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A Highly Stereoselective Addition of Lithiated Ynamides to Ellman–Davis Chiral *N*-tert-Butanesulfinyl Imines

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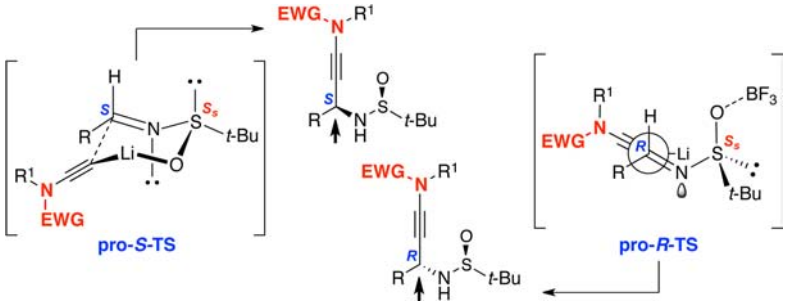
ABSTRACT



A highly diastereoselective addition of lithiated ynamides to Ellman–Davis chiral imines is described. While additions of *N*-sulfonyl ynamides are highly stereoselective even without Lewis acids, the use of BF_3–OEt_2 completely reversed the stereoselectivity. In addition, oxazolidinone-substituted ynamides behaved differently and functioned better with BF_3–OEt_2, and the chirality of the oxazolidinone ring exerts no impact on the selectivity.

The chemistry of ynamides has evolved into a burgeoning field that is attracting an immense amount of attention from the synthetic community.[1,2] Although new transformations involving ynamides have appeared in the literature at a rapid pace,[3] new and improved protocols for synthesizing ynamides,[4,5] and more provocatively, structural relatives of ynamides[6] have also been continuously reported in recent years. To continue developing useful methods for constructing *N*-heterocycles, we have been exploring *N*-tethered intramolecular transformations through usage of γ-amino-ynamides such as **1** [Scheme 1].[7]

(1) For current leading reviews on ynamides, see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840.

(2) For reviews partially accounting the chemistry of ynamides, see: (a) Ackermann, L.; Potukuchi, H. K. *Org. Biomol. Chem.* **2010**, *8*, 4503. (b) Domínguez, G.; Perez-Castells, J. *Chem. Soc. Rev.* **2011**, *40*, 3430. (c) Weding, N.; Hapke, M. *Chem. Soc. Rev.* **2011**, *40*, 4525. (d) Madelaine, C.; Valerio, V.; Maulide, N. *Chem.—Asian J.* **2011**, *6*, 2224.

(3) Given the volume, for ynamide chemistry published since September of 2012, see: (a) Karmakar, R.; Mamidipalli, P.; Yun, S. Y.; Lee, D. *Org. Lett.* **2013**, *15*, 1938. (b) Brioche, J.; Meyer, C.; Cossy, J. *Org. Lett.* **2013**, *15*, 1626. (c) Yun, S. Y.; Wang, K.-P.; Lee, N.-K.; Mamidipalli, P.; Lee, D. *J. Am. Chem. Soc.* **2013**, *135*, 4668. (d) Heffernan, S. J.; Beddoes, J. M.; Mahon, M. F.; Hennessy, A. J.; Carbery, D. R. *Chem. Commun.* **2013**, *49*, 2314. (e) Kong, Y.; Jiang, K.; Cao, J.; Fu, L.; Yu, L.; Lai, G.; Cui, Y.; Hu, Z.; Wang, G. *Org. Lett.* **2013**, *15*, 422. (f) Yavari, I.; Nematpour, M.; Sodagar, E. *Synlett* **2013**, *24*, 161. (g) Yavari, I.; Nematpour, M. *Synlett* **2013**, *24*, 165. (h) Bhunia, S.; Chang, C.-J.; Liu, R.-S. *Org. Lett.* **2012**, *14*, 5522. (i) Minko, Y.; Pasco, M.; Lercher, L.; Botoshansky, M.; Marek, I. *Nature* **2012**, *490*, 522. (j) Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208. (k) Cao, J.; Kong, Y.; Deng, Y.; Lai, G.; Cui, Y.; Hu, Z.; Wang, G. *Org. Biomol. Chem.* **2012**, *10*, 9556. (l) Greenaway, R. L.; Campbell, C. D.; Chapman, H. A.; Anderson, E. A. *Adv. Synth. Catal.* **2012**, *354*, 3187. (m) Jiang, Z.; Lu, P.; Wang, Y. *Org. Lett.* **2012**, *14*, 6266. (n) Gati, W.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Beilstein J. Org. Chem.* **2012**, *8*, 2214. (o) Smith, D. L.; Chidipudi, S. R.; Goundry, W. R.; Lam, H. W. *Org. Lett.* **2012**, *14*, 4934. (p) Heffernan, S. J.; Carbery, D. R. *Tetrahedron Lett.* **2012**, *53*, 5180.

