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An Asymmetric Aza-[3 + 3] Annulation in the Synthesis of Indolizidines: An Unexpected Reversal of Regiochemistry

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Abstract

An enantioselective and diastereoselective *aza*-[3 + 3] annulation of pyrrolidine-based *exo*-cyclic vinylogous amides and urethanes with chiral vinyl iminium salts is described. This asymmetric annulation manifold is possible because of an unexpected regiochemical reversal whereby head-to-tail annulations dominated over the predicted head-to-head. It should find prevalent synthetic applications in the enantioselective synthesis of indolizidines.

Aza-[3 + 3] annulations^{1–6} have proven to be powerful in the rapid construction of nitrogen heterocycles via domino or iterative pathways.⁷ We have been developing an *aza*-[3 + 3] annulation that proceeds through a tandem sequence of Knoevenagel condensation of vinylogous amides **1** and vinyl iminium ions **2**, followed by pericyclic ring-closure of the resulting 1-azatrienes **3** [Scheme 1].⁸ This annulation constitutes a unified strategy that has been employed in a number of complex alkaloid syntheses.^{4,9} However, while achieving highly diastereoselective annulations through the use of chiral auxiliary $[X^*]$ ^{10,11} or chiral substituents $[R^*]$ ¹² allowed us to establish the first examples of highly torquoselective pericyclic ring-closure of 1-azatrienes,^{13,14} developing a successful asymmetric variant of this annulation had remained elusive.

In particular, the use of chiral amine salts^{15,16} has not been effective because the Knoevenagel sequence mechanistically embodies a premature loss of the chiral amine $[HNR^*_2]$; and thus, the stereochemical determining step [the ring-closure of **3**] is deprived of an asymmetric inducing element in the absence of X^* or R^* . The intramolecular annulation [**5**→**6**] could be rendered asymmetric, as it circumvents this predicament with the asymmetric induction likely occurring during an *N*-1,4-addition^{11,17} to chiral vinyl iminium ion.¹⁸ To succeed in an asymmetric intermolecular annulation, we must develop either an *N*-1,4-addition [**7**] or *C*-1,4-addition [**8**] pathway.

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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>.

The latter poses a challenge because our *aza*-annulation has predominately given the *head-to-head* [C=O and C=N aligned]¹⁹ regiochemical orientation shown in **7** leading to 1,2-dihydropyridines **4**; but the annulation shown in **8** implies a reversal of regiochemistry in favor of the rare *head-to-tail* orientation.²⁰ We report herein our success in developing an asymmetric intermolecular *aza*-[3 + 3] annulation due to an unexpected reversal of regiochemistry.

Our keen interest in indolizidine, quinolizidine, and other prevalent alkaloid scaffolds^{21,22} prompted the investigation into both an intermolecular annulation using *exo*-cyclic vinylogous amides and urethanes.²³ We had found that pyrrolidine-based *exo*-cyclic vinylogous amides and urethanes such as **10**²⁴ and **11**^{25,26} underwent efficient *aza*-[3 + 3] annulation promoted by amine salt **9**^{c,11,18} to give the reasonably presumed indolizidines **13** and **14**, respectively [Scheme 2]. Both **13** and **14** would represent a *head-to-head* regiochemical orientation in the annulation.

Subsequently, we pursued these annulations with a number of chiral amines salts such as **15–16** in part to examine the counteranion effect on the reaction rate. We had found that these annulations proceed at ambient temperature in good yields by employing trifluoroacetate as the counteranion, instead of acetate or halides.^{18a} Serendipitously, it turned out that while the yields were not particularly high, the products were found enantiomerically enriched with reasonable *ee* when using MacMillian's chiral imidazolidinone salts **17** and **18**^{15,16,27} [entries 3 and 4 Scheme 2]. We were very surprised by this outcome, as we had believed that it was a *head-to-head* regiochemical orientation as usual, and rationalized that the low reaction temperature had preserved their optical integrity.

