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$Cu(OTf)_2$ catalyzed cross-coupling reaction of 1,3-dicarbonyl derivatives with 2-oxo-1-pyrrolidine compounds

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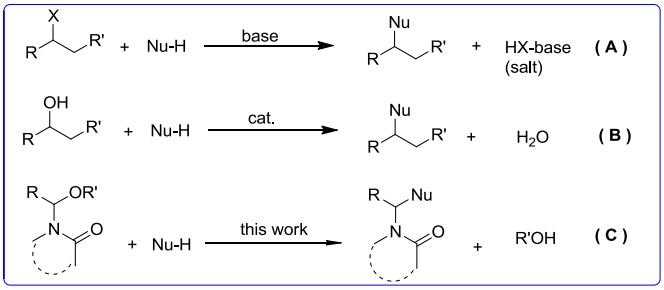
ABSTRACT

An efficient method for the cross-coupling reactions of 1,3-dicarbonyl compounds with 2-oxo-1-pyrrolidine compounds **1** was developed. $Cu(OTf)_2$ catalyzed C–C bond forming reactions using substrates **1** with 1,3-dicarbonyl compounds in chloroform, providing the corresponding compounds of 2-oxo-1-pyrrolidine bearing 1,3-dicarbonyl moiety in moderate to good yields.

1. Introduction

The functionalization of activated methylene units, such as 1,3-dicarbonyl compounds, is one of the most utilized types of carbon–carbon bond forming reactions.[1] Typically, this transformation is performed with alkyl halides in presence of at least an equimolar amount of base, which results in the generation of large quantities of waste salts[2] (Scheme 1, Path **A**). Consequently, the development of alternative methods that make use of inexpensive and readily available electrophiles, mild reaction conditions and environmentally friendly catalysts has become very topical. Recently, a lot of works were dedicated to the addition of 1,3-dicarbonyl derivatives to alcohols. It has been reported that addition of β-diketones, and β-keto esters to benzhydryl alcohols could be promoted by a stoichiometric amount of Lewis acid, such as $BF_3{\cdot}OEt_2$,[3] $InCl_3$,[4] $FeCl_3$,[5] $Bi(OTf)_3$,[1] $Yb(OTf)_3$[6] and a ruthenium complex.[7] Additionally, molecular iodine[8] and a series of Brønsted acids, such as H-montmorillote,[9] *p*-toluenesulfonic acid,[10] triflic acid[11] and phosphotungstic acid,[12] have been explored as effective catalysts for this type reaction (Scheme 1, Path **B**). However, it's not until more recently, the cross-coupling reaction of 1,3-dicarbonyl compounds 2-oxo-1-pyrrolidine compounds to construct carbon–carbon bond has remained unexplored (Scheme 1, Path **C**).



Scheme 1. State of the art on C–C bond formation of 1,3-dicarbonyl compounds.

2-Oxo-1-pyrrolidine moieties have attracted much attention for their importance as drug molecules and building blocks. 2-Oxo-1-pyrrolidine derivatives, for example, *N*-(2,6-dimethylphenyl)-2-(2-oxopyrrolidin-1-yl)acetamide, which is known as Nefiracetam, is a commonly used drug for the treatment of cerebrovascular disease (Fig. 1). Other analogues of above pharmaceuticals, especially in which another biologically active

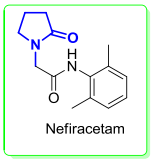


Fig. 1. Typical structure of pharmaceuticals containing 2-oxo-1-pyrrolidine fragment.

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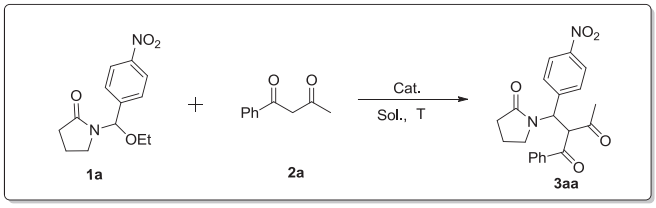
alkaloid motif incorporated, also exhibit good activities in the therapy of common diseases, such as attention deficit hyperactivity disorder (ADHD), cardiac arrhythmia and asthmatic syndrome.[13] Therefore, the discovery of new synthetic methodology and structural modification for the establishment of containing 2-oxo-1-pyrrolidine moieties pharmaceutical library was highly desirable. It's not until more recently, only we[14] and Zhang's group[15] have reported Fe(III)-promoted Friedel–Crafts reactions of *tert*-enamides with indoles for the synthesis of 2-oxo-1-pyrrolidine compounds, respectively.

As a continual of our previous work,[16] we described $Cu(OTf)_2$[17] catalyzed C–C bond forming reaction of 1,3-dicarbonyl derivatives with 2-oxo-1-pyrrolidines.

2. Results and discussion

Initial reaction was carried out using **1a** and **2a** under different conditions. As shown in Table 1, the model reaction did not occur in the absence of any catalyst (Table 1, entry 1). After screening a series of catalysts, such as metallic Lewis acid, molecular iodine, as well as Brønsted acid, it was fortunately found that 10 mol % of $Cu(OTf)_2$ was sufficient to promote the reaction (Table 1, entries 2–14). The desired C–C formation product was obtained in 63% yield after 24 h. Further optimization of the reaction conditions by changing the solvent and molar ratio were carried out using 10 mol % $Cu(OTf)_2$ as a catalyst (Table 1, entries 15–21). It was found that the model reaction could proceed effectively in $CHCl_3$ under reflux conditions. The optimized conditions were that the reaction could perform well in chloroform with a catalytic amount of $Cu(OTf)_2$ (10 mol %) (Table 1, entry 17).

Table 1
Reaction conditions screening[a]

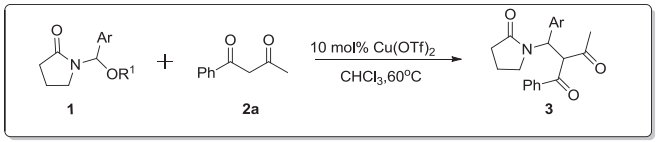


Entry	Catalyst (10 mol %)	Time (h)	Solvent	*T* (°C)	Yield[b] (%)
1	—	24	DCM	40	n.r
2	$Cu(OTf)_2$	24	DCM	40	63
3	$In(OTf)_3$	24	DCM	40	n.r[d]
4	$La(OTf)_3$	24	DCM	40	Trace
5	$Zn(OTf)_2$	24	DCM	40	24
6	$Bi(NO_3)_3$	24	DCM	40	n.r
7	$FeCl_3$	24	DCM	40	28
8	$CuBr_2$	24	DCM	40	Trace
9	$InCl_3$	24	DCM	40	<10%
10	AgOTf	24	DCM	40	Trace
11	$AgClO_4$	24	DCM	40	Trace
12	$SnCl_2$	24	DCM	40	n.r
13	I_2	24	DCM	40	Trace
14	PTSA[e]	24	DCM	40	Trace
15[c]	$Cu(OTf)_2$	24	Tol.	110	72
16[c]	$Cu(OTf)_2$	24	CH_3CN	60	24
17[c]	$Cu(OTf)_2$	24	$CHCl_3$	60	79
18[c]	$Cu(OTf)_2$	24	$ClCH_2CH_2Cl$	85	74
19[c]	$Cu(OTf)_2$	24	EtOH	78	5
20[c]	$Cu(OTf)_2$	24	THF	65	52
21[c]	$Cu(OTf)_2$	24	CH_3NO_2	100	72
22[c]	$Cu(OTf)_2$	12	$CHCl_3$	60	55

[a] General conditions: Compound **1a** (0.4 mmol), **2a** (0.4 mmol).
[b] Isolated yield.
[c] Molar ratio **1a**/**2a**=1.5: 1.
[d] n.r means no reaction.
[e] PTSA=*p*-toluenesulfonic acid.

