Article

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An Approach to Tertiary Type *β*-Hydroxyl Carboxamides Through $Sc(OTf)_3$-Catalyzed Addition of Ynamides and Ketones

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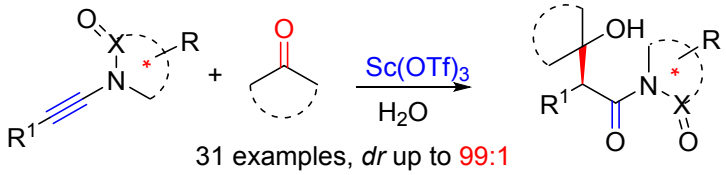
Supporting Information Placeholder



ABSTRACT

An efficient approach to access functionalized tertiary type *β*-hydroxyl carboxamides has been developed through $Sc(OTf)_3$-catalyzed addition of ynamides and substituted ketones. Water was found to be an important reaction substrate and solvent is no needed in this process. A broad range of substituted ynamides and ketones were well applicable to the reaction with excellent chemical selectivities. Moreover, several chiral *β*-hydroxyl carboxamides **3j-3r** were prepared with excellent regioselectivities and outstanding diastereoselectivities.

INTRODUCTION

The exploration of advanced methodology to access privileged structural motifs is one of the most important and urgent requirement for modern organic chemistry.[1] As a prime instance, *β*-hydroxy *α*-substituted carboxamides serve as versatile and useful subunits for numerous biologically pharmaceutical agents.[2] In particular, *β*-hydroxy *α*-substituted carboxamides can be applied to form skeletons such as oxazolines,[3] oxazoles,[4] pyrrolidines[5] and azetidines,[6] which are also used as important building blocks in synthetic chemistry[7] and flexible ligands in asymmetric organic transformations.[8] In past decades, tremendous efforts have been devoted to the development of novel synthetic approach, and several important processes including aldol reactions of aldehyde or ketone and carboxamide[9] or acylsilane,[10] hydrogenation of *β*-keto carboxamide precursors[11] or *β*-ketonitriles,[12] and ring-opening of *α*,*β*-epoxy carboxamides[13] have been established.

Recent years, ynamide has undoubtedly become one of the most fascinating building blocks in synthetic chemistry and many important chemical conversions of ynamides have been successfully achieved.[14] Among them, reactions of ynamides with ketones were reported to afford different products including acrylic amides,[15] *γ*-hydroxyenamides,[16] and *α*-halo-*γ*-hydroxyenamides[17] under the promotion of different Lewis acids (**Figure 1**). As a continuation of our interest in synthetic application of ynamides, we have reported an effective approach to access functionalized pyrido and pyrrolo[1,2-c][1,3]oxazin-1-ones through nucleophilic addition-cyclization process of *N*,O-acetal with ynamides.[18] Encouraged by these positive results, we envisioned that certain mild Lewis acids could promote, in spite of known difficulty,[19] the addition of ynamides with ketones to give *β*-hydroxyl carboxamides.

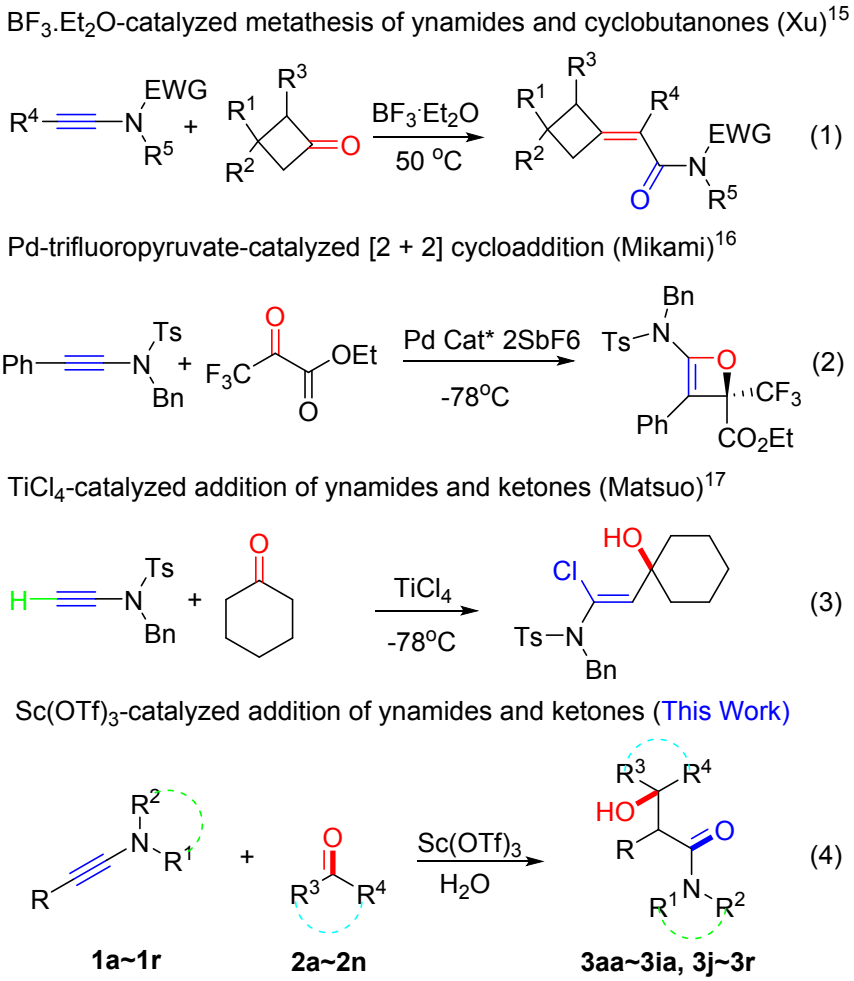


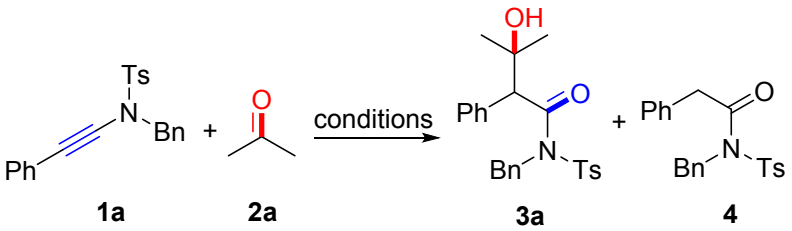
Figure 1. Lewis acid-promoted additions of ynamides with ketones.

RESULTS AND DISCUSSION

Our investigation started with the addition reaction of ynamide **1a** and ketone **2a**. First, similar conditions ($TiCl_4$ and $BF_3{\cdot}Et_2O$) used by Matsuo[17] and Xu[15] failed to promote this addition process (Table 1, entries 1-2). Initial trials with $Sc(OTf)_3$ in several solvents also turned out to be fruitless (Table 1, entries 3-5). Encouragingly, when 1 equiv. water was added, the product of carbonyl addition **3a** was obtained in 53% yield, along with the hydration product **4** in 35% yield (Table 1, entry 6). However, the replacement of water with MeOH did not produce any product (Table 1, entry 7). Notably, the neat reaction of

ynamide **1a**, $Sc(OTf)_3$, acetone and water significantly improved the yield of desired **3a** to 93% yield (Table 1, entry 8). Other Lewis acids including scandium salt ScF_3, $ScCl_3$ were screened, and the results showed that most Lewis acids gave the hydration product **4** (Table 1, entries 9-20).

