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# Highly Stereoselective Saucy–Marbet Rearrangement Using Chiral Ynamides. Synthesis of Highly Substituted Chiral Homoallenyl Alcohols

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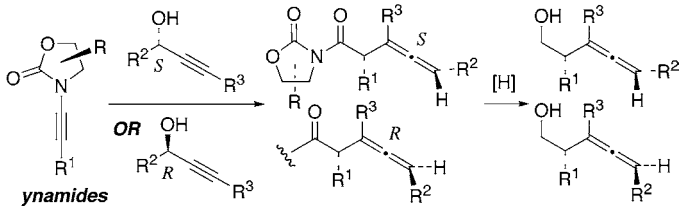
## ABSTRACT




**A highly stereoselective Saucy–Marbet rearrangement using chiral ynamides and propargyl alcohols is described here. This rearrangement can be catalyzed by *para*-nitrobenzenesulfonic acid leading to high diastereoselectivities for a range of different chiral propargyl alcohols and ynamides in a stereochemically intriguing matched, mismatched, or indifferent manner. This provides an excellent entry to highly substituted chiral homoallenyl alcohols.**

Ynamides are becoming attractive building blocks in organic synthesis.[1−15] We have been investigating reactivities of ynamides[12−15] and have demonstrated that chiral ynamides are useful in a stereoselective Ficini−Eschenmoser−Claisen rearrangement.[13,16] Given the power of the [3,3]-sigmatropic rearrangement in organic synthesis,[17] we explored the utility

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[‡] Recipient of 2001 Camille Dreyfus Teacher−Scholar Award.

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of ynamides **1** in a stereoselective Saucy−Marbet rearrangement,[18−20] an appealing entry to chiral allenes (Figure 1).

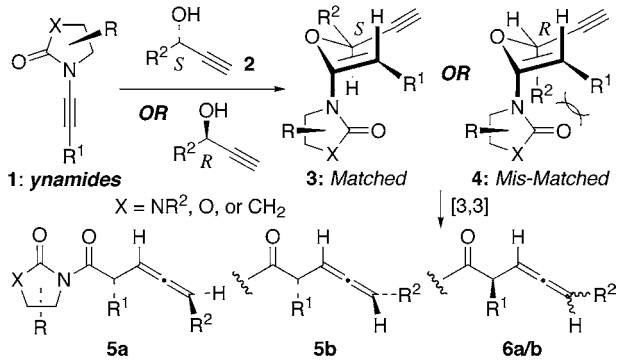
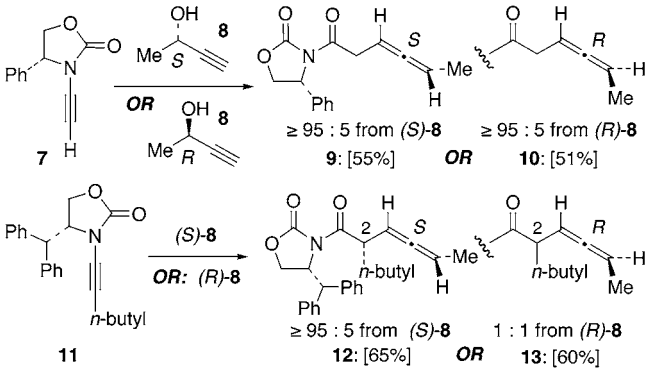



**Figure 1.**

Although Saucy and Marbet[18a] first reported the utility of propargyl alcohols in Claisen-type rearrangements in 1958, there was just one account[19] describing stereochemical issues surrounding this rearrangement using optically enriched propargyl alcohols. We were particularly interested in how reactions of **1** with (*S*)- or (*R*)-propargylic alcohol **2** would proceed in leading to either a matched (**3**) or mismatched (**4**) intermediate that would determine the stereochemical outcome of homoallenyl amides **5** and **6**. We report here a highly stereoselective Saucy−Marbet rearrangement using chiral ynamides.

We quickly established the feasibility of Saucy−Marbet rearrangement using chiral ynamides (Scheme 1).[21] Reactions

**Scheme 1**[a]




[a] Conditions: 0.01−0.20 equiv of PNBSA (*para*-nitrobenzenesulfonic acid). **7** or **11** in toluene (0.025 M), 1.0−2.0 equiv of alcohol, 100 °C, sealed tube, 12−18 h.

of ynamide **7** with (*S*)- and (*R*)-**8** using PNBSA at 100 °C gave allenes **9**[22] and **10** in 55 and 51% yields, respectively, as single diastereomers, suggesting excellent chirality transfer from chiral alcohols to the allenic axial center.[18d,19]

Reactions of **11** led to **12** as a single diastereomer using (*S*)-**8**, while **13** was isolated with 1:1 isomeric ratio when using (*R*)-**8**. Stereochemical assignment (see below) of **13** suggests that it is 1:1 at C2, thereby implying that potential mismatched intermediates were involved.

