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SYNTHESIS OF *DE NOVO* CHIRAL γ-AMINO-YNAMIDES USING LITHIATED YNAMIDES. OBSERVATION OF A UNIQUE 5-*ENDO-DIG* CYCLIZATION WITH AN INVERSION OF *S*-CENTER†

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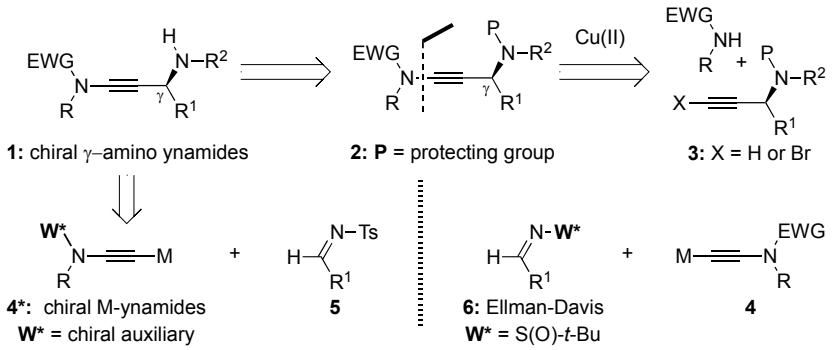
† This paper is dedicated to Professor Victor Snieckus with the deepest respect and admiration to honor the special occasion of his 77th birthday.

Abstract – We describe herein details of our efforts in developing a highly stereoselective synthesis of *de novo* chiral γ-amino-ynamides through additions of lithiated ynamides to Ellman–Davis chiral *N*-*tert*-butanesulfinyl imines. While additions of ynamides could be highly stereoselective even without Lewis acids, the use of BF_3-OEt_2 completely reversed the stereoselectivity. On the other hand, additions of oxazolidinone-substituted, oxazinanone-substituted and tetrahydropyrimidinone-substituted ynamides behaved quite differently and functioned better with BF_3-OEt_2. The chirality of the oxazolidinone ring exerts no impact on the selectivity. This work also features a unique 5-*endo-dig* cyclization of oxazolidinone-substituted γ-amino-ynamides that could be promoted with acid, leading to isothiazoles and 2,3-dihydro-isothiazole *S*-oxides.

INTRODUCTION

The field of ynamide chemistry has experienced rapid expansion in the past decade and has attracted significant attention from the synthetic community.[1-4] Consequently, novel and improved protocols for synthetizing ynamides[3] and their structural relatives[5,6] have been continuously reported in the literature

over the past few years.[3e] Recently, we have been developing *N*-tethered intramolecular transformations to construct *N*-heterocycles and encountered the need of utilizing γ-amino-ynamides such as **1** [Scheme 1],[7] and we found that this class of ynamides is actually not trivial to make.

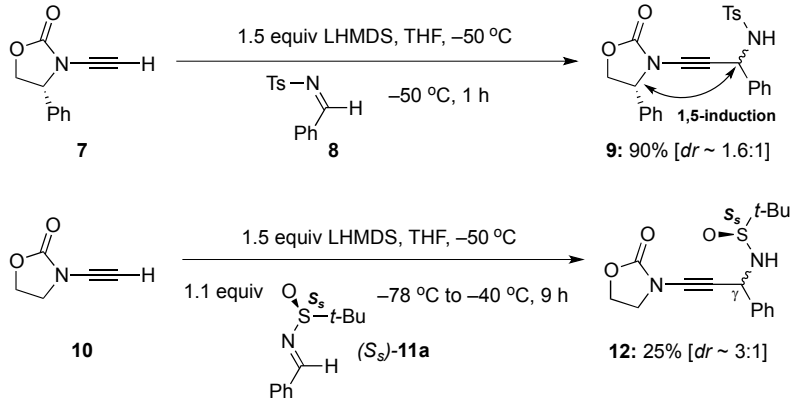


Scheme 1. Efficient syntheses of chiral γ-amino-ynamides

The existing copper-catalyzed protocols,[1,2,5] albeit attractive, may not be the most suitable approaches, because the required optically enriched propargyl amines **3** are not always readily available, and the deprotection step could pose problem to the stability of the ynamides **2**.[8] The most direct and practical accesses maybe: (a) An addition of metalated chiral ynamides **4*** to achiral imines **5**, which would constitute a long-range stereochemical induction; or (b) addition of metalated ynamides **4** to chiral imines such as Ellman-Davis chiral *N*-*tert*-butanesulfinyl imines **6**.[9,10] To the best of our knowledge, the addition of metallated ynamides to imines remains unreported,[1,11,12] although their additions to a number of other electrophiles have been developed.[13] In particular, we note here that Poisson's elegant work[11] on stereoselective additions of lithiated ynol ethers to Ellman-Davis chiral *N*-*tert*-butanesulfinyl imines provided a significant inspiration for our own pursuit of this methodology. We report herein a highly stereoselective addition of lithiated ynamides to Ellman-Davis chiral imines for synthesizing chiral γ–amino-ynamides.

RESULTS AND DISCUSSION

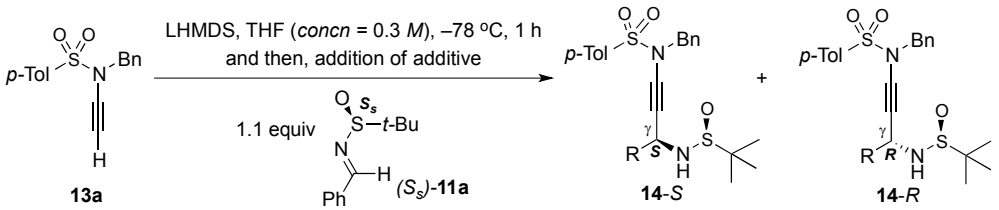
Additions to imines using lithiated ynamides such as **7**, which is substituted with an Evans chiral oxazolidinone auxiliary, was feasible but resulted a very low diastereoselectivity in γ-amino-ynamide **9** [Scheme 2]. This effectively ended any speculation of a possible remote 1,5-asymmetric induction. On the other hand, additions to Ellman-Davis chiral imine **11a** using achiral ynamides such as **10** were more selective in affording **12**, although the yield is low.



Scheme 2. A comparison of the two synthetic approaches

Subsequently, we found that *N*-sulfonyl-substituted ynamides were more suitable substrates for this asymmetric addition. Addition of lithiated ynamide **13a** to **11a** at -78 °C afforded γ-amino-ynamide **14** with a *dr* of 7:1 in favor of the (*S*)-isomer [entry 1, Table 1]. The selectivity improved significantly as the temperature turned higher [entries 2, 3 and 4], although the yield suffered when the reaction was carried at rt [entry 3]. The presence of TMEDA enhanced the yield, albeit at the expense of diastereoselectivity [entries 5 and 6]. The (*S*) relative stereochemistry at the gamma-carbon was unambiguously confirmed based on the single crystal X-ray structure of γ-amino-ynamide **14**-*S* [Figure 1].

Table 1. Screening for optimal conditions: Temperature and additive effects



entry	temp [°C]	additive [equiv]	time [h]	product	yield[a]	*dr [S:R]*[b]
1	– 78	--	15	**14**-*S*	63	7:1
2	–78 to –40	--	15	**14**-*S*	67	21:1
3	–78 to rt	--	15	**14**-*S*	35	≥25:1
4	–78 to –40	--	9	**14**-*S*	69	25:1
5	–78 to –40	TMEDA [0.25]	9	**14**-*S*	94	18:1
6	–78 to –40	TMEDA [1.0]	9	**14**-*S*	≥95	20:1
7	–78 to rt	$LiClO_4$ [1.2]	15	**14**-*S*	30	≥25:1
8	–78 to rt	$TiCl_4$ [1.2]	15	**14**-*S*	0	--
9	–78 to rt	$SnCl_4$ [1.2]	15	**14**-*S*	0	--
10	–78 to rt	$Ti(i\text{-}PrO)_2Cl_2$ [1.2]	15	**14**-*S*	26	4:1
11	–78 to rt	$Zn(OTf)_2$ [1.2]	15	**14**-*S*	35	≥25 :1
12	–78 to rt	$Cu(OTf)_2$ [1.2]	15	**14**-*S*	0	--
13	–78 to rt	BF_3-OEt_2 [1.2]	15	**14**-*R*	≥95	≤1:25
14	–78 to rt	BF_3-OEt_2 [2.0]	15	**14**-*R*	≥95	≤1:25
15	–78 to rt	BF_3-OEt_2 [0.25]	15	**14**-*R/S*	66	1:1
16	–78 to rt	BF_3-OEt_2 [0.50]	15	**14**-*R/S*	78	1:1.5
17	–78 to rt	$AlCl_3$ [1.2]	15	**14**-*S*	11	2:1
18	–78 to rt	$AlMe_2Cl$ [1.2]	15	**14**-*S*	41	≥25:1

a. Isolated yields. **b.** Ratios determined by ^1H and/ or ^{13}C NMR. The designation of *(S)* or *(R)* refers to the stereochemistry at the gamma-carbon in the product.

