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Stereoselective [2,3]-Wittig Rearrangement of (*1S,2R*)-1-Amino-Indan-2-ol Derived Amide Enolates

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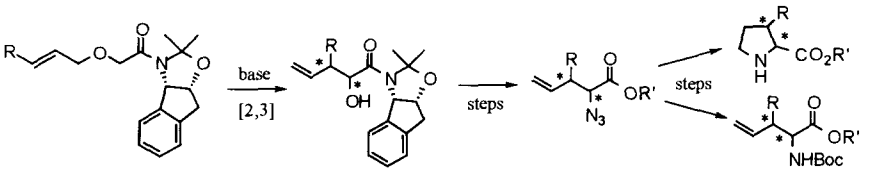
This manuscript is dedicated to the occasion of Professor Yoshito Kishi's 60th birthday

Abstract: An efficient, diastereoselective [2,3]-Wittig rearrangement of α-allyloxy-amide enolates has been developed using (*1S,2R*)-1-amino-indan-2-ol as a chiral auxiliary. After auxiliary removal, the resultant optically active α-hydroxy acids have been transformed to functionalized amino acid derivatives.

Communications from these laboratories have demonstrated the utility of (*1S,2R*)-1-amino-indan-2-ol, a subunit of HIV protease inhibitor *Crixivan*®, for controlling stereoselective carbon-carbon bond forming processes.[1] We believed an attractive extension of this methodology would arise through its use as a chiral auxiliary in a [2,3] sigmatropic rearrangement.[2] The products of the [2,3] rearrangement were envisioned to provide access to functionalized acyclic and cyclic amino acids using existing methodology.[3] Herein we disclose our use of (*1S,2R*)-1-amino-indan-2-ol as a readily available and inexpensive chiral auxiliary for the [2,3] rearrangement of α-allyloxy-amino-indanol derived amide enolates.



Substrates for the [2,3] rearrangement were routinely available in four steps from bromoacetic acid, an allylic alcohol, and (*1S,2R*)-1-amino-indan-2-ol.[4] Satisfyingly, our initial attempt at [2,3] rearrangement of the lithium enolate of amide-acetonide **3** met with encouraging results, providing a greater than 95% yield of products resulting from [2,3] sigmatropic rearrangement (Table 1, entry 1).[5,6] Subsequently a variety of enolate counter ions, reaction solvents, and additives were screened in order to optimize yield and diastereoselectivity for the [2,3] rearrangement of **3**. In agreement with the studies of Nakai and Katsuki concerning [2,3] rearrangements of amide enolates, the diastereoselectivity for the rearrangement of the enolate of **3** was observed to be a function of enolate counter ion, with syn selectivity increasing from K < Na < Li < Zr (Table 1). Although selectivity favoring **4E** was highest using the zirconium enolate protocol, these experiments suffered from low conversion of **3**. Modification of this protocol (increasing *n*-BuLi to 2.0 equiv.) lead to consumption of **3**, however a low yield of **4E**, and **4T** was still observed.[7]

Using LHMDS as a base (1.5 equiv., necessary to observe complete conversion of **3**) and employing HMPA as an additive, resulted in higher levels of syn selectivity than in the absence of HMPA (Table 1, entry 1 vs. entries 7 through 10). Unlike the zirconium enolate case, the enhanced levels of diastereoselectivity observed in the presence of HMPA did not come at the expense of yield. Optimal selectivity on a 1 mmol scale was obtained employing 15 equivalents of HMPA (Table 1, entry 10).

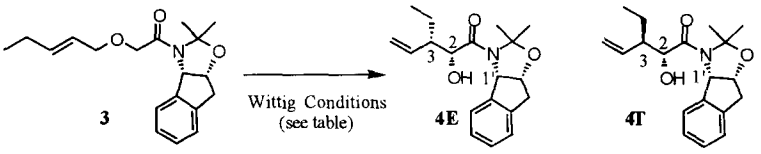


Table 1: Optimization of [2,3] Rearrangement Conditions for Amide-acetonide 3[8,9,10]

