Tetrahedron Letters 55 (2014) 193–196

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Application of acyclic chiral auxiliaries on alkylation reactions

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ARTICLE INFO

Article history:
Received 25 October 2013
Accepted 29 October 2013
Available online 7 November 2013

Keywords:
Chiral auxiliaries
Diastereoselective synthesis
Alkylation reactions
Chiral carboxylic acids
Allylic strain

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).

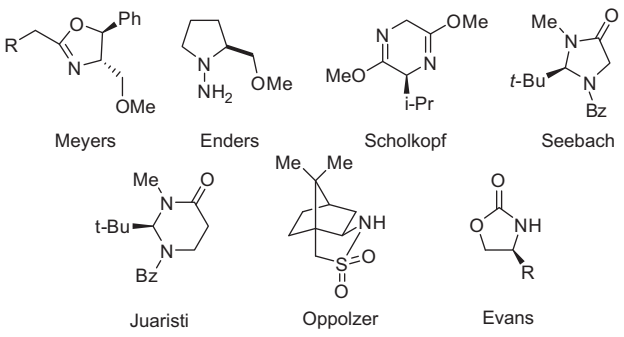

Figure 1. Representative chiral auxiliaries.

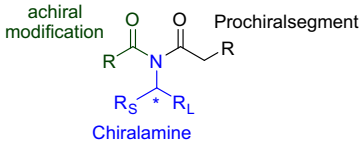

Figure 2. Proposed chiral auxiliary.

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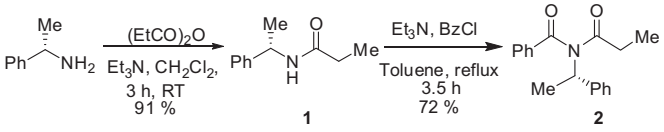
http://dx.doi.org/10.1016/j.tetlet.2013.10.148



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

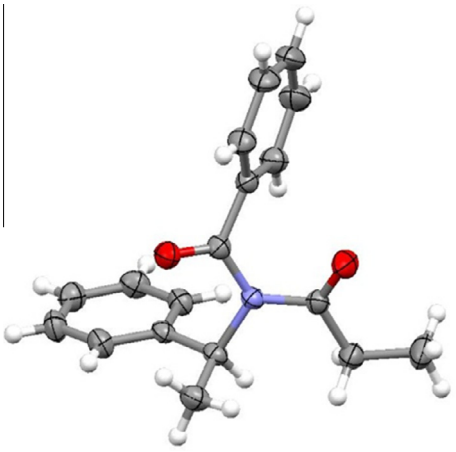
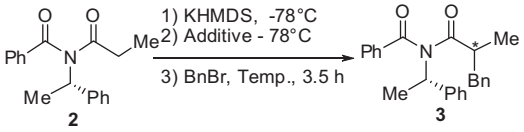


Figure 3. X-ray structure of imide **2**.

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.

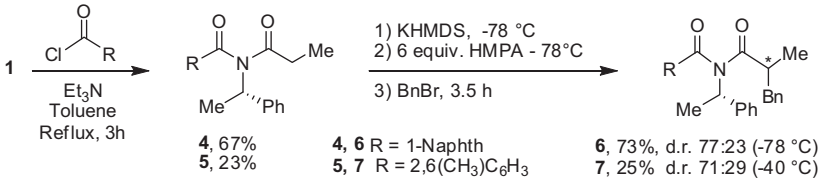
We explored the alkylation of **2** with benzyl bromide to find optimal conditions. With lithium and sodium bases no satisfactory results were obtained (Table 1, entries 1 and 2). With KHMDS a modest yield was obtained (Table 1, entry 3), but with the use of HMPA[10] as additive the reactivity of the 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).

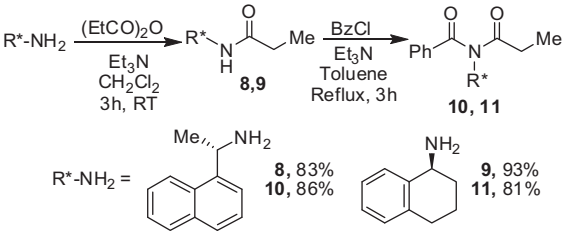
The next stage was to explore with two different chiral amines in the auxiliary: 1-(1-naphthyl)ethylamine and 1,2,3,4-tetrahydro-1-naphthylamine using the same methodology as shown in Scheme 1 to obtain compounds **10** and **11** (Scheme 3).

