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

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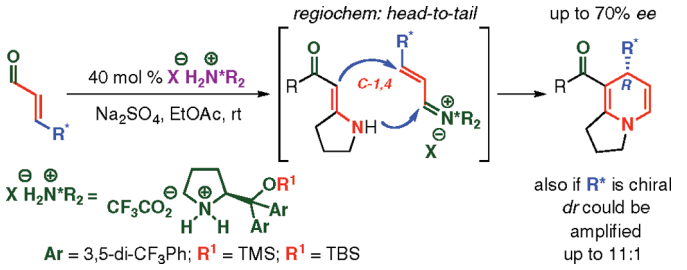
ABSTRACT



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

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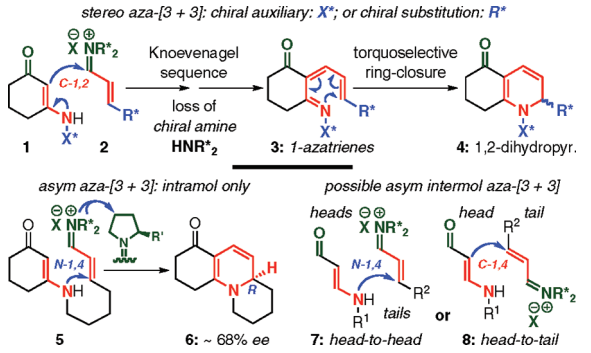
Scheme 1. Asymmetric *Aza*-[3 + 3] Annulations

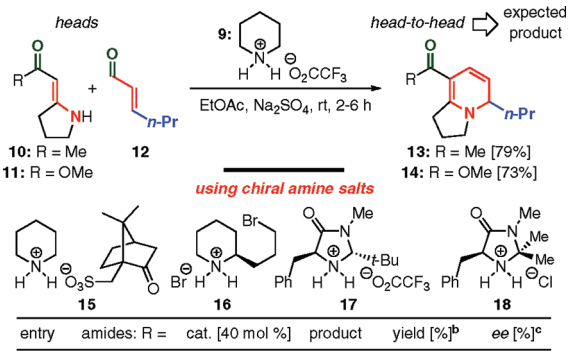


1-azatrienes,[13,14] developing a successful asymmetric variant of this annulation had remained elusive.

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.

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.

Scheme 2. Surprising Enantiomeric Inductions[a]



entry	amides: R =	cat. [40 mol %]	product	yield [%][b]	*ee* [%][c]
1	**10:** R = Me	**15**	**13**	33[d]	0
2	**11:** R = OMe	**16**	**14**	11	22
3	**10:** R = Me	**17**	**13**	46	40
4	**11:** R = OMe	**18**	**14**	20[e]	54

[a] **a** All reactions were run in EtOAc [*concn* = 0.10 *M*] with 3.0 equiv Na_2SO_4. **b** Isolated yields. **c** Determined by CSP-HPLC. **d** Time: 30 h. **e** Time: 16 h.

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**[9c,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.

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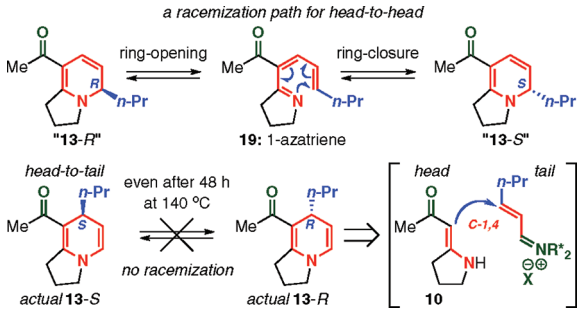
(26) See Supporting Information.

Scheme 3. Unexpected Reversal in Regiochemistry



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] we proceeded to examine various factors to optimize this asymmetric reaction.[28] We quickly found that proline-based amines were more effective for asymmetric annulation.[18a] Jørgensen's catalysts[15,16,29] **20e**–**g** with trifluoracetate as the counteranion provided the best enantiomeric excess [entries 5–7 in

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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 Na_2SO_4 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%]; CH_2Cl_2 [*ee* 48%]; THF [*ee* 42%]; acetone [*ee* 26%]; EtOH [30].