With the optimal conditions in hands, the scope of substrates was subsequently investigated. As illustrated in Table 2, the cross-coupling reactions of 1-phenylbutane-1,3-dione **2a** with 2-oxo-1-pyrrolidine derivatives **1** under the established conditions could be accomplished with good generality. The substrate **1** bearing Ar with strong electron-withdrawing groups, such as nitro, cyano and methylsulfonyl, efficiently underwent reactions

Table 2
$Cu(OTf)_2$ catalyzed cross-coupling of 1-phenylbutane-1,3-dione **2a** with 2-oxo-1-pyrrolidine derivatives **1** in chloroform[a]



Entry		Ar	R^1	Product	Time (h)	Yield[b] (%)
1	**1a**	O_2N–	Et	**3aa**	24	81(5:2)[d]
2	**1b**	–SO2–	Et	**3ba**	24	87(3:1)
3	**1c**	NC–	Et	**3ca**	24	80(10:3)
4	**1d**	O_2N–	Et	**3da**	24	81(2:1)
5	**1e**	Br–	Et	**3ea**	24	79(3:1)
6	**1f**	Br	Et	**3fa**	24	63(1:1)
7	**1g**	F–	Et	**3ga**	24	77(3:1)
8	**1h**		Et	**3ha**	48	68(4:1)
9	**1i**		Et	**3ia**	48	67(4:1)
10	**1j**	H_3CO–	Et	**3ja**	48	81[c](3:1)
11	**1k**	H_3CO	Et	**3ka**	24	68(5:1)
12	**1l**	Me_2N–	Et	**3la**	48	45(3:1)
13	**1m**	S	Et	**3ma**	48	73[c](3:2)
14	**1n**		Et	**3na**	48	63(5:1)
15	**1a**	O_2N–	CH_3	**3aa**	24	68(3:1)
16	**1j**	H_3CO–	CH_3	**3ja**	48	80(3:1)
17	**1e**	Br–	CH_3	**3ea**	48	81(3:1)
18	**1a**	O_2N–	^{i}Pr	**3aa**	48	62(3:1)

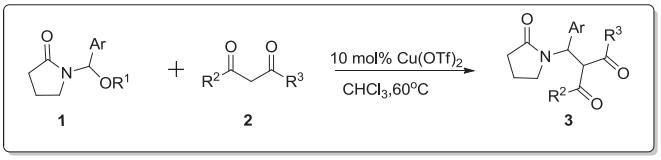
[a] Unless otherwise specified, all reactions were performed with pyrrolidin-2-ones derivatives **1** (0.6 mmol), 1-phenylbutane dione **2a** (0.4 mmol), and $Cu(OTf)_2$ (10 mol %) in $CHCl_3$ (2 ml) at 60 °C.
[b] Isolated yield after flash column chromatography.
[c] A larger amount of **1** (0.8 mmol) was employed.
[d] Ratio of the diastereomers determined by ^{1}H NMR spectroscopic analysis.

with 1-phenylbutane-1,3-dione (**2a**) to afford the desired products (**3aa**–**da**) in 80–87% yields (Table 2, entries 1–4). The substrate **1** bearing Ar with weak electron-withdrawing groups, such as halogens, also worked well, while affected a bit by the steric effect (Table 2, entries 5–7). Substrates **1** bearing Ar with electron-donating groups, such as methoxy and dimethylamino, gave the moderate results when compared to those with electron-withdrawing groups, which reflecting the electronic effect on the cross-coupling reactions (Table 2, entries 8–12). Other substrates **1** bearing aryls, such as naphthalene-2-yl and thiophen-2-yl, were also demonstrated to be good candidates for this reaction (Table 2, entries 13–14). Influence of other leaving groups on the cross-coupling of 1-phenylbutane-1,3-dione (**2a**) was investigated as well. It was found that methoxy and isopropoxy substituents exhibited comparable reactivity to ethoxy group, furnishing the expected products in good yields (Table 2, entries 15–18).

Further expansion to other β-dicarbonyl compounds **2** as nucleophile was also explored. The results were listed in Table 3. Obviously, the reaction of β-diketones including acetylacetone and dibenzoylmethane with 1-(ethoxy(4-nitrophenyl)methyl)pyrrolidin-2-one (**1a**) gave the corresponding products in good yields (Table 3, entries 1 and 3). Unexpectedly, the substrate **1** bearing strong electron-donating groups, such as methoxy in the Ar could not react with acetylacetone under standard conditions to give the target product, which might be due decompose to corresponding aldehyde as a side-product (Table 3, entry 2). What's more, β-keto esters, such as ethyl 3-oxobutanoate and ethyl 3-oxo-3-phenylpropanoate, also proceeded smoothly to give the corresponding products in 49% and 81% yields, respectively (Table 3, entries 6–7). The malonate derivatives as candidates for 1,3-dicarbonyl were selected to reacted with 1-(methoxy(4-nitrophenyl)methyl)pyrrolidin-2-one (**1a**), but no desired products were obtained (Table 3, entries 8–9).

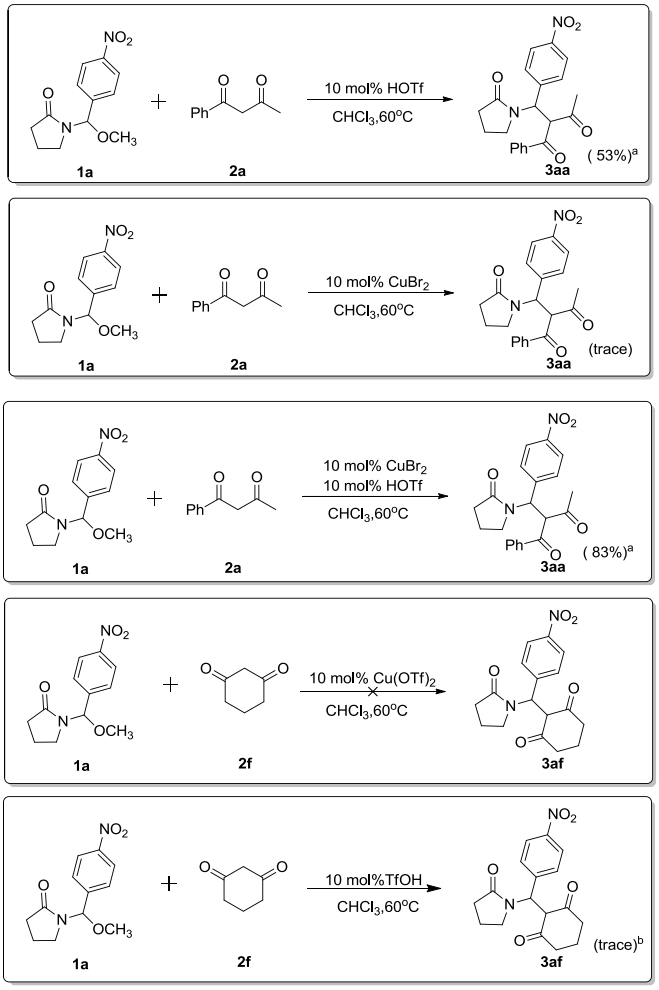
The mechanism of addition of β-dicarbonyl compounds to alcohols by Lewis acids is generally thought to involve the formation of a carbocation intermediate and subsequent S_N1 attack on the β-dicarbonyl compounds to yield the addition product. To better understand the mechanism of our reaction, five control reactions were carried out in different conditions (Scheme 2). When the reaction of **1a** and **2a** catalyzed by 10 mol % TfOH, only 53% desired product was obtained. When 10 mol % $CuBr_2$ was used as the catalyst instead of $Cu(OTf)_2$ and HOTf, only trace desired product was formed. However, an 83% yield of **3aa** was obtained by co-catalysts of 10 mol % $CuBr_2$ and 10 mol % HOTf. Then, when we carried out the reaction of **1a** and **2f** catalyzed by not only 10 mol % $Cu(OTf)_2$ but also 10 mol % HOTf under standard conditions, almost no desired product was formed. Basing on these results, a possible mechanism for this $Cu(OTf)_2$ catalyzed cross-coupling reaction of 1,3-dicarbonyl compounds was suggested in Scheme 3. By strong coordination of 1,3-dicarbonyl compounds to $Cu(OTf)_2$, the intermediate **A** was facilely formed via a ligand-exchange reaction. At the same time, elimination of one molecular HOTf occurred. Then, the C–O bond of 1-(ethoxy(4-nitrophenyl)methyl)pyrrolidin-2-one (**1a**) was activated by HOTf to generate a stable *N*-acyliminium species **B** accompanying

