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Enantioselective [2,3]-Wittig rearrangement of allyl picolyl ethers with chiral lithium amides

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Enantiomerically pure homoallylic alcohols containing pyridine substructure are useful as chiral ligands for asymmetric synthesis and as building blocks for the synthesis of biologically active chiral compounds and natural products. We have successfully performed the highly enantioselective [2,3]-Wittig rearrangement of 2-allyl picolyl ethers using chiral bidentate lithium amides to give 1-(2-pyridyl)-3-butenols with up to 95% ee, and demonstrated that the resulting chiral bidentate diamines, regenerated after the formation of lithioenamines, are excellent chiral ligands for the enantioselective [2,3]-Wittig rearrangement.

Introduction

The [2,3]-Wittig rearrangement is widely used for the stereoselective synthesis of homoallylic alcohols.[1] This base-induced transformation was first identified in 1949, when Wittig *et al.*[2] discovered that allyl fluorenyl ether underwent rearrangement to yield a homoallylic alcohol. The reaction mechanism was later clarified by Cast *et al.*[3,4]

In 1956, Suzuki[5] reported the base-induced [2,3]-Wittig rearrangement of 2-(allyloxymethyl)pyridine (**1**) to form 1-(2-pyridyl)-3-butenol (**2**) (Scheme 1). Compound **2** is of interest because it contains one of the most prevalent nitrogen-containing pyridine heterocycles found in pharmaceutical structures.[6–8] Although several asymmetric syntheses of **2** have been developed *via* the 1,2-addition of chiral allylborane and related reagents to pyridinecarboxaldehyde,[9,10] to our knowledge, its synthesis *via* the enantioselective [2,3]-Wittig rearrangement of **1** has not been reported.

Herein, we describe the unprecedented enantioselective [2,3]-Wittig rearrangement of **1** and its analogs, facilitated by bidentate chiral lithium amide bases. Chiral lithium amides have been employed in a range of asymmetric reactions, including deprotonation, alkylation, and aldol reactions.[11,12] In 2023, we demonstrated their use in the enantioselective [2,3]-Wittig rearrangement of allyloxycarboxylate enolates (Scheme 1).[13]

Although several examples of enantioselective [2,3]-Wittig rearrangements employing external chiral ligands have been reported, only one example has involved a heteroaryl allyl ether. Specifically, in 2002, Capriati *et al.*[14] reported the [2,3]-Wittig rearrangement of 2-(allyloxymethyl)benzothiazole, achieving a modest enantioselectivity of 46% ee.
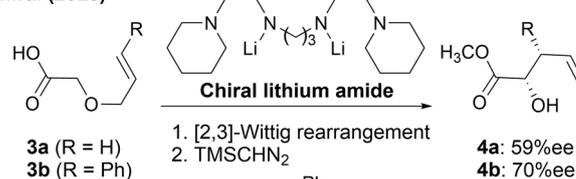
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Results and discussion

In 2019, Gladfelder *et al.*[15] reported the asymmetric alkylation of 2-alkylpyridine analogs in the presence of stoichiometric amounts of chiral lithium amide during alkylation. Based on our findings obtained from enantioselective allyloxycarboxylate enolates, we initially performed the [2,3]-Wittig rearrangement of **1** using 2.8 equivalents of *n*-butyllithium (*n*-BuLi) with 1.4 equivalents of chiral bidentate diamine (*N-tert*-butyl diamine, (*S*)-**5a**) at −80 °C for 1 day: the first equivalent of *n*-BuLi was for lithioenamine generation and the second was for enantioselective [2,3]-Wittig rearrangement (Scheme 2). The reaction proceeded 52% yield; however, the optical purity of the product was only 17% ee.
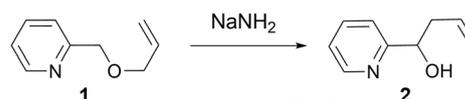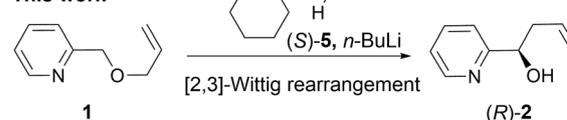

