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Design and Implementation of New Auxiliaries for Asymmetric Enolate Alkylations.‡

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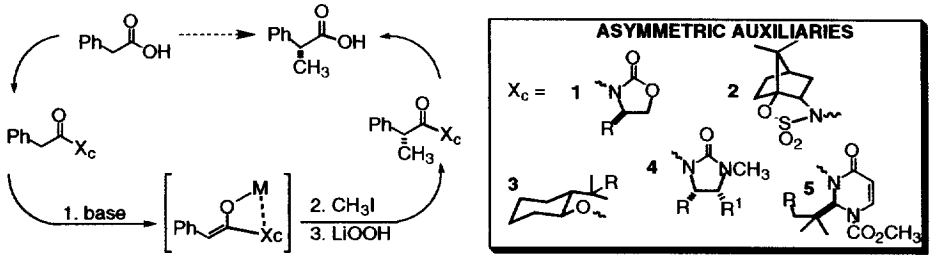
Abstract: Implementation of new, highly enantioenriched heterocycles for use in auxiliary-supported asymmetric alkylations is detailed. These new auxiliaries proved effective in enforcing pi-facial selectivity in enolate methylations with increasing diastereoselectivity resulting from bulkier aryl-steering groups. The sources for unanticipated kinetic effects and alkylation product decompositions are discussed. © 1997 Elsevier Science Ltd.

Auxiliary-mediated asymmetric alkylation of carboxylic acids is now widely applied in the research production of optically enriched carboxylic acid derivatives. Numerous auxiliaries have been introduced that provide high levels of asymmetric induction (see for example **1**-**5**, Scheme 1).[1] Following this prescript, the chiral appendage is covalently attached to the carboxylic acid allowing for the differentiation between pi-faces generated upon enolate formation. Subsequent diastereoselective alkylation and removal of the auxiliary delivers optically pure carboxylic acids. Despite the general successes of this method, enolate methylations of existing auxiliary analogues occurs less selectively. For example, the methylations of butyryl enolates **1** (R = i-Pr) and **5** (R = H) resulted in d.e. of 86%.[1c,g] Furthermore, enolate methylations of more complex substrates have been reported with significantly reduced selectivities. Since we require optically enriched α-aryl-α-methylacetic acids, we modified **5** in efforts to promote better diastereoselectivity upon enolate methylations of α-arylacetic acids. This report describes the design and alkylations with these new auxiliaries.

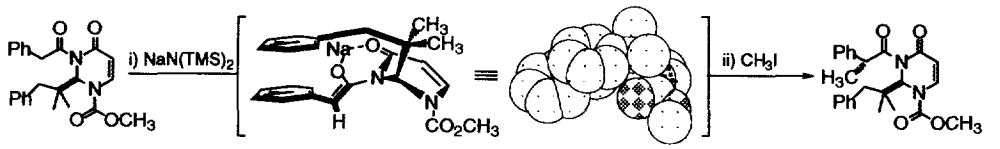


Scheme. 1. Auxiliary-mediated asymmetric alkylation (hashed arrow represents overall transformation).

Pyrimidinone **5** is a versatile scaffold that can accommodate structural modifications for improving enolate alkylation diastereoselectivity. The cyclic skeleton of the auxiliary is planar with the exception of the asymmetric carbon which supports the blocking group.[1g] The incorporation of sterically hindering aromatic units at the blocking group (**5b**: R = phenyl; **5c**: R = 1-naphthyl) can be accomplished by facile synthetic modifications. Functionalization of these new heterocycles as their phenylacetyl analogues and subsequent enolate formation (Scheme 2) and alkylation should deliver improved diastereoselectivity with a predictable stereochemical outcome. Additionally, potential pi-pi interactions between the aryl blocking group and the phenyl enolate places the blocking unit in an optimal position for the asymmetric functionalization of the

‡ Dedicated to the memory of Professor Gloria G. Lyle (1923-1996).

enolate.[2] After alkylation, the optically enriched 2-phenylpropionic acid can be liberated from the auxiliary using normal cleavage protocols.



Scheme. 2. Asymmetric alkylation (enolate structures shown in identical orientations).