Table 3
$Cu(OTf)_2$ catalyzed cross-coupling of β-dicarbonyl compounds **2** with 2-oxo-1-pyrrolidine derivatives **1** in chloroform[a]



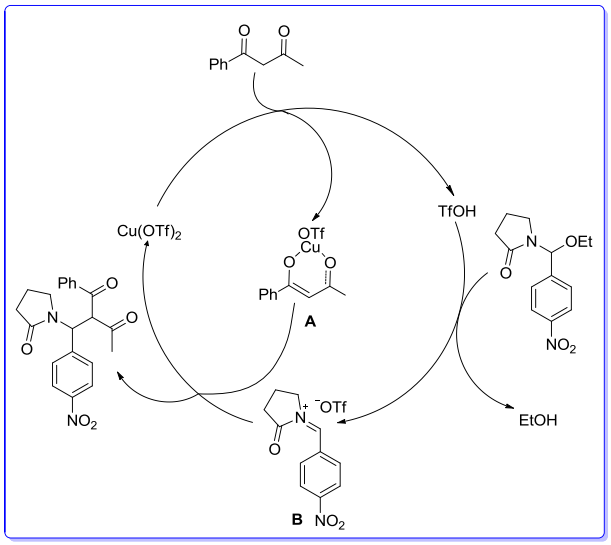
Entry		Ar	R^1		R^2	R^3	Product	Time (h)	Yield[b] (%)
1	**1a**	O_2N–	Et	**2b**	CH_3	CH_3	**3ab**	48	64
2	**1j**	H_3CO–	Et	**2b**	CH_3	CH_3	**3jb**	24	0
3	**1a**	O_2N–	Et	**2c**	Ph	Ph	**3ac**	24	79
5	**1j**	H_3CO–	Et	**2c**	Ph	Ph	**3jc**	48	61
6	**1a**	O_2N–	Et	**2d**	CH_3	OEt	**3ad**	24	49(1:1)[c]
7	**1a**	O_2N–	Et	**2e**	Ph	OEt	**3ae**	48	81(3:2)
8	**1a**	O_2N–	Et	**2f**	OH	OH	**3af**	24	0
9	**1a**	O_2N–	Et	**2g**	OEt	OEt	**3ag**	24	0

[a] Unless otherwise specified, all reactions were performed with 2-oxo-1-pyrrolidine derivatives **1a** (0.6 mmol), β-dicarbonyl compounds **2** (0.4 mmol), and $Cu(OTf)_2$ (10 mol %) in $CHCl_3$ (2 ml) at 60 °C.
[b] Isolated yield after flash column chromatography.
[c] Ratio of the diastereomers determined by ^1H NMR spectroscopic analysis.



[a] Isolated yield after flash column chromatography. [b] The desired product was monitored by LCMS.

Scheme 2. Mechanism study.



Scheme 3. Proposed mechanism.

with formation of one molecular EtOH. Under this circumstance, **B** was fast attacked by the enolate fragment from **A** to afford final product.

3. Conclusion

In summary, we have reported an efficient method for the cross-coupling of β-dicarbonyl compounds with 2-oxo-1-pyrrolidine derivatives. The reactions proceeded efficiently in the presence of a catalytic amount of $Cu(OTf)_2$ (10 mol %) in chloroform, generating 2-oxo-1-pyrrolidine derivatives bearing β-dicarbonyl moiety in moderate to good yields. The method using *N,O*-acetal compound as alkylating reagent provides a new way to synthesize of a wide variety of potential pharmaceutically active compounds bearing 2-oxo-1-pyrrolidine scaffold. Asymmetric synergistic catalyzed cross-coupling reaction of 1,3-dicarbonyl derivatives with 2-oxo-1-pyrrolidine compounds will be reported in due course.

4. Experimental section

4.1. General

Melting points were recorded on an Electrothermal digital melting point apparatus and were uncorrected. IR spectra were recorded on a Varian FT-1000 spectrophotometer using KBr optics. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian INOVA 300 or 400 MHz (^{1}H NMR) and 75 or 100 MHz (^{13}C NMR) spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. High resolution mass spectra were obtained using GCT-TOF instrument with EI or ESI source.

4.2. Typical experimental procedure for $Cu(OTf)_2$ catalyzed cross-coupling of β-dicarbonyl derivatives with 2-oxo-1-pyrrolidine compounds

1-Phenylbutane-1,3-dione (0.4 mmol, 0.0648 g), $Cu(OTf)_2$ (0.04 mmol, 0.0158 g, 10 mol %), 1-(ethoxy(phenyl)methyl)pyrrolidin-2-one (0.6 mmol, 0.1584 g), and $CHCl_3$ (2 ml) were added into a flask. Then the mixture was vigorously stirred at 60 °C until 1-phenylbutane-1,3-dione or 1-(ethoxy(phenyl)methyl)pyrrolidin-2-one was completely consumed as monitored by TLC analysis. After the completion of reaction, the residue was directly purified by flash column chromatography by using ethyl acetate and petroleum ether as eluents to afford pure product.

*4.2.1. 2-((4-Nitrophenyl)(2-oxopyrrolidin-1-yl)methyl)-1-phenylbutane-1,3-dione (**3aa**).* Yield (122.6 mg, 81%). White solid. Mp 164.5–165.3 °C. IR (KBr): ν=3428, 3065, 2958, 1674, 1514, 1424, 1267, 1175, 857 cm^{-1}. Characterized as a 5:2 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.10 (d, J=8.7 Hz, 2H), 7.96 (d, J=8.7 Hz, 2H), 7.65–7.45 (m, 5H), 6.10 (d, J=11.4 Hz, 1H), 5.88 (d, J=11.4 Hz, 1H), 3.49–3.43 (m, 1H), 3.22–3.16 (m, 1H), 2.39–2.34 (m, 2H), 2.23 (s, 3H), 1.97–1.92 (m, 2H) ppm. Isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.21 (d, J=8.6 Hz, 2H), 8.13 (d, J=8.6 Hz, 2H), 7.76 (d, J=8.2 Hz, 2H), 7.67–7.62 (m, 4H), 6.47 (d, J=11.4 Hz, 1H), 5.46 (d, J=11.4 Hz, 1H), 3.46–3.43 (m, 1H), 3.35–3.34 (m, 1H), 2.19–2.17 (m, 2H), 1.97 (s, 3H), 1.92–1.86 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=201.2, 192.7, 175.6, 147.5, 144.3, 135.8, 134.5, 129.1, 128.2, 123.9, 63.9, 55.4, 45.3, 31.2, 27.6, 18.3 ppm. Isomer ^{13}C NMR (75 MHz, $CDCl_3$): δ=201.2, 192.8, 175.6, 147.7, 145.0, 136.2, 134.2, 128.8, 128.6, 126.9, 121.7, 58.3, 48.7, 31.6, 30.5, 29.6, 18.2 ppm. HRMS: calcd for $C_{21}H_{20}N_2O_5$: $[M]^+$ 380.1372; found, 380.1264.