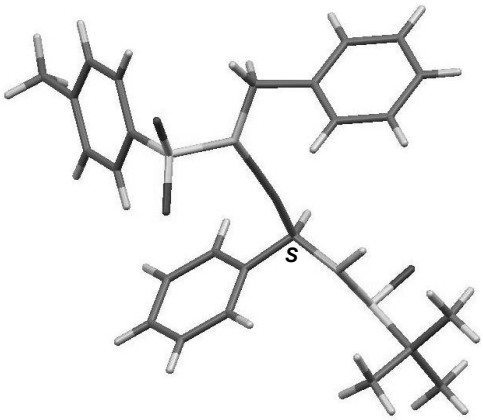


Figure 1. X-Ray structure of **14**-*S* [CCDC 955979]

We next examined effects of Lewis acids. Bidentate Lewis acids appeared to be poor promoters overall [entries 7-12] with $TiCl_4$, $SnCl_4$, and $Cu(OTf)_2$ impeding the reaction [entries 8, 9 and 12]. For monodentate Lewis acids, we found a complete reversal of stereoselectivity when using 1.2 to 2.0 equiv of BF_3-OEt_2 [entries 13 and 14],[14] and the extent of reversal depended upon the amount of BF_3-OEt_2 that was used [entries 15 and 16]. However, such a reversal could not be realized when using other monodentate Lewis acids such as $AlCl_3$ and $AlMe_2Cl$ [entries 17 and 18]. These combined outcomes suggest that this phenomenon is unique with BF_3-OEt_2.

A rationale of this stereoselectivity switch is proposed as shown in Figure 2. In the absence of a Lewis acid, the *S*-selectivity is likely derived from the Zimmerman-Traxler type chelated transition state. In contrast, with BF_3-OEt_2 coordinating to the sulfinyl oxygen atom, a synclinal or anti-periplanar approach takes precedent, thereby effectively breaking up the chelation especially when using ≥1.0 equiv. It has been suggested that other Lewis acids such as $AlMe_2Cl$ could coordinate to the imino lone pair, and thus, are not effective in deterring the pro-*S*-TS.[9] It is noteworthy that in Poisson's lithiated ynol-ether additions to Ellman-Davis chiral imines,[11] they also documented such reversal of stereochemistry when using BF_3-OEt_2.

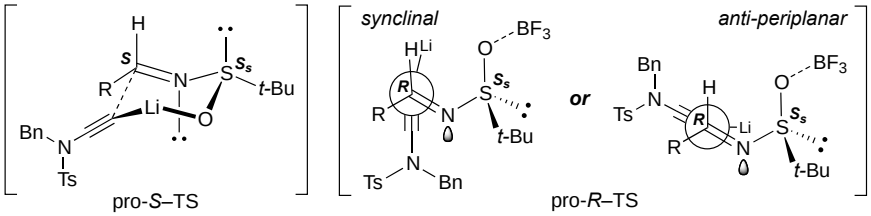
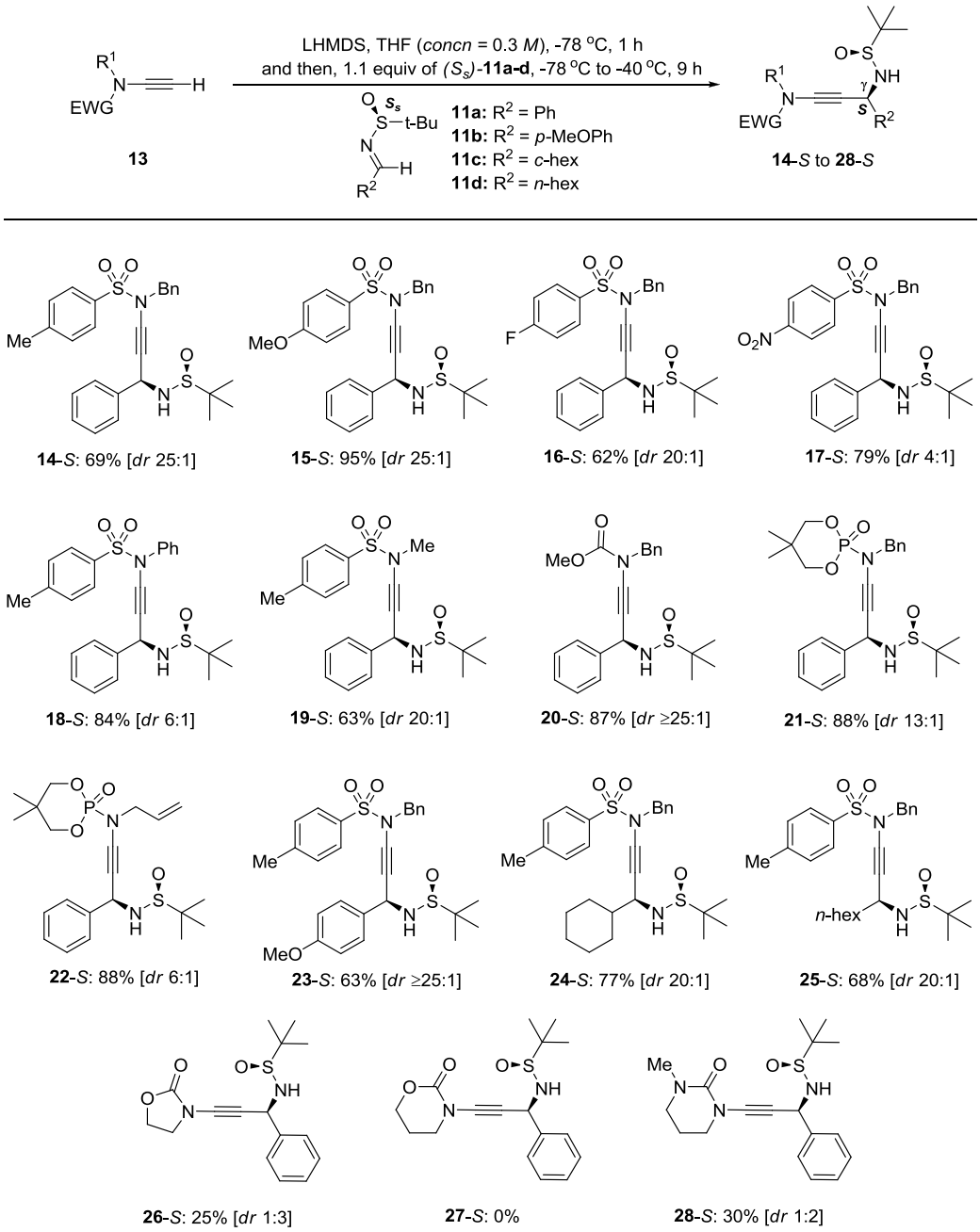


Figure 2. Chelation-**TS** versus open-**TS** *[synclinal and anti-periplanar]*

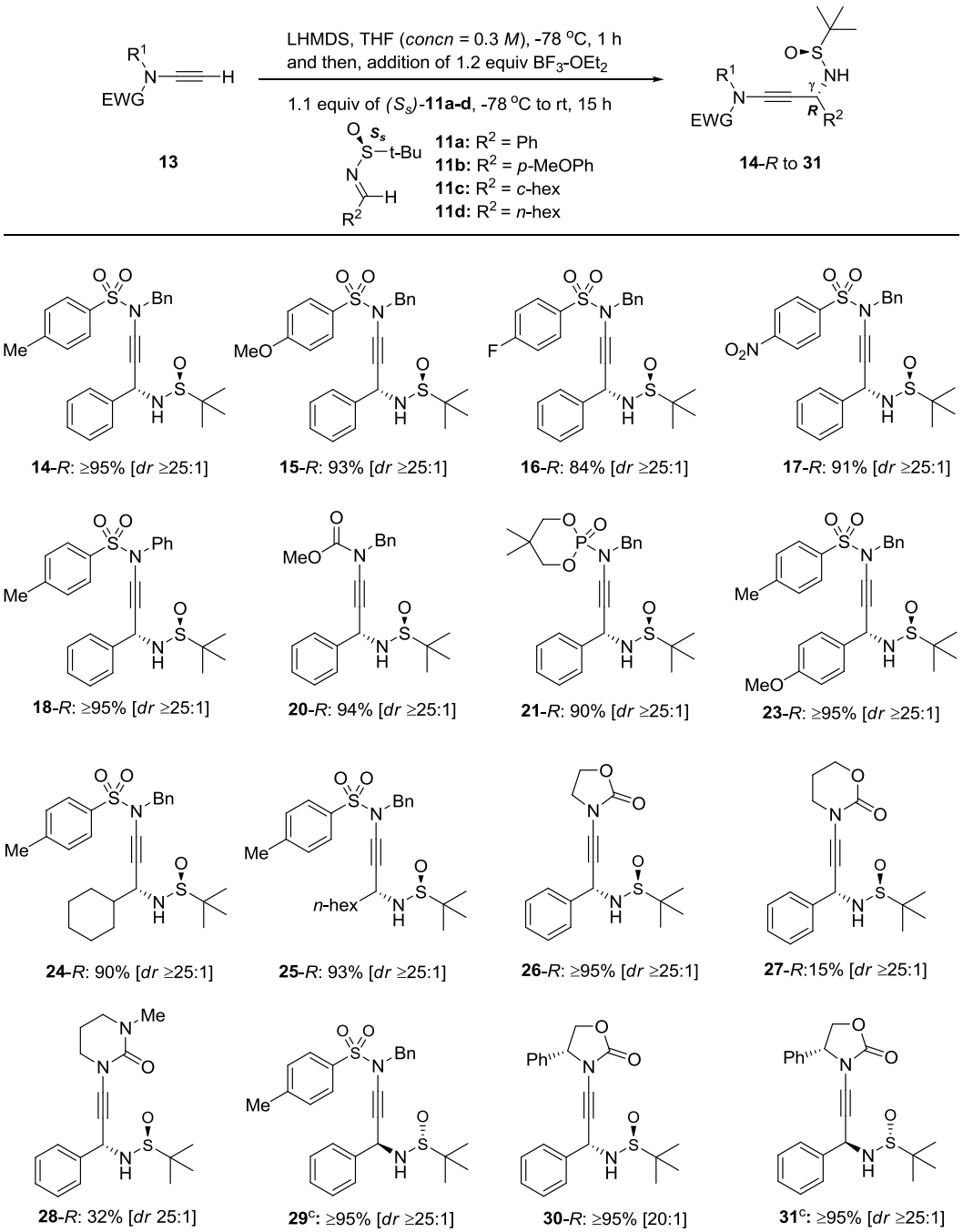
With the optimized protocols [entries 4 and 13, Table 1] in hand, our next goal was to examine the tolerance of the reaction to functionality on both ynamides **13** and Ellman-Davis chiral *N*-*tert*-butanesulfinyl imines **11** [Schemes 3 and 4]. Most of chiral γ-amino-ynamides **14-31** could be obtained in high stereoselectivities and good to high yields. Examples of the ynamide precursors included: *N*-sulfonyl-substituted γ-amino-ynamides [**14-19**, **23-25**, and **29**], carbamoyl-substituted γ-amino-ynamide [**20**], phosphoryl-substituted systems [**21** and **22**], oxazolidinone-substituted systems [**26**, **30**, and **31**], oxazinanone-substituted and tetrahydropyrimidinone-substituted γ-amino-ynamides **27** and **28**, respectively.



