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Copper-Catalyzed Regioselective Oxidative Cycloamidation of *α*-[(*β*-Dimethylamino)propenoyl]-Alkylamides: Synthetic Route to Substituted Pyrrolidine-2,4-diones

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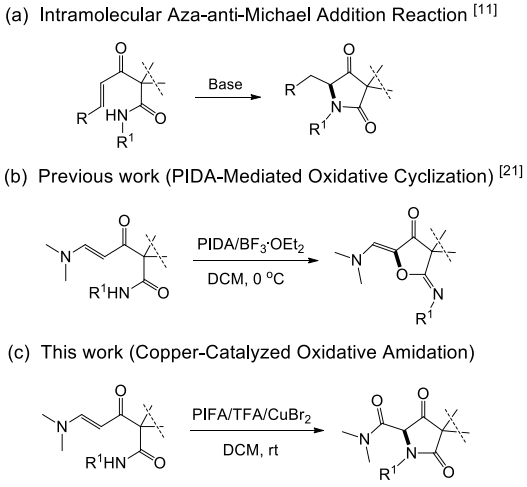
Abstract. An intramolecular oxidative amidation of varied *α*-[(*β*-dimethylamino)propenoyl]-alkylamides catalyzed by copper(II) bromide in the presence of PIFA and TFA has been described. This process features mild reaction conditions, simple execution, good yields, high regio-selectivity, and thereby, provides not only a facile and efficient protocol for the construction of C–N bond, but also a straightforward synthetic route to densely substituted pyrrolidine-2,4-diones.

Keywords: Amidation; C–N bond formation; Copper; Cyclization; Hypervalent iodine reagents; Radical reactions

Introduction

Pyrrolidine-2,4-diones, also known as tetramic acids, constitute the key core units in many naturally occurring products and synthetic compounds along with remarkable and diverse biological functions, such as antibiotic and antiviral activity.[1,2] The pharmacological importance of pyrrolidine-2,4-dione derivatives and their utility in organic transformations have intrigued researchers in search of efficient synthesis of such five-membered aza-heterocycles.[3,4] So far, extensive work has generated a variety of synthetic approaches by the construction of C–N or C–C bond through: 1) intramolecular aminolysis of *γ*-amino esters,[5] 2) Dieckmann cyclization of *N*-acyl-*α*-amino esters,[6] 3) nucleophilic cyclization of *γ*-bromo *β*-ketocarboxamides,[7] 4) acylation of the pyrrolidine-2,4-dione ring at C-3,[8] 5) Lewis acid or base-induced ring-expansion of *β*-lactams,[9] and 6) ring-contraction of diketopiperazines.[10] Recently, Liu and coworkers reported a regioselective synthesis of pyrrolidine-2,4-diones via the intramolecular aza-anti-Michael addition of amides to enones, depending on the *β*-substituent R on the enone moiety and/or the substituent R^1 on the remote amide nitrogen atom (Scheme 1a).[11] Although it seems somewhat difficult to precisely control the exact addition mode in certain cases, the polarity-reversible conjugated addition indeed provided an alternative direct route to the synthesis of pyrrolidine-2,4-diones.



Scheme 1. Cyclization of *α*-alkenoyl alkylamides

Over the past decades, hypervalent iodine reagents have emerged as a class of efficient, inexpensive and environmental benign oxidants,[12] which have been successfully used in various oxidative reactions of amides to construct N–X (X = C, N, S, O) linkages through *N*-acyl nitrenium ion intermediates.[13] During the course of our studies on the synthesis of heterocycles from *β*-oxo amide derivatives, we investigated the reaction behaviors of a variety of functionalized amides in the presence of different hypervalent iodine reagents, and achieved efficient

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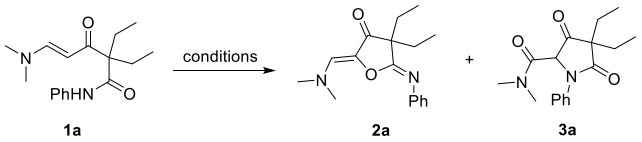
synthesis of substituted pyrrolin-4-ones,[14] benzo[*d*]-thiazoles,[15] isothiazol-3(2*H*)-ones,[16] spiro-fused pyrazolin-5-one *N*-oxides,[17] isoxazol-3(2*H*)-ones,[18] and 2,5-dihydrofurans,[19] respectively. Among these inter- or intramolecular oxidative reactions, it is worth noting that the selective N–X or O–X bond formation occurred during the transformation of amides, which is intimately dependent on the chemical structures of the substrates and/or the reaction conditions. Actually, it is one of the most challenging issues to control the bond formation of N–X or O–X in a chemoselective manner by tuning the reaction conditions in the use of amides in organic synthesis.[20]

Most recently, we found that *α*-[*β*-(dimethylamino) propenoyl]-alkylamides underwent direct regio-selective cyclization in the presence of phenyliodine-(III) diacetate (PIDA) and boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) to give dihydrofuran-3(2*H*)-ones (Scheme 1b).[21] Inspired by these results, we set out to explore if intramolecular heterocylization of such substrates might take place in different chemo- and/or regioselective manner under appropriate conditions. As part of our continued interest in the oxidation of functionalized amides mediated by hypervalent iodine(III) reagents, herein, we wish to report a novel and efficient synthesis of substituted pyrrolidine-2,4-diones involving a regioselective intramolecular amidation under very mild conditions (Scheme 1c).

Results and Discussion

A series of *α*-[*β*-(dimethylamino)propenoyl]-alkyl amides **1** were prepared according to our previously reported procedure from commercially available *β*-oxo amides in good yields.[21,22] Then, we selected 5-(dimethylamino)-2,2-diethyl-3-oxo-*N*-phenylpent-4-enamide **1a** as a model compound to initiate our study. The reaction of **1a** and PIDA (2.0 equiv) was performed in the presence of $BF_3{\cdot}OEt_2$ (0.3 equiv) and $CuBr_2$ (0.1 equiv) in dichloromethane (DCM) at room temperature. As indicated by TLC results, the reaction was completed to form a predominant product within 0.5 h, and had no significant change even by prolonging the reaction time to 24 h (Table 1, entry 1). The product was isolated and characterized as dihydrofuran-3(2*H*)-one **2a** on the basis of its spectral and analytical data. In sharp contrast, when phenyliodine(III) bis(trifluoroacetate) (PIFA), a more potent oxidant than PIDA, was employed, the reaction of **1a** delivered a new product, which was characterized as pyrrolidine-2,4-dione **3a** based on its spectral and analytical data (Table 1, entry 2).

Table 1. Selected assays performed on *α*-[*β*-(dimethylamino)propenoyl] alkylamide **1a** [a].



