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Application of acyclic chiral auxiliaries on alkylation reactions

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ABSTRACT

The application in alkylation reactions of an acyclic chiral auxiliary is described. The synthesis is straightforward from a chiral primary amine and a double acylation. A characteristic of this auxiliary is its modular design formed by an achiral part (acyl) and a chiral component (primary amine) so it can be tuned for different reactions without difficulty. The alkylation proceeds with excellent diastereoselectivity because the conformational flexibility of the enolate is restricted by the formation of a chelate and the allylic 1,3-strain.

There is a variety of methods to obtain enantiomerically pure compounds. Among these methods, chiral auxiliaries are sometimes the first choice for the total synthesis of complex molecules or in industry, because they are robust methodologies in which the stereochemical output of the product can be predicted with confidence. In addition, the products are diastereomers which are easy to analyze and more easily enriched in case of a noncomplete selectivity in the reaction.[1]

The majority of the developed auxiliaries are cyclic[2] (Fig. 1) in order to avoid the presence of different conformers that would lead to different degrees of selectivity or even promote an undesired selectivity in the product. A notable exception is Myers pseudoephedrine[3] which relies on a chelate structure to achieve selectivity.

Inspired by the broad applications of Evans oxazolidinones in different reactions[4] which are capable to induce different stereoisomers by stereodivergent pathways[5] and their use in new reactions,[6,7] we designed an acyclic auxiliary which could have the same versatility as oxazolidinones. The auxiliary is formed by a primary chiral amine that has a tertiary carbon with a large substituent and a small substituent and an acyl group (Fig. 2). A benefit of this modular design is that the achiral part (acyl) and the chiral part (chiral amine) can be easily modified without the need of an elaborated synthesis.

As a model chiral auxiliary to study the reactivity and selectivity we chose the (*S*)-phenylethylamine[8] as chiral amine and benzoyl in the achiral part with propionyl in the prochiral segment. The synthesis was straightforward and did not require anhydrous conditions. It began with the reaction between the amine and propionyl anhydride at room temperature and after 3 h the amide **1** was purified by crystallization. The benzoyl group was introduced with benzoyl chloride with refluxing toluene to obtain product **2** in 65% overall yield (Scheme 1).

We were able to obtain good quality crystals of imide **2** to obtain its structure by X-ray diffraction[9] (Fig. 3).

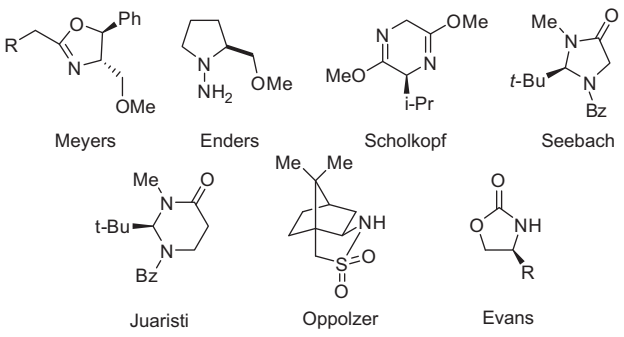

Figure 1. Representative chiral auxiliaries.

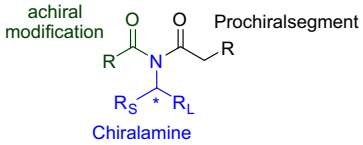

Figure 2. Proposed chiral auxiliary.

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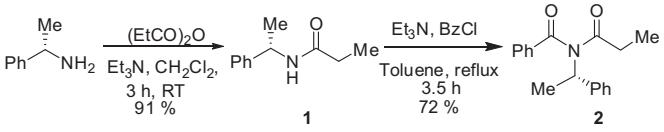


Scheme 1. Synthesis of imide **2**.

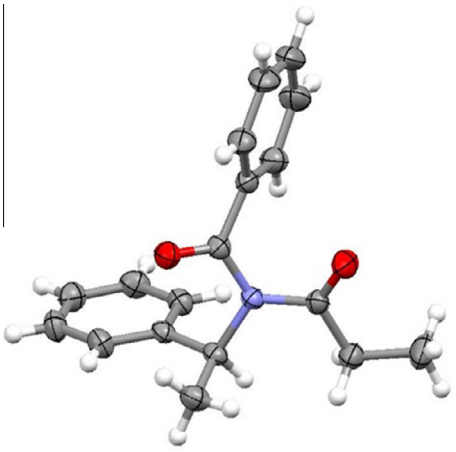
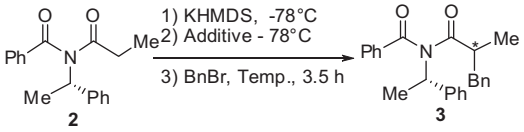


Figure 3. X-ray structure of imide **2**.