(4) For reviews on syntheses of ynamides, see: (a) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (b) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, *43*, 973. (c) Tracey, M. R.; Hsung, R. P.; Antoline, J. A.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Weinreb, S. M., Ed.; Georg Thieme Verlag KG: Stuttgart, Germany, 2005; Chapter 21.4. (d) Evano, G.; Blanchard, N.; Mathieu Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (e) Evano, G.; Jouvinb, K.; Coste, A. *Synthesis* **2013**, 17.

(5) For syntheses of ynamides published in 2012, see: (a) Jin, X.; Yamaguchi, K.; Mizuno, N. *Chem. Lett.* **2012**, *41*, 866. (b) Jin, X.; Yamaguchi, K.; Mizuno, N. *Chem. Commun.* **2012**, *48*, 4974. (c) Jouvin, K.; Heimburger, J.; Evano, G. *Chem. Sci.* **2012**, *3*, 756. (d) Jouvin, K.; Coste, A.; Bayle, A.; Legrand, F.; Karthikeyan, G.; Tadiparthi, K.; Evano, G. *Organometallics* **2012**, *31*, 7933. (e) Tong, X.; Ni, G.; Deng, X.; Xia, C. *Synlett* **2012**, *23*, 2497. (f) Wang, M.-G.; Wu, J.; Shang, Z.-C. *Synlett* **2012**, *23*, 589. (g) Laouiti, A.; Jouvin, K.; Bourdreux, F.; Rammah, M. M.; Rammah, M. B.; Evano, G. *Synthesis* **2012**, *44*, 1491.

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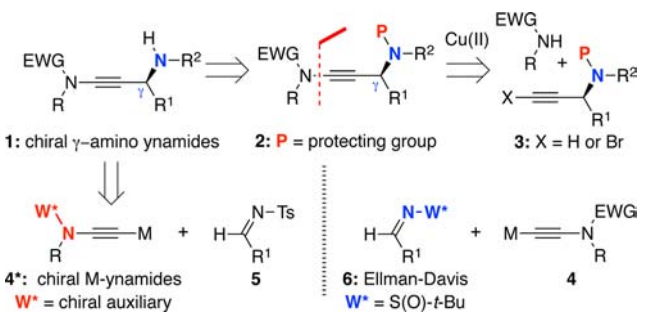
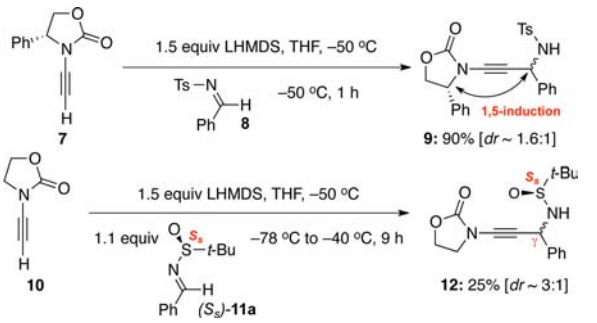
Scheme 1. Approaches to Chiral γ-Amino-Ynamides



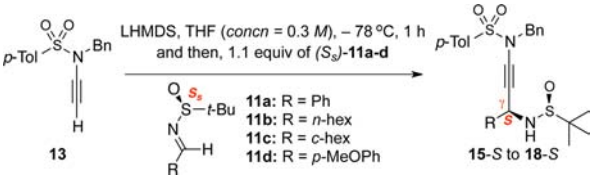
We recognized that the Cu-catalyzed protocol[1,2,4] may actually not be the most attractive approach because it would require (a) optically enriched propargyl amines **3**, which are not always readily available, and (b) a deprotection protocol that may not be compatible with ynamides **2** in addition to being tedious.[8] Yet, with *N*-protected propargyl amines **5**, the most direct access would be an addition of metalated chiral ynamide **4*** to achiral imines **5**, which would constitute a long-range stereochemical induction. The more practical approach may be adding metalated ynamides **4** to chiral imines such as Ellman–Davis chiral *N*-*tert*-butanesulfinyl imines **6**.[9,10] Metalated ynamides have been added to a number of electrophiles,[11] but to the best of our knowledge, additions to chiral imines have not been reported.[1,12,13] This method would be ideal for constructing new chiral ynamides. We wish to report here a highly stereoselective synthesis of chiral γ-amino-ynamides via the addition of lithiated ynamides to Ellman–Davis chiral imines.

