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The First Stereoselective Ficini–Claisen Rearrangement Using Chiral Ynamides

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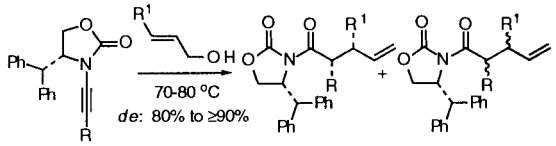
ABSTRACT



The first asymmetric Ficini–Claisen rearrangement using chiral ynamides is described. At relatively low temperatures, the Ficini–Claisen rearrangement can be efficiently promoted by *p*-nitrobenzenesulfonic acid leading to high diastereoselectivity for a range of different allylic alcohols and chiral ynamides.

The synthetic versatility of ynamines in organic synthesis was established thirty years ago.[1] The electron-donating ability of the nitrogen atom renders ynamines useful because of the highly regioselective nature in their synthetic transformation. However, there have been significantly fewer accounts of ynamine chemistry due to the high sensitivity toward hydrolysis.[1] We have been exploring reactivities of ynamides, in which the nitrogen atom is substituted with an amide functionality, thereby diminishing electron-donating ability of the nitrogen atom and offering superior stability to ynamines.[2,3] Our designs specifically feature a chiral imidazolidinone or oxazolidinone group [Figure 1].[2a] Although ynamides have been documented,[4−6] their reactivities were only unveiled recently.[2,7−9] Given the significance of the Claisen rearrangement in organic synthesis[10−13] and Ficini's pioneering work in the ynamine−Claisen reaction,[14] chiral ynamides could be ideal for an asymmetric Ficini−Claisen rearrangement [Figure 1]. To the best of our knowledge, the asymmetric Ficini−Claisen rearrangement is not known, and there are only limited accounts of the

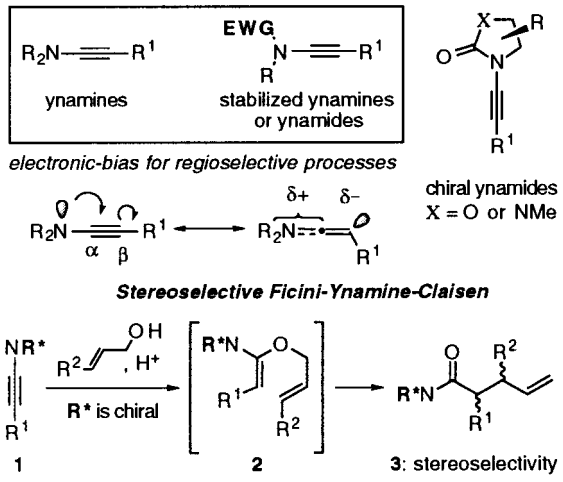


Figure 1.

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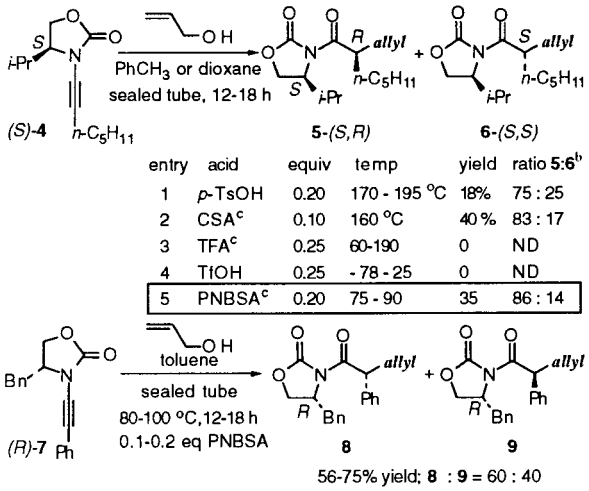
related asymmetric Eschenmoser−Claisen rearrangement.[10−14] We report here our first realization of a highly stereoselective Ficini−Claisen rearrangement.