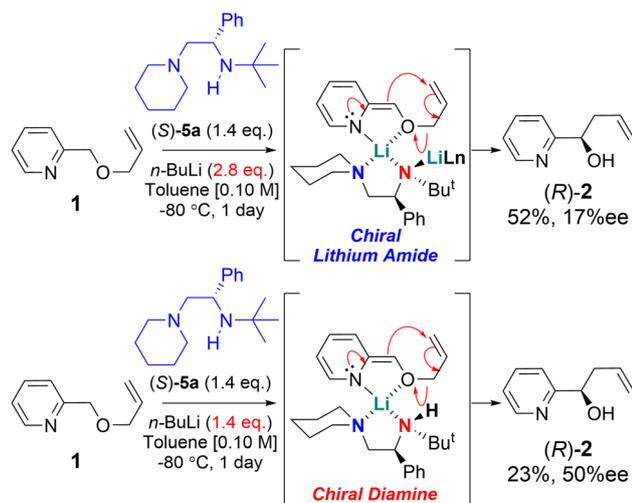**Scheme 1** The [2,3]-Wittig rearrangement of allyloxymethylacetic acids and 2-(allyloxymethyl)pyridine promoted by chiral lithium amides.

Scheme 2 Possible mechanisms of enantioselective [2,3]-Wittig rearrangement.

We hypothesized that excessive complexation with chiral lithium amide was impairing enantioselectivity. Therefore, we used 1.4 equivalent of both *n*-BuLi and chiral amine (*S*)-5a to obtain lithium-amide-free conditions during rearrangement, which significantly improved enantioselectivity (50% ee; Scheme 2).

Next, the effect of the solvent on the enantioselective [2,3]-Wittig rearrangement of 1 using bidentate chiral diamine (*S*)-5a was investigated. The results are summarized in Table 1. Moderate enantioselectivity was obtained in toluene (Table 1, entry 1); however, it was completely lost in a toluene–hexamethylphosphoramide (HMPA) mixture (2.8 eq.), 1,2-dimethoxyethane (DME), and tetrahydrofuran (THF) (Table 1, entries 2, 3, and 4, respectively). It was assumed that HMPA, DME, and THF competitively stripped the chiral amine from the lithioenamine complex *via* ligand exchange.

The effect of the bulkiness of the alkyl substituents on the nitrogen atoms was also examined. Enantioselectivity was almost the same (approximately 50% ee) when using (*S*)-5a and *N*-adamantyl diamine ((*S*)-5b) (Table 1, entries 1 and 5, respectively), but significantly lower when using *N*-neopentyl diamine ((*S*)-5c; Table 1, entry 6). In contrast, *N*-benzyl diamine ((*S*)-5d) and *N*-cyclohexyl diamine ((*S*)-5e) provided improved enantioselectivity (Table 1, entries 7 and 8, respectively), reaching 82% ee for (*S*)-5e at −100 °C (Table 1, entry 9).

Asymmetric [2,3]-Wittig rearrangements have been reported with various directing groups.[16–21] Therefore, we attempted the rearrangement of 1 using several chiral amines: (*S,S*)-PhBox (6), (*S,S*)-*t*BuBox (7), (*S,S*)-PyBox (8), the chiral diamine (−)-sparteine (9), and C_2-symmetric chiral amine (*S,S*)-10. The reactions were performed with *n*-BuLi as the base and toluene as the solvent. However, very low enantioselectivities were obtained in all cases (Table 1, entries 11–15, respectively).