*4.2.2. 2-((4-(Methylsulfonyl)phenyl)(2-oxopyrrolidin-1-yl)methyl)-1-phenylbutane-1,3-dione (**3ba**).* Yield (144.0 mg, 87%). White solid. Mp 201.3–202.8 °C. IR (KBr): ν=3427, 2968, 1674, 1424, 1293, 1151 cm^{-1}. Characterized as a 3:1 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.97 (d, J=7.7 Hz, 2H), 7.82 (d, J=7.7 Hz, 2H), 7.54–7.46 (m, 5H), 6.15 (d, J=11.4 Hz, 1H), 5.84 (d, J=11.4 Hz, 1H), 3.48–3.44 (m, 1H), 3.17–3.11 (m, 1H), 2.98 (s, 3H), 2.38–2.36 (m, 2H), 2.23 (s, 3H), 1.99–1.95 (m, 2H) ppm. Isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.13 (d, J=7.4 Hz, 2H), 7.94 (d, J=8.2 Hz, 2H), 7.78 (d, J=8.2 Hz, 2H), 7.63–7.58 (m, 3H), 6.44 (d, J=11.4 Hz, 1H), 5.49 (d, J=11.4 Hz, 1H), 3.37–3.34 (m, 1H), 3.34–3.32 (m, 1H), 3.07 (s, 3H), 2.16–2.14 (m, 2H), 1.99 (s, 3H), 1.85–1.78 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=201.5, 192.8, 175.6, 143.3, 140.4, 136.2, 134.2, 129.5, 129.1, 128.8, 127.9, 63.9, 55.3, 45.1, 44.3, 31.2, 27.5, 18.3 ppm. Isomer ^{13}C NMR (75 MHz, $CDCl_3$): δ=200.2, 192.5, 175.6, 143.8, 140.4, 136.2, 134.2, 129.5, 129.1, 128.8, 127.8, 58.2, 49.4, 48.5, 44.3, 31.6, 29.7, 18.3 ppm. HRMS: calcd for $C_{22}H_{23}NO_5S$: $[M]^+$ 413.1297; found, 413.1184.

*4.2.3. 4-(2-Benzoyl-3-oxo-1-(2-oxopyrrolidin-1-yl)butyl)benzonitrile (**3ca**).* Yield (115.6 mg, 81%). White solid. Mp 116.3–117.5 °C. IR (KBr): ν=3422, 2928, 2227, 1678, 1420, 1266, 980 cm^{-1}. Characterized as a 10:3 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.92 (d, J=7.7 Hz, 2H), 7.64 (d, J=7.7 Hz, 2H), 7.46–7.39 (m, 5H), 6.03 (d, J=11.7 Hz, 1H), 5.81 (d, J=11.7 Hz, 1H), 3.41–3.37 (m, 1H), 3.16–3.12 (m, 1H), 2.37–2.34 (m, 2H), 2.22 (s, 3H), 1.94–1.91 (m, 2H) ppm. Isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.11 (d, J=7.6 Hz, 2H), 7.70–7.59 (m, 4H), 7.54–7.52 (m, 3H), 6.42 (d, J=11.3 Hz, 1H), 5.41 (d, J=11.3 Hz, 1H), 3.46–3.44 (m, 1H), 3.31–3.29 (m, 1H), 2.22–2.14 (m, 2H), 1.96 (s, 3H), 1.85–1.82 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=201.6, 192.7, 175.6, 142.6, 136.1, 134.4, 132.8, 129.5, 128.6, 118.5, 112.4, 64.1, 55.9, 45.5, 31.8, 27.8, 18.5 ppm. Isomer ^{13}C NMR (75 MHz, $CDCl_3$): δ=200.3, 192.6, 175.8, 143.3, 136.1, 134.3, 132.8, 129.5, 129.2, 128.4, 112.5, 64.1, 58.9, 49.2, 31.9, 30.6, 18.4 ppm. HRMS: calcd for $C_{22}H_{20}N_2O_3$: $[M]^+$ 360.1474; found, 360.1546.

*4.2.4. 2-((3-Nitrophenyl)(2-oxopyrrolidin-1-yl)methyl)-1-phenylbutane-1,3-dione (**3da**).* Yield (124.6 mg, 81%). White solid. Mp 135.9–147.5 °C. IR (KBr): ν=3436, 2963, 1674, 1427, 1294, 770 cm^{-1}. Characterized as a 2:1 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.42 (s, 1H), 7.96 (d, J=7.6 Hz, 3H), 7.55–7.43 (m, 5H), 6.13 (d, J=11.7 Hz, 1H), 5.87 (d, J=11.7 Hz, 1H), 3.49–3.37 (m, 1H), 3.22–3.18 (m, 1H), 2.39–2.34 (m, 2H), 2.24 (s, 3H),

1.98–1.93 (m, 2H) ppm. Isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.23–8.11 (m, 3H), 8.06 (d, J=8.1 Hz, 1H), 7.63–7.55 (m, 5H), 6.46 (d, J=11.7 Hz, 1H), 5.51 (d, J=11.7 Hz, 1H), 3.42–3.37 (m, 1H), 2.86–2.83 (m, 1H), 2.17–2.14 (m, 2H), 2.02 (s, 3H), 1.85–1.79 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=201.4, 192.6, 175.5, 148.3, 139.2, 134.9, 134.5, 134.4, 129.9, 128.8, 123.2, 122.4, 63.9, 55.4, 45.2, 31.2, 27.6 ppm. Isomer ^{13}C NMR (75 MHz, $CDCl_3$): δ=200.0, 192.9, 175.6, 148.2, 139.7, 136.2, 134.9, 134.2, 129.9, 129.1, 128.8, 123.4, 122.3, 58.1, 48.6, 31.5, 30.6, 30.4, 18.3 ppm. HRMS: calcd for $C_{21}H_{20}N_2O_5$: $[M]^+$ 380.1372; found, 380.1263.

*4.2.5. 2-((4-Bromophenyl)(2-oxopyrrolidin-1-yl)methyl)-1-phenylbutane-1,3-dione (**3ea**).* Yield (133.3 mg, 79%). Yellow solid. Mp 118.3–119.5 °C. IR (KBr): ν=3432, 2964, 1670, 1421, 1269 cm^{-1}. Characterized as a 3:1 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.96 (d, J=7.6 Hz, 2H), 7.48–7.41 (m, 3H), 7.36 (d, J=8.2 Hz, 2H), 7.16 (d, J=8.2 Hz, 2H), 6.08 (d, J=11.7 Hz, 1H), 5.71 (d, J=11.7 Hz, 1H), 3.45–3.38 (m, 1H), 3.16–3.10 (m, 1H), 2.34–2.25 (m, 2H), 2.23 (s, 3H), 1.97–1.90 (m, 2H) ppm. Isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.11 (d, J=7.9 Hz, 2H), 7.62–7.58 (m, 3H), 7.51–7.41 (m, 4H), 6.33 (d, J=11.4 Hz, 1H), 5.40 (d, J=11.4 Hz, 1H), 3.45–3.43 (m, 1H), 3.30–3.28 (m, 1H), 2.17–2.14 (m, 2H), 1.97 (s, 3H), 1.94–1.90 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=201.9, 192.6, 173.3, 136.5, 136.1, 134.3, 131.9, 129.4, 128.9, 122.2, 64.3, 58.1, 47.6, 29.7, 18.1 ppm. Isomer ^{13}C NMR (75 MHz, $CDCl_3$): δ=200.8, 192.9, 173.3, 136.5, 136.1, 133.9, 132.0, 130.2, 129.4, 128.9, 122.5, 58.1, 48.0, 31.7, 30.9, 30.2, 18.1 ppm. HRMS: calcd for $C_{21}H_{20}BrNO_3$: $[M]^+$ 413.0627; found, 413.0693.

