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Stereoregulations of Pyrimidinone Based Chiral Auxiliary in Aldol and Alkylation Reactions: A Convenient Route to Oxyneolignans

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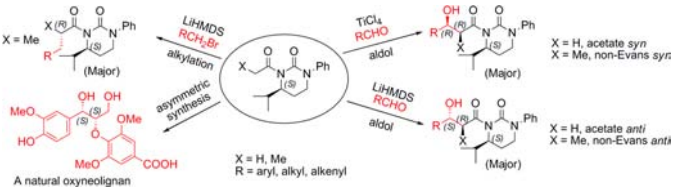
ABSTRACT



(*S*)-4-Isopropyl-1-phenyltetrahydropyrimidin-2(1*H*)-one was synthesized and evaluated as a chiral auxiliary for asymmetric acetate and propionate aldol reactions, by generation of titanium and lithium enolates, affording excellent yields and stereoselectivities for *syn* and *anti* aldol diastereomers, respectively. High stereoselectivities were also obtained in lithium mediated alkylation reactions. The application of the auxiliary was exemplified in the asymmetric synthesis of a natural oxyneolignan, (+)-(7*S*,8*S*)-4-hydroxy-3,3′,5′-trimethoxy-8′,9′-dinor-8,4′-oxyneoligna-7,9-diol-7′-oic acid.

Aldol and alkylation reactions employing a chiral auxiliary are a widely recognized approach for generating stereogenic centers during C−C bond formation.[1] Evans et al. illustrated the usefulness of an oxazolidinone based chiral auxiliary in a dialkylboron triflate mediated propionate aldol reaction, affording the *syn* selective β-hydroxy acids in high enantiomeric purity.[2] Later enolates of Li,[3] Ti,[4] and Sn[5] have also been used extensively in stereoselective aldol reactions. Despite the high selectivity in the propionate aldol reaction, the oxazolidinone auxiliary fails in acetate aldol reactions especially with aliphatic[4e] and α,β-unsaturated aldehydes.[2,4d] The auxiliary also suffers from endocyclic cleavage in cases of highly congested aldol adducts.[6] Many of these issues have been addressed later with their solutions in the form of new or improved auxiliaries.[4c,g,h] However, several problems including narrow substrate scope, modest diastereoselectivity with either aliphatic or aromatic aldehydes, limitations in reactivity, expensive reagents and metal sources, and difficulty in handling the reagents restricted the wide synthetic applicability.[2,4,5] These limitations demand development of a robust auxiliary for C−C bond forming reactions.

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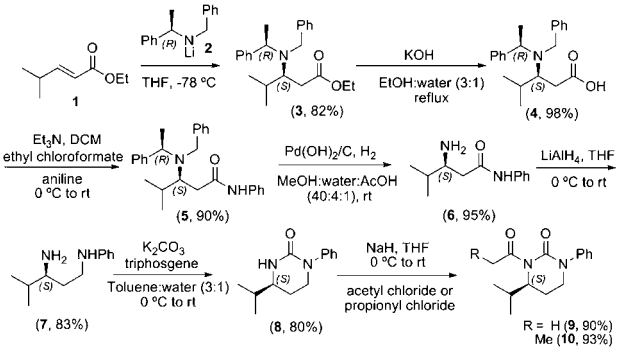
In continuation of our work[7] on metal mediated reactions, we investigated the usefulness of (*S*)-4-isopropyl-1-phenyltetrahydropyrimidin-2(1*H*)-one as a chiral auxiliary in asymmetric aldol and alkylation reactions. Apart from the excellent yields and diastereoselectivity obtained in both these reactions, the auxiliary has an *N*-phenyl group which serves as a chromophoric unit that assists in reaction monitoring and chromatographic purification. Another advantage is that the cyclic ureido frame resists endocyclic cleavage while the cyclic carbamate in oxazolidinones is prone to base hydrolysis. The auxiliary undergoes rapid enolization with a slight excess of the reagents, compared to the use of 2 equiv or more of a costly Lewis acid and chiral base.[4e,f,8] The application of the auxiliary is shown in the concise synthesis of a natural oxyneolignan.