Table 1. Optimization of Reaction Conditions. [a-e]



1a **2a** **3a** **4**

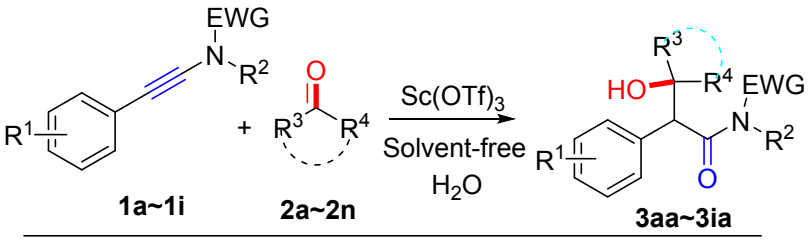
Entry[a]	Lewis Acid	Solvent[b]	Additive	Y[c] **3a**/**4**(%)
1[d]	$TiCl_4$	THF	--	--
2[d]	BF_3•Et_2O	THF	--	Complex
3[d]	$Sc(OTf)_3$	THF	--	Complex
4[d]	$Sc(OTf)_3$	DMF	--	--
5[d]	$Sc(OTf)_3$	PhMe	--	--
6	$Sc(OTf)_3$	PhMe	H_2O	53/35
7	$Sc(OTf)_3$	PhMe	MeOH[e]	--
8	$Sc(OTf)_3$	--	H_2O	93/0
9	ScF_3	--	H_2O	--
10	$Sc(AcO)_3 \cdot xH_2O$	--	H_2O	--
11	$Sc(NO_3)_3 \cdot xH_2O$	--	H_2O	20/-
12	$ScCl_3 \cdot 6H_2O$	--	H_2O	--
13	$In(OTf)_3$	--	H_2O	10/75
14	$La(OTf)_3$	--	H_2O	-/89
15	$Nd(OTf)_3$	--	H_2O	-/85
16	$Bi(OTf)_3$	--	H_2O	-/86

17	$Y(OTf)_3$	--	H_2O	-/90
18	$Zn(OTf)_2$	--	H_2O	18/76
19	$Ni(OTf)_2$	--	H_2O	--
20	$Er(OTf)_3$	--	H_2O	--

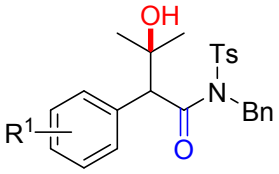
[a] The reactions were performed with ynamide **1a** (0.25 mmol), $Sc(OTf)_3$ (30 mg, 0.05 mmol), H_2O (4.5 μL, 0.25 mmol) and acetone **2a** (2.50 mmol) at rt for 2 h. [b] Solvent (1.0 mL). [c] Isolated yield. [d] Without H_2O. [e] MeOH (10.0 μL, 0.25 mmol).

Next, we turned to investigate the scope and limitation of the addition of ynamides **1a-1i** with different ketones **2a-2n** (**Scheme 1**). First, different substituted ynamides **1a-1i** were surveyed to react with acetone under the optimal condition, as summarized in Scheme 1. In general, most substituted ynamides **1a-1h** could smoothly react with acetone to give desired products **3aa-3ha** in excellent yields, except that 4-Cl-Ts substituted ynamide **1i** afforded low yield (**3ia**, 41%). Various aromatic ketones **2b-2n** were also examined under the optimal condition. The reactions of most aromatic ketones with ynamide **1a** could lead to the desired addition products **3ab-3an** in moderate yields. The steric hindered β-acetonaphthone **2m** also worked well to give **3am** in 75% yield. It is worth mentioning that cyclopentanone **2n** was also a suitable substrate, albeit with low yield (**3an**, 23%). However, the reaction with cyclohexanone turned out to be messy and did not generate any desired product. The structure of **3aa-3ia** was unambiguously confirmed by X-ray crystallographic analysis of compound **3ab** (see Supporting Information).

Scheme 1. Substrate Scope of Ynamides and Ketones. [a-d]



1a~1i **2a~2n** **3aa~3ia**

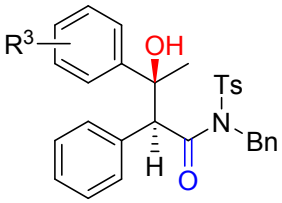


3aa R^1=H, 93%

3ba R^1=4-F-, 92%

3ca R1=4-Me-, 84%

3da R^1=4-n-C_4H_9-, 82%



3ab R^3= H, 65%

3ac R^3= 4-Br-, 75%

3ad R^3= 4-Cl-, 77%

3ae R^3= 4-CF_3-, 79%

3af R^3= 4-Me-, 72%

3ag R^3= 2-MeO-, 61%

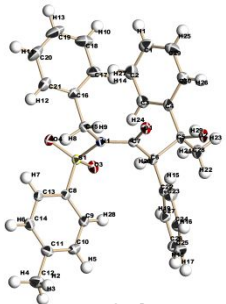
3ah R^3= 2-F-, 78%

3ai R^3= 3-CF_3-, 72%

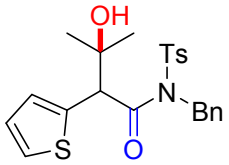
3aj R^3= 3-F-, 80%

3ak R^3= 3-Me-, 66%

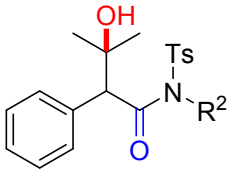
3al R^3= 3-Cl-, 73%



3ab

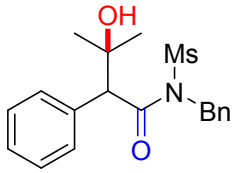


3ea 99%

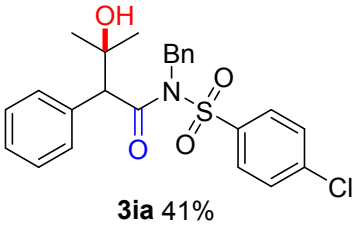


3fa R^2=Me-, 99%

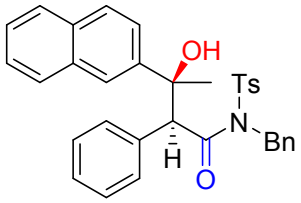
3ga R^2=n-C_4H_9-, 91%



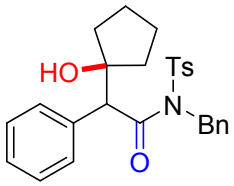
3ha 85%



3ia 41%



3am 75%[c]

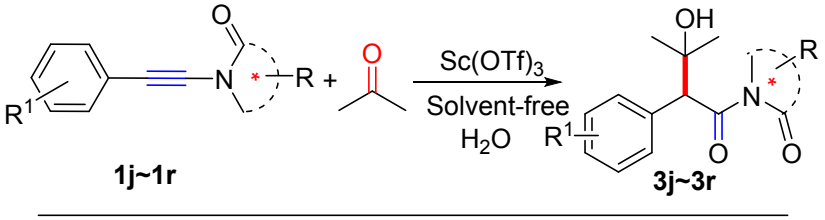


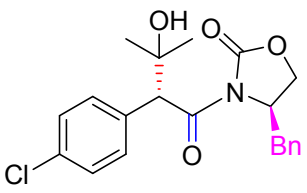
3an 23%

[a] The reactions were performed with ynamides **1a-1i** (0.25 mmol), $Sc(OTf)_3$ (30 mg, 0.05 mmol), H_2O (4.5 μL, 0.25 mmol) and ketones **2a-2n** (2.50 mmol) at rt for 2 h. [b] Isolated yield. [c] The reaction was performed in PhMe (1.0 mL). [d] *dr* > 99:1 and *dr* was determined by ^{1}H NMR of crude product.