PRELIMINARY RESULTS

We prepared optically pure **5b** and **5c** in three steps from easily attainable aldehydes and (*S*)-asparagine following the general method of Konopelski for the synthesis of **5a**.[1g] The phenylacetyl units were coupled to the auxiliaries by metallation (1.2 equiv $NaN(TMS)_2$, -78 °C, 30 min), treatment with phenylacetyl chloride (1.5 equiv, -78 °C) and gradual warming to rt (approximately 10 h). Purification by flash chromatography (silica gel, 10% EtOAc in hexanes) afforded **6** as white solids in greater than 60% yields. Each derivative of **6** (0.2 M in THF) was slowly added to $NaN(TMS)_2$ (0.9 M in THF, 1 equiv, -78 °C) and stirred (30 min). Addition of iodomethane (2 equiv) was followed by immediate warming of the reaction mixtures to the indicated temperatures (see Table). The mixtures were stirred, quenched with saturated ammonium chloride and extractively isolated. The crude materials were chromatographed by semi-preparative HPLC[3a] to afford a clean separation of the diastereomeric products.[4] Authentic samples of the minor diastereomers (**8**) were prepared by coupling metallated **5** to (*S*)-2-phenylpropionyl chloride using the previously described protocol. Diastereomeric pairs of alkylation products were similarly prepared using racemic 2-phenylpropionyl chloride. Coellution studies with these samples confirmed our prediction that the R absolute configuration was established by each alkylation. These results were corroborated by cleavage of the acyl groups from each analog of **7** (2 equiv of LiOH, 8 equiv of H_2O_2)[5] and coinjection of the acid products with the commercially available (*R*)-2-phenylpropionic acid.[6]

The enolate methylations performed at various temperatures and reactions times were analyzed by HPLC[3b] for reaction progress and diastereoselectivity (see Table). The alkylations were surprisingly sluggish at colder temperatures, however, higher temperatures enforced reaction progress. It was gratifying to note that new heterocycles **5b** and **5c** gave highly selective transformations in comparison to the less hindered **5a**.[7] In addition, an unusual kinetic effect was observed in the alkylations of the derivatized heterocycles. The diastereoselectivities were increased dramatically with increasing temperature. For example, methylation of **6b**

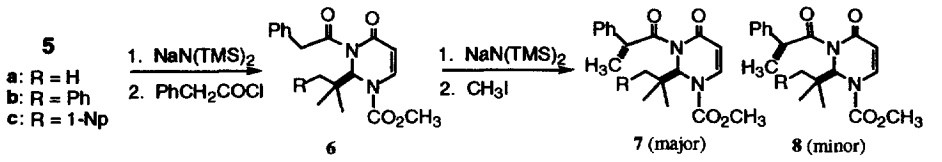


Table. Diastereoselective Methylations (Conditions as Described Above).

Heterocycle	HMPA (equiv)	°C	Rxn Time (h)	major (**7**) / minor (**8**)	% yield
6a	0	-78	19	4.3/1	2.4
"	0	-46	4	7.9/1	16.8
"	0	-23	2	8.0/1	12.3
"	0	0	0.5	10.4/1	50.9
6b	0	-78	24	1.5/1	0.6
"	2	-78	2	1.8/1	9.3
"	0.5	-78	2	3.1/1	6.3
"	0	0	0.5	16.9/1	89.6
6c	0	-78	22	3.7/1	3.0
"	0	0	0.5	>16/1	83.2

occurred with poor selectivity at -78 °C (1.5:1), however, an appreciable increase in selectivity was recorded when the reaction was performed at 0 °C (16.9:1). To examine the possible participation of enolate aggregation in the rate and selectivity trends, we performed an alkylation of **6b** in the presence of HMPA. There existed a significant increase in the rate of product formation in the presence of HMPA at -78 °C (i.e. 6.3% with 0.5 equiv of HMPA after 2 h); however, diastereoselectivity varied.

Interestingly, we noted that the ratio of diastereomers in the crude mixtures decreased upon storage in THF/ethyl acetate at a rate of 1.2% a day. For example, the product ratio of the **6a** series (at 0 °C), decreased from 7.49:1 to 5.70:1 after 15 days. It was found, when measured against an internal standard, that only the major diasteromer of the crude mixture degraded. Little to no change was seen with the minor diastereomer **8a** or the starting phenylacetyl derivative **6a**. We are investigating the possibility that **7a** is predisposed to nucleophilic substitution at the acyl carbonyl due to an out-of-plane imide distortion which diminishes conjugation between the heterocycle eneamide and the acyl carbonyl.[8]

Our results demonstrated that improved diastereoselectivities in auxiliary-mediated enolate alkylations were achieved through rational modifications of **5a**. Incorporation of an aryl unit in the blocking group of **5a** lead to improved alkylation selectivities, presumably due to the increased steric demand of the blocking group. Kinetic studies showed that unusual reaction rates and diastereoselectivities can be partially explained by enolate aggregation. Furthermore, the unexpected degradation of the major diastereomers may be related to conformational properties which increase the vulnerability of these derivatives to nucleophilic substitution. Our laboratory is continuing investigations on the temperature dependence of the methylation, the effect pi-pi stacking may have on the complexation, and the differing hydrolytic susceptibility of the diastereomers and will report these findings in the near future.