*4.2.6. 2-((2-Bromophenyl)(2-oxopyrrolidin-1-yl)methyl)-1-phenylbutane-1,3-dione (**3fa**).* Yield (102.5 mg, 63%). Yellow solid. Mp 130.7–131.5 °C. IR (KBr): ν=3246, 2964, 1976, 1688, 1440, 1284, 1171, 994, 762, 685, 534 cm^{-1}. Characterized as a 1:1 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.13 (d, J=7.8 Hz, 2H), 8.05 (d, J=7.8 Hz, 2H), 7.94 (d, J=7.8 Hz, 2H), 7.63–7.49 (m, 6H), 7.44–7.41 (m, 3H), 7.36 (t, J=7.6 Hz, 1H), 7.15–7.11 (m, 2H), 7.05 (t, J=7.6 Hz, 1H), 6.62 (d, J=11.3 Hz, 1H), 6.27 (d, J=11.4 Hz, 1H), 6.01 (d, J=11.4 Hz, 1H), 6.83 (d, J=11.3 Hz, 1H), 3.64–3.60 (m, 1H), 3.58–3.52 (m, 1H), 3.51–3.39 (m, 1H), 3.20–3.14 (m, 1H), 2.46–2.44 (m, 2H), 2.29 (s, 3H), 2.12–2.08 (m, 2H), 1.97 (s, 3H), 1.84–1.77 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=207.3, 206.1, 198.2, 197.8, 180.5, 141.7, 141.3, 139.5, 137.2, 137.1, 136.2, 136.1, 135.4, 134.7, 134.4, 133.9, 132.1, 130.3, 129.6, 129.1, 128.9, 127.7, 127.4, 69.5, 62.8, 60.2, 53.2, 49.8, 36.9, 36.5, 35.5, 32.4, 23.4, 23.3 ppm. HRMS: calcd for $C_{21}H_{20}BrNO_3$: $[M]^+$ 413.0627; found, 413.0693.

*4.2.7. 2-((4-Fluorophenyl)(2-oxopyrrolidin-1-yl)methyl)-1-phenylbutane-1,3-dione (**3ga**).* Yield (109.5 mg, 77%). White solid. Mp 106.5–107.1 °C. IR (KBr): ν=3438, 2920, 1676, 1507, 1424, 1271, 812, 695 cm^{-1}. Characterized as a 3:1 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.94 (d, J=7.7 Hz, 2H), 7.55–7.41 (m, 4H), 7.03 (t, J=8.5 Hz, 1H), 6.90 (t, J=8.5 Hz, 2H), 6.08 (d, J=11.8 Hz, 1H), 5.73 (d, J=11.8 Hz, 1H), 3.45–3.39 (m, 1H), 3.16–3.10 (m, 1H), 2.36–2.31 (m, 2H), 2.22 (s, 3H), 1.95–1.89 (m, 2H) ppm. Isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.10 (d, J=7.6 Hz, 2H), 7.58–7.50 (m, 4H), 7.26–7.24 (m, 4H), 6.32 (d, J=11.5 Hz, 1H), 5.42 (d, J=11.5 Hz, 1H), 3.39–3.37 (m, 1H), 3.31–3.27 (m, 1H), 2.16–2.14 (m, 2H), 1.91 (s, 3H), 1.78–1.70 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=197.8, 188.4, 170.9, 159.1, 156.6, 131.8, 129.8, 128.4, 125.8, 124.5, 115.0, 60.1, 50.7, 40.3, 27.3, 26.9, 13.7 ppm. Isomer ^{13}C NMR (100 MHz, $CDCl_3$): δ=196.8, 188.7, 170.9, 159.4, 156.9, 132.0, 129.5, 129.0, 125.0, 124.4, 111.3, 53.6, 45.2, 43.6, 26.3, 25.3, 13.5 ppm. HRMS: calcd for $C_{21}H_{20}FNO_3$: $[M]^+$ 353.1427; found, 353.1502.

*4.2.8. 2-((2-Oxopyrrolidin-1-yl)(phenyl)methyl)-1-phenylbutane-1,3-dione (**3ha**).* Yield (88.6 mg, 68%). White solid. Mp 110.0–111.5 °C. IR (KBr): ν=3424, 3055, 2954, 1670, 1424, 1268, 1090, 1018, 798, 692, 563 cm^{-1}. Characterized as a 4:1 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.90 (d, J=7.5 Hz, 2H), 7.45–7.38 (m, 5H), 7.20–7.14 (m, 3H), 6.13 (d, J=11.8 Hz, 1H), 5.63 (d, J=11.8 Hz, 1H), 3.43–3.35 (m, 1H), 3.05–3.03 (m, 1H), 2.28–2.26 (m, 2H), 2.17 (s, 3H), 1.88–1.84 (m, 2H) ppm. Isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.04 (d, J=7.5 Hz, 2H), 7.54–7.50 (m, 3H), 7.29–7.24 (m, 5H), 6.24 (d, J=11.5 Hz, 1H), 5.42 (d, J=11.8 Hz, 1H), 3.32–3.31 (m, 1H), 2.79–2.76 (m, 1H), 2.13–2.09 (m, 2H), 1.88 (s, 3H), 1.69–1.67 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.8, 193.3, 175.4, 137.0, 136.5, 134.3, 129.1, 128.9, 128.3, 127.9, 64.7, 55.6, 44.6, 31.5, 27.4, 18.4 ppm. Isomer ^{13}C NMR (100 MHz, $CDCl_3$): δ=201.4, 193.0, 175.4, 137.5, 136.5, 134.1, 129.1, 128.7, 128.3, 127.9, 64.6, 49.6, 47.8, 31.6, 27.4, 18.2 ppm. HRMS: calcd for $C_{21}H_{21}NO_3$: $[M]^+$ 335.1521; found, 335.1611.

*4.2.9. 2-((2-Oxopyrrolidin-1-yl)(p-tolyl)methyl)-1-phenylbutane-1,3-dione (**3ia**).* Yield (94.2 mg, 67%). White solid. Mp 125.6–126.2 °C. IR (KBr): ν=3429, 2927, 1678, 1421, 1262, 1086 cm^{-1}. Characterized as a 4:1 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.98 (d, J=7.6 Hz, 2H), 7.47–7.30 (m, 4H), 7.17–7.13 (m, 3H), 7.02 (d, J=7.9 Hz, 2H), 6.20 (d, J=11.8 Hz, 1H), 5.65 (d, J=11.8 Hz, 1H), 3.45–3.40 (m, 1H), 3.12–3.08 (m, 1H), 2.34–2.31 (m, 2H), 2.24 (s, 6H), 1.92–1.89 (m, 2H) ppm. Isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.11 (d, J=7.6 Hz, 2H), 7.60–7.57 (m, 4H), 7.04–7.02 (m, 3H), 6.26 (d, J=11.6 Hz, 1H), 5.49 (d, J=11.6 Hz, 1H), 3.39–3.35 (m, 1H), 3.26–3.25 (m, 1H), 2.18–2.14 (m, 2H), 1.96 (s, 6H), 1.71–1.69 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=202.7, 192.8, 175.1, 137.8, 136.4, 134.0, 133.7, 129.4, 128.8, 128.7, 127.6, 64.6, 54.9, 44.2, 31.3, 27.1, 18.1 ppm. Isomer ^{13}C NMR (75 MHz, $CDCl_3$): δ=201.6, 193.3, 175.1, 138.2, 136.6, 134.2, 133.7, 129.6, 128.7, 128.3, 127.6, 64.4, 58.0, 49.4, 47.4, 31.7, 27.1, 21.1, 17.6 ppm. HRMS: calcd for $C_{22}H_{23}NO_3$: $[M]^+$ 349.1678; found, 349.1759.