1a **2a** **3a**

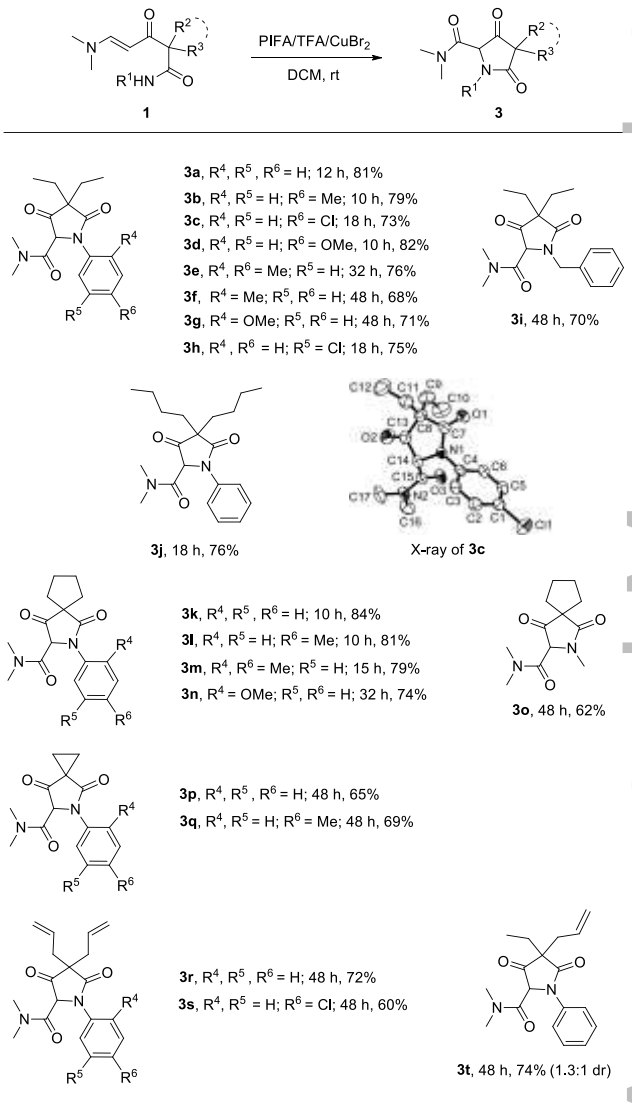
Entry	Oxidant [equiv]	Additive [equiv]	Catalyst [equiv]	Solvent	Time [h]	Yield[b] [%] **2a**	**3a**
1	PIDA (2.0)	$BF_3{\cdot}OEt_2$ (0.3)	$CuBr_2$	CH_2Cl_2	24	64	0
2	PIFA (2.0)	$BF_3.OEt_2$ (0.3)	$CuBr_2$	CH_2Cl_2	24	0	55
3	PIFA (2.0)	TFA (0.3)	$CuBr_2$	CH_2Cl_2	24	0	62
4	PIFA (2.0)	TFA (1.0)	$CuBr_2$	CH_2Cl_2	12	0	77
5	**PIFA (2.0)**	**TFA (2.0)**	**$CuBr_2$**	**CH_2Cl_2**	**12**	**0**	**81**
6	PIFA (1.5)	TFA (2.0)	$CuBr_2$	CH_2Cl_2	12	52	0
7	PIFA (2.5)	TFA (2.0)	$CuBr_2$	CH_2Cl_2	12	mixture	
8	PIFA (2.0)	TFA (2.0)	–	CH_2Cl_2	12	mixture	
9[c]	PIFA (2.0)	TFA (2.0)	$Cu(OAc)_2$	CH_2Cl_2	24	0	5
10[c]	PIFA (2.0)	TFA (2.0)	$CuSO_4$	CH_2Cl_2	24	0	trace
11	PIFA (2.0)	TFA (2.0)	$CuCl_2$	CH_2Cl_2	12	0	64
12	PIFA (2.0)	TFA (2.0)	CuBr	CH_2Cl_2	12	0	59
13	PIFA (2.0)	TFA (2.0)	CuI	CH_2Cl_2	24	0	41
14	PIFA (2.0)	TFA (2.0)	$ZnCl_2$	CH_2Cl_2	24	0	72
15	PIFA (2.0)	TFA (2.0)	$FeCl_3$	CH_2Cl_2	24	0	54
16	PIFA (2.0)	TFA (2.0)	$CuBr_2$	CH_3CN	12	0	38
17	PIFA (2.0)	TFA (2.0)	$CuBr_2$	toluene	12	14	22
18	PIFA (2.0)	TFA (2.0)	$CuBr_2$	THF	12	51	0

[a] Reagents and conditions: **1a** (1.0 mmol), catalyst (0.1 mmol), solvent (10.0 mL), rt. [b] Isolated yield of **2a** or **3a**. [c] Unidentified byproducts formed.

Next, by fixing PIFA as the oxidant, we examined the effect of additives, loading amount of additives and PIFA, catalysts, and solvents on the reaction of **1a** aiming to optimize the yield of **3a**, and some results are summarized in Table 1. It was observed that trifluoroacetic acid (TFA) was a more efficient additive than $BF_3{\cdot}OEt_2$ to promote the reaction (entry 3), and the yield of **3a** was significantly improved by the increase of TFA from 0.3 to 2.0 equivalents (entries 3-5). Notably, only product **2a** was obtained by decreasing PIFA to 1.5 equivalents (entry 6), whereas a complex mixture was formed by increasing PIFA to 2.5 equivalents (entry 7), namely the loading amount of PIFA had a significant influence on the transformation of **1a**. As indicated by TLC, the reaction of **1a** with PIFA and TFA in the absence of $CuBr_2$ proceeded quickly to form **2a** (<10 min), however, it turned into a complex mixture after prolonging the reaction time to 12 h (entry 8). These results implied that a catalyst, such as $CuBr_2$, was essential for the conversion of **1a** to **3a**. Further experiments disclosed that $CuBr_2$ was the most effective one among the tested catalysts, including $Cu(OAc)_2$, $CuSO_4$, $CuCl_2$, CuBr, CuI, $ZnCl_2$ and $FeCl_3$ (entries 5, 9-15). Disappointingly, screening of various solvents revealed that the employment of acetonitrile or toluene gave poor yield of **3a** (entries 16 and 17), and even no desired product **3a** was detected in tetrahydrofuran (entry 18). Therefore, the optimal reaction conditions were obtained when **1a** was treated with PIFA (2.0 equiv) and TFA (2.0 equiv) in the presence of $CuBr_2$ (0.1 equiv) in DCM at room temperature, whereby the yield of **3a** reached 81% (entry 5).

With the optimal reaction conditions in hand, we explored the scope and limitation of this oxidative cycloamidation reaction with a variety of *α*-[*β*-(dimethylamino)propenoyl]-alkylamides **1**. As shown in Scheme 2, the reactions of alkylamides **1b-j** bearing diethyl or di-*n*-butyl substituents at *α*-position proceeded smoothly to afford the corresponding pyrrolidine-2,4-diones **3b-j** in moderate to good yields. It is worth noting that the electron-deficient Cl (**1c** and **1h**) and electron-rich OMe groups (**1d** and **1g**) on the *N*-phenyl ring were well tolerated under the reaction conditions. For alkylamides **1e-1g**, a prolonged reaction time was required to complete the oxidative process, which might stem from the steric hindrance effect of the substituent on the *N*-phenyl ring.[13i,23] It should be mentioned that the structure of **3c** was established by X-ray diffraction analysis as shown in Scheme 2.

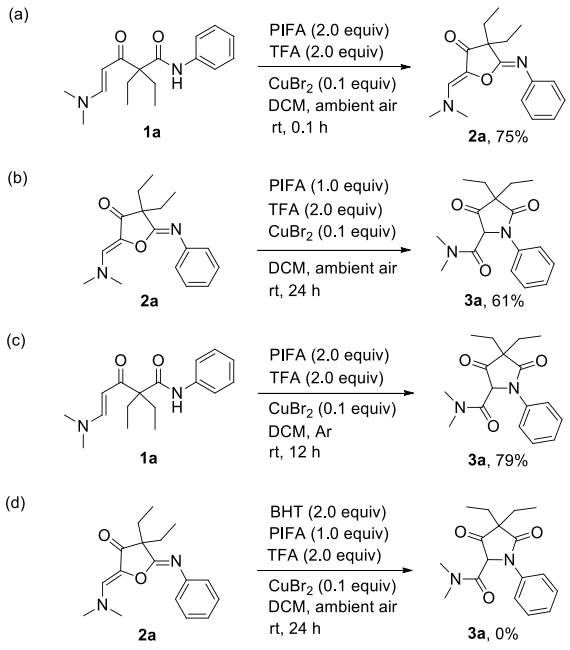
The versatility of this oxidative transformation was further evaluated by performing the reactions of cyclopentylamides **1k-o** under identical conditions, and the corresponding spiro-fused pyrrolidine-2,4-diones **3k-o** were obtained in moderate to high yields. In comparison to those *N*-arylamides **1k-n**, the reaction of *N*-alkylamide **1o** proceeded sluggishly, which is attributed to the electron effect of amide motifs. Actually, the difference of reactivity between *N*-aryl and *N*-alkyl amides had been reported in some hypervalent iodine reagent-mediated reactions.[13g,20b] Further experiments demonstrated that the modified reaction conditions with the decrease of TFA to 0.5 equivalent were suitable for cyclopropyl-amides **1p**, **1q** and *α*-mono- or *α*,*α*-diallyl acetamides **1r-t** to give the corresponding pyrrolidine-2,4-diones **3p-t** in moderate to good yields. Therefore, we developed a protocol for the operationally simple and efficient construction of N–C bond in a regioselective manner, and provied an alternative straightforward synthetic route to densely substituted pyrrolidine-2,4-diones from varied *α*-[*β*-(dimethylamino)propenoyl]-alkyl amides **1**.