The synthesis of the chiral auxiliary was achieved as illustrated in Scheme 1. (*S*)-4-Methyl-*N*-phenylpentan-1,3-diamine **7**, obtained by Michael addition[9] of the lithiated chiral secondary amine **2** on (*E*)-ethyl 4-methylpent-2-enoate **1**, and subsequent functional group transformations, was cyclized using triphosgene and K_2CO_3 to obtain (*S*)-4-isopropyl-1-phenyltetrahydropyrimidin-2(1*H*)-one **8**.

Scheme 1. Synthesis of the Chiral Auxiliary



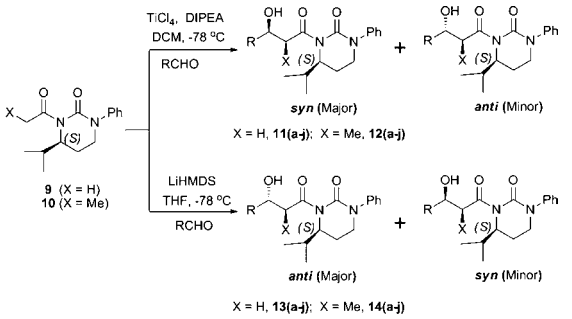
Acylation of **8** under basic conditions afforded the acetylated and propionylated products **9** and **10**, respectively. The acetylated derivative **9** was treated with $TiCl_4$ (1.05 equiv) and DIPEA (1.1 equiv) in DCM at −78 °C to generate the titanium enolate. Reaction of the enolate with benzaldehyde afforded the acetate aldol product (Scheme 2) in excellent yield. ^{1}H NMR analysis of the crude product revealed a diastereoselectivity of 97:03. The major acetate aldol diastereomer **11a** was hydrolyzed with lithium hydroperoxide. The optical rotation of the resulting free acid was compared with literature,[10a] and a *syn* relation was concluded between the hydroxy group and the stereodirecting isopropyl group of the auxiliary for **11a**. The reaction conditions when extended to **10** gave the non-Evans *syn* aldol diastereomer **12a** as the major product, confirmed by hydrolysis and comparison of the optical rotation of the resulting acid with the reported value.[10b] The reaction afforded a good yield, and a diastereoselectivity of 99:01 was determined from the ^{1}H NMR spectrum of the reaction mixture. The scope of both these aldol reactions were examined by employing various aromatic, aliphatic, and α,β-unsaturated aldehydes to afford the corresponding acetate *syn* aldols (**11a**−**j**) and non-Evans propionate *syn* aldols (**12a**−**j**) (Table 1). The effect of metal on the stereochemical outcome of the aldol reaction was evaluated by generating the lithium enolates of **9** and **10** using LiHMDS (1.05 equiv) in anhydrous THF at −78 °C. The reaction of the enolates with benzaldehyde yielded the aldol products with reversal of selectivity. A diastereoselectivity of 04:96 favoring the *anti* diastereomer **13a** was observed for the acetate aldol reaction while the propionate aldol reaction afforded the non-Evans *anti* diastereomer **14a** in a ratio of 01:99. The stereochemistry of the diastereomers **13a** and **14a** were confirmed by hydrolysis of the aldol adducts to the corresponding carboxylic acids and comparison of the optical rotation values with the literature.[10] The reaction was generalized using various aldehydes to afford the products (**13a**−**j**, **14a**−**j**) in excellent yields and stereoselectivities.