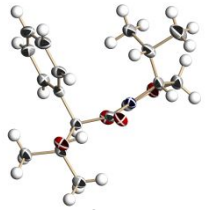
Then, we turned our attention to investigate this transformation with chiral ynamides **1j-1r**, which were prepared according to similar known approach[20] (**Scheme 2**). When (*R*)-4-benzyloxazolidin-2-one substituted ynamide **1j** was used, the desired product could be generated in 63% yield with high diastereoselectivity (*dr* > 99:1). The alkyl chain substituted ynamide **1k** also led to excellent diastereoselectivity (*dr* > 99:1), along with slightly lower yield (**3k**, 42%). Other chiral auxiliary derived ynamides also worked well. Ynamides **1l**–**1r** bearing (*R*)-4-phenyloxazolidin-2-one, (*R*)-4-isopropyloxazolidin-2-one, (4*S,5R*)-4-methyl-5-phenyloxazolidin-2-one, all offered the desired products in moderate yields with outstanding diastereoselectivities. The absolute configuration of newly generated chiral centre was fully controlled by chiral auxiliaries. Ynamides **1j**–**1o** provided *αR*-carboxamide products, while ynamides **1p**–**1r** bearing (4*S,5R*)-4-methyl-5-phenyloxazolidin-2-one afforded the desired products **3p-3r** with *αS*-configuration. The stereochemistry of compounds **3j-3r** was unambiguously assigned by X-ray crystallographic analysis of compound **3o** (see Supporting Information).

Scheme 2. Substrate Scope of Chiral Substituted Ynamides. [a-c]

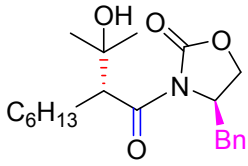




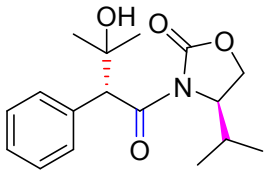
3j 68%, *dr* > 99:1



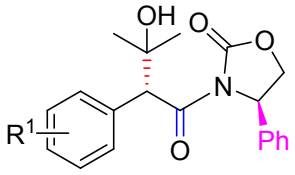
3o



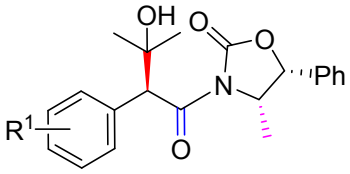
3k 42%, *dr* > 99:1



3o 59%, *dr* > 99:1



3l R^1= H, 63%, *dr* > 99:1
3m R^1= 4-MeO-, 82%, *dr* > 99:1
3n R^1= 4-Br-, 52%, *dr* > 99:1



3p R^1= H, 41%, *dr* > 99:1
3q R^1= 4-MeO-, 70%, *dr* > 99:1
3r R^1= 4-Br-, 40%, *dr* > 99:1

[a] The reactions were performed with ynamides **1j-1r** (0.25 mmol), $Sc(OTf)_3$ (30 mg, 0.05 mmol), H_2O (4.5 μL, 0.25 mmol) and acetone (2.50 mmol) at rt for 2 h. [b] Isolated yield. [c] *dr* was determined by ^1H NMR of crude product.

According to previous work[9b, 14f, 19] and our results, a possible mechanism was illustrated for this addition reaction of ynamides with ketones (**Figure 2**). First, scandium(III) triflate coordinated with the acetylene bond of **1a** to give *anti*-allene-type Sc(III) intermediate **5**. Such a metal species **5** would attack Sc-activated keto-carbonyl group to give preferred conformation intermediate **6**, which subsequently form the enol

intermediate **7**. On the other hand, slight 5 produced the hydration product **4**. Finally, isomerization of unstable enol **7** led to **3ab**.

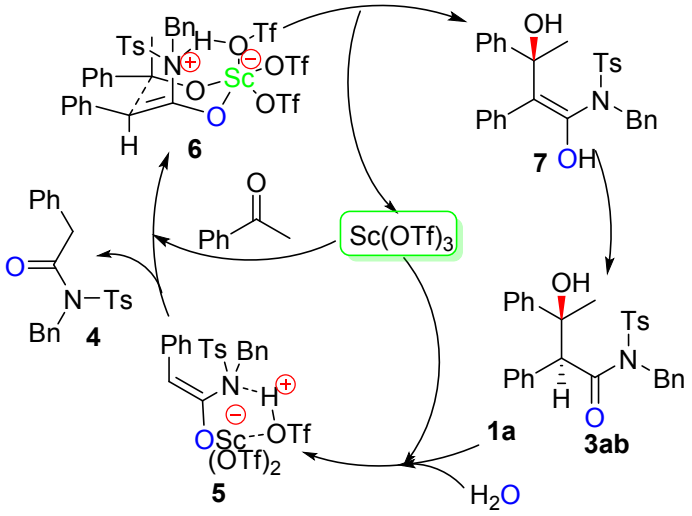
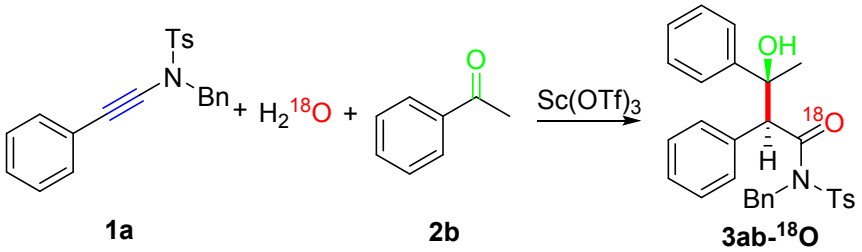


Figure 2. Proposed mechanism of the reaction.

To verify this process, **1a** was subjected to the standard reaction conditions with $H_2{}^{18}O$, the desired isotope substituted products **3ab**-^{18}O was isolated (**Scheme 3**). This showed that water was attended the reaction process.

Scheme 3. Mechanistic studies of the reaction. [a, b]



[a] The reaction was performed with ynamide **1a** (0.25 mmol), $Sc(OTf)_3$ (30 mg, 0.05 mmol), $H_2{}^{18}O$ (4.5 μL, 0.50 mmol) and ketone **2b** (2.50 mmol) at rt for 2 h. [b] The result was based on HRMS (see Supporting Information).

CONCLUSION

In summary, we established a novel and efficient approach for highly regioselective synthesis of functionalized tertiary type *β*-hydroxyl carboxamides **3aa-3ia** through a $Sc(OTf)_3$-catalyzed addition of ynamides and ketones. It is worth mentioning that water was found to be an important reaction substrate. Moreover, a series of chiral carboxamides **3j-3r** were synthesized through this approach in excellent regio-selectivities and outstanding diastereoselectivities.

EXPERIMENTAL SECTION

General Methods. Reactions were monitored by thin layer chromatography (TLC) on glass plates coated with silica gel with fluorescent indicator. Flash chromatography was performed on silica gel (300−400) with Petroleum/EtOAc as eluent. Optical rotations were measured on a polarimeter with a sodium lamp. HRMS were measured on a LCMSIT apparatus. IR spectra were recorded using film on a Fourier Transform Infrared Spectrometer. NMR spectra were recorded at 400 or 600 MHz, and chemical shifts are reported in δ (ppm) referenced to an internal TMS standard for ^1H NMR and $CDCl_3$ (77.16 ppm) for $^{13}C\{^1H\}$ NMR.

General procedure for synthesis of (3). To a solution of compound **1** (0.25 mmol，1.0 equiv), $Sc(OTf)_3$ (30 mg, 0.05 mmol, 0.2 equiv) and **2** (2.50 mmol, 10.0 equiv) at rt for 2 h. The residue was purified by flash chromatography on silica gel (PE/EA) to give **3**.

***N*-benzyl-3-hydroxy-3-methyl-2-phenyl-*N*-tosylbutanamide** (**3aa**). Colorless oil. (102 mg, 93%, PE/EA = 4:1); IR (film): ν_{max} 3502, 2976, 1674, 1357, 1167, 1088, 701,

587, 547 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.52 (m, 2H), 7.40-7.33 (m, 2H), 7.33-7.30 (m, 3H), 7.29-7.26 (m, 1H), 7.25-7.20 (m, 4H), 7.04-6.87 (m, 2H), 5.22 (d, *J* = 16.8 Hz, 1H), 6.67 (d, *J* = 16.8 Hz, 1H), 3.91 (s, 1H), 3.86 (brs, 1H), 2.44 (s, 3H), 1.06 (s, 3H), 0.82 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.9, 145.1, 136.6, 136.0, 133.3, 129.9, 129.6, 129.0, 128.5, 128.3, 128.0, 127. 9, 126.9, 72.5, 59.2, 49.5, 29.4, 27.2, 21.8 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{28}NO_4S^+$: 438.1734, found: 438.1739.