Scheme 2. Reaction Scope. *Reaction conditions for **3a-o**:* **1** (1.0 mmol), PIFA (2.0 mmol), TFA (2.0 mmol), $CuBr_2$ (0.1 mmol), DCM (10.0 mL), rt. *Modified reaction conditions for **3p-t**:* **1** (1.0 mmol), PIFA (2.0 mmol), TFA (0.5 mmol), $CuBr_2$ (0.1 mmol), DCM (10.0 mL), rt. Reaction time and Isolated yields of **3** are given.

In contrast with our previous work wherein dihydrofuran-3(2*H*)-ones were obtained from *α*-[*β*-(dimethylamino)propenoyl]-alkylamides **1** through an intramolecular O–C bond formation,[21] we achieved

the synthesis of pyrrolidine-2,4-diones from the same substrates via an intramolecular N–C bond formation in the present work. The exact origin of such selectivity between N–C and O–C bond formation is unclear,[20] but the oxidativity of different hypervalent iodine reagents did play a critical role to switch the reaction pathway, and the catalysis of transition-metal halides is of crucial importance for the N–C bond formation. To gain insight into the mechanism of the intramolecular oxidative amidation, a set of control experiments were conducted as shown in Scheme 3. In a separate experiment, **1a** was subjected to the identical conditions as described in entry 5, Table 1 for 0.1 h, and then quenched with water, which delivered **2a** in 75% yield (Scheme 3a). Subsequently, the reaction of **2a** was performed with PIFA (1.0 equiv) and TFA (2.0 equiv) in the presence of $CuBr_2$ (0.1 equiv) under ambient air conditions, and **3a** was obtained in 61% yield (Scheme 3b). In another separate experiment, it was observed that the treatment of **1a** with PIFA, TFA and $CuBr_2$ under argon atmosphere afforded **3a** in 79% yield (Scheme 3c). It is worth noting that the addition of 2,6-di-*tert*-butyl-hydroxytoluene (BHT) inhibited the reaction of **2a**, wherein no desired product **3a** was formed and **2a** was recovered in 82% yield (Scheme 3d). These results reveal that **2a** is only a relatively stable intermediate during the conversion from **1a** to **3a**, and the oxidative transformation is associated with a free radical process in which oxygen (air) is not essential.



Scheme 3. Control experiments

To get further information, the reaction of **1a** and PIFA was conducted in the presence of TFA and $CuBr_2$ under argon atmosphere, and the precipitates recovered from the reaction mixture at different reaction time were investigated by means of X-ray photoelectron spectroscopy (XPS). As illustrated in Figure 1, the black residue recovered at the initial reaction stage showed characteristic signals at 931.6 and 933.1, which could be easily assigned to the $2p^{3/2}$ binding energies of Cu^{I} and Cu^{II}, respectively.[24] In contrast, the signal at 933.1 disappeared for the off-white residue recovered at the final reaction stage. XPS analyses clearly demonstrated that the redox state of Cu^{II} species changed during the oxidative transformation process, and the formation of Cu^{I} suggested that product **3** might be derived from the reductive elimination of a Cu^{III} intermediate.[25]

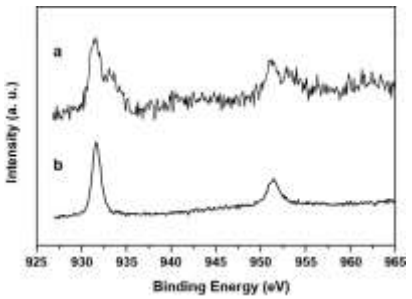


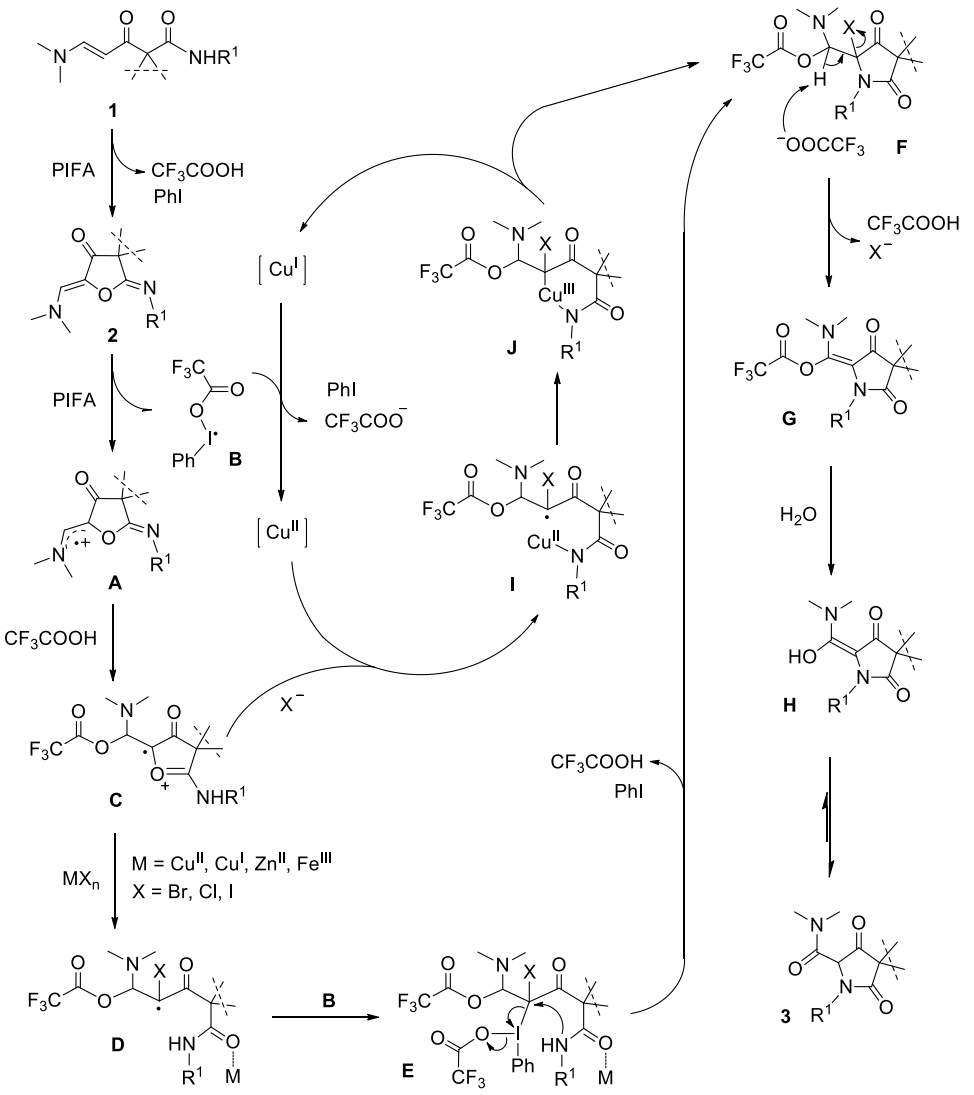
Figure 1. XPS Spectra of the insoluble residues recovered from the reaction mixture at different reaction times: (a) 0.5 h; and (b) 12 h.