Table 1. Titanium and Lithium Mediated Stereoselective Aldol Reactions

		$TiCl_4$ mediated[a]				LiHMDS mediated[b]			
		X = H, acetate		X = Me, propionate		X = H, acetate		X = Me, propionate	
entry	RCHO	*syn*:*anti*[c]	yield %[d]	*syn*:*anti*[c]	yield %[d]	*syn*:*anti*[c]	yield %[d]	*syn*:*anti*[c]	yield %[d]
1	C_6H_5CHO	97:03	**11a** (88)	99:01	**12a** (80)	04:96	**13a** (94)	01:99	**14a** (96)
2	4-MeC_6H_4CHO	98:02	**11b** (86)	99:01	**12b** (83)	03:97	**13b** (96)	02:98	**14b** (97)
3	4-$MeOC_6H_4CHO$	95:05	**11c** (78)	99:01	**12c** (72)	06:94	**13c** (72)	06:94	**14c** (88)
4	4-ClC_6H_4CHO	97:03	**11d** (87)	97:03	**12d** (85)	04:96	**13d** (95)	03:97	**14d** (98)
5	4-BrC_6H_4CHO	98:02	**11e** (85)	95:05	**12e** (80)	05:95	**13e** (88)	02:98	**14e** (93)
6	$C_6H_5CH_2CHO$	98:02	**11f** (80)	98:02	**12f** (80)	06:94	**13f** (93)	04:96	**14f** (93)
7	$C_6H_5CH{=}CHCHO$	98:02	**11g** (85)	95:05	**12g** (80)	05:95	**13g** (85)	05:95	**14g** (85)
8	$(Me)_2C{=}CHCHO$	93:07	**11h** (83)	92:08	**12h** (85)	08:92	**13h** (92)	06:94	**14h** (95)
9	$(Me)_3CCHO$	97:03	**11i** (75)	98:02	**12i** (72)	02:98	**13i** (92)	02:98	**14i** (92)
10	$(Me)_2CHCHO$	96:04	**11j** (79)	97:03	**12j** (76)	04:96	**13j** (88)	03:97	**14j** (88)

[a] The reactions were carried out at −78 °C with 1.0 equiv of **9** or **10**, 1.05 equiv of $TiCl_4$, 1.1 equiv of DIPEA, and 1.1 equiv of aldehyde in DCM (5 mL). [b] The reactions were carried out at −78 °C with 1.0 equiv of **9** or **10**, 1.05 equiv of both LiHMDS and aldehyde in anhydrous THF (5 mL). [c] Diastereoselectivity ratios are based on ^{1}H NMR spectra of the crude products. [d] Isolated yield of the major diastereomer.

Scheme 2. Stereoselective Aldol Reactions



To account for the stereoselectivity, chelated six-membered chair and nonchelated boat transition state models were considered respectively, for Ti- and Li-mediated aldol reactions (Scheme 3).[11] $TiCl_4$ is expected to form a *Z* enolate with the *N*-propionyl derivative of the auxiliary, **10**. Due to the high coordination ability of titanium, it complexes with the O-atom of aldehyde and also with any suitably positioned group on the auxiliary to form a chelated structure, as shown in **TS-A** and **TS-B**. The tight hexacoordinate species thus adopts an almost perpendicular conformation between the enolate C=C and aldehyde C=O groups. In **TS-A**, the aldehyde substituent R occupies an equatorial position to avoid a 1,3-diaxial interaction, affording the *syn* aldol diastereomer as the major product while **TS-B** leading to the *anti* aldol would have the R group positioned axially and, hence, disfavored. It may also be assumed that in **TS-A** the enolate substituent X would be forced into an eclipsed conformation with the aldehyde C=O group, to avoid a gauche interaction with the aldehyde substituent R, depending upon the steric hindrance imparted. Yet, to account for the non-Evans *anti* aldol selectivity observed with the lithium enolate, transition state models **TS-C** and **TS-D** can be envisaged. The gauche interaction between the enolate substituent X and the aldehyde group R and the freedom experienced from nonchelation promotes the formation of a boat transition state over the chair for the *Z* enolate of lithum.

Scheme 3. Stereoselectivity in Aldol Reactions

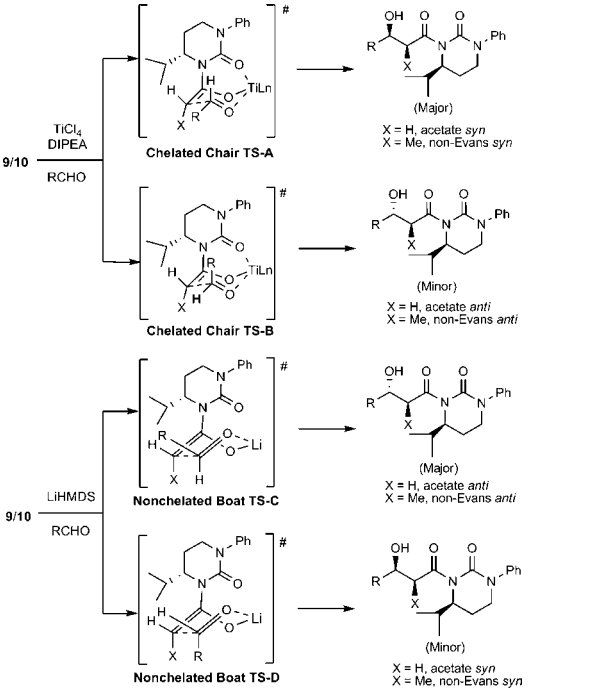
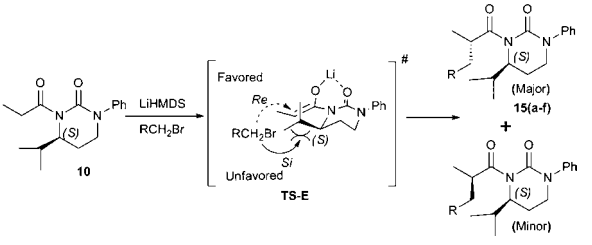