The deprotonation of 1 may lead to the preferred formation of (*Z*)-lithioenamine with a five-membered chelation structure (Fig. 1). Verification of the alkyl substituents on the pyridine ring

Table 1 Results of enantioselective [2,3]-Wittig rearrangement using chiral amines with different structural features

Entry	Solvent	Chiral amine	Yield (%)	%ee[a]	Config
1	Toluene	(*S*)-5a	23	50	*R*
2	Toluene-HMPA	(*S*)-5a	53	0	—
3	DME	(*S*)-5a	43	2	*R*
4	THF	(*S*)-5a	62	0	—
5	Toluene	(*S*)-5b	22	49	*R*
6	Toluene	(*S*)-5c	31	22	*R*
7	Toluene	(*S*)-5d	49	72	*R*
8	Toluene	(*S*)-5e	63	79	*R*
9	Toluene	(*R*)-5e	78	79	*S*
10[b]	Toluene	(*S*)-5e	71	82	*R*
11[c]	Toluene	(*S,S*)-PhBox (6)	33	7	*S*
12[c]	Toluene	(*S,S*)-*t*BuBox (7)	51	0	—
13[c]	Toluene	(*S,S*)-PyBox (8)	41	3	*S*
14	Toluene	(−)-Sparteine (9)	66	16	*S*
15	Toluene	(*S,S*)-10	83	0	—
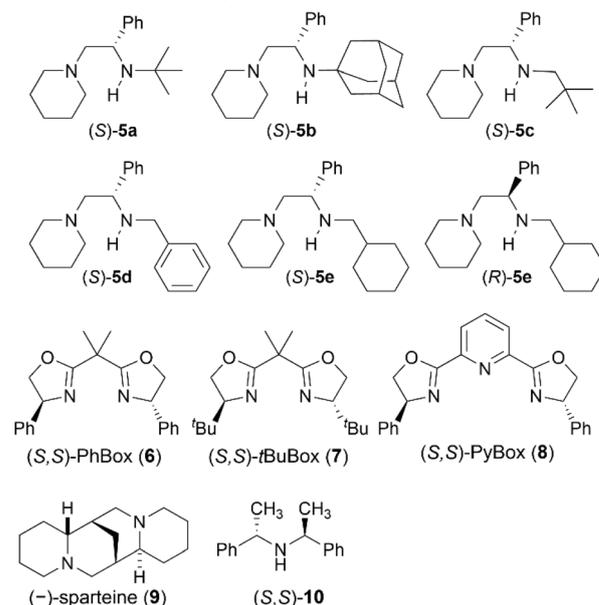
[a] Optical purity was determined by chiral HPLC (Daicel OD-3, hexane : EtOH = 100 : 0.5). [b] The reaction was performed at −100 °C. [c] The chiral amine (1.0 eq.) and *n*-BuLi (1.0 eq.) were used.

(Table 2) revealed that the enantioselectivity of 12a was improved to 92% ee (Table 2, entry 2). The presence of the 3-methyl group yielded (*Z*)-lithioenamine exclusively due to steric repulsion between the methyl and allyloxy groups (Fig. 1). In contrast, the asymmetric yield of 12c decreased significantly (Table 2, entry 3).

This decrease in the asymmetric yield was unexpected, because the 6-methyl group is located far from the reaction site; indeed, comparing the transition states of the [2,3]-Wittig
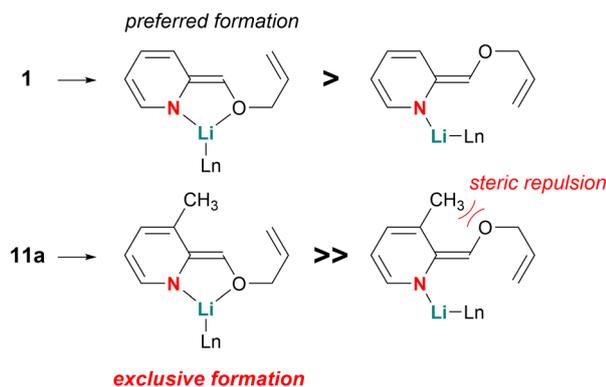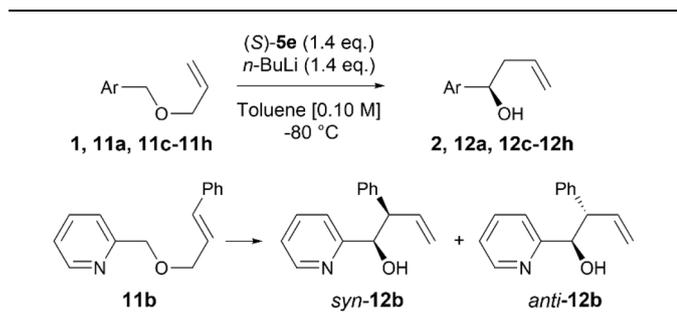
Fig. 1 (Z)-Selective formation of metalloenamine intermediates stabilized by five-membered chelation and steric repulsion.