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3. HPLC conditions are as follows with 15% EtOAc in hexanes; (a) Semi-preparative: 12 mL/min on a Rainin Silica 25 cm x 21.4 mm, 5 μm 100 Å column. (b) Analytical: 0.75 mL/min on a Rainin Silica 25 cm x 4.6 mm, 5 μm 100 Å column.

4. All ^{1}H NMR measured at 300 MHz in $CDCl_3$. **6a**: δ 7.64 (br s, 1H), 7.26 (m, 5H), 6.83 (s, 1H), 5.33 (d, J = 7.5 Hz, 1H), 4.32 (d, J = 16.2 Hz, 1H), 4.10 (d, J = 16.2 Hz, 1H), 3.83 (s, 3H), 0.92 (s, 9H). **6b**: δ 7.56 (br s, 1H), 7.25 (m, 5H), 6.69 (s, 1H), 5.13 (d, J = 7.8 Hz, 1H), 4.97 (q, J = 6.9 Hz, 1H), 3.84 (s, 3H), 1.52 (d, J = 6.6 Hz, 3H), 0.95 (s, 9H). **6c**: δ 7.65 (br s, 1H), 7.43 (d, J = 7.2 Hz, 1H) 7.27 (m, 4H), 6.62 (s, 1H), 5.33 (d, J = 4.5 Hz, 1H), 4.79 (q, J = 6.9 Hz, 1H), 3.89 (s, 3H), 1.45 (d, J = 6.9 Hz, 3H), 0.80 (s, 9H). **7a**: δ 7.72 (br s, 1H), 7.26 (m, 8H), 7.03 (m, 3H), 5.40 (d, J = 7.8 Hz, 1H), 4.36 (d, J = 16.2 Hz, 1H), 4.14 (d, J = 16.2 Hz, 1H), 3.88 (s, 3H), 2.55 (s, 2H), 0.80 (s, 3H), 0.79 (s, 3H). **7b**: δ 7.52 (br s, 1H), 7.26 (m, 5H), 7.08 (m, 2H), 6.84 (s, 1H), 5.17 (d, J = 7.8 Hz, 1H), 4.99 (q, J = 7.2 Hz, 1H), 3.86 (s, 3H), 2.59 (m, 2H), 1.53 (d, J = 6.9 Hz, 3H), 0.82 (s, 9H). **7c**: δ 7.69 (br s, 1H), 7.46 (m, 2H) 7.3-7.0 (m, 7H), 6.90 (m, 2H), 5.39 (d, J = 7.5 Hz, 1H), 4.87 (q, J = 6.9 Hz, 1H), 3.90 (s, 3H), 2.41 (m, 2H), 1.48 (d, J = 6.9 Hz, 3H), 0.70 (s, 3H), 0.61 (s, 3H). **8a**: δ 8.0-7.7 (m, 3H), 7.5-7.2 (m, 11H), 5.44 (d, J = 7.8 Hz, 1H), 4.42 (d, J = 16.2 Hz, 1H), 4.17 (d, J = 16.2 Hz, 1H), 3.91 (s, 3H), 3.08 (m, 2H), 0.83 (s, 3H), 0.80 (s, 3H. **8b**: δ 8.02 (d, J = 8.1 Hz, 1H), 7.9-7.7 (m, 2H), 7.6-7.2 (m, 10H), 7.00 (s, 1H), 5.22 (d, J = 7.8 Hz, 1H), 5.02 (q, J = 6.9 Hz, 1H), 3.89 (s, 3H), 3.13 (m, 2H), 1.57 (d, J = 7.2 Hz, 3H), 0.84 (s, 3H), 0.83 (s, 3H. **8c**: δ 7 8-7.0 (m, 14H), 5.41 (d, J = 7.8 Hz, 1H), 4.89 (q, J = 6.9 Hz, 1H), 3.94 (s, 3H), 2.93 (m, 2H), 1.51 (d, J = 6.9 Hz, 3H), 0.74 (s, 3H), 0.62 (s, 3H).

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6. Chiral HPLC conditions as follows: 98/2/0.05 hexanes/isopropanol/acetic acid at 1 mL/min; Pirkle Whelk-O 1, 25 cm x 4.6 mm, 5 μm 100 Å column on a Hewlett Packard Series 1050 with diode array detector.

7. The HPLC signal of the minor diastereomer (**8c**) was obscured by minor impurities. The reported ratio is a minimum value for the selectivity.

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