*4.2.10. 2-((4-Methoxyphenyl)(2-oxopyrrolidin-1-yl)methyl)-1-phenylbutane-1,3-dione (**3ja**).* Yield (88.0 mg, 61%). White solid. Mp 81.2–82.2 °C. IR (KBr): ν=3436, 2963, 1675, 1426, 1261, 1031, 805 cm^{-1}. Characterized as a 3:1 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.97 (d, J=7.6 Hz, 2H), 7.46 (t, J=7.5 Hz, 3H), 7.15 (d, J=8.4 Hz, 2H), 6.75 (d, J=8.4 Hz, 2H), 6.14 (d, J=11.8 Hz, 1H), 5.66 (d, J=11.8 Hz, 1H), 3.72 (s, 3H), 3.42–3.35 (m, 1H), 3.15–3.11 (m, 1H), 2.38–2.31 (m, 2H), 2.24 (s, 3H), 1.93–1.89 (m, 2H) ppm. Isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.11 (d, J=7.6 Hz, 2H), 7.59 (t, J=7.5 Hz, 3H), 7.51 (d, J=7.5 Hz, 2H), 6.87 (d, J=7.5 Hz, 2H), 6.25 (d, J=11.5 Hz, 1H), 5.46 (d, J=11.5 Hz, 1H), 3.80 (s, 3H), 3.27–3.24 (m, 1H), 3.87–3.84 (m, 1H), 2.16 (s, 3H), 2.04–2.00 (m, 2H), 1.81–1.77 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=202.8, 193.0, 175.3, 159.4, 136.5, 134.2, 129.8, 129.5, 129.1, 128.9, 114.4, 64.9, 57.9, 55.3, 44.5, 31.6, 27.3, 18.2 ppm. Isomer ^{13}C NMR (100 MHz, $CDCl_3$): δ=201.8, 193.6, 175.1, 159.7, 136.8, 134.9, 129.5, 128.9, 114.3, 64.6, 55.1, 49.6, 47.5, 31.9, 30.8, 17.8 ppm. HRMS: calcd for $C_{22}H_{23}NO_4$: $[M]^+$ 365.1627; found, 365.1701.

*4.2.11. 2-((3-Methoxyphenyl)(2-oxopyrrolidin-1-yl)methyl)-1-phenylbutane-1,3-dione (**3ka**).* Yield (99.5 mg, 68%). White solid. Mp 112.5–113.0 °C. IR (KBr): ν=3428, 2947, 1673, 1596, 1423, 1272, 1173, 1054, 989, 760 cm^{-1}. Characterized as a 5:1 diastereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.98 (d, J=7.6 Hz, 2H), 7.59 (t, J=7.5 Hz, 2H), 7.54–7.40 (m, 3H), 6.81–6.74 (m, 2H), 6.20 (d, J=11.8 Hz, 1H), 5.65 (d, J=11.8 Hz, 1H), 3.69 (s, 3H), 3.44–3.43 (m, 1H), 3.12–3.10 (m, 1H), 2.35–2.34 (m, 2H), 2.24 (s, 3H), 1.91–1.83 (m, 2H) ppm. Isomer ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.11 (d, J=7.5 Hz, 2H), 7.29–7.25 (m, 2H), 7.13–7.07 (m, 2H), 6.84–6.81 (m, 1H), 6.74–6.71 (m, 2H), 6.25 (d, J=11.6 Hz, 1H), 5.52 (d, J=11.6 Hz, 1H), 4.13–4.10 (m, 1H), 3.81 (s, 3H), 3.36–3.27 (m, 1H), 2.20–2.16 (m, 2H), 2.06–2.02 (m, 2H), 1.99 (s, 3H) ppm. ^{13}C NMR (75 MHz,

$CDCl_3$): δ=202.5, 193.2, 175.2, 159.8, 138.3, 136.3, 134.1, 129.7, 128.9, 119.6, 114.1, 113.6, 64.4, 55.2, 49.4, 44.2, 31.3, 27.1, 18.1 ppm. Isomer ^{13}C NMR (75 MHz, $CDCl_3$): δ=201.4, 192.7, 175.2, 159.7, 138.7, 136.5, 133.7, 129.9, 128.7, 120.5, 113.8, 113.5, 64.2, 58.2, 55.1, 47.4, 31.6, 29.9, 17.6 ppm. HRMS: calcd for $C_{22}H_{23}NO_4$: $[M]^+$ 365.1627; found, 365.1519.

*4.2.12. 2-((4-(Dimethylamino)phenyl)(2-oxopyrrolidin-1-yl)methyl)-1-phenylbutane-1,3-dione (**3la**).* Yield (67.4 mg, 45%). White solid. Mp 100.0–101.5 °C. IR (KBr): ν=3380, 2921, 1674, 1525, 1423, 1354, 1266, 1170, 812, 691 cm^{-1}. Characterized as a 3:1 diastereomeric mixture. ^1H NMR (400 MHz, $CDCl_3$): δ=7.96 (d, J=7.8 Hz, 2H), 7.50–7.39 (m, 3H), 7.08 (d, J=8.5 Hz, 2H), 6.52 (d, J=8.5 Hz, 2H), 6.14 (d, J=11.7 Hz, 1H), 5.57 (d, J=11.7 Hz, 1H), 3.40–3.39 (m, 1H), 3.10–3.07 (m, 1H), 2.84 (s, 6H), 2.33–2.29 (m, 2H), 2.25 (s, 3H), 1.92–1.87 (m, 2H) ppm. Isomer ^1H NMR (400 MHz, $CDCl_3$): δ=8.08 (d, J=7.7 Hz, 2H), 7.55 (t, J=6.7 Hz, 1H), 7.33 (d, J=8.2 Hz, 2H), 6.64 (d, J=8.3 Hz, 2H), 6.14 (d, J=11.7 Hz, 1H), 5.46 (d, J=11.7 Hz, 1H), 3.29–3.25 (m, 1H), 3.25–3.20 (m, 1H), 2.92 (s, 6H), 2.15–2.13 (m, 2H), 1.96 (s, 3H), 1.72–1.67 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=208.3, 198.8, 180.2, 155.5, 141.7, 139.1, 134.5, 133.9, 133.7, 129.4, 117.5, 70.1, 59.9, 49.2, 45.5, 36.6, 34.9, 32.2, 23.2 ppm. Isomer ^{13}C NMR (75 MHz, $CDCl_3$): δ=207.2, 198.8, 180.1, 155.3, 141.9, 138.3, 134.5, 139.8, 133.7, 129.6, 117.5, 62.8, 60.8, 52.2, 45.5, 36.9, 34.9, 32.2, 23.2 ppm. HRMS: calcd for $C_{23}H_{26}N_2O_3$: $[M]^+$ 378.1943; found, 378.1817.