a. Isolated yields. **b.** Ratios determined by ^{1}H and/ or ^{13}C NMR.

Scheme 3. Addition of lithiated ynamides to chiral *N*-tert-butanesulfinyl imines[a,b]

In the absence of BF_3-OEt_2, we found an interesting effect on the selectivity for sulfonyl-substituted ynamides. Most notably, the *para*-nitro substituent actually eroded the diastereoselectivity significantly [**17**-*S* in Scheme 3]. This loss of selectivity is likely due to the nitro group competing for the Li-chelation in the pro-*S*-TS. It is a phenomenon that was also observed in **18**-*S* when the R^1 substituent is a phenyl group. *N*-Sulfonyl-substituted ynamides still afforded γ-amino-ynamides **23**-*S*, **24**-*S*, and **25**-*S* in good



a. Isolated yields. **b.** Ratios determined by ^{1}H and/ or ^{13}C NMR. **c.** Using (R_s)-**11a**.

Scheme 4. Addition of lithiated ynamides to chiral *N*-tert-butanesulfinyl imines with BF_3-OEt_2[a,b]

yields with high selectivities when added to imines **11b**, **11c**, and **11d**. Carbamoyl-substituted γ-amino-ynamide **20**-*S* could be given in better yield, and phosphoryl-substituted ynamides also afforded γ-amino-ynamides in better yields but with lower selectivities [**21**-*S* and **22**-*S*]. In addition, oxazolidinone-substituted, oxazinanone-substituted and tetrahydropyrimidinone-substituted ynamides behaved rather differently, leading to products with very low yields and opposite selectivities [see **26**-*S* and **28**-*S*], and for reasons unknown to us at this moment, no reaction was observed in an attempt to synthesize γ-amino-ynamide **27**-*S*.

When using 1.2 equiv BF_3-OEt_2, *N*-sulfonyl and carbamoyl-substituted γ-amino-ynamides **14**-*R* through **31** could be synthesized with complete reversal of stereochemistry [Scheme 4]. Moreover, all chiral γ-amino-ynamides were isolated virtually in quantitative yields except for the oxazinanone-substituted γ-amino-ynamide **27**-*R* and tetrahydropyrimidinone-substituted γ-amino-ynamide **28**-*R*. The low yields of **27**-*R* and **28**-*R* may be caused by the rapid hydrolysis of the starting materials. The (*R*) relative stereochemistry at the gamma-carbon was unambiguously assigned based on the single crystal X-ray structure of γ-amino-ynamide **26**-*R* [left side in Figure 3].

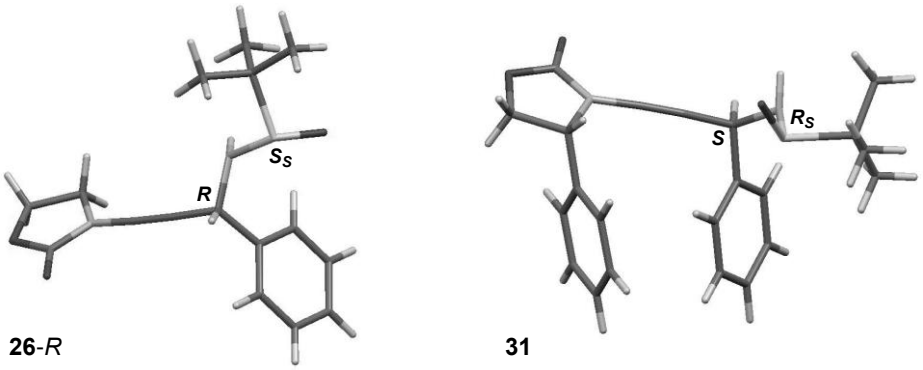
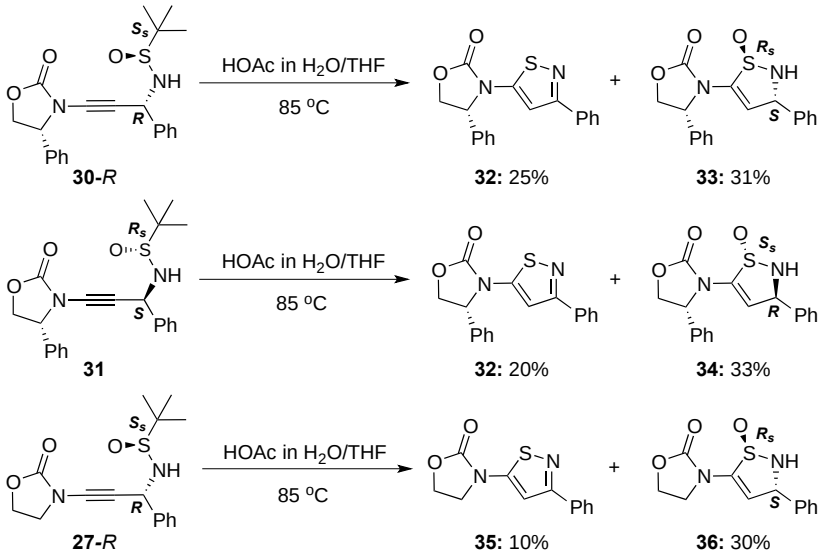


Figure 3. X-Ray structures of **26**-*R* and **31** **[**CCDC 955980 and 955981]

We anticipated a potential matched and mismatched scenario when using chiral ynamide [see products **30**-*R* and **31** in Scheme 4]. Instead, the addition of chiral lithiated ynamide to either (S_S)-**11a** or (R_S)-**11a** led to their respective addition products **30**-*R* and **31** in high yields and diastereoselectivities. These reactions suggest that the chirality on the oxazolidinone ring exerts no impact on the selectivity, but it is still noteworthy that **30**-*R* and **31** represent *de novo* ynamides that are highly rich in chirality. Stereochemistry of **31** was unambiguously assigned based on its X-ray structure [right side in Figure 3]. Very interestingly on the other hand, the relative stereochemistry at the γ–carbon of **30**-*R* was assigned through X-ray structure of its derivative 2,3-dihydro-isothiazole *S*-oxide **33** [Figure 4] obtained via a serendipitously discovered 5-*endo*-*dig* cyclization [Scheme 5].



Scheme 5. Acid-promoted 5-*endo-dig* cyclization of ynamides **27**-*R*, **30**-*R*, and **31**

This acid promoted 5-*endo-dig* cyclization deserves more comments. It occurred concomitant with the loss of the *t*-Bu group led to isothiazoles and 2,3-dihydro-isothiazole *S*-oxides respectively. The single crystal X-ray structure of 2,3-dihydro-isothiazole *S*-oxide **33** [Figure 4] not only provided the stereochemical assignment of **30**-*R* but also revealed that an inversion at the *S*-center had taken place in **33**. This cyclization appears to be unique with the oxazolidinone-substituted γ-amino-ynamides, as not all γ–amino-ynamides underwent such cyclization, and it is also consistently accompanied with a competing pathway. Aromatized products **32** and **35** are likely derived from **33 [or 34]** and **36**, respectively, through an acid promoted dehydrative process. Although we have been unable to expand the scope of or optimize this unique cyclization, to the best of our knowledge, it represents a novel transformation involving propargylic *N*-sulfinyl amines.