On the basis of the above experimental results together with our previous work,[21] a mechanism for the synthesis of pyrrolidine-2,4-diones **3** is proposed as depicted in Scheme 4. Mediated by PIFA, *α*-[*β*-(dimethylamino)propenoyl]-alkylamide **1** is quickly converted into a fairly stable dihydrofuran-3(2*H*)-one **2**,[21] which is further oxidized by PIFA via a SET process to generate a cation radical **A** and iodanyl radical **B**.[26,27] The cation **A** is captured by TFA to afford intermediate **C**,[13c-f,28] acompanied by a ring-opening reaction in the presence of transition metal halide to give a radical **D**.[29,30] The latter couples with **B** forms intermediate **E**, which undergoes cyclization to generate intermediate **F**,[31] followed by a dehydrohalogenation to afford an intervening triflate **G**. The hydrolysis of **G** during workup furnishes the final product, pyrrolidine-2,4-dione **3**, through intermediate **H**.[13e,f] When transition metal is copper, intermediate **F** can be generated via another pathway, namely, the ring-opening reaction of **C** ocurrs to give a chelated Cu^{II} species **I**,[25] followed by an oxidative cyclization to form a metallacycle **J**, and the reductive elimination of **J** leads to intermediate **F**.[25,32] During this process, the oxidation of the released Cu^{I} by PIFA or iodanyl radical **B** to Cu^{II} brings reaction to the next catalytic cycle,[32,27d] and hence the copper-involved redox cycle further facilitates the oxidative cycloamidation of **1** to **3**.

Conclusions

In summary, we have described herein an intramolecular oxidative amidation of varied *α*-[(*β*-dimethylamino)propenoyl]-alkylamides **1** catalyzed by copper(II) bromide in the presence of PIFA and TFA. This newly developed reaction features mild conditions, simple execution, wide functional group

tolerance, and good yields, and thereby, provides not only an efficient protocol for the construction of N–C bond in a regioselective manner, but also a facile, novel and straightforward synthetic route to densely substituted pyrrolidine-2,4-diones. Further studies on the mechanism involved in the reactions and the utilization and extension of the scope of the protocol are currently underway in our laboratory.



Scheme 4. Plausible reaction mechanism.

Experimental Section

General

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C at 300 MHz (or 400 MHz) and 100 MHz, respectively, with TMS as internal standard. IR spectra (KBr) were recorded on a FTIR-spectrophotometer in the range of 400-4000 cm^{-1}. High resolution mass spectra (ESI/HRMS) were recorded on a LTQ Orbitrap Velos Pro mass spectrometer. Melting points were determined on a TECH X-4 micro-melting point apparatus. The X-ray photoelectron spectroscopic (XPS) analysis was measured using Thermo ESCALAB 250. All reactions were monitored by TLC with GF254 silica gel-coated plates. The products were isolated by flash column chromatography on silica gel (300−400 mesh).

General procedure for the synthesis of 2a: To a well-stirred mixture of PIDA (644 mg, 2.0 mmol), boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$, 0.038 mL, 0.3 mmol), and $CuBr_2$ (23 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added *α*-[(*β*-dimethylamino)propenoyl]-alkylamide **1** (1.0 mmol). The reaction mixture was kept at room temperature under stirring for 24 h. The resulting mixture was poured into saturated aqueous NaCl (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The crude product was purified by column chromatography (silica gel, petroleum ether/ ethyl acetate = 7:1) to give **2a** as a pale yellow solid (183 mg, 64%).

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General procedure for the synthesis of 3a-o: To a well-stirred mixture of PIFA (860 mg, 2.0 mmol), TFA (0.152 mL, 2.0 mmol), and $CuBr_2$ (23 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added *α*-[(*β*-dimethylamino)propenoyl]-alkylamide **1** (1.0 mmol). The reaction mixture was kept at room temperature under stirring until the completion of the reaction as indicated by TLC. The resulting mixture was poured into saturated aqueous NaCl (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel with petroleum ether/ethyl acetate as the eluent to give the corresponding product **3a-o**.

General procedure for the synthesis of 3p-t: To a well-stirred mixture of PIFA (860 mg, 2.0 mmol), TFA (0.038 mL, 0.5 mmol), and $CuBr_2$ (23 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added *α*-[(*β*-dimethylamino)propenoyl]-alkyl amide **1** (1.0 mmol). The reaction mixture was kept at room temperature under stirring until the completion of the reaction as indicated by TLC. The resulting mixture was poured into saturated aqueous NaCl (50 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The crude product was purified by column chromatography on silica gel with petroleum ether/ethyl acetate as the eluent to give the corresponding product **3p-t**.

Analytical data of 2a and 3

2-[(Dimethylamino)methylene]-4,4-diethyl-5-(phenylimino)dihydrofuran-3(2*H*)-one (2a): 183 mg, 64% yield; pale yellow solid; Mp 37-38 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.30 (t, *J* = 7.5 Hz, 2H), 7.04-7.10 (m, 3H), 6.61 (s, 1H), 2.98 (s, 6H), 1.75-1.97 (m, 4H), 0.92 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 194.6, 161.0, 146.3, 128.5, 126.7, 126.4, 123.6, 122.4, 55.1, 30.6, 9.1; IR (KBr): 3066, 3044, 3011, 2962, 2919, 2876, 2844, 2813, 1693, 1625, 1619, 1594, 1487, 1458, 1436, 1423, 1381, 1361, 1346, 1284, 1250, 861, 770, 697 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2O_2Na$ 309.1573, Found 309.1561.

4,4-Diethyl-*N*,*N*-dimethyl-3,5-dioxo-1-phenylpyrrolidine-2-carboxamide (3a): 245 mg, 81% yield; white solid; mp 124-125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.49 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.2Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 5.45 (s, 1H), 3.31 (s, 3H), 2.97 (s, 3H), 1.82-1.91 (m, 4H), 0.93 (t, *J* = 7.6 Hz, 3H), 0.89 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 207.4, 174.1, 163.0, 137.1, 129.1, 126.2, 122.9, 68.2, 58.0, 37.4, 36.5, 28.1, 9.2, 8.9; IR (KBr): 3057, 3044, 2970, 2938, 2882, 2856, 1762, 1682, 1664, 1597, 1500, 1460, 1435, 1401, 1389, 1344, 1300, 1257, 758, 698. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2O_3Na$ 325.1523, Found 325.1512.

4,4-Diethyl-*N*,*N*-dimethyl-3,5-dioxo-1-(*p*-tolyl)pyrrolidine-2-carboxamide (3b): 249 mg, 79% yield; white solid; mp 159-161 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.36 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 5.41 (s, 1H), 3.29 (s, 3H), 2.96 (s, 3H), 2.33 (s, 3H), 1.81-1.89 (m, 4H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 207.7, 174.0, 163.1, 136.2, 134.5, 129.7, 123.2, 68.3, 57.9, 37.4, 36.5, 28.1, 20.9, 9.2, 9.0; IR (KBr): 3040, 2978, 2968, 2939, 2928, 2881, 1763, 1680, 1662, 1608, 1588, 1518, 1493, 1458, 1433, 1414, 1400, 1393, 1344, 1301, 1256, 847 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{24}N_2O_3Na$ 339.1679, Found 339.1667.

1-(4-Chlorophenyl)-4,4-diethyl-*N*,*N*-dimethyl-3,5-dioxopyrrolidine-2-carboxamide (3c): 246 mg, 73% yield; white solid; mp 172-173 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.44 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 9.0 Hz, 2H), 5.42 (s, 1H), 3.32 (s, 3H), 2.98 (s, 3H), 1.81-1.89 (m, 4H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 206.9, 174.1, 162.7, 135.7, 131.6, 129.2, 124.2, 68.1, 58.0, 37.5, 36.5, 28.1, 9.2, 8.9; IR (KBr): 3093, 3057, 3038, 2972, 2937, 2882, 1764, 1686, 1661, 1594, 1497, 1458, 1434, 1417, 1401, 1390, 1342, 1301, 1256, 853, 740 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{21}ClN_2O_3Na$ 359.1133, Found 359.1118.