*4.2.13. 2-((2-Oxopyrrolidin-1-yl)(thiophen-2-yl)methyl)-1-phenylbutane-1,3-dione (**3ma**).* Yield (84.1 mg, 62%). White solid. Mp 128.0–129.5 °C. IR (KBr): ν=3433, 3080, 2921, 1670, 1423, 1265, 1148, 964, 784, 697 cm^{-1}. Characterized as a 3:2 diastereomeric mixture. ^1H NMR (400 MHz, $CDCl_3$): δ=8.10 (d, J=7.8 Hz, 2H), 7.59–7.46 (m, 3H), 7.13 (d, J=5.1 Hz, 1H), 6.89–6.87 (m, 1H), 6.83–6.81 (m, 1H), 6.46 (d, J=11.7 Hz, 1H), 5.58 (d, J=11.7 Hz, 1H), 3.49–3.42 (m, 1H), 3.29–3.23 (m, 1H), 2.35–2.33 (m, 2H), 2.22 (s, 3H), 1.95–1.91 (m, 2H) ppm. Isomer ^1H NMR (400 MHz, $CDCl_3$): δ=8.11 (d, J=7.7 Hz, 2H), 7.60–7.51 (m, 3H), 7.26 (s, 1H), 7.11 (d, J=7.4 Hz, 1H), 6.97–6.94 (m, 1H), 6.18 (d, J=11.1 Hz, 1H), 5.84 (d, J=11.1 Hz, 1H), 3.50–3.48 (m, 1H), 2.87–2.85 (m, 1H), 2.17–2.07 (m, 2H), 2.07 (s, 3H), 1.83–1.74 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=201.9, 192.8, 175.1, 139.7, 136.2, 134.1, 128.9, 128.8, 126.7, 126.2, 125.4, 66.3, 49.4, 44.2, 31.2, 29.9, 18.1 ppm. Isomer ^{13}C NMR (75 MHz, $CDCl_3$): δ=200.7, 192.7, 175.1, 139.4, 136.3, 133.9, 128.9, 127.3, 126.0, 125.3, 65.5, 53.2, 47.2, 31.4, 29.6, 18.1 ppm. HRMS: calcd for $C_{19}H_{19}NO_3S$: $[M]^+$ 341.1086; found, 341.0985.

*4.2.14. 2-(Naphthalen-2-yl(2-oxopyrrolidin-1-yl)methyl)-1-phenylbutane-1,3-dione (**3na**).* Yield (96.5 mg, 63%). White solid. Mp 81.1–82.5 °C. IR (KBr): ν=3435, 3054, 2949, 673, 1419, 1267, 1170, 970, 757 cm^{-1}. Characterized as a 5:1 diastereomeric mixture. ^1H NMR (400 MHz, $CDCl_3$): δ=7.93 (d, J=8.0 Hz, 2H), 7.69 (d, J=8.0 Hz, 2H), 7.66–7.52 (m, 3H), 7.39–7.34 (m, 5H), 6.32 (d, J=11.8 Hz, 1H), 5.78 (d, J=11.8 Hz, 1H), 3.45–3.42 (m, 1H), 3.10–3.04 (m, 1H), 2.34–2.25 (m, 2H), 2.24 (s, 3H), 1.88–1.80 (m, 2H) ppm. Isomer ^1H NMR (400 MHz, $CDCl_3$): δ=8.10 (d, J=7.8 Hz, 2H), 7.81 (d, J=8.9 Hz, 2H), 7.57–7.44 (m, 9H), 6.32 (d, J=11.5 Hz, 1H), 5.64 (d, J=11.5 Hz, 1H), 3.35–3.30 (m, 1H), 3.25–3.24 (m, 1H), 2.17–2.12 (m, 2H), 1.90 (s, 3H), 1.69–1.65 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=202.5, 192.7, 175.3, 136.4, 134.1, 131.4, 128.9, 128.8, 128.7, 127.9, 127.5, 127.4, 126.5, 126.1, 125.2, 64.6, 55.5, 44.4, 31.4, 27.2, 18.1 ppm. Isomer ^{13}C NMR (75 MHz, $CDCl_3$): δ=201.4, 193.1, 175.3, 136.6, 134.8, 133.0, 128.9, 128.8, 128.7, 128.1, 127.6, 127.4, 126.3, 125.7, 125.2, 64.4, 58.3, 47.5, 31.7, 29.7, 18.1 ppm. HRMS: calcd for $C_{25}H_{23}NO_3$: $[M]^+$ 385.1678; found, 385.1557.

*4.2.15. 3-((4-Nitrophenyl)(2-oxopyrrolidin-1-yl)methyl)pentane-2,4-dione (**3ab**).* Yield (82.6.5 mg, 64%). White solid. Mp 123.2–124.2 °C. IR (KBr): ν=3409, 3111, 2966, 2866, 1687, 1519, 1419, 1354, 1265, 1168, 807,704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.81 (d, J=8.7 Hz, 2H), 7.54 (d, J=8.7 Hz, 2H), 5.67 (d, J=11.9 Hz, 1H), 5.17 (d, J=11.9 Hz, 1H), 337–3.31 (m, 1H), 3.24–3.17 (m, 1H), 2.35–2.25 (m, 5H), 2.12 (s, 3H), 1.97–1.86 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=205.7, 205.4, 180.7, 152.9, 149.4, 134.2, 129.4, 74.8, 60.8, 51.2, 36.5, 36.4, 33.6, 23.4 ppm. HRMS: calcd for $C_{16}H_{18}N_2O_5$: $[M]^+$ 318.1216; found, 318.1302.

*4.2.16. 2-((4-Nitrophenyl)(2-oxopyrrolidin-1-yl)methyl)-1,3-diphenylpropane-1,3-dione (**3ac**).* Yield (139.5 mg, 79%). White solid. Mp 86.4–87.1 °C. IR (KBr): ν=3441, 3054, 2920, 1670, 1520, 1278, 1104, 1005, 857, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.02 (t, J=8.0 Hz, 4H), 7.80 (d, J=7.7 Hz, 2H), 7.68 (d, J=7.7 Hz, 2H), 7.53–7.29 (m, 7H), 5.53 (d, J=11.0 Hz, 1H), 3.57–3.55 (m, 1H), 3.46–3.44 (m, 1H), 2.23–2.18 (m, 2H), 1.90–1.86 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=193.3, 176.2, 147.5, 145.1, 136.2, 135.8, 134.0, 133.8, 129.6, 128.8, 128.7, 132.7, 60.3, 57.5, 49.8, 31.9, 29.6 ppm. HRMS: calcd for $C_{26}H_{22}N_2O_5$: $[M]^+$ 442.1529; found, 442.1414.

*4.2.17. 2-((4-Methoxyphenyl)(2-oxopyrrolidin-1-yl)methyl)-1,3-diphenylpropane-1,3-dione (**3jc**).* Yield (106.0 mg, 61%). White solid. Mp 176.2–177.9 °C. IR (KBr): ν=3449, 3056, 2937, 1671, 1512, 1437, 1268, 1188, 1023, 760, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.02 (d, J=7.7 Hz, 2H), 7.83 (d, J=7.7 Hz, 2H), 7. 51–7.28 (m, 9H), 6.71 (d, J=8.7 Hz, 2H), 5.44 (d, J=11.0 Hz, 1H), 3.69 (s, 3H), 3.54–3.48 (m, 1H), 3.45–3.42 (m, 1H), 2.24–2.20 (m, 2H), 1.85–1.64 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=194.2, 176.1, 159.7, 136.7, 133.6, 130.1, 129.9, 129.1, 128.9, 128.7, 114.1, 60.4, 58.8, 55.4, 49.4, 32.4, 18.5 ppm. HRMS: calcd for $C_{27}H_{25}NO_4$: $[M]^+$ 427.1784; found, 427.1691.