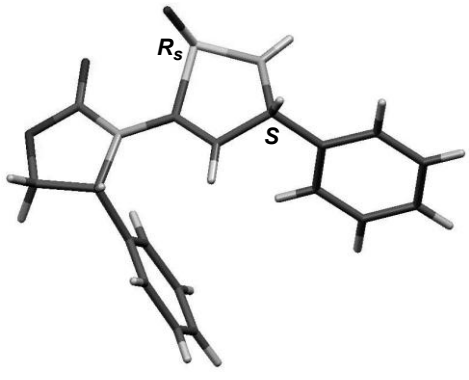


Figure 4. X-Ray structure of **33 [**CCDC 955982]

CONCLUSION

We have described herein details in developing an expeditious and convenient method for synthesizing chiral γ-amino-ynamides via a highly stereoselective addition of lithiated ynamides to Ellman–Davis Chiral *N*-*tert*-Butanesulfinyl Imines. Our work demonstrates that additions of ynamides can be highly stereoselective even without Lewis acids, although the use of BF_3-OEt_2 completely reversed the stereoselectivity. Additions of oxazolidinone-substituted, oxazinanone-substituted and tetrahydropyrimidinone-substituted ynamides appear to require BF_3-OEt_2, and the chirality of the oxazolidinone ring does not play a role in the asymmetric induction. This work also features a rare acid promoted 5-*endo*-*dig* cyclization of the oxazolidinone-substituted γ-amino-ynamides concomitant with the loss of the *t*-Bu group and an inversion at the *S*-center to afford isothiazoles and 2,3-dihydro-isothiazole *S*-oxides.

EXPERIMENTAL

General Procedure for Additions of Lithiated Ynamides to Chiral Imines.

To a flamed-dried vial were added ynamide **13a** (135.2 mg, 0.47 mmol) and THF (1.58 mL, ynamide *concn* = 0.30 *M*). To this solution was added LHMDS (0.71 mL, 1.0 *M* in THF) at -78 °C. After the mixture was stirred at -78 °C for 1.0 h, a solution of imine *(S_s)*-**11a**[15] (109.1 mg, 0.52 mmol) in THF (1 mL) was added over 1 min. The reaction mixture was then allowed to warm to -40 °C slowly and monitored using TLC analysis. When it was 9.0 h post addition of the imine, TLC analysis showed complete consumption of the starting material. The mixture was re-cooled to -78 °C, and H_2O (2 mL) was added to quench the reaction. The quenched mixture was extracted with equal volume of EtOAc, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified using silica gel flash column chromatography [Gradient eluent: 8:1~1:1 Hexane/EtOAc + 3% Et_3N] to afford **14**-*S* (161.6 mg, 0.33 mmol) in 69% yield.

14-*S*: R_f = 0.18 [3:1 Hexane/EtOAc]; pale yellow solid; mp 129–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 2.41 (s, 3H), 3.51 (d, 1H, *J* = 5.6 Hz), 4.44 (d, 1H, *J* = 14.0 Hz), 4.51 (d, 1H, *J* = 14.0 Hz), 5.23 (d, 1H, *J* = 5.6 Hz), 7.24-7.29 (m, 12H), 7.72 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 22.4, 50.6, 55.2, 56.2, 70.2, 79.9, 127.6, 127.7, 128.1, 128.2, 128.4, 128.5, 129.0, 129.7, 134.2, 134.4, 139.0, 144.5; IR (film) cm^{-1} 2249m, 1597m, 1494m, 1455m, 1363s, 1168s; mass spectrum (ESI): *m/z* (% relative intensity) 495 $(M+H)^+$ (100); HRMS (ESI): *m/z* calcd for $C_{27}H_{31}N_2O_3S_2$ $[M+H]^+$: 495.1771; found 495.1758.

Ynamide **15**-*S* (228.9 mg, 0.45 mmol) was prepared from the corresponding ynamide (142.8 mg, 0.47

mmol) and imine *(S_s)*-**11a** (109.1 mg, 0.52 mmol) in 95% yield.

15-*S*: R_f = 0.28 [1:1 Hexane/EtOAc]; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H), 3.53 (d, 1H, *J* = 5.6 Hz), 3.83 (s, 3H), 4.43 (d, 1H, *J* = 13.6 Hz), 4.51 (d, 1H, *J* = 14.0 Hz), 5.23 (d, 1H, *J* = 5.6 Hz), 6.89 (d, 2H, *J* = 8.8 Hz), 7.28 (d, 10H, *J* = 3.6 Hz), 7.75 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 50.8, 55.3, 55.7, 56.3, 70.3, 80.3, 114.4, 114.9, 127.7, 128.2, 128.4, 128.55, 128.60, 129.1, 130.1, 134.4, 139.2, 163.7; IR (film) cm^{-1} 2248m, 1595m, 1497m, 1363m, 1262m, 1162s; mass spectrum (APCI): m/e (% relative intensity) 511 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{27}H_{31}N_2O_4S_2$ $[M+H]^+$: 511.1720; found 511.1718.

Ynamide **16**-*S* (147.0 mg, 0.29 mmol) was prepared from the corresponding ynamide (135.0 mg, 0.47 mmol) and imine *(S_s)*-**11a** (109.1 mg, 0.52 mmol) in 62% yield.

16-*S*: R_f = 0.19 [4:1 Petroleum Ether/EtOAc]; yellow solid; mp 81-82 ^{o}C; ^{1}H NMR (600 MHz $CDCl_3$) δ 1.17 (s, 9H), 3.52 (d, 1H, *J*= 6.0 Hz), 4.46 (d, 1H, *J* = 12.0 Hz), 4.56 (d, 1H, *J* = 12.0 Hz), 5.24 (d, 1H, *J* = 6.0 Hz), 7.09 (t, 2H, *J* = 8.4 Hz), 7.26-7.29 (m, 10 H), 7.83 (dd, 2H, *J* = 5.4, 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.5, 51.0, 55.5, 56.3, 70.5, 79.9, 116.4 (d, $^2J_{F\text{-}C}$ = 22.7 Hz), 127.6, 128.2, 128.5, 128.58, 128.63, 129.1, 130.68 (d, $^3J_{F\text{-}C}$ = 9.6 Hz), 133.53 (d, $^4J_{F\text{-}C}$ = 2.7 Hz), 134.1, 139.0, 165.7 (d, $^1J_{F\text{-}C}$ = 254.7 Hz); IR (KBr) cm^{-1} 2246m, 1590m, 1491m, 1360m, 1239m, 1176s; mass spectrum (ESI): m/e (% relative intensity) 499 (100) $(M+H)^+$.

A separable 4:1 mixture of ynamides **17**-*S* (157.3 mg, 0.30 mmol) and **17**-*R* (39.3 mg, 0.07 mmol) were prepared from the corresponding ynamide (149.9 mg, 0.47 mmol) and imine *(S_s)*-**11a** (109.1 mg, 0.52 mmol) in 79% yield.

17-*S*: R_f = 0.62 [1:1 Hexane/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 3.52 (d, 1H, *J* = 6.8 Hz), 4.52 (d, 1H, *J* = 13.6 Hz), 4.61 (d, 1H, *J* = 14.0 Hz), 5.25 (d, 1H, *J* = 6.8 Hz), 7.26-7.42 (m, 12H), 7.99 (d, 2H, *J* = 8.8 Hz), 8.23 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 51.3, 56.0, 56.6, 71.0, 79.4, 124.4, 127.5, 128.76, 128.81, 128.84, 129.1, 129.2, 129.3, 133.7, 138.9, 142.8, 150.5; IR (film) cm^{-1} 2251w, 1613m, 1531s, 1371m, 1348m, 1313m, 1172s; mass spectrum (ESI): m/e (% relative intensity) 526 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{26}H_{28}N_3O_5S_2$ $[M+H]^+$: 526.1465; found 526.1459.

A separable 6:1 mixture of ynamides **18**-*S* (150.2 mg, 0.31 mmol) and **18**-*R* (25.0 mg, 0.05 mmol) were prepared from the corresponding ynamide (118.2 mg, 0.44 mmol) and imine *(S_s)*-**11a** (100.3 mg, 0.48 mmol) in 84% yield.

18-*S*: R_f = 0.46 [1:1 Hexane/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 2.40 (s, 3H), 3.63 (d, 1H, *J* = 5.6 Hz), 5.35 (d, 1H, *J* = 5.6 Hz), 7.18 (d, 2H, *J* = 8.4 Hz), 7.26-7.41 (m, 8H),

7.48-7.52 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 22.7, 51.1, 56.5, 69.7, 80.6, 126.3, 128.0, 128.4, 128.45, 128.51, 128.8, 129.3, 129.7, 133.0, 138.7, 139.3, 145.1; IR (film) cm^{-1} 2254m, 1596m, 1492m, 1455m, 1373m, 1175s; mass spectrum (ESI): m/e (% relative intensity) 481 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{26}H_{29}N_2O_3S_2$ $[M+H]^+$: 481.1615; found 481.1622.

Ynamide **19**-*S* (125.5 mg, 0.31 mmol) were prepared from the corresponding ynamide (99.2 mg, 0.47 mmol) and imine *(S$_s$)*-**11a** (109.1 mg, 0.52 mmol) in 63% yield.
19-*S*: R_f = 0.22 [1:1 Hexane/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9H), 2.41 (s, 3H), 3.06 (s, 3H), 3.62 (d, 1H, *J* = 6.0 Hz), 5.28 (d, 1H, *J* = 6.0 Hz), 7.25-7.39 (m, 5H), 7.46-7.48 (m, 2H), 7.69-7.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 22.6, 39.0, 51.2, 56.4, 68.1, 81.6, 127.8, 128.0, 128.4, 128.8, 129.9, 133.2, 139.3, 144.9; IR (film) cm^{-1} 2251m, 1597m, 1454m, 1364s, 1171s; mass spectrum (ESI): m/e (% relative intensity) 419 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{21}H_{27}N_2O_3S_2$ $[M+H]^+$: 419.1458; found 419.1460.