Table 2. Lithium Mediated Stereoselective Alkylation Reactions[a]



entry	condition[b]	RCH_2Br	*dr*[c]	yield %[d]
1	**A**	$C_6H_5CH_2Br$	>99:1	**15a** (30)
2	**B**	$C_6H_5CH_2Br$	>99:1	**15a** (98)
3	**B**	$4\text{-}BrC_6H_4CH_2Br$	>99:1	**15b** (95)
4	**B**	$4\text{-}MeC_6H_4CH_2Br$	>99:1	**15c** (98)
5	**B**	EtO_2CCH_2Br	>99:1	**15d** (96)
6	**B**	$CH_2{=}CHCH_2Br$	>99:1	**15e** (94)
7	**B**	$MeCH_2Br$	>99:1	**15f** (98)

[a] The reactions were carried out with 1.0 equiv of **10**, 1.05 equiv of both LiHMDS and organic halide in anhydrous THF (5 mL). [b] Condition A = 1.05 equiv of LiHMDS, −78 °C to rt. Condition B = 1.05 equiv of both LiHMDS and TMEDA, −60 °C to rt. [c] Diastereoselectivity ratios are based on ^1H NMR spectra of the crude products. [d] Isolated yield of the major diastereomer.

Thus in **TS-C**, the R group is accommodated in such a position that it encounters less steric repulsions from the enolate substituent X and the auxiliary, favoring the *anti* aldol as the major product. But in the case of **TS-D**, gauche

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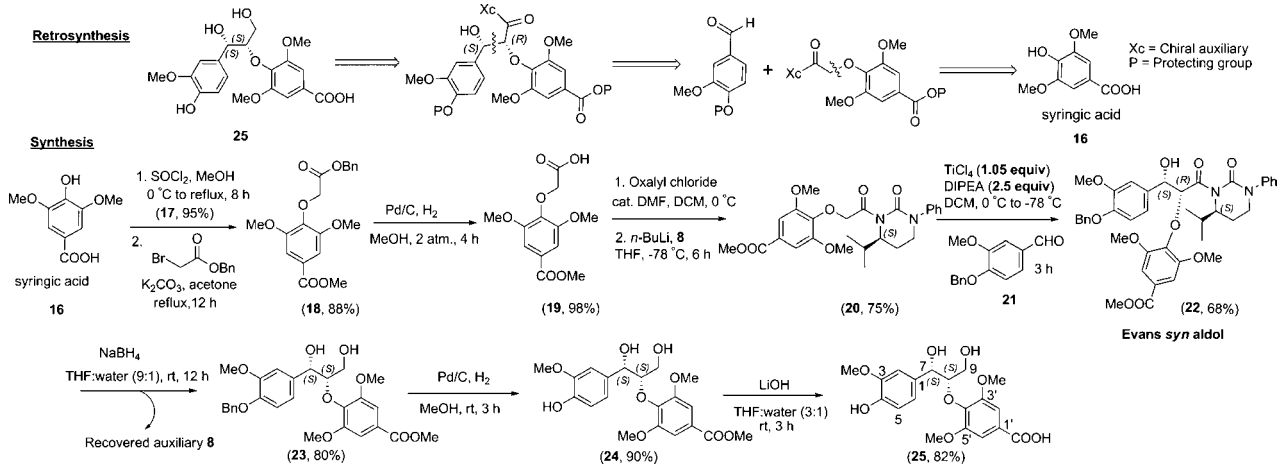
Scheme 4. Synthesis of (+)-(7*S*,8*S*)-4-Hydroxy-3,3′,5′-trimethoxy-8′,9′-dinor-8,4′-oxyneoligna-7,9-diol-7′-oic Acid **25**



interaction between the X and R groups arising from the eclipsed conformation disfavors the *syn* aldol formation.

