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5,5-Dimethyl-2-phenylamino-2-oxazoline as an effective chiral auxiliary for asymmetric alkylations

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Abstract—The novel chiral auxiliaries, 5,5-diphenyl-2-phenylamino-2-oxazoline and 5,5-dimethyl-2-phenylamino-2-oxazoline, were prepared from L-valine methyl ester. The 5,5-dimethyl compound was shown to be a particularly effective chiral auxiliary for asymmetric alkylation affording high yields and diastereoselectivities.

1. Introduction

Chiral auxiliary-derived asymmetric alkylations have been extensively studied and are now important and general methods for asymmetric carbon–carbon bond formation.[1] The asymmetric alkylations of the enolates of *N*-acyloxazolidinones **1**, developed by Evans, are widely used for the preparation of enantiopure α-substituted carboxylic acids and their derivatives.[2] However, the removal of Evans' auxiliaries with alkali lead to undesired endocyclic cleavage rather than the required exocyclic cleavage if the *N*-acyl fragment is sterically demanding. To suppress the troublesome endocyclic hydrolysis, hazardous lithium hydroperoxide has been used in place of the hydroxide.[3] Davies et al. addressed the removal problem of Evans' auxiliaries by the introduction of auxiliaries **2** with dimethyl groups at 5-C in chiral 2-oxazolidinones.[4] Dimethyl substituents have dual functions, sterically blocking nucleophilic attack to 2-oxazolidinone carbonyl and in addition serving to direct the conformation of the stereocontrolling group at 4-C. Therefore, Davies' auxiliaries do not suffer from the undesired endocyclic cleavage and give good to excellent diastereoselectivities in alkylation reactions.[4a–c] Later, Gibson and Seebach modified and independently reported the asymmetric alkylations of *N*-acyl-5,5-diaryl-2-oxazolidinones **3**.[5,6]

Recently, we documented the asymmetric alkylation of *N*-acyl-2-phenylimino-2-oxazolidine with as a high yield and diastereoselectivity as the chiral 2-oxazolidinones.[7] We expected that the introduction of dialkyl or diaryl groups at the 5-C position of our auxiliaries would have a beneficial effect on the enolate chemistry and diastereoselectivity, impacting the conformation of the stereocontrolling group at 4-C. We herein report the synthesis of the novel chiral auxiliaries, 5,5-diphenyl and 5,5-dimethyl-2-phenylamino-2-oxazolines, and the asymmetric alkylations of their *N*-acyl derivatives.

2. Results and discussion

The 2-phenylamino-2-oxazolines **6a–b** were readily prepared in two steps from the appropriate 1,2-aminoalcohols **4a–b**, which were derived from commercially available valine methyl ester hydrochloride.[6b,8] The reaction of the aminoalcohols with phenyl isothiocyanate afforded the *N*-(2-hydroxyethyl)thioureas **5a–b** in good yield, and the cyclization of the thioureas to the 2-phenylamino-2-oxazolines by a one-pot reaction using *p*-TsCl and NaOH yielded the chiral auxiliaries **6a–b** (Scheme 1).[9]

We first studied the alkylation of their propanoic acid derivatives. N-Acylations of the chiral auxiliaries **6a–b** were carried out by deprotonation with *t*-BuOK, followed by treatment with propionyl chlorides to afford the regiocontrolled *N-endo* products **7a–b** (Scheme 2).[7]

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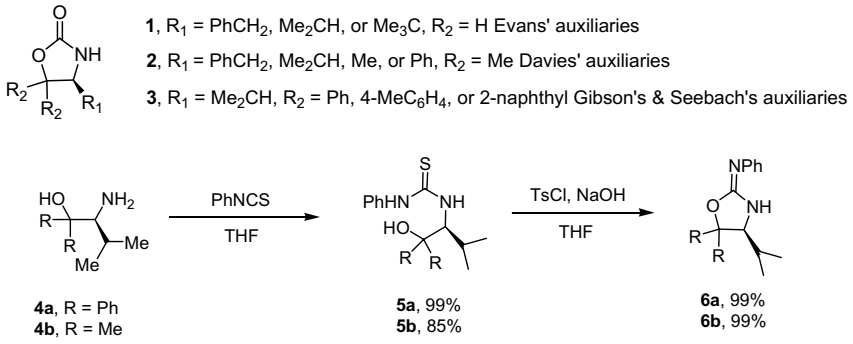
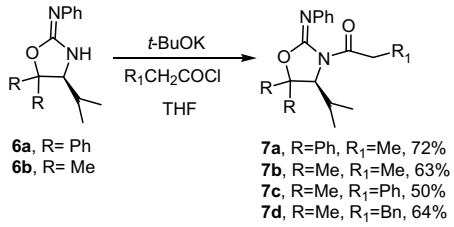
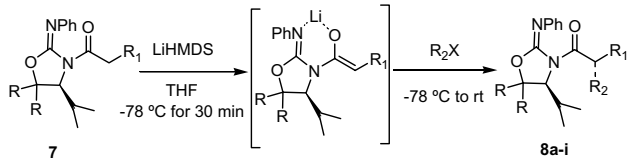


Scheme 1. Synthesis of chiral auxiliaries.