(2*S*, 3*S*)-*N*-Benzyl-3-hydroxy-2,3-diphenyl-*N*-tosylbutanamide (3ab). White solid. (81 mg, 65%, PE/EA = 8:1); M.P. 117-119°C; IR (film): ν_{max} 3473, 2929, 1779, 1674, 1495, 1356, 1168, 1087, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 7.26-7.17 (m, 9H), 7.16-7.09 (m, 3H), 6.97-6.83 (m, 2H), 5.01 (s, 1H), 4.98-4.86 (m, 1H), 4.41 (d, *J* = 15.2 Hz, 1H), 2.41 (s, 3H), 1.11 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.5, 147.5, 144.9, 135.9, 135.5, 133.0, 130.5, 129.6, 128.8, 128.6, 128.4, 128.1, 128.1, 127.6, 126.8, 126.7, 124.9, 76.3, 58.9, 49.2, 28.7, 21.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{30}NO_4S^+$: 500.1890, found: 500.1892.

(2*S*, 3*S*)-*N*-Benzyl-3-(4-bromophenyl)-3-hydroxy-2-phenyl-*N*-tosylbutanamide (3ac). White solid. (108 mg, 75%, PE/EA = 8:1); M.P. 134-136°C; IR (film): ν_{max} 3483, 2974, 1688, 1363, 1167, 1087, 995, 750, 588 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.22 (m, 10H), 7.21-7.12 (m, 4H), 7.10-6.97 (m, 2H), 6.96-6.82 (m, 2H), 5.05 (s, 1H), 5.01-4.84 (m, 1H), 4.41 (d, *J* = 16.4 Hz, 1H), 2.42 (s, 3H), 1.08 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.3, 146.6, 145.0, 135.6, 135.3, 132.5, 131.2, 130.4, 129.5, 128.8, 128.6, 128.1, 128.0, 127.7, 126.8, 126.7, 120.6, 76.0, 58.5, 49.1, 28.5, 21.7 ppm;

HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{29}BrNO_4S^+$: 578.0995, 580.0975, found: 578.0996, 580.0983.

(2*S*, 3*S*)-*N*-Benzyl-3-(4-chlorophenyl)-3-hydroxy-2-phenyl-*N*-tosylbutanamide (3ad). White solid. (103 mg, 77%, PE/EA = 8:1); M.P. 110-112°C; IR (film): ν_{max} 3425, 1655, 1493, 1356, 1167, 1088, 813, 753, 585 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.24 (m, 8H), 7.22-7.03 (m, 8H), 7.02-6.87 (m, 2H), 5.04 (s, 1H), 4.94 (brs, 1H), 4.40 (d, *J* = 16.4 Hz, 1H), 2.42 (s, 3H), 1.08 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.4, 146.1, 145.1, 135.8, 135.4, 132.6, 132.5, 130.5, 129.6, 128.8, 128.7, 128.4, 128.2, 128.1, 127.8, 126.9, 126.4, 76.1, 58.6, 49.2, 28.6, 21.8 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{29}ClNO_4S^+$: 534.1500, found: 534.1503.

(2*S*, 3*S*)-*N*-Benzyl-3-hydroxy-2-phenyl-*N*-tosyl-3-(4-(trifluoromethyl)phenyl)butanamide (3ae). White solid. (112 mg, 79%, PE/EA = 8:1); M.P. 139-141°C; IR (film): ν_{max} 3454, 2924, 1666, 1327, 1165, 1121, 1083, 700, 587 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43-7.35 (m, 4H), 7.35-7.28 (m, 4H), 7.28-7.24 (m, 2H), 7.24-7.15 (m, 4H), 7.15-7.08 (m, 2H), 7.05-6.85 (m, 2H), 5.16 (s, 1H), 4.94 (brs, 1H), 4.40 (d, *J* = 16.4 Hz, 1H), 2.41 (s, 3H), 1.09 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.3, 151.6, 145.2, 135.3, 132.4, 130.7 (q, *J* = 670.4, 331.4 Hz), 130.5, 129.6, 128.8, 128.8, 128.3, 128.1, 127.9, 126.9, 125.4, 125.3, 125.2, 123.0, 76.3, 58.5, 49.2, 28.7, 21.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{31}H_{29}F_3NO_4S^+$: 568.1764, found: 568.1767.

(2*S*, 3*S*)-*N*-Benzyl-3-hydroxy-2-phenyl-3-(*p*-tolyl)-*N*-tosylbutanamide (3af). White solid. (96 mg, 72%, PE/EA = 8:1); M.P. 112-114°C; IR (film): ν_{max} 3448, 2924,

1638, 1454, 1357, 1167, 1085, 699, 588 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.24 (m, 7H), 7.23-7.04 (m, 7H), 7.03-6.98 (m, 2H), 6.97-6.85 (m, 2H), 4.98 (s, 1H), 4.97-4.83 (m, 1H), 4.42 (d, *J* = 16.8 Hz, 1H), 2.41 (s, 3H), 2.35 (s, 3H), 1.09 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.5, 144.9, 144.6, 136.0, 135.9, 135.5, 133.1, 130.6, 129.5, 129.1, 128.7, 128.6, 128.1, 128.0, 127.6, 126.9, 124.8, 76.2, 58.9, 49.2, 28.8, 21.7, 21.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + Na]^+$ Calcd for $C_{31}H_{31}NO_4SNa^+$: 536.1866, found: 536.1863.

(2*S*, 3*S*)-*N*-Benzyl-3-hydroxy-3-(2-methoxyphenyl)-2-phenyl-*N*-tosylbutanamide (3ag). White solid. (84 mg, 61%, PE/EA = 8:1); M.P. 141-143°C; IR (film): ν_{max} 3458, 2924, 2854, 1666, 1455, 1359, 1167, 1082, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.47 (m, 1H), 7.33-7.20 (m, 6H), 7.18-7.12 (m, 4H), 7.12-7.05 (m, 3H), 6.90-6.83 (m, 1H), 6.82-6.75 (m, 3H), 5.54 (brs, 1H), 5.45 (s, 1H), 4.79 (d, *J* = 16.4 Hz, 1H), 4.54 (d, *J* = 16.0 Hz, 1H), 3.68 (s, 3H), 2.39 (s, 3H), 1.22 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.3, 155.2, 144.6, 136.0, 135.6, 134.6, 133.7, 130.8, 129.5, 128.6, 128.5, 128.4, 128.0, 127.7, 127.2, 126.3, 120.9, 111.1, 76.0, 55.2, 55.1, 49.1, 25.1, 21.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + Na]^+$ Calcd for $C_{31}H_{31}NO_5SNa^+$: 552.1815, found: 552.1821.

(2*S*, 3*S*)-*N*-Benzyl-3-(2-fluorophenyl)-3-hydroxy-2-phenyl-*N*-tosylbutanamide (3ah). White solid. (101 mg, 78%, PE/EA = 8:1); M.P. 118-120°C; IR (film): ν_{max} 3434, 2924, 2854, 1638, 1458, 1364, 1168, 1083, 580 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.47 (m, 1H), 7.43-7.30 (m, 3H), 7.29-7.23 (m, 3H), 7.22-7.17 (m, 3H), 7.17-7.10 (m, 4H), 7.05-6.99 (m, 1H), 6.96-6.79 (m, 3H), 5.52 (s, 1H), 4.92 (d, *J* = 16.8 Hz, 1H), 4.58 (d, *J* = 16.8 Hz, 1H), 2.42 (s, 3H), 1.17 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz,

$CDCl_3$) δ 174.9, 158.8 (d, *J* = 242.8 Hz), 144.8, 135.8, 135.6, 133.7 (d, *J* = 12.2 Hz), 132.7, 130.6, 129.4, 128.9 (d, *J* = 8.6 Hz), 128.8, 128.6, 128.3 (d, *J* = 4.3 Hz), 128.2, 128.1, 127.5, 126.3, 124.3, 116.1 (d, *J* = 24.2 Hz), 75.0, 74.9, 56.6, 49.3, 26.0, 25.9, 21.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{29}FNO_4S^+$: 518.1796, found: 518.1799.