entry[a]	Base	Solvent	Additive (equiv.)	% 4E (2R,3S)	% 4T (2R,3R)	Assay Yield of 4E+4T[6]
1	LHMDS	THF	None	79	21	95 %
2	LHMDS	Et_2O	None	78	22	93 %
3	KHMDS	THF	None	66	34	91 %
4	NaHMDS	THF	None	73	27	80 %
5	*n*-BuLi	THF	None	76	24	94 %
6[b]	*n*-BuLi	THF	Cp_2ZrCl_2 (1.2)	94	6	73 %
7	LHMDS	THF	HMPA (3.0)	86	14	95 %
8	LHMDS	THF	(5.0)	87	13	96 %
9	LHMDS	THF	(10.0)	88	12	95 %
10	LHMDS	THF	(15.0)	89	11	97 %
11	LHMDS	THF	TMEDA (10.0)	80	20	90 %
12	LHMDS	THF	DMPU (16.0)	85	15	92 %

[a] Except when noted, all reactions were run on a 1 mmol scale at a concentration of 0.1 *M*, with 1.5 equivalents of base, and an initial reaction temperature of -78 °C. The reaction mixture was subsequently aged for 2 h at this temperature, warmed to -10 °C over the course of approximately 2 h and assayed by GC. [b] 1.2 equivalents of base were used.

The scalability of the above protocol was demonstrated on a *0.2 mol* scale of **3** (HMPA charge of 5 equivalents) providing a 91% GC assay yield of [2,3] products containing the *2R* configuration (**86% 4E**: **14% 4T**). The reaction was quenched with 0.1 *N* sodium phosphate buffer (pH = 6.8) and the aqueous layer extracted with *iso*-propyl acetate (iPAc). The organic layer was washed three times with H_2O (in order to remove the residual HMPA), and concentrated to give a yellow-orange oil. Filtration through a short deactivated silica gel column (8 X weight of crude oil, 1 % Et_3N in 10 % EtOAc in hexane) gave 80 % yield of a 85:15 **4E**:**4T** mixture as an oily solid. Further enrichment in **4E** was achieved by trituration with pentane (4 °C) to give an overall 67 % yield (94:6 **4E**:**4T**) from **3** as a white powder.

The stereochemistry of **4E** was established by a single-crystal X-ray diffraction study to be *2R,3S* relative to the known configuration of the aminoindanol auxiliary (*1S,2R*).[9] The (*2R,3R*) stereochemistry of **4T** was deduced by removing the C.3 stereocenter via olefin hydrogenation of a 9:1 **4E**:**4T** mixture (10% Pd/C, EtOH). The resultant product was determined to be diastereomerically pure by ^1H, and ^{13}C NMR, thereby securing the 2*R* configuration for both **4E** and **4T**.

In an effort to extend the scope this methodology, amide-acetonides **5-8** were made available following the previously described method, and their respective [2,3]-Wittig rearrangements carried out under identical conditions (Table 2). In general, substrates possessing the *trans*-disubstituted olefin geometry (*i.e.* **5**, **3**, **8**) afforded excellent selectivity for the *2R,3S* configuration (syn).[11,12] In contrast, the rearrangement of the lithium enolate of amide **6**, containing a *cis*-disubstituted olefin geometry, resulted in low *2R,3R* selectivity (*ca.* 2:1 anti:syn).[13] Amide **7**, possessing a terminal olefin, afforded greater than 98 % *2R* selectivity. Summarizing our results outlined in Tables 1 and 2, it is apparent that for all substrates studied a 91-98 % diastereofacial bias in relation to the auxiliary (*2R* selectivity) has been observed.

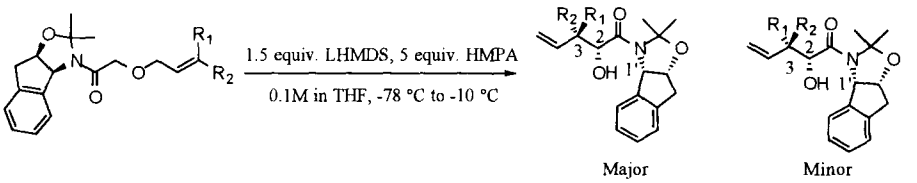
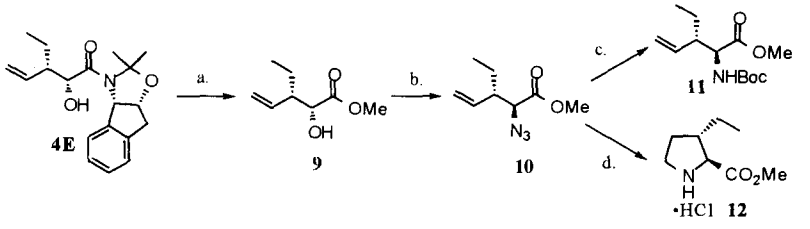