Table 2 Substituent effects on the pyridine ring of 2-(allyloxymethyl) pyridine analogs

Entry	Substrate	Product	Time (day)	Yield (%)	%ee	Config
1	**1**	**2**	1	63	79	R
2	**11a**	**12a**	1	64	92	R[a]
3	**11b**	syn-**12b**	1	59 (syn)	77 (syn)	—[b]
		anti-**12b**		32 (anti)	81 (anti)	—[b]
4	**11c**	**12c**	3	37	36	R[a]
5	**11d**	**12d**	3	66	14	R
6	**11e**	**12e**	1	83	73	R
7	**11f**	**12f**	1	0	—	—
8	**11g**	**12g**	1	11	14	S
9	**11h**	**12h**	1	0	—	—
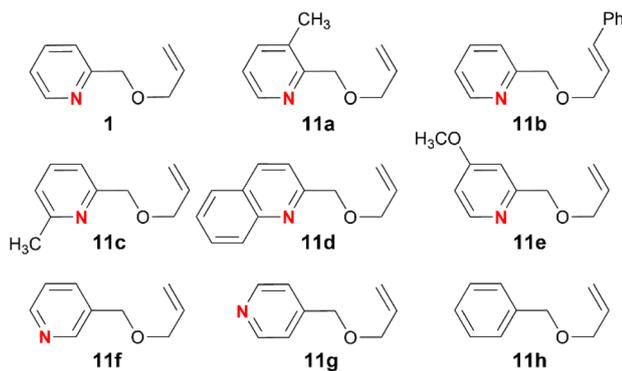
[a] The absolute configurations of **12a** and **12c** were deduced by the comparison of the ¹H-NMR spectra of Mosher's esters. See SI. [b] The absolute configuration of syn- and anti-**12b** have not been determined.

rearrangement by density functional theory (DFT) revealed that the 3-methyl group of Li-**11a** (Fig. 2, transition state TS-2) is located on the opposite side of the chiral diamine and, therefore, does not cause steric interference. Nevertheless, the 6-methyl group of Li-**11c** (Fig. 2, TS-3) is very close to the substituents on the chiral diamine, resulting in significant steric repulsion.

