diazoesters may be critical for the C–N bond formation.

ASSOCIATED CONTENT

- **Data Availability Statement**

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Condition optimizations, experimental procedures, compound characterization, and NMR spectra

AUTHOR INFORMATION

Corresponding Authors

Bingnan Du – *School of Food Science and Pharmaceutical Engineering, Nanjing Normal University, Nanjing, China ;* ORCID: 0000-0001-5503-3916; E-mail: bn.du@njnu.edu.cn

Wing-Yiu Yu – *State Key Laboratory of Chemical Biology and Drug Discovery, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong;* ORCID: 0000-0003-3181-8908; E-mail: wing-yiu.yu@polyu.edu.hk

Authors

Yiu-Wai Yeung – *State Key Laboratory of Chemical Biology and Drug Discovery, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong;* ORCID: 0000-0001-7678-8963

Chun-Ming Chan – *State Key Laboratory of Chemical Biology and Drug Discovery, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong;* ORCID: 0000-0003-3859-8477

Yu-Ting Chen – *State Key Laboratory of Chemical Biology and Drug Discovery, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong*

Marco Chan – *State Key Laboratory of Chemical Biology and Drug Discovery, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong*

Mingyu Luo – *State Key Laboratory of Chemical Biology and Drug Discovery, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong*

Xin Gao – *School of Food Science and Pharmaceutical Engineering, Nanjing Normal University, Nanjing, China*

Notes

The authors declare no competing financial interest.

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