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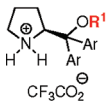
Table 1. Optimization Employing Proline-Based Amine Salts[a]



20a: Ar = Ph; R^1 = H
20b: Ar = Ph; R^1 = Me
20c: Ar = Ph; R^1 = TMS
20d: Ar = 3,5-di-CF_3Ph; R^1 = H
20e: Ar = 3,5-di-CF_3Ph; R^1 = TMS
20f: Ar = 3,5-di-CF_3Ph; R^1 = TES
20g: Ar = 3,5-di-CF_3Ph; R^1 = TBS
20h: Ar = naphthyl; R^1 = H
20i: Ar = Ph, Cy; R^1 = H

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

[a] All reactions were run in EtOAc [*concn* = 0.10 *M*] with 1.4 equiv of enal **12** and 3.0 equiv of Na_2SO_4. [b] The trifluoroacetate salts were all generated *in situ* by addition of 40 mol % TFA to the reaction mixture. [c] Isolated yields. [d] Determined by CSP-HPLC.

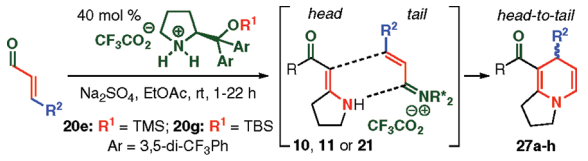
Table 1]. Overall, steric bulk of the R^1 group on the tertiary hydroxyl and of the aryl moiety appeared to be critical for the asymmetric induction. Consequently, catalysts **20e** and **20g**, asymmetric intermolecular *aza*-[3 + 3] annulations of *exo*cyclic vinylogous amide **10**, as well as urethanes **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.

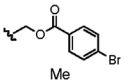
To unambiguously determine both the regioselectivity and stereochemistry of this annulation, we were left with the only option of attaining an X-ray structure. To this end, we synthesized chiral enal **28a** from the acid of (*S*)-naproxen and submitted it to our annulation conditions with vinylogous 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 nonzero *dr* values,[12,23] we observed a much enhanced diastereoselectivity of 11:1 for annulation product **29** when using chiral catalyst **20e** [Table 3, 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**. 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

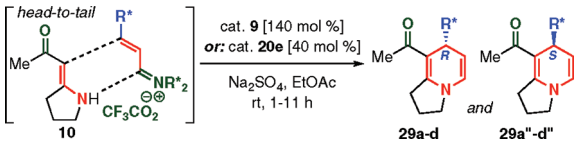
Table 2. Scope of the Asymmetric Aza-Annulation[a]

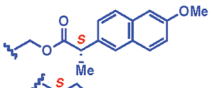
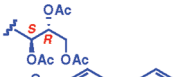
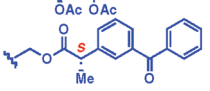


entry	amides	enals [R^2 =]	cat.	product	yield [%][b]	*ee* [%][c]
1	**10:** R = Me	**22** Me	**20e**	**27a**	51	54
2	**10**	**22**	**20g**	**27a**	46	62
3	**10**	**12** *n*-Pr	**20e**	**27b**	65	70
4	**10**	**12**	**20g**	**27b**	75	66
5	**10**	**23** Ph	**20e**	**27c**	52	62
6	**10**	**23**	**20g**	**27c**	40	58
7	**10**	**24** $CH_2OTBDPS$	**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** Me	**20e**	**27f**	40	52
11	**11**	**22**	**20g**	**27f**	53	56
12	**11**	**12** *n*-Pr	**20e**	**27g**	56	70
13	**11**	**12**	**20g**	**27g**	51	54
14	**21:** R = OEt	**26** *n*-Pentyl	**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 ^{1}H NMR. [e] Not determined. [f] Inseparable by CSP-HPLC.

Table 3. 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**		*ent*-**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 Na_2SO_4. [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 ^{1}H NMR. [f] Enal (2.8 equiv) was used.

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.

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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 ref 23]. Azepane-based *exo*-cyclic vinylogous amide gave 16% *ee* but very low yield in the annulation.

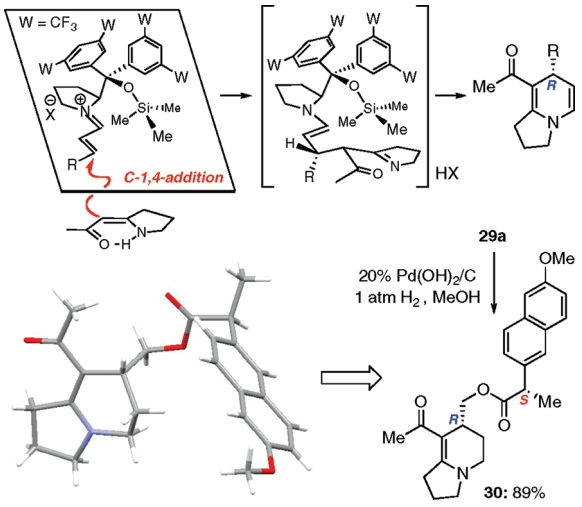

Figure 1. X-ray Structure of **30**.

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