X-ray Crystal Data for 3c: white crystal, M = 336.81, orthorhombic, Pbca, a = 15.199(2) Å, b = 8.9579(13) Å, c = 25.874(4) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 3522.7(9) Å^3, Z = 8, T = 273.15 K, F000 = 1424.0, F000' = 1425.78, R = 0.0621(2148), wR_2 = 0.1579(3616). CCDC deposition number: 1858809. These data can be obtained free of charge *via* www.ccdc.cam. ac.uk/conts/retrieving. html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (0) 1223 762911; or deposit @ccdc.cam.ac. uk).

4,4-Diethyl-1-(4-methoxyphenyl)-*N*,*N*-dimethyl-3,5-dioxopyrrolidine-2-carboxamide (3d): 272 mg, 82% yield, white solid; mp 178-179 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.38 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 5.36 (s 1H), 3.80 (s, 3H), 3.26 (s, 3H), 2.96 (s, 3H), 1.81-1.89 (m, 4H), 0.92 (t, *J* = 7.5 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 207.8, 174.1, 163.2, 158.0, 129.9, 125.5, 114.3, 68.7, 57.6, 55.4, 37.4, 36.4, 28.1, 9.2, 8.9; IR (KBr): 3075, 3049, 2973, 2940, 2928, 2883, 2839, 1762, 1680, 1660, 1609, 1591, 1518, 1496, 1460, 1431, 1414, 1401, 1303, 1251, 850 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{24}N_2O_4Na$ 355.1628, Found 355.1623.

1-(2,4-Dimethylphenyl)-4,4-diethyl-*N*,*N*-dimethyl-3,5-dioxopyrrolidine-2-carboxamide (3e): 250 mg, 76% yield; white solid; mp 137-138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.10-7.15 (m, 2H), 7.01 (d, *J* = 7.5 Hz, 1H), 5.35 (s, 1H), 3.14 (s, 3H), 2.91 (s, 3H), 2.37 (s, 3H), 2.31 (s, 3H), 1.82-1.92 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 208.2, 173.8, 163.5, 138.0, 136.3, 132.6, 132.0, 127.2, 68.9, 57.2, 37.4, 36.4 28.1, 27.8, 21.0, 18.5, 9.3, 9.0; IR (KBr): 2973, 2940, 2930, 2883, 2867, 1762, 1682, 1658, 1615, 1582, 1508, 1460, 1436, 1419, 1391, 1307, 1256, 861, 811 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{26}N_2O_3Na$ 353.1836, Found 353.1819.

4,4-Diethyl-*N*,*N*-dimethyl-3,5-dioxo-1-(*o*-tolyl)pyrrolidine-2-carboxamide (3f): 214 mg, 68% yield; white solid; mp 151-153 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.19-7.30 (m, 4H), 5.38 (s, 1H), 3.15 (s, 3H), 2.91 (s, 3H), 2.42 (s, 3H), 1.84-1.93 (m, 4H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 208.1, 173.7, 163.4, 136.9, 135.3, 131.4, 128.2, 126.5, 68.9, 57.3,

37.5, 36.4, 28.2, 27.9, 18.6, 9.4, 9.0; IR (KBr): 3052, 3029, 2973, 2942, 2883, 2861, 1761, 1686, 1658, 1604, 1583, 1497, 1459, 1437, 1420, 1404, 1388, 1307, 1258, 761 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{24}N_2O_3Na$ 339.1679, Found 339.1665.

4,4-Diethyl-1-(2-methoxyphenyl)-*N*,*N*-dimethyl-3,5-dioxopyrrolidine-2-carboxamide (3g): 235 mg, 71% yield; white solid; mp 145-146 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 5.54 (s, 1H), 3.83 (s, 3H), 3.16 (s, 3H), 2.90 (s, 3H), 1.78-1.90 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.0, 174.8, 163.4, 154.2, 131.8, 129.2, 124.2, 121.0, 111.4, 67.9, 56.8, 55.5, 37.3, 36.2, 28.3, 28.2, 9.1, 9.0; IR (KBr): 3082, 3021, 2972, 2966, 2937, 2880, 2847, 1762, 1706, 1657, 1621, 1598, 1501, 1459, 1442, 1401, 1381, 1267, 758 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{24}N_2O_4Na$ 355.1628, Found 355.1612.

1-(3-Chlorophenyl)-4,4-diethyl-*N*,*N*-dimethyl-3,5-dioxopyrrolidine-2-carboxamide (3h): 252 mg, 75% yield; white solid; mp 112-113 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.28-7.36 (m, 2H), 7.20 (dt, J_1 = 6.9 Hz, J_2 = 1.8 Hz, 1H), 5.43 (s, 1H), 3.34 (s, 3H), 2.99 (s, 3H), 1.81-1.89 (m, 4H), 0.91 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.7, 174.1, 162.6, 138.3, 134.7, 130.0, 126.2, 122.8, 120.6, 67.9, 58.1, 37.5, 36.5, 28.1, 28.1, 9.2, 8.9; IR (KBr): 3068, 3044, 2985, 2971, 2945, 2927, 2883, 2863, 1765, 1703, 1650, 1593, 1481, 1450, 1447, 1433, 1406, 1390, 1336, 1257, 878, 788, 749, 705 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{21}ClN_2O_3Na$ 359.1133, Found 359.1120.

1-Benzyl-4,4-diethyl-*N*,*N*-dimethyl-3,5-dioxopyrrolidine-2-carboxamide (3i): 221 mg, 70% yield; white solid; mp 105-106 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32-7.34 (m, 3H), 7.21 (d, J = 6.3 Hz, 2H), 5.55 (d, J = 14.4 Hz, 1H), 4.49 (s, 1H), 3.91 (d, J = 14.4 Hz, 1H), 3.01 (s, 3H), 2.94 (s, 3H), 1.69-1.88 (m, 4H), 0.84 (t, J = 7.5 Hz, 3H), 0.77 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.1, 174.3, 162.8, 135.2, 128.9, 128.1, 65.1, 57.2, 44.5, 37.1, 36.3, 28.1, 27.9, 9.2, 9.0; IR (KBr): 3063, 3030, 2971, 2939, 2883, 1762, 1694, 1682, 1652, 1587, 1496, 1453, 1425, 1416, 1388, 1349, 1308, 1259, 761, 701 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{24}N_2O_3Na$ 339.1679, Found 339.1666.

4,4-Dibutyl-*N*,*N*-dimethyl-3,5-dioxo-1-phenylpyrrolidine-2-carboxamide (3j): 272 mg, 76% yield; white solid; mp 140-142 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, J = 7.5 Hz, 2H), 7.39 (t, J = 7.2 Hz, 2H), 7.22 (t, J = 7.5 Hz, 1H), 5.46 (s, 1H), 3.31 (s, 3H), 2.97 (s, 3H), 1.73-1.89 (m, 4H), 1.07-1.39 (m, 8H), 0.86 (t, J = 7.2 Hz, 3H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.6, 174.3, 162.9, 137.2, 129.1, 126.2, 122.9, 68.1, 57.0, 37.5, 36.5, 35.3, 35.1, 26.9, 26.1, 22.9, 13.7, 13.6; IR (KBr): 3064, 3042, 2961, 2933, 2874, 2862, 1765, 1703, 1652, 1598, 1498, 1457, 1438, 1405, 1385, 1299, 1254, 755, 694 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{30}N_2O_3Na$ 381.2149, Found 381.2139.

***N*,*N*-Dimethyl-1,4-dioxo-2-phenyl-2-azaspiro[4.4]nonane-3-carboxamide (3k):** 252 mg, 84% yield; white solid; mp 133-135 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 7.53 (d, J = 8.1 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.18 (t, J = 7.5 Hz, 1H), 6.22 (s, 1H), 3.27 (s, 3H), 2.84 (s, 3H), 1.91-2.01 (m, 3H), 1.68-1.85 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.5, 175.7, 163.7, 137.2, 129.1, 125.9, 122.4, 67.3, 57.7, 38.4, 37.4, 36.5, 34.5, 27.0, 26.9; IR (KBr): 3059, 3040, 2961, 2942, 2870, 1762, 1686, 1664, 1595, 1493, 1455, 1415, 1400, 1293, 1254, 752, 698 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{20}N_2O_3Na$ 323.1366, Found 323.1353.