(2*S*, 3*S*)-*N*-Benzyl-3-hydroxy-2-phenyl-*N*-tosyl-3-(3-(trifluoromethyl)phenyl)butanamide (3ai). White solid. (102 mg, 72%, PE/EA = 8:1); M.P. 128-130°C; IR (film): ν_{max} 3451, 2924, 1702, 1459, 1328, 1164, 1083, 702, 544 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.47-7.42 (m, 1H), 7.41-7.28 (m, 5H), 7.27-7.23 (m, 3H), 7.22-7.14 (m, 4H), 7.13-7.07 (m, 2H), 7.03-6.85 (m, 2H), 5.04 (s, 1H), 4.94-4.81 (m, 1H), 4.41 (d, *J* = 16.4 Hz, 1H), 2.39 (s, 3H), 1.12 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.3, 148.8, 145.1, 135.7, 135.4, 132.6, 130.6, 129.6, 128.8, 128.7, 128.2, 128.0, 127.8, 126.8, 125.6, 123.7 (d, *J* = 4.3 Hz), 122.9, 122.0 (d, *J* = 3.5 Hz), 76.3, 58.5, 49.3, 28.8, 21.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{31}H_{29}F_3NO_4S^+$: 568.1764, found: 568.1767.

(2*S*, 3*S*)-*N*-Benzyl-3-(3-fluorophenyl)-3-hydroxy-2-phenyl-*N*-tosylbutanamide (3aj). White solid. (104 mg, 80%, PE/EA = 8:1); M.P. 116-118°C; IR (film): ν_{max} 3447, 2960, 1638, 1493, 1358, 1167, 1084, 699, 457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.22 (m, 9H), 7.20-7.10 (m, 5H), 7.01-6.92 (m, 2H), 6.91-6.82 (m, 2H), 5.05 (s, 1H), 5.03-4.86 (m, 1H), 4.42 (d, *J* = 16.4 Hz, 1H), 2.41 (s, 3H), 1.07 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.3, 162.8 (d, *J* = 244.2 Hz), 150.5 (d, *J* = 5.8 Hz), 145.1, 135.8, 135.4, 132.6, 130.5, 129.8 (d, *J* = 8.0 Hz), 129.6, 128.9, 128.7, 128.2, 128.1, 127.8, 126.8, 120.4, 113.6 (d, *J* = 21.0 Hz), 112.4 (d, *J* = 22.6 Hz), 76.1, 58.6, 49.2, 28.7,

21.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{29}FNO_4S^+$: 518.1796, found: 518.1793.

(2*S*, 3*S*)-*N*-Benzyl-3-hydroxy-2-phenyl-3-(*m*-tolyl)-*N*-tosylbutanamide (**3ak**). White solid. (88 mg, 66%, PE/EA = 8:1); M.P. 130-132°C; IR (film): ν_{max} 3449, 2924, 2854, 1638, 1460, 1376, 1167, 749, 420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H), 7.24-7.14 (m, 5H), 7.13-7.06 (m, 3H), 7.04-7.00 (m, 1H), 6.96-6.81 (m, 2H), 4.97 (s, 1H), 4.89 (d, *J* = 16.0 Hz, 1H), 4.41 (d, *J* = 16.8 Hz, 1H), 2.40 (s, 3H), 2.28 (s, 3H), 1.11 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.5, 147.6, 144.9, 137.9, 135.8, 135.6, 133.2, 130.6, 129.6, 128.8, 128.6, 128.3, 128.0, 127.5, 126.7, 125.7, 122.0, 76.3, 58.8, 49.2, 28.8, 21.8, 21.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + Na]^+$ Calcd for $C_{31}H_{31}NO_4SNa^+$: 536.1866, found: 536.1867.

(2*S*, 3*S*)-*N*-Benzyl-3-(3-chlorophenyl)-3-hydroxy-2-phenyl-*N*-tosylbutanamide (**3al**). White solid. (97 mg, 73%, PE/EA = 8:1); M.P. 132-134°C; IR (film): ν_{max} 3424, 2960, 1655, 1494, 1356, 1166, 1084, 700, 546 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56-7.21 (m, 10H), 7.20-7.11 (m, 5H), 7.10-7.05 (m, 1H), 7.02-6.91 (m, 2H), 5.02 (s, 1H), 4.98-4.83 (m, 1H), 4.41 (d, *J* = 16.4 Hz, 1H), 2.41 (s, 3H), 1.08 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.3, 149.9, 145.1, 135.7, 135.4, 134.4, 132.6, 130.5, 129.6, 128.9, 128.7, 128.2, 128.1, 127.8, 127.0, 126.8, 125.4, 123.1, 76.1, 58.5, 49.2, 28.8, 21.8 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{29}ClNO_4S^+$: 534.1500, found: 534.1506.

(2*S*, 3*S*)-*N*-Benzyl-3-hydroxy-3-(naphthalen-2-yl)-2-phenyl-*N*-tosylbutanamide (**3am**). White solid. (107 mg, 75%, PE/EA = 8:1); M.P. 136-138°C; IR (film): ν_{max} 3447,

1638, 1494, 1359, 1166, 1084, 750, 582, 457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87-7.82 (m, 1H), 7.82-7.60 (m, 3H), 7.55-7.47 (m, 2H), 7.42-7.31 (m, 4H), 7.30-7.24 (m, 2H), 7.23-7.04 (m, 3H), 7.00-6.60 (m, 5H), 5.20 (s, 1H), 4.86 (brs, 1H), 4.39 (d, *J* = 16.0 Hz, 1H), 2.31 (s, 3H), 1.21 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.5, 145.0, 144.8, 135.6, 135.4, 133.3, 133.0, 132.4, 130.6, 129.5, 128.7, 128.6, 128.1, 127.8, 127.6, 126.6, 126.1, 125.9, 123.8, 123.4, 76.6, 58.7, 49.1, 28.7, 21.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + Na]^+$ Calcd for $C_{34}H_{31}NO_4SNa^+$: 572.1866, found: 572.1866.

***N*-Benzyl-2-(1-hydroxycyclopentyl)-2-phenyl-*N*-tosylacetamide** (**3an**). Colorless oil. (27 mg, 23%, PE/EA = 8:1); IR (film): ν_{max} 3483, 2926, 1688, 1587, 1363, 1167, 1014, 750, 588 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.52 (m, 2H), 7.39-7.34 (m, 2H), 7.34-7.28 (m, 3H), 7.26-7.19 (m, 5H), 7.01-6.97 (m, 2H), 5.22 (d, *J* = 16.8 Hz, 1H), 4.62 (d, *J* = 16.8 Hz, 1H), 3.86 (s, 1H), 3.73 (s, 1H), 2.43 (s, 3H), 1.75-1.56 (m, 3H), 1.42-1.30 (m, 2H), 1.29-1.20 (m, 2H), 1.18-1.10 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.0, 145.0, 136.6, 136.0, 133.9, 129.5, 129.5, 129.1, 128.5, 128.3, 128.0, 127.8, 126.8, 83.2, 58.4, 49.4, 40.0, 37.7, 23.5, 23.1, 21.8 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{30}NO_4S^+$: 464.1890, found: 464.1893.