It was unclear how these novel ynamides would behave in the Claisen rearrangement given their improved stability and the lack of precedent in non-transition metal mediated reactions of ynamides.[2b,7−9] It was quickly found that reactions of the ynamide (*S*)-**4** with allyl alcohol using standard conditions, high temperature in the presence of *p*-TsOH, provided the desired Ficini−Claisen products **5**-(*S*,*R*) and **6**-(*S*,*S*)[15] but with low yields as well as low stereoselectivity [Scheme 1]. Extensive hydrolysis of (*S*)-**4** was observed, and no rearrangement occurred at temperatures below 170 °C.

With only mildly encouraging preliminary results in hand, it became necessary to search for conditions that would lower

Scheme 1[a]



entry	acid	equiv	temp	yield	ratio 5:6[b]
1	*p*-TsOH	0.20	170 - 195 °C	18%	75 : 25
2	CSA[c]	0.10	160 °C	40 %	83 : 17
3	TFA[c]	0.25	60-190	0	ND
4	TfOH	0.25	- 78 - 25	0	ND
5	PNBSA[c]	0.20	75 - 90	35	86 : 14

[a] CSA = camphorsulfonic acid. TFA = trifluoroacetic acid. PNBSA = *p*-nitrobenzenesulfonic acid.

the reaction temperature and minimize hydrolysis of the ynamide. It was found that protic acids CSA, TFA, and TfOH were not useful [Scheme 1]. However, in the presence of 0.20 equiv of *p*-nitrobenzensulfonic acid [PNBSA], reactions of ynamides (*S*)-**4** and (*R*)-**7** proceeded at 80 °C leading to Claisen products **5**/**6** and **8**/**9**, respectively, in consistent yields and diastereoselectivity. It is reasonable to assume that the temperature of 80 °C was necessary to promote protonation of the ynamide and/or addition of allyl alcohol but not the ensuing [3,3]-sigmatropic rearrangement. Most significantly, these represent much milder conditions than most of those used in Johnson−Claisen and Eschenmoser−Claisen rearrangements.[11,12]

With the optimized reactivity using PNBSA in hand, it was readily apparent that the chiral auxiliary had a noticeable effect on the diastereoselectivity. The ynamides (*S*)-**4** and (*R*)-**7** provided only poor to modest diastereoselectivity. Thus, a variety of ynamides with different chiral auxiliaries were prepared[2a] and examined.

As shown in Table 1, reactions of ynamides **10**−**12**, containing the Sibi auxiliary,[16] with simple allyl alcohol proceeded in good yields in the presence of just 0.10 equiv of PNBSA and a reaction temperature at only 70 °C, leading to rearranged product **14**−**16**, respectively, with high diastereoselectivity [entries 1−3]. The stereochemistry was assigned by X-ray analysis of the major isomer of **14** and ^{1}H NMR correlation with other rearrangement products.

Other the other hand, the ynamide **13**, containing a cyclohexyl group, appeared to slow the reaction and had to be heated at a much higher temperature, leading to **17** with a lower de in comparison with **16** obtained from **12** [entry 3 versus 4]. Subsequent work quickly established that ynamides containing the Sibi auxiliary are unique in provid-

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Table 1

entry	ynamides	Claisen product	temp[a]	yield[b]	ratio[c]
1	(*R*)-**10**: R = *n*-pentyl	**14**: R = *n*-pentyl	70 °C	60%	93 : 7
2	(*R*)-**11**: R = *n*-butyl	**15**: R = *n*-butyl	70	70	96 : 4
3	(*R*)-**12**: R = *i*-Pr	**16**: R = *i*-Pr	70	74	91 : 9
4	(*R*)-**13**: R = cyclohexyl	**17**: R = cyclohexyl	125	86	80 : 20
5	**4**	**5**	75	50	86 : 14
6	**18**	**23**	110	69	68 : 32
7	**19**	**24**	110	75	85 : 15
8	(*S*)-**20**: R = Ph	**25**: R = Ph	115	60	60 : 40
9	(*S*)-**21**: R = *n*-C_5H_{11}	**26**: R = *n*-C_5H_{11}	85	65	87 : 13
10	**22**	**27**[d]	25-50	80	87 : 13
11	(*R*)-**11**: R = *n*-butyl, **28**	**31**	80	67	92 : 8
12	(*R*)-**11**, **29**	**32**	80	90	93 : 7
13	(*R*)-**11**, **30**	**33**	85	90	90 : 10