Table 1
Alkylation of imide **2** with different additives



Entry	Additive (equiv)	Temp. (°C)	Yield (%)	dr[a]
1	—[b]	−55	NR	—
2	—[c]	−55	28	73:27
3	—	−55	60	70:30
4	HMPA (3)	−78	68	83:17
5	HMPA (6)	−78	98	86:14
6	HMPA (12)	−78	84	81:19
7	HMPA (6)	−40	71	80:20

[a] Obtained by ^{1}H NMR.
[b] LiHMDS was used.
[c] NaHMDS was used.

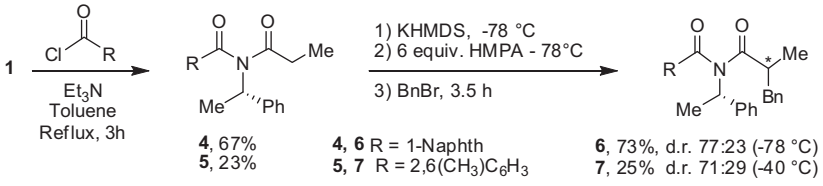
We explored the alkylation of **2** with benzyl bromide to find optimal conditions. With lithium and sodium bases no satisfactory results were obtained (Table 1, entries 1 and 2). With KHMDS a modest yield was obtained (Table 1, entry 3), but with the use of HMPA[10] as additive the reactivity of the enolate was higher so the alkylation was performed at lower temperatures (Table 1, entries 4–7). To our delight with 6 equiv. of the additive full conversion to the alkylated product **3** was obtained (Table 1, entry 5). Larger amounts of HMPA or higher temperatures diminished yield and diastereoselectivity (Table 1, entries 6 and 7).

Once we found the optimal conditions for the alkylation reaction, we next explored the effect of other fragments in the achiral part of the molecule. 1-Naphthylcarbonyl and 2,6-dimethylphenylcarbonyl were evaluated and we found lower reactivity and selectivity so we continue to use benzoyl in the achiral part (Scheme 2).

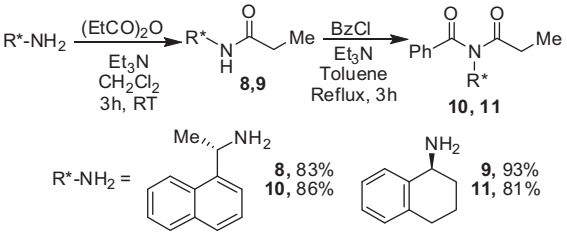
The next stage was to explore with two different chiral amines in the auxiliary: 1-(1-naphthyl)ethylamine and 1,2,3,4-tetrahydro-1-naphthylamine using the same methodology as shown in Scheme 1 to obtain compounds **10** and **11** (Scheme 3).

The alkylation of these compounds was performed under the same conditions as imide **2**. Using imide **10** conduced to a lower reactivity of the enolate and no improvement in selectivity (Table 2, entries 1 and 2). With imide **11** the alkylation proceeds with almost complete selectivity when the reaction was done at −78 °C (Table 2, entry 3).[11]

With the optimized auxiliary in hand, we deemed into the task to show the broad scope of this auxiliary with different groups in

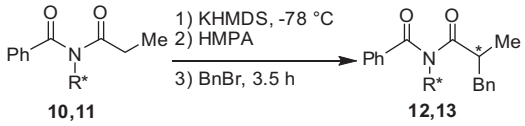


Scheme 2. Synthesis and alkylation of imides with different acyl groups.



Scheme 3. Synthesis of imides **10** and **11**.

Table 2
Alkylation of imides **10** and **11**



Entry	Compound	Temp. (°C)	Yield (%)	dr[a]
1	12	−78	29	85:15
2	12	−40	63	84:16
3	13	−78	83	98:2
4	13	−40	85	95:5

[a] Obtained by ^{1}H NMR.