Ynamide **20**-*S* (72.9 mg, 0.18 mmol) were prepared from the corresponding ynamide (39.8 mg, 0.21 mmol) and imine *(S$_s$)*-**11a** (48.4 mg, 0.23 mmol) in 87% yield.
20-*S*: R_f = 0.25 [1:1 Hexane/EtOAc]; pale yellow solid; mp 85-86 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 9H), 3.57 (d, 1H, *J* = 6.0 Hz), 3.82 (s, 3H), 4.63 (s, 2H), 5.31 (d, 1H, *J* = 5.6 Hz), 7.26-7.39 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.6, 51.0, 53.7, 54.2, 56.3, 70.1, 80.3, 127.8, 128.15, 128.23, 128.59, 128.62, 128.84, 135.9, 139.4, 155.7; IR (film) cm^{-1} 2260m, 1726s, 1444m, 1383m, 1285m, 1220m; mass spectrum (ESI): m/e (% relative intensity) 399 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{22}H_{27}N_2O_3S$ $[M+H]^+$: 399.1737; found 399.1726.

A 13:1 mixture of ynamides **21**-*S/R* (203.6 mg, 0.42 mmol) were prepared from the corresponding ynamide (132.3 mg, 0.47 mmol) and imine *(S$_s$)*-**11a** (109.1 mg, 0.52 mmol) in 88% yield.
21-*S*: R_f = 0.28 [1:1 CH_2Cl_2/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.10 (s, 3H), 1.16 (s, 9H), 3.51 (d, 1H, *J* = 6.0 Hz), 4.05-4.16 (m, 4H), 4.42-4.51 (m, 2H), 5.21 (dd, 1H, *J* = 2.8, 5.2 Hz), 7.25-7.41 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 21.5, 22.6, 32.2 (d, *J* = 6.6 Hz), 51.1 (d, *J* = 1.4 Hz), 54.7 (d, *J* = 5.8 Hz), 56.2, 65.4 (d, *J* = 5.8 Hz), 78.5 (dd, *J* = 7.3, 36.4 Hz), 82.4 (d, *J* = 4.8 Hz), 127.6, 128.1, 128.5, 128.6, 129.0, 136.2 (d, *J* = 1.9 Hz), 139.5; ^{31}P NMR (202 MHz, $CDCl_3$) δ -1.99; IR (film) cm^{-1} 2970w, 2247m, 1455m, 1281m, 1052s; mass spectrum (ESI): m/e (% relative intensity) 489 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{25}H_{34}N_2O_4PS$ $[M+H]^+$: 489.1972; found 489.1985.

A 6:1 mixture of ynamides **22**-*S* and **22**-*R* (183.1 mg, 0.42 mmol) were prepared from the corresponding

ynamide (108.6 mg, 0.47 mmol) and imine *(S$_s$)*-**11a** (109.1 mg, 0.52 mmol) in 88% yield.
22-*S*: R$_f$ = 0.32 [1:1 CH_2Cl_2/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 3H), 1.10 (s, 3H), 1.20 (s, 9H), 3.64 (d, 1H, *J* = 5.6 Hz), 3.92 (dd, 2H, *J* = 6.8, 8.0 Hz), 4.04-4.15 (m, 4H), 5.25-5.36 (m, 2H), 5.87-5.97 (m, 1H), 7.28-7.36 (m, 3H), 7.47 (d, 2H, *J* = 7.2 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 21.5, 22.6, 32.2 (d, *J* = 6.9 Hz), 51.1 (d, *J* = 1.6 Hz), 53.5 (d, *J* = 5.3 Hz), 56.2, 64.6 (d, *J* = 5.4 Hz), 78.4 (dd, *J* = 6.9, 25.3 Hz), 82.5 (d, *J* = 4.6 Hz), 119.2, 127.6, 128.2, 128.6, 132.4 (d, *J* = 2.3 Hz), 139.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ -2.10; IR (film) cm^{-1} 2974w, 2248m, 1455m, 1279m, 1052s; mass spectrum (APCI): m/e (% relative intensity) 439 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{21}H_{31}N_2O_4PS$ $[M+H]^+$: 439.1815; found 439.1801.

Ynamide **23**-*S* (129.9 mg, 0.25 mmol) was prepared from the corresponding ynamide **13a** (111.7 mg, 0.39 mmol) and imine *(S$_s$)*-**11b**[16] (103.1 mg, 0.43 mmol) in 63% yield.
23-*S*: *R$_f$* = 0.28 [1:1 Hexane/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 9H), 2.41 (s, 3H), 3.48 (d, 1H, *J* = 5.2 Hz), 3.78 (s, 3H), 4.44 (d, 1H, *J* = 14.0 Hz), 4.50 (d, 1H, *J* = 13.6 Hz), 5.17 (d, 1H, *J* = 5.2 Hz), 6.80 (d, 2H, *J* = 8.8 Hz), 7.18-7.28 (m, 9H), 7.72 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 22.6, 50.2, 55.36, 55.40, 56.2, 70.6, 79.8, 113.9, 127.9, 128.4, 128.6, 129.05, 129.14, 129.8, 131.3, 134.4, 134.6, 144.7, 159.5; IR (film) cm^{-1} 2248w, 1611w, 1456m, 1364m, 1250m, 1169s; mass spectrum (ESI): m/e (% relative intensity) 525 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{28}H_{33}N_2O_4S_2$ $[M+H]^+$: 525.1877; found 525.1881.

Ynamide **24**-*S* (183.3 mg, 0.37 mmol) was prepared from the corresponding ynamide **13a** (135.2 mg, 0.47 mmol) and imine *(S$_s$)*-**11c**[16] (112.3 mg, 0.52 mmol) in 77% yield.
24-*S*: *R$_f$* = 0.51 [1:1 Hexane/EtOAc]; pale yellow solid; mp 119–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81-0.90 (m, 2H), 0.99-1.20 (m, 3H), 1.17 (s, 9H), 1.43-1.46 (m, 1H), 1.56-1.67 (m, 5H), 2.43 (s, 3H), 3.09 (d, 1H, *J* = 6.4 Hz), 3.88 (t, 1H, *J* = 6.0 Hz), 4.42 (d, 1H, *J* = 13.6 Hz), 4.50 (d, 1H, *J* = 14.0 Hz), 7.27-7.33 (m, 7H), 7.79 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 22.6, 25.8, 25.9, 26.2, 27.8, 29.4, 43.3, 53.0, 55.4, 56.1, 70.1, 78.6, 127.9, 128.3, 128.5, 129.0, 129.8, 134.5, 134.6, 144.6; IR (film) cm^{-1} 2925brm, 2852w, 2250w, 1361m, 1168s, 1070m; mass spectrum (ESI): m/e (% relative intensity) 501 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{27}H_{37}N_2O_3S_2$ $[M+H]^+$: 501.2241; found 501.2235.

Ynamide **25**-*S* (162.2 mg, 0.32 mmol) was prepared from the corresponding ynamide **13a** (135.2 mg, 0.47 mmol) and imine *(S$_s$)*-**11d**[17] (113.3 mg, 0.52 mmol) in 68% yield.
25-*S*: *R$_f$* = 0.52 [1:1 Hexane/EtOAc]; white solid; mp 69–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t,

3H, *J* = 7.0 Hz), 1.16 (s, 9H), 1.18-1.29 (m, 8H), 1.48-1.64 (m, 2H), 2.43 (s, 3H), 3.13 (d, 1H, *J* = 5.6 Hz), 4.02-4.07 (m, 1H), 4.43 (d, 1H, *J* = 13.6 Hz), 4.50 (d, 1H, *J* = 13.6 Hz), 7.27-7.32 (m, 7H), 7.77 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 21.7, 22.6, 22.7, 25.5, 28.9, 31.8, 37.0, 47.7, 55.5, 56.0, 71.2, 78.2, 127.9, 128.4, 128.6, 129.1, 129.8, 134.6, 134.7, 144.7; IR (film) cm^{-1} 2926brm, 2856m, 2252w, 1456m, 1364m, 1169s; mass spectrum (ESI): m/e (% relative intensity) 503 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{27}H_{39}N_2O_3S_2$ $[M+H]^+$: 503.2397; found 503.2396.

A 1:3 mixture of ynamides **26**-*S* and **26**-*R* (37.2 mg, 0.12 mmol) were prepared from the corresponding ynamide (52.7 mg, 0.47 mmol) and imine *(S$_s$)*-**11a** (109.1 mg, 0.52 mmol) in 25% yield.
26-*S/R***:** R_f = 0.22 [EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) [*for* **26**-*S/R*] δ 1.19 (s, 9H), 1.21 (s, 27H), 3.69 (d, 3H, *J* = 4.0 Hz), 3.79 (d, 1H, *J* = 6.8 Hz), 3.90-3.94 (m, 8H), 4.39-4.43 (m, 8H), 5.36 (d, 1H, *J* = 6.8 Hz), 5.43 (d, 1H, *J* = 4.0 Hz), 7.30-7.39 (m, 12H), 7.52-7.56 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) [*for* **26**-*S/R*] δ 22.6, 46.7, 46.8, 51.2, 51.3, 56.1, 56.5, 63.17, 63.24, 69.5, 70.2, 76.8, 127.7, 127.8, 128.4, 128.6, 128.7, 128.9, 138.7, 139.0, 156.0; IR (film) cm^{-1} [*for* **26**-*S/R*] 2264m, 1765s, 1477m, 1417m, 1200m. mass spectrum (APCI): m/e (% relative intensity) 321 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{16}H_{20}N_2O_3S$ $[M+H]^+$: 321.1267; found 321.1266.