Scheme 2. N-Acylation reactions.

Asymmetric alkylations were performed using **7a**–**b**.[10] Lithium enolates were formed by treating **7a**–**b** with LiHMDS (2 equiv) at −78 °C for 30 min and the subsequent addition of the alkyl halide (3–5 equiv) led to the formation of the corresponding α-alkylated products in excellent diastereoselectivities (Scheme 3 and Table 1). The alkylation reaction with benzyl bromide and allyl bromide using the 5,5-diphenyl substituted compound **7a** gave the required products in 72–75% yields (entries 1 and 2), which are slightly lower than those obtained using the unsubstituted auxiliary (82–88%).[7] The reaction with ethyl iodide afforded product **8c** in higher yield (75%), as compared with the 55% obtained for the unsubstituted auxiliary,[7] but required 4 equiv of base to complete the reaction (entry 3).



Scheme 3. Alkylation of *N*-acyl 2-phenylimino-2-oxazolidines.

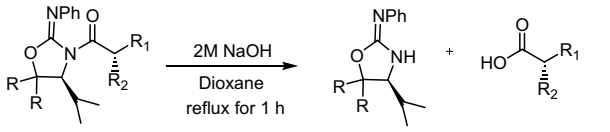
On the other hand, the 5,5-dimethyl-2-phenylamino-2-oxazoline (**6b**) was shown to have greater potential as a chiral auxiliary for asymmetric alkylations. The alkylation of **7b** with benzyl bromide and allyl bromide afforded the products **8d**–**e** in quantitative yields with excellent diastereomeric excess (de) (entries 4 and 5).[11] The ethylation reaction also furnished product **8f** with a high yield of 88% (entry 6). In addition, the lithium enolate of **7b** reacted with the even less reactive *n*-PrI to give product **8g** in moderate yield (61%, entry 7). These results show that the 5,5-dimethyl groups of **7b** play an important role in controlling the stereoselectivity, in a similar manner to that observed with the chiral 5,5-disubstituted-2-oxazolidinones.[4] 5,5-Dimethyl-2-phenylamino-2-oxazoline **7b** was shown to be the most effective auxiliary for asymmetric alkylation in our 2-phenylamino-2-oxazoline series.

We next investigated the alkylation reaction of other *N*-acyl-5,5-dimethyl-2-phenyliminooxazolidines. Auxiliary **6b** was acylated with phenylacetyl chloride and hydrocinnamoyl chloride in the presence of *t*-BuOK to give compounds **7c** and **7d**, respectively (Scheme 2). The formation of the enolate was achieved with LiHMDS, followed by treatment with methyl iodide to give products **8h**–**i** in high yields (74% and 90%, respectively) and both with an excellent de of 99%.[12] In the

Table 1. Diastereoselective alkylation of *N*-acyl 2-phenylimino-2-oxazolidines **7a**–**d**

Entry	Substrate	R	R_1	R_2X	Product[a]	Yield[b] (%)	de[c] (%)
1	**7a**	Ph	Me	$C_6H_5CH_2Br$	**8a**	75	>99
2	**7a**	Ph	Me	$CH_2{=}CHCH_2Br$	**8b**	72	96
3	**7a**	Ph	Me	CH_3CH_2I	**8c**	75	>99
4	**7b**	Me	Me	$C_6H_5CH_2Br$	**8d**	99	>99
5	**7b**	Me	Me	$CH_2{=}CHCH_2Br$	**8e**	99	>99
6	**7b**	Me	Me	CH_3CH_2I	**8f**	88	>99
7	**7b**	Me	Me	$CH_3CH_2CH_2I$	**8g**	61	>99
8	**7c**	Me	Ph	CH_3I	**8h**	74	>99
9	**7d**	Me	Bn	CH_3I	**8i**	90	>99

[a] The configuration as verified by correlation with authentic sample after removal of the chiral auxiliary.
[b] Isolated yield after purification.
[c] Determined by HPLC (Spherisorb ODS column).



