Published in final edited form as:

Org Lett. 2013 May 17; 15(10): 2514–2517. doi:10.1021/ol400989x.

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 $\text{BF}_3\text{-OEt}_2$ completely reversed the stereoselectivity. In addition, oxazolidinone-substituted ynamides behaved differently and functioned better with $\text{BF}_3\text{-OEt}_2$, and the chirality of the oxazolidinone ring exerts no impact on the selectivity.

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 ynamides⁶ 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 the usage of γ -amino-ynamides such as **1** [see Scheme 1].⁷ We recognized that copper-catalyzed protocols^{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 On the other hand, with *N*-protected propargyl amines **5**, the most direct access would be an addition of metallated chiral ynamide **4*** to achiral imines **5**, which would constitute a long-range stereochemical induction. The more practical approach may be adding metallated ynamides **4** to chiral imines such as Ellman–Davis chiral *N*-*tert*-butanesulfinyl imines **6**.^{9,10} Metallated 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.

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Supporting Information Available: Experimental procedures, X-ray data as well as NMR spectra and characterizations are available for all new compounds and free of charge via Internet <http://pubs.acs.org>.

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. On the other hand, additions to Ellman-Davis chiral imine **11a** using achiral ynamides such as **10**, the selectivity was actually promising, although the yield was not impressive.

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, as the same addition, when carried out at -50 °C [entry 2] or -40 °C [entries 3 and 4], the selectivity improved significantly. Although the selectivity was at the highest when reaction was run at rt, the yield suffered [entry 5]. Additive such as TMEDA enhanced the yield but at the expensive 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 single crystal X-ray structure of **15-S** [Figure 1].

The success in achieving a high level of diastereoselectivity led us to examine effects of Lewis acids and we found a complete reversal of stereoselectivity when using 1.2 to 2.0 equiv of BF₃·OEt₂ [entries 3 and 4 in Table 2].¹⁵ The extent of reversal appears to depend on the amount of BF₃·OEt₂ used [entries 14]. This phenomenon appears to be unique with BF₃·OEt₂, as not all mono-dentate Lewis acids would present such reversal [entries 5-7]. On the other hand, bi-dentate Lewis acids were poor promoter overall [entries 7-12] with TiCl₄, SnCl₄, 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 BF₃·OEt₂ [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. On the other hand, a synclinal or anti-periplanar approach takes place with BF₃·OEt₂ coordinating to the sulfinyl oxygen atom, thereby effectively breaking up the chelation especially when using 1.0 equiv. It has been suggested that other Lewis acids such as AlMe₂Cl could coordinate to the imino lone pair, and thus, are not effective in deterring the pro-*S*-TS.⁹

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 BF₃·OEt₂ [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 on the selectivity. This phenomenon also occurred when the R substituent is a Ph group as shown in **22-S**. On the other hand, a complete reversal of stereochemistry took place when using BF₃·OEt₂ regardless of sulfonamide substitutions.

Success with these *N*-sulfonyl-substituted ynamides prompted us to return to oxazolidinone-substituted ynamides that were found unsuccessful earlier. Both selectivity and efficiency could be rescued through the use of 1.2 equiv BF₃·OEt₂ and gave the desired addition product **23-R** in quantitative yield [Scheme 3]. X-Ray structure of **23-R** confirms that the stereochemical outcome is the same as those from using *N*-sulfonyl ynamides.

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 -carbon 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 both **24** and **26** represent *de novo* ynamides that are rich in chirality.

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 BF₃·OEt₂ could alter the stereochemical outcome. Additions of oxazolidinone-substituted ynamides appear to require BF₃·OEt₂, but 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank NIH [GM066055] for funding and thank Dr. Victor Young of The University of Minnesota for providing X-ray structural data.

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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. Single crystal X-ray structure of **ii** provided stereochemical assignment of **26** (*S_s*,*R*) and confirmed that an inversion at the “S” center had taken place in **ii**.

Scheme 1.
Approaches to Chiral γ -Amino-Ynamides.

Scheme 2.
Initial Assessment of The Two Approaches.

Figure 1.
X-Ray Structure of **15-S**.

Figure 2.
Chelation-TS Versus Open-TS.

Figure 3. Effects of the Sulfonyl Substitutions.^{a,b}**a.** Isolated Yields. **b.** Ratios determined by ¹H and/or ¹³C NMR.

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

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

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

The designation of (S) or (R) refers to the stereochemistry at the gamma carbon in the product.

^a Isolated Yields.^b Ratios determined by ¹H and/or ¹³C NMR.

Table 2

Reversal of Stereoselectivity Using $\text{BF}_3\text{-OEt}_2$.

$ \begin{array}{c} \text{O}=\text{O} \\ \diagup \quad \diagdown \\ \text{p-Tol}-\text{N}-\text{Bn} \\ \text{S} \\ \text{ } \\ \text{H} \end{array} \xrightarrow[\text{and then, addition of Lewis acid}]{\text{LHMDS, THF (concn} = 0.3 \text{ M), } -78^\circ\text{C, 1 h}} \begin{array}{c} \text{O}=\text{O} \\ \diagup \quad \diagdown \\ \text{p-Tol}-\text{N}-\text{Bn} \\ \text{S} \\ \text{ } \\ \text{R} \end{array} \xrightarrow{\text{1.1 equiv of (S}_s\text{)-11a-d, } -78^\circ\text{C to rt, 15 h}} \begin{array}{c} \text{O} \\ \diagup \\ \text{R}-\text{C} \\ \diagdown \\ \text{H} \end{array} \begin{array}{c} \text{O} \\ \diagup \\ \text{N}-\text{Bn} \\ \diagdown \\ \text{S} \\ \text{ } \\ \text{H} \end{array} \begin{array}{c} \text{15-R to 18-R} \end{array} $					
entry	R =	Lewis Acid [equiv]	product	yield ^a	dr [S:R] ^b
1	Ph	$\text{BF}_3\text{-OEt}_2$ [0.25]	15- <i>R/S</i>	66	1:1
2	Ph	$\text{BF}_3\text{-OEt}_2$ [0.50]	15- <i>R/S</i>	78	1:1.5
3	Ph	$\text{BF}_3\text{-OEt}_2$ [1.2]	15- <i>R</i>	95	1:25
4	Ph	$\text{BF}_3\text{-OEt}_2$ [2.0]	15- <i>R</i>	95	1:25
5	Ph	AlCl_3 [1.2]	15- <i>S</i>	11	2:1
6	Ph	AlMe_2Cl [1.2]	15- <i>S</i>	41	25:1
7	Ph	LiClO_4 [1.2]	15- <i>S</i>	30	25:1
8	Ph	TiCl_4 [1.2]	15- <i>R</i>	0	--
9	Ph	SnCl_4 [1.2]	15- <i>R</i>	0	--
10	Ph	$\text{Ti}(\text{i-PrO})_2\text{Cl}_2$ [1.2]	15- <i>S</i>	26	4:1
11	Ph	$\text{Zn}(\text{OTf})_2$ [1.2]	15- <i>S</i>	35	25:1
12	Ph	$\text{Cu}(\text{OTf})_2$ [1.2]	15- <i>R</i>	0	--
13	<i>n</i> -hex	$\text{BF}_3\text{-OEt}_2$ [1.2]	16- <i>R</i>	93	1:25
14	<i>c</i> -hex	$\text{BF}_3\text{-OEt}_2$ [1.2]	17- <i>R</i>	90	1:25
15	<i>p</i> -MeOPh	$\text{BF}_3\text{-OEt}_2$ [1.2]	18- <i>R</i>	95	1:25

^a Isolated Yields.

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