***N*-Benzyl-2-(4-fluorophenyl)-3-hydroxy-3-methyl-*N*-tosylbutanamide** (**3ba**). Corlorless oil. (105 mg, 92%, PE/EA = 4:1); IR (film): ν_{max} 3451, 1674, 1508, 1355, 1167, 1088, 811, 577, 546 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61-7.52 (m, 2H), 7.38-7.28 (m, 5H), 7.26-7.21 (m, 2H), 7.04-6.96 (m, 2H), 6.95-6.85 (m, 2H), 5.19 (d, *J* = 16.4 Hz, 1H), 4.72 (d, *J* = 16.4 Hz, 1H), 3.94 (brs, 1H), 3.84 (s, 1H), 2.44 (s, 3H), 1.04 (s, 3H), 0.81 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.9, 162.5 (d, *J* = 245.6 Hz), 145.2, 136.4, 136.1, 131.6 (d, *J* = 7.9 Hz), 129.7, 129.2 (d, *J* = 2.8 Hz), 128.1, 128.0,

127.1, 115.4, 115.2, 72.4, 58.3, 49.6, 29.3, 27.1, 21.8 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{27}FNO_4S^+$: 456.1639, found: 456.1644.

***N*-benzyl-3-hydroxy-3-methyl-2-(*p*-tolyl)-*N*-tosylbutanamide** (**3ca**). Colorless oil. (95 mg, 84%, PE/EA = 4:1); IR (film): ν_{max} 3442, 1671, 1454, 1356, 1167, 1117, 804, 699, 546 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.53 (m, 2H), 7.43-7.28 (m, 5H), 7.27-7.20 (m, 2H), 7.07-6.98 (m, 2H), 6.93-6.83 (m, 2H), 5.22 (d, *J* = 16.8 Hz, 1H), 4.65 (d, *J* = 16.8 Hz, 1H), 3.88 (s, 1H), 3.76 (brs, 1H), 2.44 (s, 3H), 2.32 (s, 3H), 1.04 (s, 3H), 0.80 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.0, 145.0, 137.6, 136.6, 136.1, 130.2, 129.7, 129.5, 129.2, 129.0, 128.3, 127.9, 126.8, 72.4, 58.8, 49.4, 29.4, 27.2, 21.8, 21.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{30}NO_4S^+$: 452.1890, found: 452.1896.

***N*-Benzyl-2-(4-butylphenyl)-3-hydroxy-3-methyl-*N*-tosylbutanamide** (**3da**). Colorless oil. (101 mg, 82%, PE/EA = 4:1); IR (film): ν_{max} 3511, 2929, 1675, 1456, 1356, 1167, 1087, 813, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.54 (m, 2H), 7.40-7.34 (m, 2H), 7.34-7.30 (m, 3H), 7.25-7.20 (m, 2H), 7.05-7.01 (m, 2H), 6.93-6.87 (m, 2H), 5.22 (d, *J* = 16.8 Hz, 1H), 4.67 (d, *J* = 16.8 Hz, 1H), 3.92 (s, 1H), 3.79 (brs, 1H), 2.61-2.56 (m, 2H), 2.44 (s, 3H), 1.60-1.53 (m, 2H), 1.40-1.33 (m, 2H), 1.05 (s, 3H), 0.98-0.92 (m, 3H), 0.81 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.1, 145.0, 142.6, 136.7, 136.1, 130.4, 129.8, 129.5, 129.0, 128.6, 128.3, 127.9, 126.9, 72.5, 58.9, 49.5, 35.4, 33.7, 29.4, 27.2, 22.5, 21.8, 14.1 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{36}NO_4S^+$: 494.2360, found: 494.2358.

***N*-Benzyl-3-hydroxy-3-methyl-2-(thiophen-2-yl)-*N*-tosylbutanamide** (**3ea**). White solid. (110 mg, 99%, PE/EA = 4:1); M.P. 99-101°C; IR (film): ν_{max} 3449, 1656, 1355, 1243, 1167, 1087, 814, 701, 545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.54 (m, 2H), 7.37-7.33 (m, 4H), 7.33-7.27 (m, 1H), 7.26-7.17 (m, 3H), 6.87 (dd, *J* = 4.0, 3.2 Hz, 1H), 6.67 (d, *J* = 2.8 Hz, 1H), 5.19 (d, *J* = 16.4 Hz, 1H), 4.84 (d, *J* = 16.4 Hz, 1H), 4.38 (s, 1H), 3.82 (s, 1H), 2.42 (s, 3H), 1.03 (s, 3H), 0.92 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.6, 145.2, 136.4, 136.0, 134.9, 129.7, 128.9, 128.2, 128.0, 127.4, 126.4, 126.1, 72.5, 54.6, 49.7, 28.8, 27.0, 21.8 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{26}NO_4S_2^+$: 444.1298, found: 444.1291.

3-Hydroxy-*N*,3-dimethyl-2-phenyl-*N*-tosylbutanamide (**3fa**). Colorless oil. (90 mg, 99%, PE/EA = 4:1); IR (film): ν_{max} 3450, 1656, 1358, 1262, 1167, 1080, 749, 673, 548 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.45 (m, 2H), 7.31-7.25 (m, 3H), 7.23-7.14 (m, 4H), 4.24 (s, 1H), 3.98 (s, 1H), 3.20 (s, 3H), 2.41 (s, 3H), 1.28 (s, 3H), 0.98 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.8, 145.0, 135.6, 133.7, 130.2, 129.7, 128.5, 127.8, 72.6, 59.4, 33.3, 29.7, 27.2, 21.7 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{24}NO_4S^+$: 362.1421, found: 362.1427.

***N*-Butyl-3-hydroxy-3-methyl-2-phenyl-*N*-tosylbutanamide** (**3ga**). Colorless oil. (92 mg, 91%, PE/EA = 4:1); IR (film): ν_{max} 3495, 2962, 1668, 1357, 1168, 1085, 909, 701, 548 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59-7.50 (m, 2H), 7.29-7.20 (m, 5H), 7.17-7.09 (m, 2H), 4.09 (brs, 1H), 4.04 (s, 1H), 3.77 (ddd, *J* = 14.8, 10.4, 5.6 Hz, 1H), 3.57 (ddd, *J* = 14.8, 10.4, 5.2 Hz, 1H), 2.42 (s, 3H), 1.64-1.53 (m, 2H), 1.37-1.28 (m, 2H), 1.26 (s, 3H), 0.96 (s, 3H), 0.95-0.90 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.6, 144.9, 136.4, 133.8, 130.1, 129.6, 128.4, 127.9, 127.8, 72.6, 59.2, 46.7, 32.2, 29.7, 27.3,

21.7, 20.2, 13.8 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{30}NO_4S^+$: 404.1890, found: 404.1884.

***N*-benzyl-3-hydroxy-3-methyl-*N*-(methylsulfonyl)-2-phenylbutanamide (3ha)**. Colorless oil. (76 mg, 85%, PE/EA = 4:1); IR (film): ν_{max} 3449, 2926, 1719, 1656, 1362, 1166, 1086, 814, 662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.34 (m, 5H), 7.33-7.28 (m, 5H), 5.05 (d, *J* = 16.8 Hz, 1H), 4.77 (d, *J* = 16.8 Hz, 1H), 4.02 (s, 1H), 3.99 (brs, 1H), 3.00 (s, 3H), 1.22 (s, 3H), 0.90 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.0, 136.3, 133.6, 130.1, 129.2, 128.9, 128.3, 128.2, 127.1, 72.7, 59.1, 49.0, 42.6, 29.7, 27.3 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{24}NO_4S^+$: 362.1421 found: 362.1425.