8a, R= Ph, R_1= Me, R_2 =Bn	**6a**, 88%	**9a**, 74%
8b, R= Ph, R_1= Me, R_2 =Allyl	**6a**, 99%	**9b**, 88%
8d, R= Me, R_1= Me, R_2 =Bn	**6b**, 98%	**9a**, 82%
8i, R= Me, R_1 = Bn, R_2 = Me	**6b**, 97%	**9c**, 85%

Scheme 4. Hydrolysis and recovery of chiral auxiliaries.

case of **7d**, 4 equiv of base was employed to force the reaction to completion. These high diastereoselectivities might be due to the conformational control of the stereodirecting isopropyl group depending on the dimethyl group at 5-C as proposed by Davies' group.[4c]

The alkylated products **8** were hydrolyzed by 2 M sodium hydroxide in dioxane to furnish the corresponding alkylated carboxylic acids **9a–c** (74–88%) and the recovered chiral auxiliaries **6a–b** (88–99%) (Scheme 4). As expected, no products resulting from endocyclic cleavage were observed in the cleavage reaction. Herein, compound **8d** ($R = Me$, $R_1 = Me$, $R_2 = Ph$) with the dimethyl group also gave a better yield of both the recovered chiral auxiliary and chiral acid than the corresponding diphenyl substituted compound **8a** ($R = Ph$, $R_1 = Me$, $R_2 = Ph$) (Scheme 3). The absolute configurations and enatiomeric purity of acids **9a–c** were determined by comparing the measured optical rotations with the known values.[13]

In summary, we have developed a new chiral auxiliary, 5,5-dimethyl-2-phenylamino-2-oxazolidine, which has great potential for asymmetric alkylations. The alkylated products were obtained in high yields with excellent diastereoselectivities. The chiral auxiliary was easily recovered by hydrolysis with sodium hydroxide affording the chiral α-alkylated carboxylic acids.

Acknowledgment

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10. *General procedure for asymmetric alkylation of N-acyl 5,5-disubstituted 2-phenylimino-2-oxazolidines*. To a dry round-bottomed flask under nitrogen was added compound **7** (0.1 g) in anhydrous THF (4 mL). The solution was cooled to −78 °C. A solution of lithium bis(trimethylsilylamide) (LiHMDS) in THF (1.0 M, 2–4 equiv) was added dropwise, and the solution was allowed to stir for 30 min. The mixture was treated with halide (3–8 equiv). After stirring for 30 min at −78 °C and 1 h at 0 °C, the reaction mixture was quenched with saturated ammonium chloride (4 mL) and water (20 mL) and extracted with ether. The combined extracts were dried over magnesium sulfate, filtered, and concentrated. HPLC analysis of the crude product revealed the isomer ratios. Purification by flash chromatography (hexane/EtOAc 8:2) afforded the major diastereomer **8**.
Compound **8a**: Yield 75%; oil; $[\alpha]_D^{20}$ +21.8 (*c* 0.73, $CHCl_3$); $R_f = 0.5$ (ethyl acetate/hexane 1:4); ^1H NMR ($CDCl_3$) δ 7.39–7.14 (20H, m), 5.50 (1H, d, $J = 3.3$ Hz), 4.41–4.44 (m, 1H), 3.30 (1H, dd, $J = 10.4$ Hz, 6.3 Hz), 2.58 (1H, dd, $J = 10.4$ Hz, 6.3 Hz), 1.96–1.91 (1H, m), 0.81 (3H, d, $J = 6.9$ Hz), 0.76 (3H, d, $J = 6.8$ Hz), 0.73 (3H, d, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 176.4, 145.7, 145.4, 142.6, 139.8, 138.6, 129.2, 128.7, 128.6, 128.2, 128.1, 128.1, 127.6, 125.9, 125.7, 125.4, 123.5, 122.8, 89.9, 64.2, 39.5, 38.3, 29.6, 21.5, 16.4, 15.8.
Compound **8b**: Yield 72%; oil; $[\alpha]_D^{20}$ +10.8 (*c* 0.3, $CHCl_3$); $R_f = 0.5$ (ethyl acetate/hexane 1:4); ^1H NMR ($CDCl_3$) δ 7.41–7.13 (15H, m), 5.85–5.79 (m, 1H), 5.50 (1H, d, $J = 3.3$ Hz), 5.13–4.99 (m, 2H), 4.20–4.08 (m, 1H), 2.65–2.60 (m, 1H), 2.18–2.04 (m, 1H), 1.99–1.95 (1H, m), 0.90 (3H, d, $J = 6.9$ Hz), 0.84 (3H, d, $J = 6.8$ Hz), 0.74 (3H, d, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 176.4, 145.7, 145.4, 142.7, 138.7, 136.2, 129.2, 128.7, 128.7, 128.3, 128.2, 127.6, 125.8, 125.5, 123.5, 122.8, 116.4, 90.0, 64.3, 37.7, 36.3, 29.7, 21.6, 16.6, 16.0.
Compound **8c**: Yield 75%; white solid; mp 116–118 °C; $[\alpha]_D^{20}$ +6.3 (*c* 3.4, $CHCl_3$); $R_f = 0.5$ (ethyl acetate/hexane 1:4); ^1H NMR ($CDCl_3$) δ 7.41–7.10 (15H, m), 5.50 (1H, d, $J = 3.3$ Hz), 4.00–3.93 (m, 1H), 2.00–1.91 (m, 1H), 1.88–1.82 (m, 1H), 1.45–1.36 (1H, m), 0.95 (3H, d, $J = 6.9$ Hz),