Table 2: [2,3]-Wittig Rearrangement Substrates

Substrate	R1	R2	Crude Assay Yield	Major (config.)	Minor (config.)	Isolated Yield (major:minor)
5	H	Me	97 %	90 % (*2R,3S*)	10% (*2R,3R*)	67% (94:6)
3	H	Et	96 %	87 %(*2R,3S*)	13 % (*2R,3R*)	67 % (94:6)
6	Et	H	93 %	32 %(*2R,3S*)	68 % (*2R,3R*)	not attempted
7	H	H	95 %	> 98 % (*2R*)	NA	88 % (NA)
8[12]	H	Ph	87 %	91 % (*2R,3R*)	9 % (*2R,3S*)	68 % (93:7)

The utility of our [2,3]-Wittig products was demonstrated through conversion of **4E** to functionalized amino acids **11** and **12**. Auxiliary solvolysis was routinely carried out on a 94:6 ratio of **4E**:**4T** or better, and was achieved in refluxing aqueous methanol (3:1 v/v MeOH: 12 *N* HCl) to afford a 74 % distilled yield of hydroxy-methyl ester **9** with a 90 % HPLC assay recovery of amino-indanol. Conversion of **9** to azide **10** occurred in two steps under standard conditions (overall 70% yield).[14] Reduction of **10** under Staudinger conditions and Boc protection of the crude amine gave **11** in 80 % yield after purification. Alternatively, treatment of **10** with dicyclohexylborane afforded (*2S,3S*)-3-ethyl proline•HCl (**12**) in 78 % yield after acidic hydrolysis of the intermediate aminoborane with aqueous HCl.[15]

In conclusion, we have utilized (*1S,2R*)-1-amino-indan-2-ol as a practical chiral auxiliary for controlling the stereochemical outcome of the [2,3]-Wittig rearrangement of a variety of α-allyloxy amino-indanol derived amide enolates. The utility of the hydroxy-amide product has been demonstrated by its conversion to functionalized cyclic and acyclic amino acid derivatives.



Reagents and Conditions: a. MeOH: 12*N* HCl (3:1), 1 h (74 %); b. i) MsCl, Et_3N, CH_2Cl_2 (92 %), ii) NaN_3, DMSO (76 %); c. i) PPh_3, 1*N* HCl, THF, ii) Boc_2O, 5*N* NaOH, THF (80 %); d. Cx_2BH, THF, then 1*N* HCl, (78 %).

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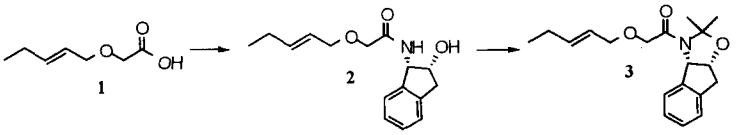
References and Notes

1. Maligres, P. E.; Weissman, S. A.; Upadhyay, V.; Cianciosi, S. J.; Reamer, R. A.; Purick, R. M.; Sager, J.; Rossen, K.; Eng, K. K.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron* **1996**, *52*, 3327. Davies, I. W.; Senanayake, C. H.; Castonguay, L.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7619. *ibid.*, **1996**, *37*, 1725.

2. a) Nakai, T.; Mikami, K. *Organic Reactions, vol. 46*, John Wiley & Sons, Inc.; New York, NY; 1994; pp 105-210. b) For the [2,3]-Wittig rearrangement of oxazolines derived from *cis*-2-amino-1-acenaphthenol, see: Sudo, A.; Hashimoto, Y.; Kimoto, H.; Hayashi, K.; Saigo, K. *Tetrahedron Asym.* **1994**, *5*, 1333.

3. a) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151. b) Waid, P. P.; Flynn, G. A.; Huber, E. W.; Sabol, J. S. *Tetrahedron Lett.* **1996**, *37*, 4091.