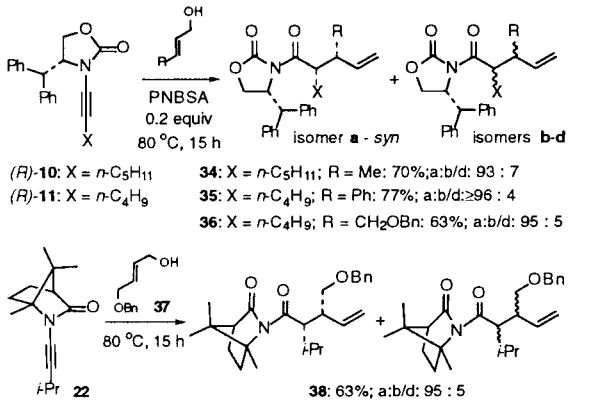
[a] Reactions were carried out in anhydrous toulene in the presence of 0.1 equiv of PNBSA and heated in sealed tube for 12−18 h. 2-Propen-1-ol was used for entries 1−10. [b] All yields were isolated yields. [c] Ratios were determined by using ^1H and ^{13}C NMR and/or GC analysis. [d] For assignment, see ref 20.

ing high diastereoselectivity. All other ynamides, **4** and **18** with the Evans auxiliary,[17] **19** with the Seebach auxiliary,[18] **20**−**21** with amino indanol based auxiliary, and **22** with the Boeckman auxiliary,[19] led to the desired rearranged products in good yields but with slightly inferior diastereoselectivity [entries 5−10].

It is noteworthy that reactions of the ynamide **22** could proceed efficiently at a temperature as low as 25 °C [entry 10]. We also observed the corresponding ketene aminal [see **2** in Figure 1] from **22** after the addition of allyl alcohol prior to rearrangement. It was rather unstable for isolation but can be assigned as *E* based on NOE experiments.[20b] In addition, with ynamides **18** and **20** containing a phenyl substituent, the stereoselectivity suffered greatly relative to that with an alkyl substituent [entries 6 and 8]. Finally, the generality of this stereoselective Ficini−Claisen rearrangement could be established using different allyl alcohols. Reactions of **28**−**30** with **11** led to Claisen products **31**−**33**, respectively, in excellent yields and with high diastereoselectivity [entries 11−13].

We next turned our attention to various substituted allylic alcohols to construct more elaborate systems. As shown in Scheme 2, reactions of *trans*-crotyl and cinnamyl alcohols

Scheme 2



with chiral ynamides **10** and **11** provided the desired Claisen products **34** and **35** in 70% and 77% yields, respectively. The overall stereoselectivities were very high in favor of the *syn* isomer **a**, though there can be four possible diastereomers. Furthermore, the allylic alcohol **37** was also efficient in the rearrangement, leading to a more functionalized Claisen product **36**, again in favor of the *syn* isomer **36a** despite four isomeric possibilities. Reactions of *cis*-crotyl alcohol and *cis*-**37** also provided the *syn* diastereoselectivity for the major isomers but with poorer ratios and yields. Finally, the ynamide **22** was found to give the desired Claisen product in good diastereoselectivity. To subsequently broaden the synthetic scope of this rearrangement, *trans*-allyl alcohols **39**−**41** were used, leading to a series of structurally interesting Claisen products **42**−**44** [Scheme 3].

A plausible mechanistic model based on the stereochemical assignment has been proposed in Figure 2. Protonation of the ynamide **45** would lead to the ketene iminium salt **46**, and subsequent addition of an allyl alcohol from the same side as the hetero cumulene[21] hydrogen would give the *E*-ketene aminal or Claisen precursor **47**. The observed stereoselectivity in the Claisen product **48** can then be reasoned through the chair transition state shown in the Claisen precursor **47**, assuming a conformation similar to

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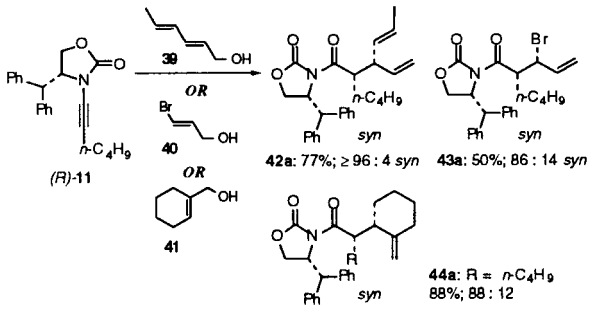
Scheme 3



that of Evan's model for asymmetric aldol reactions using chiral oxazolidinones.[17] This conformation would minimize the dipole interaction between the urethane C═O and vinyl C−O bond, thereby setting up two sterically differentiated π-faces of the ketene aminal.