0.91 (3H, d, $J = 6.9$ Hz), 0.85 (3H, d, $J = 6.8$ Hz), 0.72 (3H, d, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 177.1, 145.7, 145.5, 142.8, 138.7, 128.7, 128.6, 128.2, 128.1, 127.6, 125.8, 125.4, 123.5, 122.8, 89.9, 64.3, 38.2, 29.6, 26.7, 21.7, 16.6, 16.0, 11.8.

Compound **8d**: Yield 99%; oil; $[\alpha]_D^{20}$ +126.0 (c 0.4, $CHCl_3$); $R_f = 0.5$ (ethyl acetate/hexane 1:4); ^{1}H NMR ($CDCl_3$) δ 7.34–7.07 (10H, m), 4.70 (1H, m), 4.30 (1H, d, $J = 3.2$ Hz), 3.39 (1H, dd, $J = 13.1$ Hz, 6.1 Hz), 2.60 (1H, dd, $J = 13.1$ Hz, 8.8 Hz), 2.10–2.05 (1H, m), 1.45 (3H, s), 1.33 (3H, s), 1.12 (3H, d, $J = 6.7$ Hz), 0.92 (3H, d, $J = 6.8$ Hz), 0.90 (3H, d, $J = 6.7$ Hz); ^{13}C NMR ($CDCl_3$) δ 177.1, 146.5, 145.9, 129.3, 128.6, 128.1, 126.0, 123.2, 123.0, 83.3, 65.9, 40.0, 38.7, 29.7, 28.3, 21.5, 21.3, 16.8, 16.1.

Compound **8e**: Yield 99%; oil; $[\alpha]_D^{20}$ +119.0 (c 0.65, $CHCl_3$); $R_f = 0.5$ (ethyl acetate/hexane 1:4); ^{1}H NMR ($CDCl_3$) δ 7.31–7.25 (2H, m), 7.08–7.02 (3H, m), 5.96–5.82 (m, 1H), 5.16–5.02 (m, 2H), 4.41–4.35 (m, 1H), 4.29 (1H, d, $J = 3.1$ Hz), 2.73–2.64 (m, 1H), 2.27–2.15 (m, 1H), 2.16–2.07 (1H, m), 1.46 (3H, s), 1.33 (3H, s), 1.17 (3H, d, $J = 6.8$ Hz), 1.03 (3H, d, $J = 6.7$ Hz), 0.99 (3H, d, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 177.0, 146.4, 145.8, 136.1, 128.5, 123.2, 123.0, 116.4, 83.3, 65.9, 38.2, 36.6, 29.7, 28.3, 21.6, 21.2, 17.0, 16.2.

Compound **8f**: Yield 88%; oil; $[\alpha]_D^{20}$ +107.0 (c 0.44, $CHCl_3$); $R_f = 0.5$ (ethyl acetate/hexane 1:4); ^{1}H NMR ($CDCl_3$) δ 7.31–7.26 (2H, m), 7.08–7.02 (3H, m), 4.29 (1H, d, $J = 3.1$ Hz), 4.19 (m, 1H), 2.14–2.11 (m, 1H), 1.96–1.89 (1H, m), 1.54–1.41 (1H, m), 1.46 (3H, s), 1.32 (3H, s), 1.17 (3H, d, $J = 6.8$ Hz), 1.04 (3H, d, $J = 6.7$ Hz), 1.02 (3H, d, $J = 6.9$ Hz), 1.00 (3H, t);^{13}C NMR ($CDCl_3$) δ 177.7, 146.4, 145.9, 128.5, 123.2, 123.0, 83.2, 65.9, 38.4, 29.6, 28.3, 27.2, 21.6, 21.3, 17.0, 16.2, 11.7.