The high level of diastereoselectivity for the rearrangement is quite general (Table 1). Entries 1−8 illustrate that careful

**Table 1.**

| entry | ynamides and alkynols[a] | rearrangement products | yield[b] | ratio[c] |
|---|---|---|---|---|
| 1 | (*R*)-**14** (*S*)-**8** | **21**: R = Ph; $R^1$ = *n*-butyl; $R^2$ = Me | 67% | ≥ 96 : 4 |
| 2 | (*R*)-**14** (*S*)-**18** | **22**: R = Ph; $R^1$ = *n*-butyl; $R^2$ = *n*-pentyl | 64 | 95 : 5 |
| 3 | (*R*)-**14** (*S*)-**19** | **23**: R = Ph; $R^1$ = *n*-butyl; $R^2$ = *c*-hex | 79 | ≥ 96 : 4 |
| 4 | (*R*)-**15** (*S*)-**8** | **24**: R = Ph; $R^1$ = *c*-hex; $R^2$ = Me | 61 | ≥ 96 : 4 |
| 5 | (*R*)-**16** (*S*)-**8** | **25**: R = Ph; $R^1$ = $R^2$ = Me | 54 | ≥ 96 : 4 |
| 6 | (*R*)-**16** (*R*)-**20** | **26**: R = Ph; $R^1$ = Me; $R^2$ = Ph | 53 | ≥ 96 : 4 |
| 7 | (*R*)-**17** (*S*)-**8** | **27**: R = Bn; $R^1$ = *n*-hexyl; $R^2$ = Me | 77 | 87 : 13 |
| 8 | (*R*)-**11** (*R*)-**20** | **28**: R = $CHPh_2$; $R^1$ = *n*-butyl; $R^2$ = Ph | 65 | 91 : 9 |
| 9 | (*S*)-**14** (*R*)-**8** | *ent*-**21**: R = Ph; $R^1$ = *n*-butyl; $R^2$ = Me | 66 | ≥ 96 :4 |
| 10 | (*S*)-**14** (*R*)-**18** | *ent*-**22**: R = Ph; $R^1$ = *n*-butyl; $R^2$ = *n*-pentyl | 71 | ≥ 96 : 4 |
| 11 | **29** (*S*)-**8** | **30** | 42[d] | 77 : 23 |
| 12 | (*R*)-**8** | **31** | 57[d] | 63 : 37 |
| 13 | **14** (*R*)-**20** | **32** | 80 | ≥ 96 : 4 |
| 14 | (*S*)-**20** | **33** | 78 | 90 : 10 |
| 15 | **14** (*S*)-**20** | **34** | 77 | ≥ 96 : 4 |
| 16 | (*R*)-**20** | **35** | 75 | 89 : 11 |
| 17 | (*R*)-**14** (*S*)-**36** | **38**: $R^2$ = *n*-pentyl; $R^3$ = Ph | 77 | ≥ 96 : 4 |
| 18 | (*R*)-**14** (*S*)-**37** | **39**: $R^2$ = *c*-hex; $R^3$ = *n*-butyl | 71 | ≥ 96 : 4 |

[a] Reactions were carrried out in anhydrous toluene in the presence of 0.10−0.20 equiv of PNBSA and heated at 100 °C in a sealed tube for 12−18 h. [b] All yields were isolated yields. [c] Ratios were determined by using $^1$H and/or $^{13}$C NMR. [d] Reaction was run at 80 °C for entry 11 and 60 °C for entry 12.

matching of (*R*)-oxazolidinone-substituted ynamides **14**−**17** and **11** with (*S*)-propargylic alcohols (except for **20**, which is *R*) led to allenes **21**−**28** with high diastereoselectivity. Stereochemistry of **21** was assigned using X-ray structural analysis, and this serves as a basis for all other assignments

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of configuration in the rearranged products. Matching of (*S*)-oxazolidinone-substituted ynamides **14** with (*R*)-**8** and (*R*)-**18** led to *ent*-**21** and *ent*-**22**, respectively, in high selectivities (entries 9 and 10).