A 1:2 mixture of ynamides **28**-*S* and **28**-*R* (39.2 mg, 0.11 mmol) were prepared from the corresponding ynamide (52.5 mg, 0.38 mmol) and imine *(S$_s$)*-**11a** (87.5 mg, 0.42 mmol) in 30% yield.
28-*S/R***:** R_f = 0.54 [acetone]; pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) [*for **28**-S/R*] δ 1.20 (s, 9H), 1.21 (s, 18H), 2.00-2.05 (m, 6H), 2.98 (s, 9H), 3.25-3.30 (m, 6H), 3.57 (d, 3H, *J* = 4.5 Hz), 3.68 (t, 6H, *J* = 5.7 Hz), 5.36 (d, 1H, *J* = 6.5 Hz), 5.43 (d, 2H, *J* = 4.0 Hz), 7.27-7.38 (m, 9H), 7.39-7.60 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) [*for* **28**-*S/R*] δ 14.9, 21.80, 21.83, 22.7, 34.5, 36.2, 47.97, 47.90, 50.0, 50.2, 51.7, 51.8, 56.0, 56.3, 66.5, 67.3, 83.1, 127.91, 127.92, 128.1, 128.2, 128.6, 128.8, 139.6, 139.9, 153.9; IR (film) cm^{-1} [*for* **28**-*S/R*] 2958brm, 2254m, 1668s, 1498m, 1441m, 1407m, 1319m; mass spectrum (ESI): m/e (% relative intensity) 348 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{18}H_{26}N_3O_2S$ $[M+H]^+$: 348.1741; found 348.1746.

General Procedure for Additions with BF_3-OEt_2.

To a flamed-dried vial were charged with ynamide **13a** (135.2 mg, 0.47 mmol) and THF (1.58 mL, ynamide *concn* = 0.3 *M*). To this solution at -78 ^{o}C was added LHMDS (0.71 mL, 1.0 *M* in THF). After the mixture was stirred at -78 ^{o}C for 1.0 h, a solution of imine *(S$_s$)*-**11a** (109.1 mg, 0.52 mmol) in THF (1 mL) pre-treated with BF_3-Et_2O (0.070 mL, 0.59 mmol) was added over 1 min. The resulting mixture was warmed to rt slowly, stirred overnight (~15 h), and monitored using TLC analysis. After complete

consumption of the starting material, re-cooling of the mixture to -78 ^{o}C, H_2O (2 mL) was added to quench the reaction. The quenched mixture was extracted with equal volume of EtOAc, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified using silica gel flash column chromatography [Gradient eluent: 8:1~1:1 Hex:EtOAc + 3% Et_3N] to afford **14**-*R* (234.4 mg, 0.47 mmol) in ≥95% yield.

14-*R*: R_f = 0.30 [1:1 Hexane/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 9H), 2.43 (s, 3H), 3.32 (d, 1H, *J* = 4.0 Hz), 4.45 (d, 1H, *J* = 13.6 Hz), 4.55 (d, 1H, *J* = 14.0 Hz), 5.30 (d, 1H, *J* = 4.0 Hz), 7.24-7.31 (m, 12H), 7.70 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 22.6, 51.5, 55.5, 56.0, 69.8, 80.2, 127.8, 128.0, 128.5, 128.6, 128.7, 128.9, 129.1, 129.9, 134.5, 134.7, 139.3, 144.8; IR (film) cm^{-1} 2250m, 1598m, 1455m, 1365s, 1169s; mass spectrum (APCI): m/e (% relative intensity) 495 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{27}H_{31}N_2O_3S_2$ $[M+H]^+$: 495.1771; found 495.1751.

Ynamide **15**-*R* (225.0 mg, 0.44 mmol) were prepared from the corresponding ynamide (142.8 mg, 0.47 mmol) and imine *(S$_s$)*-**11a** (109.1 mg, 0.52 mmol) in 93% yield.

15-*R*: R_f = 0.18 [1:1 Hexane/EtOAc]; pale yellow solid; mp 104–105 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 9H), 3.40 (d, 1H, *J* = 3.5 Hz), 3.83 (s, 3H), 4.44 (d, 1H, *J* = 14.0 Hz), 4.54 (d, 1H, *J* = 14.0 Hz), 5.29 (d, 1H, *J* = 3.5 Hz), 6.90 (d, 2H, *J* = 9.0 Hz), 7.28 (d, 10H, *J* = 8.0 Hz), 7.74 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.5, 51.3, 55.3, 55.7, 55.8, 69.7, 80.3, 114.3, 127.6, 128.3, 128.4, 128.5, 128.7, 128.9, 129.0, 130.0, 134.4, 139.2, 163.7; IR (film) cm^{-1} 2251m, 1595m, 1497m, 1364m, 1262m, 1163s; mass spectrum (ESI): m/e (% relative intensity) 511 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{27}H_{31}N_2O_4S_2$ $[M+H]^+$: 511.1720; found 511.1702.

Ynamide **16**-*R* (197.0 mg, 0.40 mmol) were prepared from the corresponding ynamide (135.0 mg, 0.47 mmol) and imine *(S$_s$)*-**11a** (109.1 mg, 0.52 mmol) in 84% yield.

16-*R*: R_f = 0.16 [7:3 Petroleum Ether/ EtOAc]; mp 84-85 ^{o}C; ^{1}H NMR (600 MHz $CDCl_3$) 1.14 (s, 9H), 3.37 (d, 1H, *J*= 3.6 Hz), 4.49 (d, 1H, *J* = 13.8 Hz), 4.58 (d, 1H, *J* = 13.8 Hz), 5.31 (d, 1H, *J* = 3.6 Hz), 7.09 (t, *J* = 8.4 Hz), 7.27-7.34 (m, 10H,), 7.77-7.79 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) 22.5, 51.2, 55.6, 55.9, 69.9, 79.9, 116.3 (d, $^2J_{F\text{-}C}$ = 22.5 Hz), 127.6, 128.47, 128.53, 128.6, 128.8, 128.9, 130.6 (d, $^3J_{F\text{-}C}$ = 9.5 Hz), 133.6 (d, $^4J_{F\text{-}C}$ = 3.0 Hz), 134.1, 139.0, 165.6 (d, $^1J_{F\text{-}C}$ = 254.9 Hz); IR (KBr) cm^{-1} 2247w, 1590m, 1493m, 1366s, 1241m, 1178s; mass spectrum (ESI): m/e (% relative intensity) 521 (100) $(M + Na)^+$.

Ynamide **17**-*R* (62.3 mg, 0.12 mmol) were prepared from the corresponding ynamide (39.7 mg, 0.13 mmol) and imine *(S$_s$)*-**11a** (28.9 mg, 0.14 mmol) in 91% yield.

17-*R*: R_f = 0.31 [1:1 Hexane/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 3.45 (s, 1H), 4.55 (d, 1H, *J* = 14.0 Hz), 4.63 (d, 1H, *J* = 14.0 Hz), 5.33 (d, 1H, *J* = 3.6 Hz), 7.26-7.34 (m, 12H), 7.88 (d, 2H, *J* = 8.4 Hz), 8.19 (d, 2H, *J* = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 51.0, 56.1, 56.2, 70.4, 79.6, 124.3, 127.7, 128.8, 128.85, 128.88, 129.0, 129.08, 129.12, 133.8, 139.0, 143.0, 150.5; IR (film) cm^{-1} 2251m, 1531s, 1366m, 1349s, 1313m, 1174s; mass spectrum (ESI): m/e (% relative intensity) 526 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{26}H_{28}N_3O_5S_2$ $[M+H]^+$: 526.1465; found 526.1443.

Ynamide **18**-*R* (114.3 mg, 0.24 mmol) were prepared from the corresponding ynamide (65.8 mg, 0.24 mmol) and imine *(S$_s$)*-**11a** (55.9 mg, 0.27 mmol) in ≥95% yield.

18-*R*: R_f = 0.24 [1:1 Hexane/EtOAc]; pale yellow solid; mp 84–85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (s, 9H), 2.40 (s, 3H), 3.48 (d, 1H, *J* = 4.0 Hz), 5.42 (d, 1H, *J* = 3.5 Hz), 7.19-7.40 (m, 11H), 7.50-7.51 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 22.7, 51.5, 56.1, 68.9, 80.6, 126.2, 127.9, 128.35, 128.40, 128.7, 129.0, 129.2, 129.6, 133.0, 138.7, 139.4, 145.0; IR (film) cm^{-1} 2251m, 1595m, 1491m, 1455m, 1371s; mass spectrum (ESI): m/e (% relative intensity) 481 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{26}H_{29}N_2O_3S_2$ $[M+H]^+$: 481.1615; found 481.1631.