***N*,*N*-Dimethyl-1,4-dioxo-2-(*p*-tolyl)-2-azaspiro[4.4]nonane-3-carboxamide (3l):** 254 mg, 81% yield; white solid; mp 185-186 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 5.50 (s, 1H), 3.28 (s, 3H), 2.97 (s, 3H), 2.32 (s, 3H), 2.21-2.32 (m, 1H), 2.05-2.13 (m, 1H), 1.79-2.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.7, 175.6, 163.8, 135.8, 134.6, 129.7, 122.6, 67.5, 57.6, 38.4, 37.4, 36.5, 34.4, 27.0, 26.9, 20.9; IR (KBr): 3061, 3034, 2952, 2869, 1764, 1697, 1647, 1613, 1517, 1446, 1422, 1409, 1388, 1299, 1259, 815 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{22}N_2O_3Na$ 337.1523, Found 337.1513.

2-(2,4-Dimethylphenyl)-*N*,*N*-dimethyl-1,4-dioxo-2-azaspiro[4.4]nonane-3-carboxamide (3m): 259 mg, 79% yield; white solid; mp 172-173 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.19 (d, J = 7.5 Hz, 1H), 7.09 (s, 1H), 7.01 (d, J = 8.1 Hz, 1H), 5.34 (s, 1H), 3.10 (s, 3H), 2.92 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H), 2.21-2.29 (m, 1H), 1.76-2.13 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.5, 175.4, 164.4, 138.1, 135.9, 132.5, 131.9, 127.3, 126.7, 68.1, 56.7, 38.2, 37.4, 36.4, 34.1, 27.0, 26.8, 21.0, 18.0; IR (KBr): 3028, 3014, 2999, 2955, 2936, 2866, 1761, 1704, 1654, 1609, 1497, 1457, 1447, 1405, 1390, 1295, 1255, 822, 768 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{24}N_2O_3Na$ 351.1679, Found 351.1667.

2-(2-Methoxyphenyl)-*N*,*N*-dimethyl-1,4-dioxo-2-azaspiro[4.4]nonane-3-carboxamide (3n): 244 mg, 74% yield; white solid; mp 132-134 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.61 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 7.29 (td, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H), 7.02 (td, J_1 = 7.5 Hz, J_2 = 0.9 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 5.66 (s, 1H), 3.84 (s, 3H), 3.14 (s, 3H), 2.90 (s, 3H), 2.21-2.30 (m, 1H), 2.04-2.14 (m, 1H), 1.78-2.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.9, 176.5, 164.3, 154.1, 131.2, 129.0, 124.3, 121.1, 111.5, 67.0, 56.3, 55.6, 37.8, 37.2, 36.3, 34.6, 27.0, 26.9; IR (KBr): 3088, 3066, 3020, 2960, 2953, 2928, 2869, 2833, 1764, 1703, 1657, 1598, 1502, 1461, 1437, 1413, 1401, 1386, 1301, 1267, 752 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{22}N_2O_4Na$ 353.1472, Found 353.1452.

***N*,*N*,2-Trimethyl-1,4-dioxo-2-azaspiro[4.4]nonane-3-carboxamide (3o):** 147 mg, 62% yield; white solid; mp 140-141 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 4.95 (s, 1H), 3.26 (s, 3H), 3.02 (s, 3H), 2.95 (s, 3H), 1.94-2.09 (m, 2H), 1.73-1.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.1, 176.2, 163.4, 67.7, 56.1, 37.4, 37.3, 36.4, 34.0, 28.3, 26.8, 26.7; IR (KBr): 2963, 2947, 2874, 1763, 1686, 1651, 1483, 1452, 1435, 1393, 1311, 1289, 1254 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{18}N_2O_3Na$ 261.1210, Found 261.1207.

***N*,*N*-Dimethyl-4,7-dioxo-5-phenyl-5-azaspiro[2.4]heptane-6-carboxamide (3p):** 176 mg, 65% yield; white solid; mp 159-160 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, J =

7.8 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.20 (t, *J* = 7.2 Hz, 1H), 5.68 (s, 1H), 3.32 (s, 3H), 2.99 (s, 3H), 1.82-1.95 (m, 2H), 1.68-1.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 202.2, 171.3, 163.5, 137.4, 129.1, 125.7, 121.9, 67.6, 37.4, 36.5, 32.2, 23.4, 21.4; IR (KBr): 3111, 3079, 3061, 2967, 1755, 1709, 1651, 1596, 1495, 1458, 1439, 1404, 1383, 1348, 1300, 1254, 1028, 761, 694 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{16}N_2O_3Na$ 295.1053, Found 295.1045.

***N*,*N*-Dimethyl-4,7-dioxo-5-(*p*-tolyl)-5-azaspiro[2.4]heptane-6-carboxamide (3q):** 197 mg, 69% yield; white solid; mp 193-194 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.38 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 5.65 (s, 1H), 3.29 (s, 3H), 2.98 (s, 3H), 2.33 (s, 3H), 1.80-1.93 (m, 2H), 1.67-1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 202.4, 171.2, 163.6, 135.6, 134.8, 129.7, 122.2, 67.8, 37.4, 36.5, 32.2, 2.3.2, 21.3, 20.9; IR (KBr): 3034, 2969, 2935, 2869, 1755, 1707, 1651, 1515, 1436, 1423, 1406, 1386, 1348, 1301, 1255, 1019, 823 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{18}N_2O_3Na$ 309.1210, Found 309.1200.

4,4-Diallyl-*N*,*N*-dimethyl-3,5-dioxo-1-phenylpyrrolidine-2-carboxamide (3r): 234 mg, 72% yield; white solid; mp 146-147 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.43-7.47 (m, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 5.62-5.88 (m, 2H), 5.35 (s, 1H), 5.08-5.18 (m, 4H), 3.27 (s, 3H), 2.96 (s, 3H), 2.45-2.63 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 205.4, 172.9, 163.0, 137.0, 131.4, 131.2, 129.1, 126.4, 123.1, 120.2, 119.4, 68.2, 56.8, 38.9, 38.4, 37.4, 36.5; IR (KBr): 3076, 3044, 3004, 2979, 2940, 2913, 2835, 1769, 1699, 1654, 1598, 1500, 1458, 1431, 1418, 1406, 1374, 1252, 996, 920, 766, 693 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{22}N_2O_3Na$ 349.1523, Found 349.1511.

4,4-Diallyl-1-(4-chlorophenyl)-*N*,*N*-dimethyl-3,5-dioxo-pyrrolidine-2-carboxamide (3s): 216 mg, 60% yield; white solid; mp 89-91 °C; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.40 (d, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 9.0 Hz, 2H), 5.60-5.84 (m, 2H), 5.31 (s, 1H), 5.07-5.18 (m, 4H), 3.28 (s, 3H), 2.96 (s, 3H), 2.45-2.62 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 204.9, 172.9, 162.6, 135.5, 131.8, 131.2, 131.0, 129.2, 124.4, 120.4, 119.6, 68.2, 56.8, 39.0, 38.5, 37.5, 36.5; IR (KBr): 3090, 3054, 3038, 2983, 2935, 2868, 1769, 1685, 1663, 1643, 1594, 1498, 1445, 1418, 1401, 1386, 1256, 993, 924, 829 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{21}ClN_2O_3Na$ 383.1133, Found 383.1121.