*4.2.18. Ethyl 2-((4-nitrophenyl)(2-oxopyrrolidin-1-yl)methyl)-3-oxobutanoate (**3ad**).* Yield (68.2 mg, 49%). Yellow oil. IR (KBr): ν=3454, 2932, 1689, 1523, 1354, 1272, 1021, 856, 530 cm^{-1}. Characterized as a 1:1 diastereomeric mixture. ^1H NMR (400 MHz, $CDCl_3$): δ=8.19 (dd, J=8.1, 4.8 Hz, 2H, ArH), 7.57 (dd, J=8.1, 4.8 Hz, 2H, ArH), 5.55 (dd, J=25.7, 11.9 Hz, 1H, CH), 5.45 (d, J=11.6 Hz, 1H, CH), 4.24 (dd, J=7.1, 4.2 Hz, 1H, OCH_2), 4.04 (dd, J=7.1, 4.2 Hz, 1H, OCH_2), 3.48–3.33 (m, 1H), 3.27–3.22 (m, 1H), 2.37 (s, 1.5H, $COCH_3$), 2.35–2.19 (m, 2H), 2.17 (s, 1.5H, $COCH_3$), 1.89–1.80 (m, 2H), 1.28 (t, J=7.1 Hz, 1.5H, OCH_2CH_3), 1.10 (t, J=7.1 Hz, 1.5H, OCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ=205.6, 204.8, 180.7, 180.3, 171.6, 171.5, 152.9, 152.7, 149.6, 148.7, 134.2, 133.8, 129.2, 128.8, 67.6, 67.2, 66.1, 60.6, 51.7, 51.4, 36.6, 35.8, 35.4, 34.7, 33.7, 23.5, 23.4, 19.2, 19.0 ppm. HRMS: calcd for $C_{17}H_{20}N_2O_6$: $[M]^+$ 348.1321; found, 348.1212.

*4.2.19. Ethyl 2-benzoyl-3-(4-nitrophenyl)-3-(2-oxopyrrolidin-1-yl) propanoate (**3ae**).* Yield (134.9 mg, 81%). White solid. Mp 37.4–38.1 °C. IR (KBr): ν=3456, 3072, 2958, 1727, 1521, 1348, 1268, 1013, 850, 692 cm^{-1}. Characterized as a 3:2 diastereomeric mixture. ^1H NMR (400 MHz, $CDCl_3$): δ=8.07 (d, J=8.5 Hz, 2H), 7.96 (d, J=8.5 Hz, 2H), 7.57 (d, J=8.4 Hz, 2H), 7. 61–7.39 (m, 3H), 5.87 (d, J=11.5 Hz, 1H), 5.76 (d, J=11.5 Hz, 1H), 4.17–4.10 (m, 2H), 3.54–3.49 (m, 1H), 3.36–3.33 (m, 1H), 2.35–2.31 (m, 2H), 1.85–1.64 (m, 2H), 1.14 (t, J=8.4 Hz, 3H) ppm. Isomer ^1H NMR (400 MHz, $CDCl_3$): δ=8.18 (d, J=8.4 Hz, 2H), 8.10 (d, J=8.4 Hz, 2H), 7. 61–7.39 (m, 5H), 6.21 (d, J=11.5 Hz, 1H), 5.35 (d, J=11.5 Hz, 1H), 3.91–3.87 (m, 2H), 3.54–3.49 (m, 1H), 3.33–3.24 (m, 1H), 2.33–2.24 (m, 1H), 2.31–2.51 (m, 2H), 1.80–1.67 (m, 2H), 0.89 (t, J=8.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.8, 175.8, 167.5, 147.9, 144.8, 134.4, 129.8, 129.3, 129.0, 128.9, 124.1, 62.5, 58.7, 55.2, 46.4, 31.6, 29.8, 14.1 ppm. Isomer ^{13}C NMR (100 MHz, $CDCl_3$): δ=191.4, 175.5, 167.2, 147.6, 144.7, 134.3, 129.8, 129.1, 129.0, 128.9, 124.0, 62.1, 56.3, 55.6, 49.2, 31.9, 18.6, 13.8 ppm. HRMS: calcd for $C_{22}H_{22}N_2O_6$: $[M]^+$ 410.1478; found, 410.1557.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2012.07.017.

References and notes

1. Rueping, M.; Nachtsheim, B. J.; Kuenkei, A. *Org. Lett.* **2007**, *9*, 825–827.
2. *Comprehensive Organic Synthesis*; Trost, B. M., Freming, I., Eds.; Pergamon: Oxford, 1991; p 3.
3. Bisaro, F.; Prestat, G.; Vitale, M.; Poli, G. *Synlett* **2002**, 1823–1826.
4. Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793–796.
5. Yuan, Y.; shi, Z.; Feng, X.; Liu, X. *Appl. Organomet. Chem.* **2007**, *21*, 958–964; Jana, U.; Biswas, S.; Maiti, S. *Tetrahedron Lett.* **2007**, *48*, 4065–4069; Kischel, J.; Mertins, K.; Michalik, D.; zapf, A.; Beller, M. *Adv. Synth. Catal.* **2007**, *349*, 865–870.
6. Noji, M.; Konno, Y.; Ishii, K. *J. Org. Chem.* **2007**, *72*, 5161–5167.
7. Liu, P. N.; Zhou, Z. Y.; Lau, C. P. *Chem.—Eur. J.* **2007**, *13*, 8610–8619.
8. Rao, W.; Tay, A. H. L.; Goh, P. J.; Choy, J. M. L.; Ke, J. K.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 122–126.
9. Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2605–2609; Motokura, K.; Nakagiri, N.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Org. Chem.* **2007**, *72*, 6006–6015.
10. Sanz, R.; Martinez, A.; Miguel, D.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Adv. Synth. Catal.* **2006**, *348*, 1841–1845; Sanz, R.; Miguel, D.; Martinez, A.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Org. Lett.* **2007**, *9*, 727–730.
11. Sanz, R.; Miguel, D.; Martinez, A.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Org. Lett.* **2007**, *9*, 2027–2030.
12. Wang, G. W.; Shen, Y. B.; Wu, X. L. *J. Org. Chem.* **2008**, 4999–5004.
13. Kenda B.; Quesnel Y.; Ates A.; Michel P.; Turet L.; Mercier J. WO2006128693, 2006; Gobert J.; Geerts J.-P.; Bodson G. EP0162036, 1985; Schmiesing R. J.; Murray R. J. U.S. Patent 5,334,720, 1994.
14. Jiang, R.; Wu, X.-J.; Zhu, X.; Xu, X.-P.; Ji, S.-J. *Eur. J. Org. Chem.* **2010**, 5946–5950.
15. Niu, T. M.; Huang, L. H.; Wu, T. X.; Zhang, Y. H. *Org. Biomol. Chem.* **2011**, *9*, 273–277.
16. Jiang, R.; Xu, H.-Y.; Xu, X.-P.; Chu, X.-Q.; Ji, S.-J. *Org. Biomol. Chem.* **2011**, *9*, 5659–5669.
17. $Cu(OTf)_2$ belongs to the most reactive and used catalyst with Lewis acid properties, has been widely used in organic synthesis. Famous examples, see: (a) Guo, C.; Song, J.; Luo, S. W.; Gong, L. Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 5558–5562; (b) Shao, L. X.; Zhang, Y. P.; Qi, M. H.; Shi, M. *Org. Lett.* **2007**, *9*, 117–120; (c) Zhang, Z. P.; Wang, S. P.; Cai, X. B.; Liu, H. J.; Yu, J. J.; Cui, Y. Y. *Adv. Synth. Catal.* **2007**, *349*, 2097–2102; (d) Zhou, J.; Tang, Y. *Chem. Commun.* **2004**, 432–433; (e) Asao, N.; Kashaara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3504–3506; (f) Taylor, J. G.; Whittall, N.; Hii, K. K. *Chem. Commun.* **2005**, 5103–5105; (g) For $Cu(OTf)_2$ catalyzed α-amidoalkylation reaction inside of the piperidine six-member ring see: Onomura, O.; Kanda, Y.; Nakamura, Y.; Maki, T.; Matsumura, Y. *Tetrahedron Lett.* **2002**, *43*, 3229–3231.