4. As an example, amide-acetonide **3** was available on 0.5 mole scale in the following manner.



A THF suspension of NaH (60 % in mineral oil) at 0 °C, was sequentially treated with THF solutions of *trans*-2-penten-1-ol and bromoacetic acid over a 1 h period. Upon completion of the additions the resultant thick reaction mixture was heated to reflux for 8 h. After aqueous quench, acid/base extraction and distillation, an 80 % yield of **1** was obtained. Activation of **1** was achieved in *iPAc* using Vilsmeier conditions ($POCl_3$, DMF). The resultant *iPAc* solution was used directly under Schotten-Baumann conditions (2.5 *N* NaOH) to acylate (*1S,2R*)-1-amino-indan-2-ol. Hydroxy-amide **2** was isolated after concentration of the *iPAc* layer and trituration of the crude solids with cold pentane (73 % yield from **1**). Treatment of **2** with methoxypropene and catalytic $MeSO_3H$, in iPAc, gave a 94 % yield of amide **3** [b.p. = 223-230 °C, 9 torr; $[\alpha]^{23}_D$= +144° (*c* 2.0, $CHCl_3$)].

5. The propensity of α-allyloxy-*cis*-amino-indanol derived amide enolates to undergo [2,3] rearrangement is a marked difference in reactivity when compared to similar amide enolates containing the Evans oxazolidinone auxiliary (which do not undergo [2,3] rearrangement), see: Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885. We attribute this difference to an increase of carbon-based anionic character in the former case.

6. Assay yield was determined by GC area percent. For Table 1 (entries 1-3, 5, and 7-12) the remaining materials consisted of one diastereomer of [2,3] rearrangement as determined by ^1H and ^{13}C NMR. The absolute stereochemistry of this product was not proven, but is assumed to be (*2S,3R*). On a preparative scale this minor product was separated by silica gel chromatography.

7. The [2,3] rearrangements of the zirconium enolates of a variety of *trans*-2,5-bis-(methoxymethoxymethyl) pyrrolidine amides have been reported to give excellent syn selectivity, with moderate to good isolated yields, see: Uchikawa, M.; Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 4577.

8. Diastereomeric ratios of **4E**:**4T** were routinely assayed on a HP 6890 GC with FID, using a splitless injection of a heptane solution onto a 5m HP-1/30m DB-23 joined column (He carrier).

9. An analytically pure sample of **4E** [white crystalline, m.p.= 97.5-98 °C, $[\alpha]^{23}_D$= +133° (*c* 1.0, $CHCl_3$)] was available by normal phase, preparative HPLC on a YMC-pack CN column. The authors have deposited the coordinates of **4E** in the Cambridge Crystallographic Database.

10. Both amide **3** and hydroxy-amide **4E** exist at room temperature, in $CDCl_3$, as a 97:3 mixture of rotomers as determined by magnetization transfer upon irradiation of the H_1' proton of the amino-indanol auxiliary.

11. The absolute stereochemistry of the [2,3]-Wittig rearranged products of amides **5**, and **7** were determined after conversion to L-isoleucine and L-norvaline respectively, followed by GC comparison of their trifluoroacetamide methyl esters to authentic samples on a Alltech Chirasil-Val column (25m) as per: Abe, I.; Izumi, K.; Kuramoto, S.; Musha, S. *J. High Res. Chromo. Chromo. Comm.* **1981**, 549.

12. For the major [2,3] rearrangement product of amide **8** (R_2=Ph), the priority for assigning absolute stereochemistry changes (R_2>vinyl) relative to all other examples in Table 2 (R_2<vinyl). The relative stereochemistry of this major product was assigned based on nOes observed upon irradiation of the ortho aromatic protons of the lactone resulting from auxiliary hydrolysis (aqueous acidic dioxane) and iodolactonization. Its absolute stereochemistry was not determined.

13. Similar low anti selectivity was observed for the [2,3] rearrangement of (*cis*-2-butenyloxy)-pyrrolidine amide enolates, see footnote 4 of: Mikami, K.; Takahashi, O.; Kasuga, T.; Nakai, T. *Chem. Lett.* **1985**, 1729.

14. Attempts to achieve this transformation in one pot with diphenyl phosphorazidate and DBU lead to significant amounts of the elimination product, see: Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886.

15. Azide **10** (92 % de) underwent hydroboration-cycloalkylation to afford **12** as a 88:12 (76 % de) mixture of trans:cis proline ring isomers, as determined by ^1H NMR. The source of this leak in stereospecificity is currently under investigation.

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