Consequently, we attempted the racemization via a sequence of ring-opening and ring-closure [Scheme 3], which represents another major impediment to developing asymmetric intermolecular *aza*-annulation, as 1,2-dihydropyridines are prone to such ring-opening process even at 50 °C.¹¹ However, we found no racemization even after heating **13** at 140 °C for 48 h! This outcome and later X-ray assignment confirmed that **13** [and **14**] are in fact *aza*-[3 + 3] annulation products representing a rare *head-to-tail* regiochemical orientation.¹⁹

Recognizing that this could prove to be an invaluable entry to enantioselective synthesis of indolizidine alkaloids,²¹ and, we proceeded to examine various factors to optimize this asymmetric reaction.²⁸ We quickly found that proline-based amines were the more effective for asymmetric annulation.^{18a} Jørgensen's catalysts^{15,16,29} **20e–g** with trifluoroacetate as the counter-anion provided the best enantiomeric excess [entries 5–7 in Table 1]. Overall, steric bulk of the R¹ group on the tertiary hydroxyl and of the aryl moiety appeared to be critical for the asymmetric induction. Consequently, catalysts **20e** and **20g**, asymmetric intermolecular *aza*-[3 + 3] annulations of *exo*-cyclic vinylogous amide **10** as well as urethanes **11** and **21** with a variety of enals were examined [Table 2]. Most proceeded to give indolizidines **27a–h** in modest to good yields and enantioselectivity.

To unambiguously determine both the regioselectivity and stereochemistry of this annulation, we were left with the only option of attaining an X-ray structure. To this end, we synthesized chiral enal **28a** from the acid of (*S*)-naproxen, submitted it to our annulation conditions with vinylogous amide **10** using either achiral catalyst **9** or chiral catalyst **20e**. While the intent was to isolate both diastereomers using **9** [56:44 see entry 1 in Table 3] and separate them for submission to the crystallization process, **29a** and **29a'** were unfortunately very difficult to separate.

Although chiral enals would give non-zero *dr* values,^{12,23} we observed a much enhanced diastereoselectivity of 11:1 for annulation product **29** when using chiral catalyst **20e** [entry

2]; and that ratio was reversed when using *ent*-**20e** [entry 3]. Another intriguing phenomenon was seen from the annulations of chiral enals **28b** [entries 4 and 5] and **28c** [entries 6 and 7] in which the diastereoselective ratio was reversed when using **9**. It is noteworthy that while the high level of amplification in the stereoselectivity of the annulation of **28a** should be useful, the observed “matched” and “mismatched” cases suggest that the asymmetric induction is dictated through the chiral amine.

The X-ray structure of **30** [hydrogenated **29a**] allowed us to unambiguously determine both the regioselectivity and stereochemistry [Figure 1]. The matching of the derivatives of **30**²⁶ with the major enantiomer of **27d** led to the assignment of its absolute configuration. Consequently, a model for the asymmetric induction could be reasonably proposed here, although a precise rationale behind the stereoselectivity amplification when using chiral aldehydes remains unknown to us. In addition, while we are not certain as to the reason for the regiochemical divergence in the annulations of *exo*-cyclic versus *endo*-cyclic vinylogous amides, *exo*-cyclic ones have behaved precariously, leading to alternative and/or unexpected reactions pathways.³⁰ Nevertheless, we now finally possess a window for understanding how an asymmetric intermolecular *aza*-[3 + 3] annulation can be achieved.

We have described here the first successful enantioselective *aza*-[3 + 3] annulation of pyrrolidine-based *exo*-cyclic vinylogous amides and urethanes with chiral vinyl iminium salts. This asymmetric *aza*-annulation manifold is possible because of an unexpected regiochemical reversal whereby *head-to-tail* annulations dominated over the predicted *head-to-head*. Further mechanistic understanding and applications in enantioselective synthesis of indolizidines are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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28. Solvents have a noticeable effect on the enantioselectivity with EtAOc being the best solvent. Reactions [*concn* = 0.10 M] were run with **10**, 1.4 equiv of **12**, 3.0 equiv of Na₂SO₄ and 40 mol % of amine catalyst **20e** at RT for 3 h. Solvents were and the respective *ee* values evaluated were: benzene [*ee* 58%]; EtOAc [*ee* 70%]; CH₂Cl₂ [*ee* 48%]; THF [*ee* 42%]; acetone [*ee* 26%]; EtOH [30].
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30. Piperidine-based *exo*-cyclic vinylogous amides and urethanes surprisingly gave carbo-[3 + 3] annulation products, leading to as quinolines synthesis [see reference 23]. Azepane-based *exo*-cyclic vinylogous amide gave 16% *ee* but very low yield in the annulation.