Although to a lesser extent, chiral lactam-substituted[23] ynamide **29** also experienced matching with (*S*)-**8** to afford **30** in a 77:23 ratio and mismatching with (*R*)-**8** to provide **31** in a 63:27 ratio (entries 11 and 12). We should note that the stereochemistry shown here for the major isomers of **30** and **31** is assigned on the basis of the observation that chiral lactam-substituted[23] ynamides such as **29** provided the same stereochemical outcome as those chiral oxazolidinone-substituted ynamides in the Ficini ynamide Claisen rearrangement.[13]

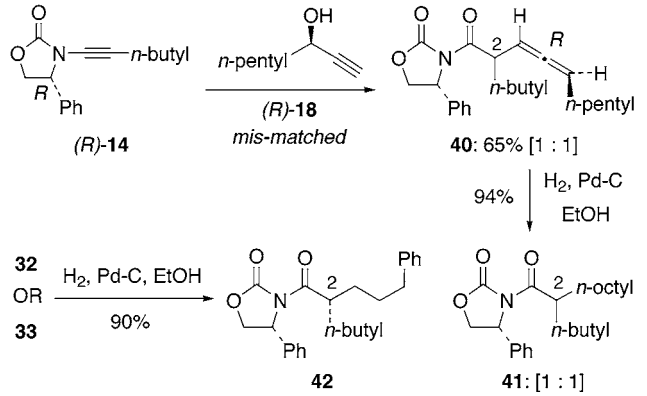
On the other hand, these rearrangements do not all experience either matching or mismatching. Entries 13−16 illustrate that reactions of both (*R*)-**14** and (*S*)-**14** with (*R*)-**20** and (*S*)-**20** gave rearranged products **32**−**35**, respectively, with high diastereoselectivities, although the matched cases (entries 13 and 15) are still noticeably higher. This indifference allows us to have access to all four possible diastereomeric homoallenyl amides.

Finally, trisubstituted chiral homoallenyl amides **38** and **39** could also be obtained in high selectivities using (*R*)-**36** and (*S*)-**37**,[24] respectively (entries 17 and 18).

Intrigued by the mismatched and indifferent cases, we further explored this issue mechanistically. The isomeric mixture **40** obtained with a 1:1 ratio from reaction of (*R*)-**14** with (*R*)-**18** was hydrogenated to give **41**, which remained as a 1:1 mixture (Scheme 2), suggesting that the diastereoselectivity suffered only at C2 in mismatched cases, whereas the allene stereochemistry was transferred in high degrees of integrity from the chiral propargyl alcohol. On the other hand, hydrogenation of both **32** and **33** led to the same amide **42**, implying that stereoselectivity at C2 was the same when it was indifferent to match or mismatch.

On the basis of our previous work with Ficini−Claisen rearrangement,[13] in the matched cases, [3,3]-sigmatropic rearrangement would likely proceed through the (*E*)-ketene

**Scheme 2**




aminal intermediate **43** in which the C2 stereochemistry is dictated by the preference of the rearrangement occurring at the *Re*-face of **43** (Figure 2).[13] The allene stereochemistry is

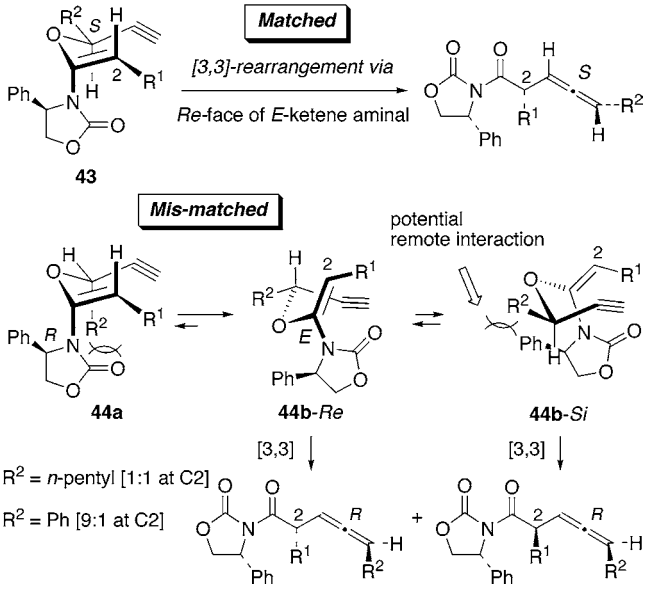



**Figure 2.**

directly transferred from the chiral propargyl alcohol, and this should be true for both matched and mismatched cases.

For mismatched and indifferent cases, to address the C2 stereochemistry, it could be proposed that the rearrangement would go through the same type of (*E*)-ketene aminal that is now mismatched as shown in **44a** due to pseudo 1,3-diaxial interactions between the $R^2$ and the auxiliary groups. Thus, it may be proposed that ketene aminal **44b** is the active conformation for the rearrangement with the $R_2$ group being equatorial (Figure 2). Because of this conformational preference, in the mismatched or indifferent cases, the [3,3]-sigmatropic rearrangement could occur at either or both *Re*- and *Si*-faces of **44b**, thereby providing some explanation for the observed stereochemical outcome at C2.[25]

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(22) All new compounds are characterized by $^1$H NMR, $^{13}$C NMR, FTIR, mass spectroscopy, and $[\alpha]^{20}_D$.