***N*-Benzyl-*N*-((4-chlorophenyl)sulfonyl)-3-hydroxy-3-methyl-2-phenylbutanamide (3ia)**. Colorless oil. (47 mg, 41%, PE/EA = 4:1); IR (film): ν_{max} 3443, 2925, 1767, 1668, 1356, 1164, 1027, 695, 545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66-7.59 (m, 2H), 7.43-7.37 (m, 4H), 7.36-7.27 (m, 4H), 7.26-7.22 (m, 2H), 7.01-6.92 (m, 2H), 5.23 (d, *J* = 17.2Hz, 1H), 4. 66 (d, *J* = 17.2 Hz, 1H), 3.79 (s, 1H), 3.76 (s, 1H), 1.08 (s, 3H), 0.82 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.8, 140.6, 137.3, 136.3, 133.1, 129.9, 129.8, 129.2, 128.7, 128.2, 128.1, 126.8, 72.5, 59.3, 49.5, 29.4, 27.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{25}ClNO_4S^+$: 458.1187, found: 458.1183.

(*R*)-4-Benzyl-3-((*R*)-2-(4-chlorophenyl)-3-hydroxy-3-methylbutanoyl)oxazolidin-2-one (3j). Colorless oil. (66 mg, 68%, PE/EA = 2:1); $[\alpha]_D^{24}$ = 3.1 (*c* 0.55, $CHCl_3$); IR (film): ν_{max} 3442, 1779, 1635, 1490, 1376, 1212, 1105, 1015, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.43 (m, 2H), 7.37-7.32 (m, 2H), 7.25-7.16 (m, 3H), 6.97-6.92 (m,

2H), 5.03 (s, 1H), 4.83-4.76 (m, 1H), 4.23 (dd, *J* = 9.2, 8.4 Hz, 1H), 4.11 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.90 (s, 1H), 3.64 (dd, *J* = 13.6, 3.6 Hz), 2.59 (dd, *J* = 13.6, 8.8 Hz, 1H), 1.41 (s, 3H), 1.04 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.6, 152.7, 134.6, 134.0, 132.9, 132.1, 129.5, 129.0, 128.6, 127.6, 72.4, 66.0, 56.2, 54.8, 37.3, 30.1, 27.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ $C_{21}H_{23}ClNO_4^+$: 388.1310, found: 388.1314.

(*R*)-4-Benzyl-3-((*R*)-2-(2-hydroxypropan-2-yl)octanoyl)oxazolidin-2-one (3k). Colorless oil. (38 mg, 42%, PE/EA = 2:1); $[\alpha]_D^{25}$ = -3.1 (*c* 0.50, $CHCl_3$); IR (film): ν_{max} 3436, 2920, 2852, 1655, 1638, 1386, 1052, 670, 575 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 2H), 7.31-7.28 (m, 1H), 7.27-7.23 (m, 2H), 4.85-4.75 (m, 1H), 4.20-4.13 (m, 2H), 4.10 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.40 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.80 (s, 1H), 2.66 (dd, *J* = 12.8, 10.0 Hz, 1H), 1.98-1.85 (m, 1H), 1.65-1.56 (m, 1H), 1.38-1.32 (m, 2H), 1.30 (s, 3H), 1.29-1.26 (m, 6H), 1.25 (s, 3H), 0.92-0.85 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 176.7, 154.3, 135.4, 129.5, 129.2, 127.5, 72.6, 66.1, 55.7, 52.2, 38.3, 31.8, 30.2, 29.6, 29.3, 28.0, 25.5, 22.7, 14.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{32}NO_4^+$: 362.2326, found: 362.2326.

(*R*)-3-((*R*)-3-Hydroxy-3-methyl-2-phenylbutanoyl)-4-phenyloxazolidin-2-one (3l). Colorless oil. (54 mg, 63%, PE/EA = 2:1); $[\alpha]_D^{24}$ = 59.2 (*c* 0.92, $CHCl_3$); IR (film): ν_{max} 3450, 2309, 1783, 1580, 1438, 1340, 1053, 671, 620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.26-7.21 (m, 4H), 7.19-7.13 (m, 2H), 6.93-6.84 (m, 2H), 5.50 (dd, *J* = 8.8, 4.8 Hz, 1H), 5.08 (s, 1H), 4.67 (dd, *J* = 9.6, 8.8 Hz, 1H), 4.07 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.77 (s, 1H), 1.41 (s, 3H), 1.01 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.2, 152.9, 138.0, 133.8, 130.8, 129.1, 128.8, 128.2, 127.8, 125.7, 72.2, 69.6, 57.7,

57.5, 30.1, 27.3 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_4^+$: 340.1543, found: 340.1545.

(*R*)-3-((*R*)-3-Hydroxy-2-(4-methoxyphenyl)-3-methylbutanoyl)-4-phenyloxazolidin-2-one (**3m**). White solid. (75 mg, 82%, PE/EA = 2:1); M.P. 110-112°C; $[\alpha]_D^{21}$ = 74.1 (*c* 2.00, $CHCl_3$); IR (film): ν_{max} 3449, 2083, 1780, 1637, 1511, 1345, 1246, 1182, 1120 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.21 (m, 3H), 7.11-7.05 (m, 2H), 6.92-6.86 (m, 2H), 6.80-6.74 (m, 2H), 5.49 (dd, *J* = 9.2, 5.2 Hz, 1H), 5.02 (s, 1H), 4.66 (dd, *J* = 9.6, 8.8 Hz, 1H), 4.07 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.80 (s, 3H), 3.73 (brs, 1H), 1.39 (s, 3H), 1.00 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.4, 159.3, 152.9, 138.1, 131.8, 129.1, 128.8, 125.9, 125.7, 113.6, 72.2, 69.6, 57.7, 56.7, 55.4, 29.9, 27.2 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{24}NO_5^+$: 370.1649, found: 370.1655.

(*R*)-3-((*R*)-2-(4-Bromophenyl)-3-hydroxy-3-methylbutanoyl)-4-phenyloxazolidin-2-one (**3n**). White solid. (54 mg, 52%, PE/EA = 2:1); M.P. 130-132°C; $[\alpha]_D^{24}$ = 113.3 (*c* 0.55, $CHCl_3$); IR (film): ν_{max} 3443, 1778, 1637, 1486, 1380, 1202, 1104, 760, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 3H), 7.27-7.23 (m, 2H), 7.07-7.01 (m, 2H), 6.92-6.88 (m, 2H), 5.48 (dd, *J* = 8.8, 4.8 Hz, 1H), 5.03 (s, 1H), 4.68 (dd, *J* = 9.6, 8.8 Hz, 1H), 4.12 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.70 (s, 1H), 1.40 (s, 3H), 0.99 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.8, 152.9, 137.9, 132.9, 132.4, 131.3, 129.2, 129.0, 125.7, 122.1, 72.0, 69.7, 57.8, 56.9, 30.0, 27.3 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{21}BrNO_4^+$: 418.0649, 420.0628, found: 418.0649, 420.0621.

(*R*)-3-((*R*)-3-Hydroxy-3-methyl-2-phenylbutanoyl)-4-isopropyloxazolidin-2-one (3o). White solid. (45 mg, 59%, PE/EA = 2:1); M.P. 122-124°C; $[\alpha]_D^{25}$ = 30.2 (*c* 0.26, $CHCl_3$); IR (film): ν_{max} 3443, 2967, 1777, 1668, 1373, 1203, 1027, 720, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.40 (m, 2H), 7.33-7.25 (m, 3H), 5.08 (s, 1H), 4.57-4.50 (m, 1H), 4.30-4.23 (m, 1H), 4.15-4.07 (m, 1H), 4.03 (s, 1H), 2.25-2.15 (m, 1H), 1.41 (s, 3H), 1.03 (s, 3H), 0.85-0.78 (m, 3H), 0.45-0.35 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.1, 153.2, 134.6, 130.5, 128.2, 127.8, 72.3, 62.9, 58.0, 57.0, 30.2, 27.8, 27.3, 17.9, 14.0 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{24}NO_4^+$: 306.1700, found: 306.1702.