Ynamide **20**-*R* (112.1 mg, 0.28 mmol) were prepared from the corresponding ynamide (56.6 mg, 0.30 mmol) and imine *(S$_s$)*-**11a** (68.9 mg, 0.33 mmol) in 94% yield.

20-*R*: R_f = 0.17 [1:1 Hexane/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 3.47 (d, 1H, *J* = 4.0 Hz), 3.78 (s, 3H), 4.59 (d, 1H, *J* = 14.4 Hz), 4.65 (d, 1H, *J* = 14.8 Hz), 5.37 (d, 1H, *J* = 4.0 Hz), 7.28-7.33 (m, 8H), 7.35-7.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 51.4, 53.7, 54.1, 55.9, 69.3, 80.4, 127.7, 128.1, 128.4, 128.6, 128.7, 135.9, 139.5, 155.8; IR (film) cm^{-1} 2259m, 1724s, 1444m, 1365m, 1286m, 1221m; mass spectrum (ESI): m/e (% relative intensity) 399 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{22}H_{27}N_2O_3S$ $[M+H]^+$: 399.1737; found 399.1724.

Ynamide **21**-*R* (208.4 mg, 0.43 mmol) were prepared from the corresponding ynamide (132.3 mg, 0.47 mmol) and imine **11a** (109.1 mg, 0.52 mmol) in 90% yield.

21-*R*: R_f = 0.28 [1:1 CH_2Cl_2/EtOAc]; white solid; mp 143–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.09 (s, 3H), 1.16 (s, 9H), 3.41 (d, 1H, *J* = 3.2 Hz), 4.05-4.12 (m, 4H), 4.42-4.50 (m, 2H), 5.29 (t, 1H, *J* = 3.0 Hz), 7.28-7.40 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 21.4, 22.6, 32.1 (d, *J* = 6.9 Hz), 51.1, 54.8 (d, *J* = 6.9 Hz), 55.8, 64.6 (d, *J* = 5.4 Hz), 78.4 (dd, *J* = 6.9, 19.1 Hz), 82.8 (d, *J* = 5.3 Hz), 127.5, 128.1, 128.4, 128.5, 128.78, 128.84, 136.2 (d, *J* = 2.3 Hz), 139.6; ^{31}P NMR (162 MHz, $CDCl_3$) δ -1.81; IR (film) cm^{-1} 2962brw, 2249m, 1456m, 1281m, 1060s; mass spectrum (ESI): m/e (% relative intensity) 489 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{25}H_{34}N_2O_4PS$ $[M+H]^+$: 489.1972; found

489.1970.

Ynamide **23**-*R* (258.0 mg, 0.49 mmol) were prepared from the corresponding ynamide (135.2 mg, 0.47 mmol) and imine *(S$_s$)*-**11b** (124.8 mg, 0.52 mmol) in ≥95% yield.
23-*R*: R_f = 0.15 [1:1 Hexane/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 2.38 (s, 3H), 3.34 (d, 1H, *J* = 3.6 Hz), 3.73 (s, 3H), 4.41 (d, 1H, *J* = 14.0 Hz), 4.51 (d, 1H, *J* = 14.0 Hz), 5.22 (d, 1H, *J* = 3.6 Hz), 6.77 (d, 2H, *J* = 8.4 Hz), 7.17-7.25 (m, 9H), 7.69 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 22.37, 22.45, 50.7, 55.2, 55.3, 55.7, 69.8, 79.7, 113.9, 127.7, 128.2, 128.5, 128.77, 128.84, 129.7, 131.2, 134.3, 134.4, 144.6, 159.5; IR (film) cm^{-1} 2249w, 1611w, 1511m, 1364m, 1248m, 1169s; mass spectrum (ESI): m/e (% relative intensity) 525 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{28}H_{33}N_2O_4S_2$ $[M+H]^+$: 525.1877; found 525.1902.

Ynamide **24**-*R* (213.6 mg, 0.43 mmol) were prepared from the corresponding ynamide (135.2 mg, 0.47 mmol) and imine *(S$_s$)*-**11c** (112.3 mg, 0.52 mmol) in 90% yield.
24-*R*: R_f = 0.20 [1:1 Hexane/EtOAc]; white solid; mp 92–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84-1.07 (m, 5H), 1.12 (s, 9H), 1.44-1.49 (m, 1H), 1.55-1.68 (m, 5H), 2.43 (s, 3H), 3.15 (d, 1H, *J* = 5.2 Hz), 3.99 (t, 1H, *J* = 5.0 Hz), 4.42 (d, 1H, *J* = 14.0 Hz), 4.54 (d, 1H, *J* = 14.0 Hz), 7.28-7.32 (m, 7H), 7.76 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 22.5, 25.7, 25.9, 26.1, 27.5, 29.6, 43.8, 53.4, 55.4, 55.8, 69.2, 78.8, 127.8, 128.3, 128.5, 128.9, 129.7, 134.5, 134.6, 144.6; IR (film) cm^{-1} 2925m, 2852w, 2251w, 1452m, 1363m, 1168s; mass spectrum (ESI): m/e (% relative intensity) 501 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{27}H_{37}N_2O_3S_2$ $[M+H]^+$: 501.2241; found 501.2234.

Ynamide **25**-*R* (186.7 mg, 0.37 mmol) were prepared from the corresponding ynamide (114.1 mg, 0.40 mmol) and imine *(S$_s$)*-**11b** (95.6 mg, 0.44 mmol) in 93% yield.
25-*R*: R_f = 0.25 [1:1 Hexane/EtOAc]; white solid; mp 69–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 7.0 Hz), 1.13 (s, 9H), 1.21-1.29 (m, 8H), 1.50-1.67 (m, 2H), 2.43 (s, 3H), 3.12 (d, 1H, *J* = 5.2 Hz), 4.09-4.14 (m, 1H), 4.42 (d, 1H, *J* = 13.6 Hz), 4.52 (d, 1H, *J* = 14.0 Hz), 7.24-7.31 (m, 7H), 7.75 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.7, 22.5, 22.6, 25.6, 28.8, 31.7, 37.5, 48.4, 55.5, 55.7, 70.6, 78.1, 127.8, 128.3, 128.5, 128.9, 129.7, 134.5, 134.7, 144.6; IR (film) cm^{-1} 2925m, 2857m, 2250w, 1597w, 1456m, 1364m, 1168s; mass spectrum (ESI): m/e (% relative intensity) 503 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{27}H_{39}N_2O_3S_2$ $[M+H]^+$: 503.2397; found 503.2393.

Ynamide **26**-*R* (145.2 mg, 0.45 mmol) were prepared from the corresponding ynamide (52.7 mg, 0.47 mmol) and imine *(S$_s$)*-**11a** (109.1 mg, 0.52 mmol) in ≥95% yield.

26-*R*: R_f = 0.22 [EtOAc]; pale yellow solid; mp 131–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 3.69 (d, 1H, *J* = 4.0 Hz), 3.90-3.94 (m, 2H), 4.41 (t, 2H, *J* = 8.0 Hz), 5.43 (d, 1H, *J* = 4.0 Hz), 7.30-7.39 (m, 3H), 7.54 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 46.8, 51.2, 56.1, 63.2, 69.5, 76.8, 127.8, 128.6, 128.9, 139.0, 156.0; IR (film) cm^{-1} 2979brw, 2924w, 2264m, 1764s, 1477m, 1418m, 1201m; mass spectrum (ESI): m/e (% relative intensity) 321 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{16}H_{21}N_2O_3S$ $[M+H]^+$: 321.1273; found 321.1279.

Ynamide **27**-*R* (24.3 mg, 0.07 mmol) were prepared from the corresponding ynamide (59.3 mg, 0.47 mmol) and imine *(S_s)*-**11a** (109.1 mg, 0.52 mmol) in 15% yield.

27-*R*: R_f = 0.43 [1:1 acetone/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (s, 9H), 2.08-2.13 (m, 2H), 3.64 (d, 1H, *J* = 4.0 Hz), 3.77 (t, 2H, *J* = 6.2 Hz), 4.33 (t, 2H, *J* = 5.4 Hz), 5.43 (d, 1H, *J* = 4.4 Hz), 7.28-7.39 (m, 3H), 7.57 (d, 2H, *J* = 7.2 Hz)**;** ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 22.7, 50.0, 51.3, 56.2, 67.7, 68.1, 81.2, 128.0, 128.6, 128.9, 139.2, 151.8; IR (film) cm^{-1} 2955brw, 2265w, 1721s, 1476m, 1423m, 1278m; mass spectrum (ESI): m/e (% relative intensity) 335 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{17}H_{23}N_2O_3S$ $[M+H]^+$: 335.1424; found 335.1417.

Ynamide **28**-*R* (42.1 mg, 0.12 mmol) were prepared from the corresponding ynamide (52.5 mg, 0.38 mmol) and imine *(S_s)*-**11a** (87.5 mg, 0.42 mmol) in 32% yield.

28-*R*: R_f = 0.54 [acetone]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 9H), 1.99 (pent, 2H, *J* = 5.8 Hz), 2.94 (s, 3H), 3.25 (t, 2H, *J* = 5.8 Hz), 3.63-3.66 (m, 3H), 5.40 (d, 1H, *J* = 4.8 Hz), 7.23-7.34 (m, 3H), 7.55 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 22.7, 36.2, 47.9, 50.2, 51.7, 56.0, 66.6, 83.2, 127.9, 128.2, 128.8, 139.9, 154.0; IR (film) cm^{-1} 2955m, 2257w, 1662s, 1498s, 1441m, 1408m, 1319m, 1207m; mass spectrum (ESI): m/e (% relative intensity) 348 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{18}H_{26}N_3O_2S$ $[M+H]^+$: 348.1741; found 348.1728.