4-Allyl-4-ethyl-*N*,*N*-dimethyl-3,5-dioxo-1-phenylpyrrolidine-2-carboxamide (3t): 232 mg, 74% yield, 1.3:1 dr; white solid; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.47 (t, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 6.9 Hz, 1H), 5.64-5.87 (m, 1H), 5.45 (s, 0.4H, dia.2), 5.35 (s, 0.6H, dia.1), 5.06-5.18 (m, 2H), 3.30 (s, 1.3H, dia.2), 3.28 (s, 1.7H, dia.1), 2.96 (s, 3H), 2.43-2.63 (m, 2H), 1.84-1.89 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 1.7H, dia.1), 0.88 (t, *J* = 7.2 Hz, 1.3H, dia.2); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 206.7 & 206.1 (dia.1/dia.2), 173.5, 162.9, 137.0, 131.5, 129.1, 126.3, 123.2 & 122.9 (dia.1/dia.2), 120.1 & 119.1 (dia.1/dia.2), 68.2, 57.8 & 57.3 (dia.1/dia.2), 39.2, 37.4, 36.5, 28.0 & 27.4 (dia.1/dia.2), 8.9 & 9.1 (dia.1/dia.2); IR (KBr): 3076, 3067, 3043, 2969, 2938, 2880, 1765, 1699, 1652, 1598, 1496, 1458, 1434, 1406, 1382, 1297, 1254, 996, 923, 760, 692 cm^{-1}. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{22}N_2O_3Na$ 337.1523, Found 337.1511.

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References

[1] For reviews, see: a) H.-G. Henning, A. Gelbin, *Adv. Heterocycl. Chem.* **1993**, 57, 139-185; b) B. J. L. Royles, *Chem. Rev.* **1995**, *95*, 1981-2001; c) R. Schobert, A. Schlenk, *Bioorg. Med. Chem.* **2008**, *16*, 4203-4221; d) P.-Q. Huang, *Synlett* **2006**, 1133-1149; e) A. S. Ivanov, *Chem. Soc. Rev.* **2008**, *37*, 789-811; f) D. Boettger, C. Hertweck, *ChemBioChem* **2013**, *14*, 28-42.

[2] a) T. B. Kakule, S. Zhang, J. Zhan, E. W. Schmidt, *Org. Lett.* **2015**, *17*, 2295-2297; b) R. G. Haase, R. Schobert, *Org. Lett.* **2016**, *18*, 6352-6355; c) C. M. Haskins, D. W. Knight, *Chem. Commun.* **2005**, 3162-3164; d) T. Wakimoto, T. Mori, H. Morita, I. Abe, *J Am. Chem. Soc.* **2011**, *133*, 4746-4749; e) X. Li, Q. Zheng, J. Yin, W. Liu, S. Gao, *Chem. Commun.* **2017**, *53*, 4695-4697; f) J. Li, S. Liu, S. Niu, W. Zhuang, Y. Che, *J. Nat. Prod.* **2009,** *72*, 2184-2187.

[3] a) E. J. Corey, W. Li, T. Nagamitsu, *Angew. Chem. Int. Ed.* **1998**, *37*, 1676-1679; *Angew. Chem.* **1998**, *110*, 1784-1787; b) H. H. Dhanjee, Y. Kobayashi, J. F. Buergler, T. C. McMahon, M. W. Haley, J. M. Howell, K. Fujiwara, J. L. Wood, *J. Am. Chem. Soc.* **2017**, *139*, 14901-14904; c) X.-B. Li, L. Li, R.-X. Zhu, W. Li, W.-Q. Chang, L.-L. Zhang, X.-N. Wang, Z.-T. Zhao, H.-X. Lou, *J. Nat. Prod.* **2015**, *78*, 2155-2160; d) J. C. Carlson, S. Li, D. A. Burr, D. H. Sherman, *J. Nat. Prod.* **2009,** *72*, 2076-2079; e) J. Y. Li, G. Strobel, J. Harper, E. Lobkovsky, J. Clardy, *Org. Lett.* **2000**, *2*, 767-770.

[4] a) X. Cheng, F. Liang, F. Shi, L. Zhang, Q. Liu, *Org. Lett.* **2009**, *11*, 93-96; b) A. Padwa, J. P. Snyder, E. A. Curtis, S. M. Sheehan, K. J. Worsencroft, C. O Kappe, *J. Am. Chem. Soc.* **2000**, *122*, 8155-8167; c) R. A. Shenvi, E. J. Corey, *J. Am. Chem. Soc.* **2009**, *131*, 5746-5747; d) J. J. Leban, K. L. Colson, *J. Org. Chem.* **1996,** *61*, 228-231; e) S. Fustero, M. García de la Torre, J. F. Sanz-Cervera, C. Ramírez de Arellano, J. Piera, A. Simón, *Org. Lett.* **2002**, *4*, 3651-3654; f) C.-P. Xu, P.-Q. Huang, S. Py, *Org. Lett.* **2012**, 14, 2034-2037.

[5] a) M. Hosseini, H. Kringelum, A. Murray, J. E. Tønder, *Org. Lett.* **2006**, *8*, 2103-2106; b) T. Wakimoto, T. Mori, H. Morita, I. Abe, *J. Am. Chem. Soc.* **2011**, *133*, 4746-4749; c) Y.-C. Jeong, M. G.

Moloney, *J. Org. Chem.* **2011**, *76*, 1342-1354; d) K. Aikawa, M. Asano, K. Ono, N. Habuka, J. Yano, K. Wilson, H. Fujita, H. Kandori, T. Hara, M. Morimoto, T. Santou, M. Yamaoka, M. Nakayama, A. Hasuoka, *Bioorg. Med. Chem.* **2017**, *25*, 3330-3349.

[6] a) B. A. Kulkarni, A. Ganesan, *Angew. Chem. Int. Ed.* **1997**, *36*, 2454-2455; *Angew. Chem.* **1997**, *109*, 2565-2567; b) J. W. Sims, E. W. Schmidt, *J. Am. Chem. Soc.* **2008**, *130*, 11149-11155; c) P. C. Bulman Page, A. S. Hamzah, D. C. Leach, S. M. Allin, D. M. Andrews, G. A. Rassias, *Org. Lett.* **2003**, *5*, 353-355; d) R. Yendapally, J. G. Hurdle, E. I. Carson, R. B. Lee, R. E. Lee, *J. Med. Chem.* **2008,** *51*, 1487-1491; e) N. A. Butt, C. J. Moody, *Org. Lett.* **2011**, *13*, 2224-2227.

[7] A. Miyadera, K. Satoh, A. Imura, *Chem. Pharm. Bull.* **2000**, *48*, 563-565.

[8] a) A. P. Michael, E. J. Grace, M. Kotiw, R. A. Barrow, *J. Nat. Prod.* **2002,** *65*, 1360-1362; b) T. Sengoku, Y. Nagae, Y. Ujihara, M. Takahashi, H. Yoda, *J. Org. Chem.* **2012**, *77*, 4391-4401; c) K. Kempf, A. Raja, F. Sasse, R. Schobert, *J. Org. Chem.* **2013**, *78*, 2455-2461.

[9] a) B. Alcaide, P. Almendros, A. Luna, S. Cembellín, M. Arnó, L. R. Domingo, *Chem. Eur. J.* **2011**, *17*, 11559-11566; b) B. Alcaide, P. Almendros, A. Luna, M. R. Torres, *Adv. Synth. Catal.* **2010**, *352*, 621-626; c) B. Alcaide, Y. Martín-Cantalejo, J. Rodríguez-López, M. A. Sierra, *J. Org. Chem.* **1993**, *58*, 4767-4770.

[10] a) D. Farran, I. Parrot, J. Martinez, G. Dewynter, *Angew. Chem. Int. Ed.* **2007**, *46*, 7488-7490; *Angew. Chem.* **2007**, *119*, 7632-7634; b) G. Chaubet, T. Coursindel, X. Morelli, S. Betzi, P. Roche, Y. Guari, A. Lebrun, L. Toupet, Y. Collette, I. Parrot, J. Martinez, *Org. Biomol. Chem.* **2013**, *11*, 4719-4726.

[11] a) X. Bi, J. Zhang, Q. Liu, J. Tan, B. Li, *Adv. Synth. Catal.* **2007**, *349*, 2301-2306; b) Y. Li, X. Xu, J. Tan, P. Liao, J. Zhang, Q. Liu, *Org. Lett.* **2010**, *12*, 244-247.