The low asymmetric yield of quinoline derivative **11d** can also be explained by steric repulsion between the extra benzene ring of quinoline and the chiral diamine (Table 2, entry 5 and Fig. 2, TS-4). The rearrangement of O-cinnamyl derivative **11b** proceeded with good enantioselectivity (77% ee (syn) and 81% ee (anti)), although the diastereoselectivity was modest (syn : anti = 65 : 35) (Table 2, entry 3). As predicted, **11f**, **11g**, and **11h** all had very low
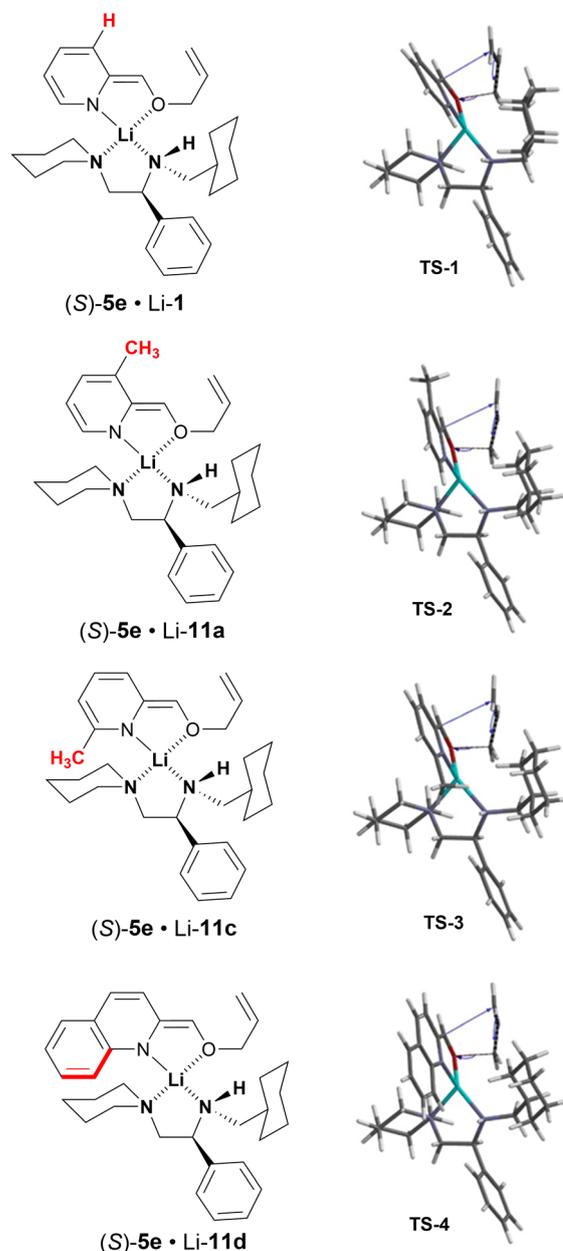

Fig. 2 Plausible transition states of [2,3]-Wittig rearrangement obtained by DFT calculation.

Table 3 Effect of *in situ* silylation (internal quench) of lithium alkoxide on enantioselective [2,3]-Wittig rearrangement

Entry	(S)-5e	n-BuLi	TMSCl	LiCl	Yield (%)	%ee
1	1.4 eq.	1.4 eq.	—	—	71	82
2	1.4 eq.	1.4 eq.	—	1.4 eq.	73	84
3	1.4 eq.	1.4 eq.	1.4 eq.	—	43	95
4	2.8 eq.	2.8 eq.	1.4 eq.	—	69	95

reactivity at −80 °C owing to the lack of effective electron-withdrawing directing group for the [2,3]-Wittig rearrangement.

Because the product of this [2,3]-Wittig rearrangement is a lithium alkoxide, it may interfere with the transition state of the ongoing reaction and reduce the enantioselectivity. To explore this further, the Wittig rearrangement was carried out in the presence of trimethylsilyl chloride (TMSCl) to trap the formed lithium alkoxide as a silyl ether (**13**), followed by acidic workup. Notably, a significant improvement in enantio-selectivity to 95% ee was achieved (Table 3, entries 3 and 4). However, the enantioselectivity did not improve when only LiCl was added (Table 3, entry 2). Thus, lithium alkoxide capture was effective for obtaining high enantioselectivity.

Conclusion

In conclusion, we demonstrated the highly enantioselective [2,3]-Wittig rearrangement of allyl picolyl ethers using chiral bidentate lithium amides. This asymmetric transformation provides easy access to chiral chemicals, materials, and pharmaceuticals containing pyridine heterocycles. Further studies are underway to expand the scope of this reaction.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI. Supplementary information: experimental procedures, NMR spectra and HPLC data. See DOI: **https://doi.org/10.1039/d5ra06385j**.

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