The usefulness of the auxiliary was then examined in the alkylation reaction.[1e−i] Deprotonation of **10** with LiHMDS at −78 °C, followed by addition of benzyl bromide either at the same temperature or 0 °C, witnessed very sluggish reactions (Table 2, entry 1). Further attempts were made to enhance the deprotonation by chelating the cation using tetramethylethylenediamine (TMEDA) so that the hexamethyldisilylamide anion is sufficiently basic for proton abstraction. Addition of equimolar amounts of LiHMDS and TMEDA to a solution of **10** in THF at −60 °C followed by benzyl bromide resulted in a dramatic improvement in the reaction (Table 2, entry 2). The benzylated product **15a** was obtained in excellent yield (98%) and diastereoselectivity (>99% *de*). The alkylated product **15a** was hydrolyzed with lithium hydroperoxide. The optical rotation of the free acid on comparison with the literature[1e] revealed an *anti* relation between the alkyl group and the stereodirecting isopropyl group of the auxiliary for **15a**. The reaction conditions were then generalized with substituted benzyl bromides bearing electron-donating/-withdrawing groups and various aliphatic bromides (Table 2, entries 2−7). The observed stereoselectivity in the alkylation reaction can be explained by the proposed transition state model **TS-E** (Table 2). Kinetic deprotonation using LiHMDS at low temperature favors the formation of a *Z* enolate. The *si* face of the enolate is shielded by the bulky isopropyl group of the auxiliary which disfavors the approach of the electrophile. The *re* face on the other hand is less hindered and hence more accessible, resulting in high stereoselectivity for the alkylation reactions.

The scope of the auxiliary was further illustrated in the synthesis of a natural oxyneolignan **25**, recently isolated from the stem of *Sinocalamus affinis* and identified as (+)-(7*S*,8*S*)-4-hydroxy-3,3′,5′-trimethoxy-8′,9′-dinor-8,4′-oxyneoligna-7,9-diol-7′-oic acid.[13] Synthesis of the oxyneolignan was accomplished from commercially available syringic acid **16** (Scheme 4). The methyl ester of syringic acid **17** was alkylated using benzyl bromoacetate and subjected to catalytic hydrogenolysis to give 2-(2,6-dimethoxy-4-(methoxycarbonyl)phenoxy)acetic acid **19**. The corresponding acid chloride was then coupled with the auxiliary **8** to obtain the acylated derivative **20**. Subsequent reaction of the enolate generated from **20** using $TiCl_4$ (1.05 equiv) and DIPEA (2.5 equiv) with 4-(benzyloxy)-3-methoxybenzaldehyde **21** gave the Evans *syn* aldol[8c,12] diastereomer **22** (*dr* = 9:1). Reductive hydrolysis of the diastereomer **22** yielded the desired intermediate **23**. Finally, cleavage of the aryloxy benzyl group by Pd-catalyzed hydrogenolysis followed by base hydrolysis of the ester afforded the oxyneolignan, (+)-(7*S*,8*S*)-4-hydroxy-3,3′,5′-trimethoxy-8′,9′-dinor-8,4′-oxyneoligna-7,9-diol-7′-oic acid **25**. The structure and stereochemistry of the oxyneolignan **25** were confirmed spectroscopically and by comparing the optical rotation with the literature.[13]

In conclusion, the stereoregulations imparted by the (*S*)-4-isopropyl-1-phenyltetrahydropyrimidin-2(1*H*)-one chiral auxiliary in asymmetric aldol and alkylation reactions were evaluated. The products were obtained in high yields and excellent stereoselectivity. The synthetic utility of the auxiliary was illustrated by a concise synthesis of a newly isolated natural oxyneolignan in nine steps and 24% overall yield.

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Supporting Information Available. Experimental procedures; ^{1}H NMR, ^{13}C NMR, and HRMS (ESI) data of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) When 2.5 equiv of DIPEA was used, the Evans *syn* aldol adduct was formed with excellent selectivity. The amine probably coordinates to titanium disfavoring the chelated transition state.

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The authors declare no competing financial interest.