[12] For reviews, see: a) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2002**, *102*, 2523-2584; b) P. J. Stang, *J. Org. Chem.* **2003**, *68*, 2997-3008; c) H. Tohma, Y. Kita, *Adv. Synth. Catal.* **2004**, *346*, 111-124; d) F. Collet, C. Lescot, P. Dauban, *Chem. Soc. Rev.* **2011**, *40*, 1926-1936; e) M. L. Louillat, F. W. Patureau, *Chem. Soc. Rev.* **2014**, *43*, 901-910; f) L. F. Silva Jr., B. Olofsson, *Nat. Prod. Rep.* **2011**, *28*, 1722-1754; g) A. Yoshimura, V. V. Zhdankin, *Chem. Rev.* **2016**, *116*, 3328-3435.

[13] a) Y. Kikugawa, M. Kawase, *Chem. Lett.* **1990**, 581-582; b) D. J. Wardrop, W. Zhang, *Org. Lett.* **2001**, *3*, 2353-2356; c) N. Itoh, T. Sakamoto, E. Miyazawa, Y. Kikugawa, *J. Org. Chem.* **2002**, *67*, 7424-7428; d) Y. Kikugawa, A. Nagashima, T. Sakamoto, E. Miyazawa, M. Shiiya, *J. Org. Chem.* **2003**, *68*, 6739-6744; e) S. Serna, I. Tellitu, E. Dominguez, I. Moreno, R. SanMartin, *Org. Lett.* **2005**, *7*, 3073-3076; f) A. Correa, I. Tellitu, E. Dominguez, R. SanMartin, *J. Org. Chem.* **2006**, *71***,** 8316-8319; g) A Correa, I. Tellitu, E. Dominguez, R. SanMartin, *Org. Lett.* **2006**, *8*, 4811-4813; h) J. Huang, Y. Liang, W. Pan, Y. Yang, D. Dong, *Org. Lett.* **2007**, *9*, 5345-5348; i) L. Mao, Y. Li, T. Xiong, K. Sun, Q. Zhang, *J. Org. Chem.* **2013**, *78*, 733-737; j) S. Maiti, T. K. Achar, P. Mal, *Org. Lett.* **2017**, 19, 2006-2009.

[14] J. Huang, Y. Liang, W. Pan, Y. Yang, D. Dong, *Org. Lett.* **2007**, *9*, 5345-5348.

[15] P. Huang, X. Fu, Y. Liang, R. Zhang, D. Dong, *Aust. J. Chem.* **2012**, *65*, 121-128.

[16] J. Huang, Y. Lu, B. Qiu, Y. Liang, N. Li, D. Dong, *Synthesis* **2007**, 2791-2796.

[17] K. Wang, X. Fu, J. Liu, Y. Liang, D. Dong, *Org. Lett.* **2009**, *11*, 1015-1018.

[18] J. Yuan, C. B. Rao, Q. Zhang, R. Zhang, Y. Liang, N. Zhang, D. Dong, *Synthesis* **2018**, *50*, 1875-1882.

[19] X. Liu, X. Xin, D. Xiang, Y. Liang, X. Xin, W. Li, D. Dong, *RSC Adv.* **2013**, *3*, 1346-1349.

[20] a) Y. Yamane, K. Miyazaki, T. Nishikata, *ACS Catal.* **2016**, *6*, 7418-7425. b) A. Correa, I. Tellitu, E. Dominguez, R. SanMartin, *J. Org. Chem.* **2006**, *71*, 3501-3505; c) D. Anand, O. P. S. Patel, R. K. Maurya, R. Kant, P. P. Yadav, *J. Org. Chem.* **2015**, *80*, 12410-12419; d) A. Padwa, J. P. Snyder, E. A. Curtis, S. M. Sheehan, K. J. Worsencroft, C. O. Kappe, *J. Am. Chem. Soc.* **2000,** *122*, 8155-8167; e) U. Farid, T. Wirth, *Angew. Chem. Int. Ed.* **2012**, *51*, 3462 –3465; *Angew. Chem.* **2012**, *124*, 3518-3522.

[21] J. Yuan, Q. Zhang, M. Yu, P. Huang, R. Zhang, D. Dong, *Org. Lett.* **2015**, *17*, 5012-5015.

[22] a) R. Zhang, Y. Liang, G. Zhou, K. Wang, D. Dong, *J. Org. Chem.* **2008**, *73*, 8089-8092; b) P. Huang, N. Zhang, R. Zhang, D. Dong, *Org. Lett.* **2012**, *14*, 370-373.

[23] J. Sun, D. Zhang-Negrerie, Y. Du, K. Zhao, *J. Org. Chem.* **2015**, *80*, 1200-1206.

[24] C.-Y. Liu, Y. Li, J.-Y. Ding, D.-W Dong, F.-S. Han, *Chem. Eur. J.* **2014**, *20*, 2373-2381.

[25] a) L. M. Huffman, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 9196-9197; b) A. Casitas, A. E. King, T. Parella, M. Costas, S. S. Stahl, X. Ribas, *Chem. Sci.* **2010**, *1*, 326–330; c) D. E. Mancheno, A. R. Thornton, A. H. Stoll, A. Kong, S. B. Blakey, *Org. Lett.* **2010**, *12*, 4110-4113; d) S. Sanjaya, S. Chiba, *Org. Lett.* **2012**, *14*, 5342-5345.

[26] a) H. Hamamoto, Y. Shiozaki, H. Nambu, K. Hata, H. Tohma, Y. Kita, *Chem. Eur. J.* **2004**, *10*, 4977-4982; b) T. Dohi, K. Morimoto, Y. Kiyono, H. Tohma, Y. Kita, *Org. Lett.* **2005**, *7*, 537-540; c) T. Takada, M. Arisawa, M. Gyoten, R. Hamada, H. Tohma, Y. Kita, *J. Org. Chem.* **1998**, *63*, 7698-7706; d) T. Dohi, K. Morimoto, A. Maruyama, Y. Kita, *Org. Lett.* **2006**, *8* 2007-2010.

[27] a) Y. Du, R. Liu, G. Linn, K. Zhao, *Org. Lett.* **2006**, *8*, 5919-5922; b) J. Huang, Y. He, Y. Wang, Q. Zhu, *Chem. Eur. J.* **2012**, *18*, 13964-13967; c) R. Narayana, S. Mannaa, A. P. Antonchick, *Synlett* **2015**, *26*, 1785-1803; d) J.-R. Chen, X.-Y. Yu, W.-J. Xiao, *Synthesis* **2015**, *47*, 604-629.

[28] F. Wang, W. Sun, Y. Wang, Y. Jiang, T.-P. Loh, *Org. Lett.* **2018**, *20*, 1256-1260.

[29] J. Clarke, K. J. Bonney, M. Yaqoob, S. Solanki, H. S. Rzepa, A. J. P. White, D. S. Millan, D. C. Braddock. *J. Org. Chem.* **2016**, *81*, 9539-9552.

10.1002/adsc.201801237

[30] a) Y. Kita, Y. Nishii, T. Higuchi, K. Mashima. *Angew. Chem. Int. Ed.* **2012**, *51*, 5723-5726. *Angew. Chem.* **2012**, *124*, 5821-5824; b) C. C. D. Wybon, C. Mensch, K. Hollanders, C. Gadais, W. A. Herrebout, S. Ballet, B. U. W. Maes. *ACS Catal.* **2018**, *8*, 203-218; c) E. S. Elton, T. Zhang, R. Prabhakar, A. M. Arif, L. M. Berreau. *Inorg. Chem.* **2013**, *52*, 11480-11492.
[31] a) J. Yu, J. Tian, C. Zhang, *Adv. Synth. Catal.* **2010**, *352*, 531-546; b) Y. Sun, R. Fan, *Chem. Commun.* **2010**, *46*, 6834-6836.
[32] B. L. Tran, B. Li, M. Driess, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 2555-2563.

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FULL PAPER Copper-Catalyzed Regioselective Oxidative Cycloamidation

Copper-Catalyzed Regioselective Oxidative Cycloamidation of α-[(β-Dimethylamino)propenoyl]-Alkylamides: Synthetic Route to Substituted Pyrrolidine-2,4-diones

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