Scheme 2. Initial Assessment of The Two Approaches



We quickly established that although synthetically feasible, additions to imines using lithiated ynamides such as **7**, which is substituted with an Evans chiral oxazolidinone auxiliary, provided no significant diastereoselectivity in γ-amino-ynamide **9** [Scheme 2].[14] This effectively ends the speculation of a possible 1,5-asymmetric induction. Yet, for additions to Ellman–Davis chiral imine **11a** using achiral ynamides such as **10**, the selectivity was actually promising, although the yield was not impressive.

Table 1. A Temperature Effect on Stereoselectivity



entry	R=	temp [°C]	additive [equiv]	time [h]	product	yield[a]	*dr* [S:R][b]
1	Ph	– 78	–	15	**15**-*S*	63	7:1
2	Ph	– 78 to –50	–	15	**15**-*S*	60	11:1
3	Ph	– 78 to –40	–	15	**15**-*S*	67	21:1
4	Ph	– 78 to –40	–	9	**15**-*S*	69	25:1
5	Ph	– 78 to rt	–	15	**15**-*S*	35	≥25:1
6	Ph	– 78 to –40	TMEDA [0.25]	9	**15**-*S*	94	18:1
7	Ph	– 78 to –40	TMEDA [1.0]	9	**15**-*S*	≥95	20:1
8	*n*-hex	– 78 to –40	–	9	**16**-*S*	68	20:1
9	*c*-hex	– 78 to –40	–	9	**17**-*S*	77	20:1
10	*p*-MeOPh	– 78 to –40	–	9	**18**-*S*	63	≥25:1

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

(6) For syntheses of novel structural analogs of ynamides, see: (a) Yne-Sulfoxyimines: Wang, L.; Huang, H.; Priebbenow, D. L.; Pan, F.-F.; Bolm, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 3478. (b) Yne-hydrazides: Beveridge, R. E.; Batey, R. A. *Org. Lett.* **2012**, *14*, 540. (c) Yne-imines: Laouiti, A.; Rammah, M. M.; Rammah, M. B.; Marrot, J.; Couty, F.; Evano, G. *Org. Lett.* **2012**, *14*, 6. (d) Ynimides: Souto, J. A.; Becker, P.; Iglesias, A.; Muñiz, K. *J. Am. Chem. Soc.* **2012**, *134*, 15505. (e) Ynimides: Sueda, T.; Oshima, A.; Teno, N. *Org. Lett.* **2011**, *13*, 3996. (f) Ynimides: Sueda, T.; Kawada, A.; Urashi, Y.; Teno, N. *Org. Lett.* **2013**, *15*, 1560. (g) Diamino-acetylenes: Petrov, A. R.; Daniliuc, C. G.; Jones, P. G.; Tamm, M. *Chem.—Eur. J.* **2010**, *16*, 11804. (h) Amidinyl-ynamides: Li, J.; Neuville, L. *Org. Lett.* **2013**, *15*, 1752.

(7) DeKorver, K. A.; Hsung, R. P.; Song, W.-Z.; Walton, M. C.; Wang, X.-N. *Org. Lett.* **2012**, *14*, 3214.

(8) For an example of coupling using unprotected secondary propargylic amines, see: Hashmi, A. S. K.; Schuster, A. M.; Zimmer, M.; Rominger, F. *Chem.—Eur. J.* **2011**, *17*, 5511.

(9) For reviews, see: (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600. (b) Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162. (c) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831. (d) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (e) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (f) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (g) Sorochinsky, A. E.; Soloshonok, V. A. *J. Fluorine Chem.* **2010**, *131*, 127.