Ynamide **29** (233.2 mg, 0.47 mmol) were prepared from the corresponding ynamide (135.2 mg, 0.47 mmol) and imine *(R_s)*-**11a** (109.1 mg, 0.52 mmol) in ≥95% yield.

29: R_f = 0.30 [1:1 Hexane/EtOAc]; colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (s, 9H), 2.41 (s, 3H), 3.35 (d, 1H, *J* = 4.0 Hz), 4.45 (d, 1H, *J* = 13.5 Hz), 4.54 (d, 1H, *J* = 14.0 Hz), 5.29 (d, 1H, *J* = 4.0 Hz), 7.24-7.29 (m, 12H), 7.70 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 22.5, 51.4, 55.4, 55.9, 69.7, 80.1, 127.7, 127.8, 128.4, 128.5, 128.6, 128.8, 129.0, 129.8, 134.4, 134.6, 139.1, 144.7; IR (film) cm^{-1} 2250m, 1598w, 1494w, 1455m, 1363s, 1167s; mass spectrum (ESI): m/e (% relative intensity) 495 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{27}H_{31}N_2O_3S_2$ $[M+H]^+$: 495.1771; found 495.1756.

Ynamide **30**-*R* (188.0 mg, 0.47 mmol) were prepared from the corresponding ynamide (88.7 mg, 0.47 mmol) and imine *(S$_s$)*-**11a** (109.1 mg, 0.52 mmol) in ≥95% yield.

30-*R*: R_f = 0.49 [1:1 CH_2Cl_2/EtOAc]; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 3.40 (d, 1H, *J* = 4.4 Hz), 4.24 (dd, 1H, *J* = 7.2, 8.8 Hz), 4.72 (t, 1H, *J* = 8.8 Hz), 5.06 (t, 1H, *J* = 7.8 Hz), 5.27 (d, 1H, *J* = 4.0 Hz), 7.25-7.30 (m, 5H), 7.35-7.37 (m, 2H), 7.43-7.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 51.3, 55.9, 62.0, 70.8, 71.1, 75.6, 127.1, 127.6, 128.5, 128.8, 129.4, 129.6, 136.0, 139.0, 155.5; IR (film) cm^{-1} 2267m, 1773s, 1475m, 1457m, 1409m, 1181m; mass spectrum (ESI): m/e (% relative intensity) 397 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{22}H_{25}N_2O_3S$ $[M+H]^+$: 397.1581; found 397.1580.

Ynamide **31** (183.9 mg, 0.46 mmol) were prepared from the corresponding ynamide (88.7 mg, 0.47 mmol) and imine *(S$_s$)*-**11a** (109.1 mg, 0.52 mmol) in ≥95% yield.

31: R_f = 0.26 [1:1 CH_2Cl_2/EtOAc]; white solid; mp 150–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 3.48 (d, 1H, *J* = 4.4 Hz), 4.27 (dd, 1H, *J* = 7.2, 9.2 Hz), 4.74 (t, 1H, *J* = 9.0 Hz), 5.10 (dd, 1H, *J* = 7.2, 8.8 Hz), 5.29 (d, 1H, *J* = 4.4 Hz), 7.23-7.24 (m, 5H), 7.37-7.39 (m, 2H), 7.44-7.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 51.4, 55.9, 62.0, 70.8, 71.3, 75.7, 127.3, 127.7, 128.4, 128.7, 129.4, 129.6, 136.1, 138.6, 155.5; IR (film) cm-1 2267m, 1773s, 1457m, 1406m, 1182m; mass spectrum (APCI): m/e (% relative intensity) 397 (42) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{22}H_{25}N_2O_3S$ $[M+H]^+$: 397.1581; found 397.1598.

General Procedure for Acid Promoted 5-*endo*-*dig* Cyclization.

To a vial were added ynamide **30**-*R* (113.2 mg, 0.29 mmol), THF (0.50 mL), H_2O (0.050 mL), and HOAc (0.050 mL). The vial was sealed and heated to 85 ^{o}C. When the reaction was judged to be complete by TLC after 14.5 h, the mixture was cooled to rt and concentrated under reduced pressure. The crude residue was purified using silica gel flash column chromatography [Two isocratic eluent: (a) 4:1 Hexane/EtOAc and then (b) 1:1 Acetone/EtOAc] to afford **32** (23.0 mg, 0.07 mmol) in 25% yield and **33** (29.7 mg, 0.09 mmol) in 31% yield.

32: R_f = 0.23 [3:1 Hexane/EtOAc]; white solid; mp 207-208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (dd, 1H, *J* = 5.6, 8.8 Hz), 4.95 (t, 1H, *J* = 9.0 Hz), 5.36 (dd, 1H, *J* = 5.6, 9.2 Hz), 6.59 (s, 1H), 7.33-7.46 (m, 8H), 7.67-7.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.4, 71.8, 106.2, 126.4, 126.7, 128.8, 129.3, 129.9, 130.0, 134.8, 136.7, 155.3, 160.8, 164.7; IR (film) cm^{-1} 1745s, 1539m, 1389m, 1208m; mass spectrum (ESI): m/e (% relative intensity) 323 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{18}H_{15}N_2O_2S$ $[M+H]^+$: 323.0849; found 323.0854.

33: R_f = 0.11 [1:1 CH_2Cl_2/EtOAc]; white solid; mp 198-199 °C. ^{1}H NMR (500 MHz, DMSO) δ 3.30 (dd, 1H, *J* = 3.5, 8.5 Hz), 3.95 (t, 1H, *J* = 9.0 Hz), 4.41 (dd, 1H, *J* = 3.5, 8.5 Hz), 4.51 (s, 1H), 4.63 (s, 1H), 5.95-5.97 (m, 2H), 6.25-6.45 (m, 8H); ^{13}C NMR (100 MHz, DMSO) δ 60.8, 67.0, 71.2, 117.5, 126.4, 127.3, 128.2, 128.6, 128.8, 129.3, 138.1, 138.6, 144.8, 154.0; IR (film) cm^{-1} 2959w, 2927w, 1768m, 1714s, 1645m, 1402m, 1187m; mass spectrum (ESI): m/e (% relative intensity) 341 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{18}H_{17}N_2O_3S$ $[M+H]^+$: 341.0955; found 341.0954.

34: R_f = 0.14 [1:1 Hexane/EtOAc]; white solid; mp 159-160 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 (dd, 1H, *J* = 6.5, 8.5 Hz), 4.64 (s, 1H), 4.83 (t, 1H, *J* = 8.7 Hz), 5.35 (dd, 1H, *J* = 6.5, 9.0 Hz), 5.69 (s, 1H), 5.91 (d, 1H, *J* = 1.0 Hz), 7.10-7.12 (m, 2H), 7.24-7.46 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 60.1, 69.3, 71.0, 118.6, 126.6, 127.3, 129.1, 129.2, 129.6, 129.8, 136.4, 137.8, 143.6, 154.9; IR (film) cm^{-1} 2926w, 1745s, 1462m, 1373m, 1241s; mass spectrum (ESI): m/e (% relative intensity) 341 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{18}H_{17}N_2O_3S$ $[M+H]^+$: 341.0955; found 341.0946.

35: R_f = 0.70 [1:1 CH_2Cl_2/EtOAc]; white solid; 180 °C (decomposed). ^{1}H NMR (500 MHz, DMSO) δ 3.37 (t, 2H, *J* = 8.0 Hz), 3.83 (t, 2H, *J* = 8.0 Hz), 6.61-6.68 (m, 4H), 7.20 (d, 2H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, DMSO) δ 45.4, 64.2, 105.8, 126.5, 128.8, 129.3, 134.3, 155.3, 161.5, 164.0; IR (film) cm^{-1} 2918brm, 1740s, 1542w, 1373m, 1240s; mass spectrum (ESI): m/e (% relative intensity) 247 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{12}H_{11}N_2O_2S$ $[M+H]^+$: 247.0536; found 247.0529.

36: R_f = 0.13 [1:1 CH_2Cl_2/EtOAc]; white solid; mp 190-191 °C. ^{1}H NMR (400 MHz, DMSO) δ 2.99 (dd, 1H, *J* = 7.6, 16.8 Hz), 3.18 (dd, 1H, *J* = 8.8, 17.6 Hz), 3.67 (t, 2H, *J* = 8.0 Hz), 4.93 (t, 1H, *J* = 1.6 Hz), 5.22 (dd, 1H, *J* = 1.2, 2.0 Hz), 6.43-6.56 (m, 5H); ^{13}C NMR (100 MHz, DMSO) δ 45.3, 63.0, 67.1(d, *J* = 1.5 Hz), 115.7 (d, *J* = 7.6 Hz), 127.3, 128.1, 128.6, 139.0, 145.0, 154.0; IR (film) cm^{-1} 2984w, 2916w, 1739s, 1373m, 1239s, 1046m; mass spectrum (ESI): m/e (% relative intensity) 265 (100) $(M+H)^+$; HRMS (ESI): *m/z* calcd for $C_{12}H_{13}N_2O_3S$ $[M+H]^+$: 265.0642; found 265.0653.

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