Figure 1.
The X-Ray Structure of **30**.

Scheme 1.
Asymmetric Aza-[3 + 3] Annulations.

a. All reactions were run in EtOAc [*concn* = 0.10 M] with 3.0 equiv Na₂SO₄. **b.** Isolated yields. **c.** Determined by CSP-HPLC. **d.** Time: 30 h. **e.** Time: 16 h.

Scheme 3.
An Unexpected Reversal in Regiochemistry.

^aOptimization Employing Proline-Based Amine Salts.

entry	amides: R =	cat. [40 mol %] ^b	product	yield [%] ^c	ee [%] ^d
1	11 : R = OMe	20a	14	44	20
2	11 : R = OMe	20b	14	22	38
3	10 : R = Me	20c	13	77	59
4	11 : R = OMe	20d	14	62	38
5	11 : R = OMe	20e	14	56	70
6	10 : R = Me	20e	13	65	70
7	10 : R = Me	20f	13	57	70
8	11 : R = OMe	20g	14	51	54
9	10 : R = Me	20g	13	75	66
10	10 : R = Me	20h	13	44	10
11	11 : R = OMe	20i	14	28	20

^aAll reactions were run in EtOAc [*concn* = 0.10 *M*] with 1.4 equiv of enal **12** and 3.0 equiv of Na₂SO₄.

^b The trifluoroacetate salts were all generated *in situ* by addition of 40 mol % TFA to the reaction mixture.

^cIsolated yields.^d Determined by CSP-HPLC.

Table 2

entry	amides	enals [$\text{R}^2 =$]	cat.	product	yield [%] ^b	ee [%] ^c
1	10: R = Me	22	20e	27a	51	54
2	10	22	20g	27a	46	62
3	10	12	20e	27b	65	70
4	10	12	20g	27b	75	66
5	10	23	20e	27c	52	62
6	10	23	20g	27c	40	58
7	10	24	20e	27d	57	60
8	10	24	20g	27d	<10 ^d	n.d. ^e
9	10	25	20e	27e	48	— ^f
10	11: R = OMe	22	20e	27f	40	52
11	11	22	20g	27f	53	56
12	11	12	20e	27g	56	70
13	11	12	20g	27g	51	54
14	21: R = OEt	26	20e	27h	41	54
15	21	26	20g	27h	44	62

^a All reactions were run in EtOAc [*concn* = 0.10 M] with 1.4 equiv of the respective enal, 3.0 equiv of Na_2SO_4 and 40 mol % of the amine catalyst. The TFA salts were generated *in situ* by addition of 40 mol % TFA to the reaction mixture.

^b Isolated yields.

^c Determined by CSP-HPLC.

^d Observed in crude ^1H NMR.

e Not determined.

f Inseparable by CSP-HPLC.

Table 3

An Amplified Diastereoselective Aza-[3 + 3] Annulation.^a

entry	chiral enals [R* =]	cat. ^b	product ^c	yield [%] ^d	dr ^e
1	28a	9	29a/a''	57	56:44
2	28a	20e	29a/a''	62	92:8
3	28a	en 20e	29a/a''	70	21:79
4	28b	9	29b/b''	58 ^f	70:30
5	28b	20e	29b/b''	69 ^f	23:77
6	28c	9	29c/c''	58	78:12
7	28c	20e	29c/c''	49	32:68
8	28d	9	29d/d''	50	55:45
9	28d	20e	29d/d''	67	67:33

^a All reactions were run in EtOAc [*concn* = 0.10 M] with 1.4 equiv of the respective chiral enal and 3 equiv of Na₂SO₄.

^b The TFA salt of **20e** was generated in situ by addition of 40 mol % TFA to the reaction mixture.

^c The two diastereomers are inseparable.

^d Isolated yields.

^e Ratios determined by crude ¹H NMR.

^f 2.8 equiv enal was used.