(10) Given the volume on additions to Ellamn–Davis chiral imines, for leading examples using metallated acetylides, see: (a) Wang, B.; Zhang, P.-P. *Tetrahedron Lett.* **2012**, *53*, 119. (b) Ye, L.; He, W.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3236. (c) Chen, B.-L.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2009**, *75*, 941. (d) Hodgson, D. M.; Kloesges, J.; Evans, B. *Synthesis* **2009**, 1923. (e) aHarried, S. S.; Croghan, M. D.; Kaller, M. R.; Lopez, P.; Zhong, W.; Hungate, R.; Reider, P. J. *J. Org. Chem.* **2009**, *74*, 5975. (f) Voituriez, A.; Pérez-Luna, A.; Ferreira, F.; Botuha, C.; Chemla, F. *Org. Lett.* **2009**, *11*, 931. (g) Chen, X.-Y.; Qiu, X.-L.; Qing, F.-L. *Tetrahedron* **2008**, *64*, 2301. (h) Turcaud, S.; Berhal, F.; Royer, J. *J. Org. Chem.* **2007**, *72*, 7893. (i) Patterson, A. W.; Ellman, J. A. *J. Org. Chem.* **2006**, *71*, 7110. (j) Davis, F. A.; Nolt, M. B.; Wu, Y.; Prasad, K. R.; Li, D.; Yang, B.; Bowen, K.; Lee, S. H.; Eardley, J. H. *J. Org. Chem.* **2005**, *70*, 2184. (k) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051. (l) Shaw, A. W.; deSolms, S. J. *Tetrahedron Lett.* **2001**, *42*, 7173. (m) Tang, T. P.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772.

(11) (a) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368. (b) Rodriguez, D.; Martinez-Esperon, M. F.; Castedo, L.; Saá, C. *Synlett* **2007**, 1963. (c) Yne-hydrazides: Beveridge, R. E.; Batey, R. A. *Org. Lett.* **2012**, *14*, 540.

Subsequently, we observed that *N*-sulfonyl-substituted ynamides appear to work better in this asymmetric addition. Addition of lithiated ynamide **13** to **11a** at −78 °C afforded **15** with a *dr* of 7:1 in favor of the (*S*)-isomer [entry 1, Table 1]. There appears to be a noticeable temperature effect; when the same addition was carried out at −50 °C [entry 2] or −40 °C [entries 3 and 4], the selectivity improved significantly. Although the selectivity was the highest when the reaction was run at rt, the yield suffered [entry 5]. An additive such as TMEDA enhanced the yield, but at the expense of diastereoselectivity [entries 6 and 7]. The generality of this asymmetric addition can be revealed through the use of chiral imines (S_s)-**11c**−**d** [entries 8−10]. The (*S*) stereochemistry was confirmed using the single crystal X-ray structure of **15**-*S* [Figure 1].

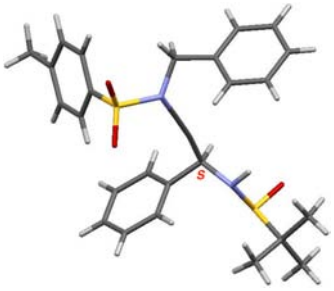
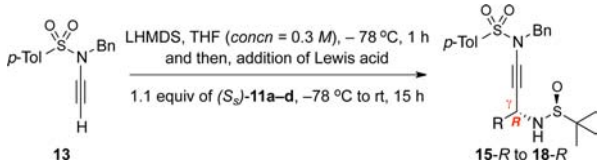


Figure 1. X-ray structure of **15**-*S*.

Table 2. Reversal of Stereoselectivity Using BF_3−OEt_2



entry	R=	Lewis acid [equiv]	product	yield[a]	*dr* [*S*:*R*][b]
1	Ph	BF_3-OEt_2 [0.25]	**15**-*R*/*S*	66	1:1
2	Ph	BF_3-OEt_2 [0.50]	**15**-*R*/*S*	78	1:1.5
3	Ph	BF_3-OEt_2 [1.2]	**15**-*R*	≥95	≤1:25
4	Ph	BF_3-OEt_2 [2.0]	**15**-*R*	≥95	≤1:25
5	Ph	$AlCl_3$ [1.2]	**15**-*S*	11	2:1
6	Ph	$AlMe_2Cl$ [1.2]	**15**-*S*	41	≥25:1
7	Ph	$LiClO_4$ [1.2]	**15**-*S*	30	≥25:1
8	Ph	$TiCl_4$ [1.2]	**15**-*R*	0	–
9	Ph	$SnCl_4$ [1.2]	**15**-*R*	0	–
10	Ph	Ti (i-PrO)$_2Cl_2$ [1.2]	**15**-*S*	26	4:1
11	Ph	$Zn(OTf)_2$ [1.2]	**15**-*S*	35	≥25:1
12	Ph	$Cu(OTf)_2$ [1.2]	**15**-*R*	0	–
13	*n*-hex	BF_3-OEt_2 [1.2]	**16**-*R*	93	≤1:25
14	*c*-hex	BF_3-OEt_2 [1.2]	**17**-*R*	90	≤1:25
15	*p*-MeOPh	BF_3-OEt_2 [1.2]	**18**-*R*	≥95	≤1:25