Compound **8g**: Yield 75%; brown oil; $[\alpha]_D^{20}$ +108.2 (c 0.35, $CHCl_3$); $R_f = 0.5$ (ethyl acetate/hexane 1:4); ^{1}H NMR ($CDCl_3$) δ 7.31–7.25 (2H, m), 7.07–7.02 (3H, m), 4.32–4.28 (m, 1H), 4.29 (1H, d, $J = 3.1$ Hz), 2.14–2.09 (m, 1H), 1.45–1.41 (3H, m), 1.54–1.41 (1H, m), 1.45 (3H, s), 1.39 (3H, s), 1.16 (3H, d, $J = 6.8$ Hz), 1.04 (3H, d, $J = 6.7$ Hz), 1.00 (3H, d, $J = 6.9$ Hz), 0.99 (3H, t); ^{13}C NMR ($CDCl_3$) δ 178.0, 146.4, 145.9, 128.5, 123.2, 123.0, 83.2, 65.9, 36.7, 36.2, 29.6, 28.3, 21.7, 21.3, 20.4, 17.0, 16.7, 14.1.

Compound **8h**: Yield 75%; oil; $[\alpha]_D^{20}$ +108.8 (c 0.67, $CHCl_3$); $R_f = 0.5$ (ethyl acetate/hexane 1:4); ^{1}H NMR ($CDCl_3$) δ 7.32–6.88 (10H, m), 5.65 (1H, q, $J = 6.7$ Hz), 4.30 (1H, d, $J = 3.2$ Hz), 2.14–2.07 (1H, m), 1.56 (3H, d, $J = 6.7$ Hz), 1.34 (3H, s), 1.10 (3H, d, $J = 6.7$ Hz), 1.02 (3H, d, $J = 6.8$ Hz), 0.86 (3H, s); ^{13}C NMR ($CDCl_3$) δ 174.8, 146.9, 145.8, 141.3, 129.1, 128.5, 128.4, 128.3, 126.8, 123.2, 122.7, 83.6, 67.0, 42.9, 29.7, 27.8, 21.7, 21.3, 19.5, 17.0.

Compound **8i**: Yield 90%; oil; $[\alpha]_D^{20}$ +70.1 (c 0.34, $CHCl_3$); $R_f = 0.5$ (ethyl acetate/hexane 1:4); ^{1}H NMR ($CDCl_3$) δ 7.32–7.00 (10H, m), 4.86–4.79 (1H, m), 4.11 (1H, d, $J = 3.2$ Hz), 3.07 (1H, dd, $J = 13.3$ Hz, 9.0 Hz), 2.60 (1H, dd, $J = 13.3$ Hz, 6.0 Hz), 2.10–2.04 (1H, m), 1.35 (3H, s), 1.32 (3H, d, $J = 6.7$ Hz), 1.03 (3H, d, $J = 6.7$ Hz), 1.00 (3H, d, $J = 6.7$ Hz), 0.83 (3H, s); ^{13}C NMR ($CDCl_3$) δ 177.0, 146.6, 146.0, 140.1, 129.0, 128.5, 128.2, 126.0, 123.2, 122.8, 83.3, 65.8, 39.8, 38.7, 29.6, 27.4, 21.6, 21.2, 18.3, 17.0.

11. Davies' group reported that the benzylation of *N*-acyl derivatives in their chiral auxiliary furnished the desired product in 93% yield with 95% de.[4b]
12. The diastereoselectivities of same reactions with the Davies' oxazolidinones were 94% de in **8h**[4d] and 95% de in **8i**.[4a]
13. The crude auxiliary was recovered by extracting the reaction mixture with ethyl acetate. The required carboxylic acid was isolated almost quantitatively by extracting with CH_2Cl_2 after acidifying the aqueous layer to pH 2. Specific rotation: **9a**: $[\alpha]_D^{24}$ −24.0 (c 0.17, $CHCl_3$), lit.[14] $[\alpha]_D^{20}$ −23.1 (c 1, $CHCl_3$); **9b**: $[\alpha]_D^{24}$ −8.0 (c 0.14, $CHCl_3$); lit.[15] $[\alpha]_D^{20}$ −8.2 (c 1, $CHCl_3$); **9c**: $[\alpha]_D^{24}$ +24.2 (c 0.19, $CHCl_3$); lit.[16] $[\alpha]_D^{20}$ +25.5 (c 1, $CHCl_3$).
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