The larger the substituent [i.e., a dibenzylidene group] on the chiral auxiliary is three-dimensionally, the more differentiated the two π-faces can be, thereby leading to greater diastereoselectivity. The ensuing [3,3]-sigmatropic rearrangement should then occur at the less hindered backside leading to the desired major isomer. The observation of the *E*-ketene aminal[20b] that underwent subsequent rearrangement to give **27** from the reaction of **22** lent strong support to the postulation of the Claisen precursor **47**.

This mechanistic model could also in part rationalize the observed lack of diastereoselectivity when R^1 = Ph [entries 6 and 8 in Table 1]. A Ph group could assume coplanarity with the π-face of the ketene aminal, thereby diminishing

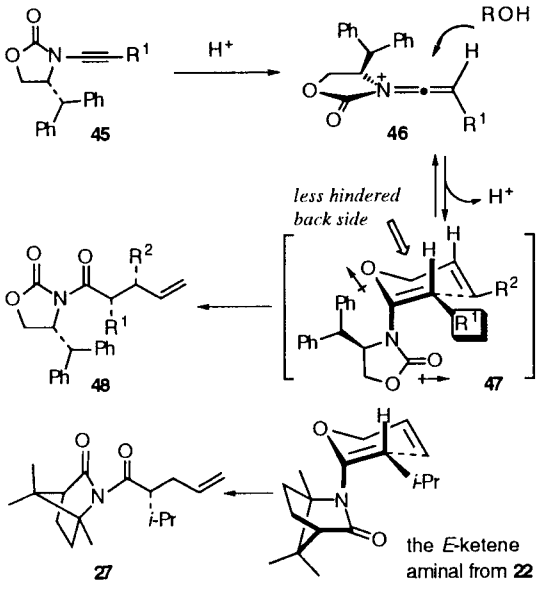
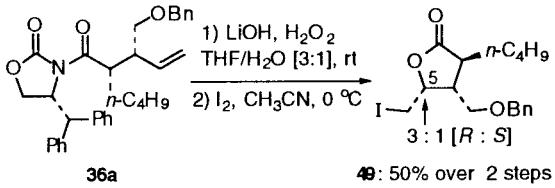


Figure 2.

Scheme 4



the overall steric presence of the front face and π-facial selectivity during the rearrangement.

The observation that *cis*-crotyl alcohol also led to *syn* diastereoselectivity is puzzling, although it has been documented in the Claisen literature.[11,12] This could be a result of a boat transition state for the [3,3]-sigmatropic rearrangement instead of the chair shown in **47**,[22] or an acid-induced isomerization of the ketene aminal from *E* to *Z* in **47**,[23] or isomerization of *cis*-crotyl alcohol to *trans* prior to the allyl alcohol addition.

Finally, as shown in Scheme 4, the auxiliary of **36a** may be effectively removed and recovered using standard conditions.[24] A subsequent iodolactonization[25] of the corresponding carboxylic acid led to synthetically useful lactones **49** in ~50% yield from **36a** with an isomeric ratio of 3:1 in favor of the *R*-epimer at C-5. The relative stereochemistry of **49** was assigned using NOE experiments. These assignments also confirm the *syn* stereoselectivity assigned to the Claisen products shown in Schemes 2 and 3.

We have described here the first asymmetric Ficini−Claisen rearrangements using chiral ynamides. These rearrangements proceed with high diastereoselectivity at relatively low temperatures and are efficiently promoted by using catalytic PNBSA. Studies involving synthetic applications and mechanism are underway.

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Supporting Information Available: Experimental procedures as well as NMR spectral, characterization data, and X-ray data are given for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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