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

The success in achieving a high level of diastereoselectivity led us to examine the effects of Lewis acids, and we found a complete reversal of stereoselectivity when using 1.2 to 2.0 equiv of BF_3−OEt_2 [entries 3 and 4, Table 2].[15] The extent of reversal appears to depend on the amount of BF_3−OEt_2 used [entries 14]. This phenomenon appears to be unique with BF_3−OEt_2, as not all monodentate Lewis acids would present such a reversal [entries 5−7]. Yet, bidentate Lewis acids were poor promoters overall [entries 7−12] with $TiCl_4$, $SnCl_4$, and $Cu(OTf)_2$ appearing to impede the reaction [entries 7, 8, and 12]. Again, chiral γ-amino-ynamides **16**-*R*−**18**-*R* could be obtained through additions to (S_s)-**11c**−**d** in the presence of BF_3−OEt_2 [entries 13−15].

A rationale of this stereochemical switch is shown in Figure 2. The *S*-selectivity in the absence of a Lewis acid is likely derived from a Zimmerman−Traxler type chelated transition state. Yet, a synclinal or antiperiplanar approach takes place with BF_3−OEt_2 coordinating to the sulfinyl O-atom, 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]

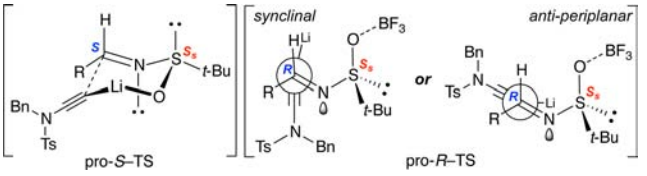


Figure 2. Chelation-TS versus open-TS.

Consequently, variations on the sulfonamide substitutions were examined, and we found an interesting effect on the selectivity. Most notably, the *para*-nitro substituent eroded the selectivity significantly in the absence of BF_3−OEt_2 [see **20**-*S* in Figure 3]. This loss of selectivity is likely due to the nitro group competing for the Li-chelation in the pro-*S*−*TS*, thereby suggesting that the sulfonamido group can impact the selectivity. This phenomenon also

(12) For an elegant account on additions of lithiated ynol-ethers to Ellman−Davis chiral imines, see: Verrier, C.; Carret, S.; Poisson, J.-F. *Org. Lett.* **2012**, *14*, 5122.

(13) For additions of lithiated ynol-ethers to imines, see: (a) Mak, X. Y.; Ciccolini, R. P.; Robinson, J. M.; Tester, J. W.; Danheiser, R. L. *J. Org. Chem.* **2009**, *74*, 9381. (b) Hashmi, A. S. K.; Rudolph, M.; Huck, J.; Frey, W.; Bats, J. W.; Hamzic, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5848.

(14) See Supporting Information.

(15) For leading examples of related reversals of stereoselectivity, see: (a) Louvel, J.; Chemla, F.; Demont, E.; Ferreira, F.; Pérez-Luna, A.; Voituriez, A. *Adv. Synth. Catal.* **2011**, *353*, 2137. (b) Viso, A.; Fernández de la Pradilla, R.; Flores, A.; García, A.; Tortosa, M.; López-Rodríguez, M. L. *J. Org. Chem.* **2006**, *71*, 1442. (c) Jiang, W.; Chen, C.; Marinkovic, D.; Tran, J. A.; Chen, C. W.; Arellano, L. M.; White, N. S.; Tucci, F. C. *J. Org. Chem.* **2005**, *70*, 8924. (d) Kuduk, S. D.; DiPardo, R. M.; Chang, R. K.; Ng, C.; Bock, M. G. *Tetrahedron Lett.* **2004**, *45*, 6641. (e) Also see ref 13.

occurred when the R substituent is a Ph group as shown in **22-*S***. Yet, a complete reversal of stereochemistry took place when using $BF_3{-}OEt_2$ regardless of sulfonamide substitutions.