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(24) Obtained via CBS reductions of their corresponding ketones: Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551 and 7925.

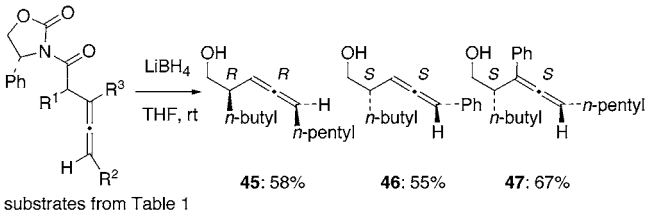
When it is completely mismatched, i.e., $R^2$ = *n*-pentyl in the reaction of (*R*)-**18** with ynamide (*R*)-**14** to produce allene **40** (shown in Scheme 2), rearrangement could be proposed to proceed through both *Re*- and *Si*-faces of **44b**, and PM3 calculations using the program Spartan Model only showed a small energetic difference of ~0.6 kcal/mol.[26] The ensuing [3,3]-rearrangement at both *Re*- and *Si*-faces of **44b** would then lead to a 1:1 isomeric ratio at C2 as observed for allene **40**.[13]

However, when $R^2$ = Ph, as in (*R*)- or (*S*)-**20**, the ensuing rearrangement may prefer to go through the *Re*-face of **44b** because PM3 calculations provide $\Delta E$ = 1.0 kcal/mol in favor of **44b**-*Re*. This preference could be proposed as a result of *the unfavorable remote interaction* between the $R^2$ group, when it is more bulky (i.e., Ph versus *n*-pentyl), with the auxiliary shown in **44b**-*Si*, although we are not certain if this is the actual reason the energetic preference is in favor of **44b**-*Re*. Nevertheless, this preference could result in a 9:1 isomeric ratio at C2 in favor of the same major isomer as those found in the matched case (**32**/**34** vs **33**/**35**, entries 13−16, Table 1).

Moreover, this preliminary assertion was further supported when (*S*)-**19** ($R^2$ = *c*-hex) was reacted with (*S*)-**14** in a potentially mismatched manner: instead of giving a 1:1 ratio as it should in completely mismatched cases, it led to the corresponding allene with an improved ratio of 7:3 (64% yield).[26] Further studies are underway to examine in more details of these various proposed conformations and intermediates.

Finally, given the attractiveness of homoallenyl alcohols as chiral synthons in synthesis,[27] selected substrates from Table 1 were readily reduced using $LiBH_4$ to give homoallenyl alcohols **45**−**47** in good yields (Scheme 3).

**Scheme 3**




We have described here a highly stereoselective Saucy−Marbet rearrangement using chiral ynamides and propargyl alcohols. This provides an excellent entry to highly substituted chiral homoallenyl alcohols.

**Acknowledgment.** Authors thank NSF (CHE-0094005) for support and Dr. Victor Young for X-ray structural analysis.

**Supporting Information Available:** Experimental procedures, $^1H$ NMR spectra, characterizations, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) We initially considered that the 1:1 isomeric ratio observed at C2 could also be a result of the *E*/*Z* ratio of the ketene aminal **44b** while rearranging from the same *Re*-face. Although this remains an option, PM3 calculations (Spartan Model) indicated that (*E*)-ketene aminals of **44b** are more stable than the corresponding (*Z*)-ketene aminals (~2.3−3.2 kcal/mol) for a range of different $R^1$ and $R^2$ groups.

(26) These calculations were carried out with some constraints. Specifically, the terminal alkyne carbon and C2 in **44b**-*Re* and **44b**-*Si* were placed within proximity (2.31 Å) of bond formation in transition states. PM3 calculations showed an energetic difference of 1.3 kcal/mol in favor of **44b**-Re when $R^2$ = *c*-hex.

(27) For some examples, see: (a) Trost, B. M.; Pinkerton, A. B.; Seidel, M. *J. Am. Chem. Soc.* **2001**, *123*, 12466. (b) Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Org. Lett.* **2000**, *2*, 441. (c) Oh, C. H.; Rhim, C. Y.; Song, C. H.; Ryu, J. H. *Chem. Lett.* **2002**, 1140. (d) Yoneda, E.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* **2001**, *42*, 5459. (e) Ma, S.; Gao, W. *J. Org. Chem.* **2002**, *67*, 6104. (f) Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470.