(4*S*,5*R*)-3-((*S*)-3-Hydroxy-3-methyl-2-phenylbutanoyl)-4-methyl-5-phenyloxazolidin-2-one (3p). Colorless oil. (36 mg, 41%, PE/EA = 2:1); $[\alpha]_D^{25}$ = -78.4 (*c* 0.86, $CHCl_3$); IR (film): ν_{max} 3504, 2917, 1780, 1676, 1455, 1345, 1233, 1121, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.41 (m, 2H), 7.39-7.28 (m, 6H), 7.22-7.15 (m, 2H), 5.67 (d, *J* = 4.8 Hz, 1H), 5.01 (s, 1H), 4.92-4.82 (m, 1H), 3.93 (s, 1H), 1.44 (s, 3H), 1.06 (s, 3H), 0.75-0.66 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.6, 152.3, 134.2, 133.2, 130.6, 129.0, 128.8, 128.3, 127.8, 125.8, 78.9, 72.4, 57.4, 54.7, 30.1, 27.3, 14.0 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{24}NO_4^+$: 354.1700, found: 354.1698.

(4*S*,5*R*)-3-((*S*)-3-Hydroxy-2-(4-methoxyphenyl)-3-methylbutanoyl)-4-methyl-5-phenyloxazolidin-2-one (**3q**). Colorless oil. (67 mg, 70%, PE/EA = 2:1); $[\alpha]_D^{23}$ = -91.6 (*c* 0.55, $CHCl_3$); IR (film): ν_{max} 3442, 1778, 1638, 1511, 1380, 1246, 1181, 1036, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.32 (m, 5H), 7.22-7.17 (m, 2H), 6.88-6.84 (m, 2H), 5.67 (d, *J* = 7.2 Hz, 1H), 4.94 (s, 1H), 4.90-4.82 (m, 1H), 3.90 (s, 1H), 3.80 (s, 3H),

1.42 (s, 3H), 1.05 (s, 3H), 0.72 (d, J = 6.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.9, 159.3, 152.3, 133.3, 131.6, 129.0, 128.8, 126.3, 125.8, 113.7, 78.9, 72.5, 56.6, 55.3, 54.7, 30.0, 27.2, 14.0 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{26}NO_5^+$: 384.1806, found: 384.1814.

(4*S*,5*R*)-3-((*S*)-2-(4-Bromophenyl)-3-hydroxy-3-methylbutanoyl)-4-methyl-5-phenyloxazolidin-2-one (**3r**). Colorless oil. (43 mg, 40%, PE/EA = 2:1); $[\alpha]_D^{24}$ = -74.4 (*c* 0.55, $CHCl_3$); IR (film): ν_{max} 3442, 2076, 1780, 1636, 1366, 1196, 1121 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49-7.43 (m, 2H), 7.41-7.35 (m, 3H), 7.34-7.30 (m, 2H), 7.23-7.18 (m, 2H), 5.68 (d, J = 7.6 Hz, 1H), 4.95 (s, 1H), 4.90-4.82 (m, 1H), 3.86 (s, 1H), 1.43 (s, 3H), 1.04 (s, 3H), 0.73 (d, J = 6.4 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 174.3, 152.3, 133.4, 133.1, 132.3, 131.5, 129.1, 128.9, 125.8, 122.2, 79.0, 72.3, 56.8, 54.8, 30.1, 27.2, 14.0 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{23}BrNO_4^+$: 432.0805, 434.0785, found: 432.0810, 434.0759.

Procedure for Synthesis of (3aa) (Gram Scale).

To a solution of compound **1a** (1.08 g, 3.0 mmol, 1.0 equiv), $Sc(OTf)_3$ (0.36 g, 0.6 mmol, 0.2 equiv) and **2a** (2.2 mL, 30.0 mmol, 10.0 equiv) at rt for 2 h. The residue was purified by flash chromatography on silica gel (PE/EA = 4:1) to give **3aa** as colorless oil (1.16 g, 88%).

General Procedure for Synthesis of (1a-1r).[20] To a mixture of an amide (2 mmol), K_3PO_4 (4 mmol), $CuSO_4 \cdot 5H_2O$ (0.2 mmol), and 1,10-phenanthroline (0.4 mmol,) in toluene under a N_2 atmosphere was added a solution 1-bromoalkyne (2.2 mmol) in toluene. The reaction was stirred at 75 °C for 24 h under a N_2 atmosphere. The reaction

mixture was cooled to room temperature, diluted with EtOAc, and filtered through Celite, and the filtrate was concentrated in vacuo. The crude products were purified by flash chromatography on silica gel (PE/EA) to afford the desired ynamide.

Data for new compounds of Ynamides.

***N*-benzyl-*N*-((4-butylphenyl)ethynyl)-4-methylbenzenesulfonamide (1d).** White solid. (635 mg, 76%, PE/EA = 20:1); M.P. 116-118°C; IR (film): ν_{max} 2929, 1779, 1674, 1535, 1356, 1236, 1187, 689, 501 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ7.75-7.60 (m, 2H), 7.38-7.23 (m, 7H), 7.13-7.06 (m, 2H), 7.01-6.84 (m, 2H), 5.08-5.06 (m, 1H), 3.83-3.81 (m, 1H), 2.59-2.52 (m, 2H), 2.43 (s, 3H), 1.61-1.50 (m, 2H), 1.37-1.25 (m, 2H), 0.91 (dd, *J* = 7.6, 6.8 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.6, 145.0, 142.0, 136.8, 136.7, 130.4, 129.8, 129.2, 128.8, 128.7, 128.6, 128.1, 127.9, 127.8, 49.8, 42.7, 35.4, 33.7, 22.5, 21.8, 14.1 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{28}NO_2S^+$: 418.1835, found: 418.1840.

(*R*)-3-((4-Bromophenyl)ethynyl)-4-phenyloxazolidin-2-one (1n). White solid. (468 mg, 68%, PE/EA = 10:1); M.P. 130-132°C; $[\alpha]_D^{26}$ = -178.6 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 2929, 1779, 1574, 1495, 1258, 1168, 1087, 701, 567 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50-7.43 (m, 3H), 7.41-7.32 (m, 4H), 7.13-7.08 (m, 2H), 5.14 (dd, *J* = 7.6, 6.8 Hz, 1H), 4.79 (dd, *J* = 9.2, 8.4 Hz, 1H), 4.32 (dd, *J* = 8.8, 7.2 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.5, 136.0, 133.0, 131.6, 129.8, 129.5, 127.0, 122.4, 121.3, 79.2, 72.1, 70.9, 62.3 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{13}BrNO_2^+$:342.0124, 344.0104, found: 342.0120, 343.0108.

(*R*)-3-((4-Methoxyphenyl)ethynyl)-4-phenyloxazolidin-2-one (1r). White solid. (583 mg, 82%, PE/EA = 10:1); M.P. 110-112°C; $[\alpha]_D^{26}$ = 22.5 (*c* 1.00, $CHCl_3$); IR (film): ν_{max} 3453, 2329, 1779, 1674, 1495, 1356, 968, 687, 501 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.52-7.35 (m, 5H), 7.34-7.24 (m, 4H), 5.77 (d, *J* = 8.0, 1H), 5.71 (d, *J* = 7.6 Hz, 1H), 4.50-4.42 (m, 0.9H), 4.24-4.16 (m, 0.1H), 1.00 (d, *J* = 6.4 Hz, 2.7H), 0.80 (d, *J* = 6.4 Hz, 0.3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, rotamers) δ 159.0, 155.3, 135.0, 133.8, 133.1, 131.7, 129.2, 128.9, 128.6, 126.1, 122.5, 122.4, 121.4, 81.0, 80.0, 79.3, 71.5, 58.4, 52.4, 17.7, 15.1 ppm; HRMS (ESI-Orbitrap) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{15}BrNO_2^+$: 356.0281, found 356.0281.

ASSOCIATED CONTENT

Supporting Information

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

Crystallographic data for **3ab** (CIF)

Crystallographic data for **3o** (CIF)

HRMS data for **3ab**-^{18}O (PDF).

X-ray structures for **3ab** and **3o** and copies of ^1H and ^{13}C spectra (PDF).

Accession Codes

CCDC 1951962, 1951970 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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