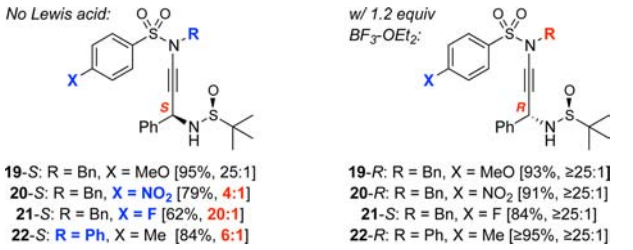
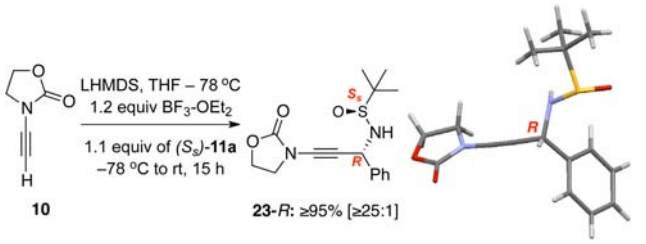


Figure 3. Effects of the sulfonyl substitutions. Isolated yields reported. Ratios determined by ^1H and/or ^{13}C NMR.

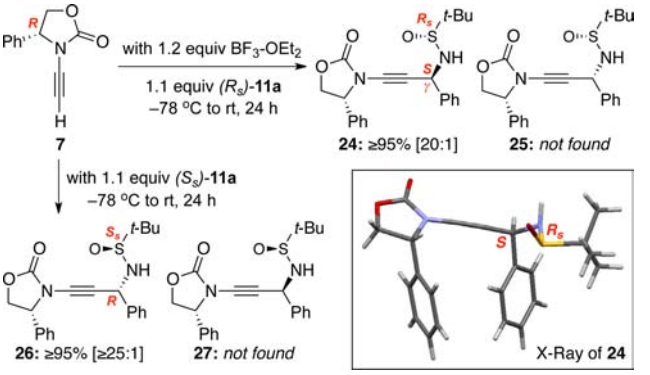
Success with these *N*-sulfonyl-substituted ynamides prompted us to return to oxazolidinone-substituted ynamides that were found to be unsuccessful earlier. Both selectivity and efficiency could be rescued through the use of 1.2 equiv $BF_3{-}OEt_2$ and gave the desired addition product **23-*R*** in quantitative yield [Scheme 3]. The X-ray structure of **23-*R*** confirms that the stereochemical outcome is the same as those from using *N*-sulfonyl ynamides.

Scheme 3. Reexamining the Addition of Ynamide **10**



When using chiral ynamide **7**, we anticipated a potential matched and mismatched scenario. However, as shown in Scheme 4, the addition of lithiated **7** to either (R_s)-**11a** or (S_s)-**11a** led to their respective addition products **24** and **26** in good yield and high diastereoselectivity. While the relative stereochemistry at the γ-C of **24** was unambiguously assigned based on its X-ray structure, **26** was assigned through its derivative obtained via an unusual 5-*endo-dig* *S*-cyclization.[16] These reactions suggest that the chirality on the oxazolidinone ring does not play a role in the asymmetric induction. It is noteworthy that **24** and **26** represent *de novo* ynamides that are rich in chirality.

Scheme 4. Matching–Mismatching with Chiral Ynamide **7**



We have described here a highly diastereoselective addition of lithiated ynamides to Ellman–Davis chiral *N-tert*-butanesulfinyl imines that expands synthetic tools for constructing chiral ynamides. Our work demonstrates that additions of *N*-sulfonyl ynamides are highly stereoselective even without Lewis acids, although the use of $BF_3{-}OEt_2$ could alter the stereochemical outcome. Additions of oxazolidinone-substituted ynamides appear to require $BF_3{-}OEt_2$, but the chirality on the oxazolidinone ring does not impact the selectivity. Applications of these *de novo* chiral γ-amino-ynamides in developing new synthetic transformations are currently underway.

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Supporting Information Available. Experimental procedures, X-ray data, and NMR spectra and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(16) An acid promoted 5-*endo-dig* cyclization concomitant with the loss of the *t*-Bu group led to isothiazole **i** and 2,3-dihydro-isothiazole *S*-oxide **ii** in 25% and 31% yield, respectively. The single crystal X-ray structure of **ii** provided the stereochemical assignment of **26** (S_s,*R*) and confirmed that an inversion at the "S" center had taken place in **ii**.