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

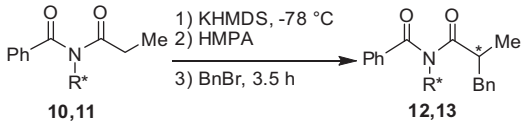


Scheme 2. Synthesis and alkylation of imides with different acyl groups.



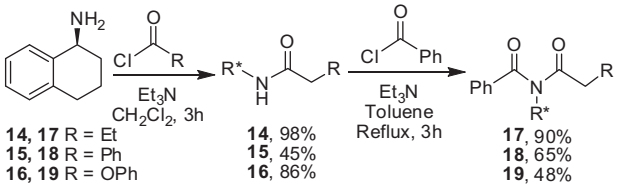
Scheme 3. Synthesis of imides **10** and **11**.

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

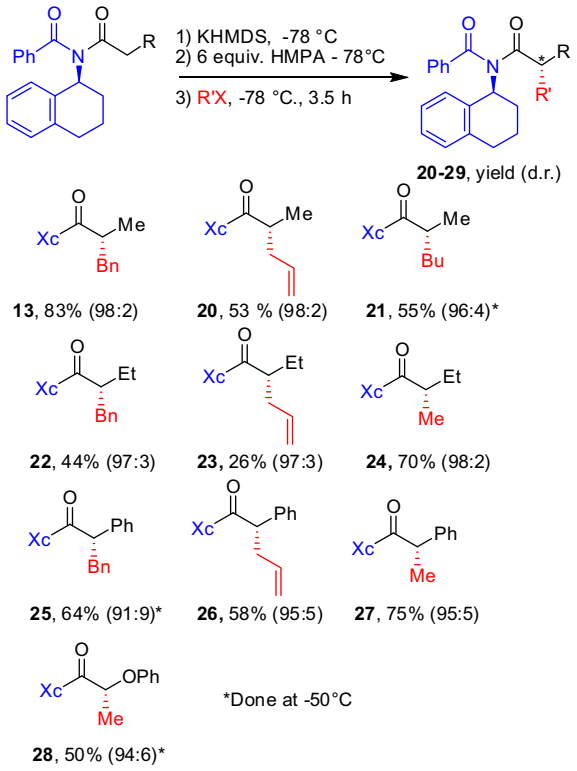


Entry	Compound	Temp. (°C)	Yield (%)	dr[a]
1	12	−78	29	85:15
2	12	−40	63	84:16
3	13	−78	83	98:2
4	13	−40	85	95:5

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



Scheme 4. Synthesis of chiral imides with different prochiral groups.



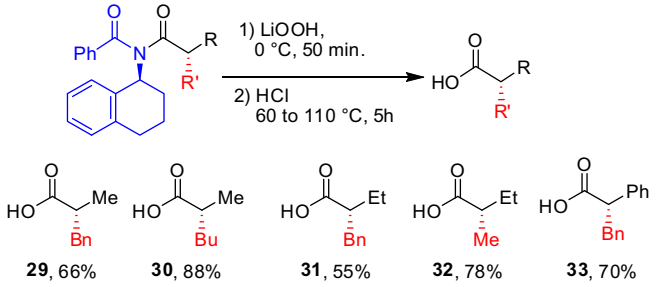
Scheme 5. Alkylation of the optimized auxiliary.

the prochiral group. For that purpose we obtained imides **17**–**19** with ethyl, phenyl, and phenoxy as R groups (Scheme 4).

Having these three new imides the alkylation was done under the same conditions with benzyl bromide, allyl bromide, methyl iodide, and iodobutane, in all cases a very good diastereoselectivity was observed when the reaction was performed at −78 °C (Scheme 5).

The removal of the auxiliary was done in two steps in order to avoid the separation of the chiral acid and benzoic acid. The first was the chemoselective removal of the benzoyl group with lithium hydroperoxide. The second was the hydrolysis of the amide in acidic conditions in 5 h. After a conventional work-up taking advantage of the acidic properties of the product the pure acid was obtained. After analysis of its optical rotation to the reported compound we could assign configuration of the generated stereocenter.[12] In all cases the alkylhalide was added to the Si face of the enolate (Scheme 6).

In order to explain the selectivity in the alkylation reaction we postulate that potassium with coordinating molecules of HMPA forms a chelate with the amide of the auxiliary. The rotation around the stereocenter of the auxiliary and the nitrogen is conformationally restricted because of the allylic 1,3-strain[13] so the conformer with the C–H *anti* to the N–C(O) of the amide is unfavorable because of the interactions with the phenyl group. The other



Scheme 6. Auxiliary removal.

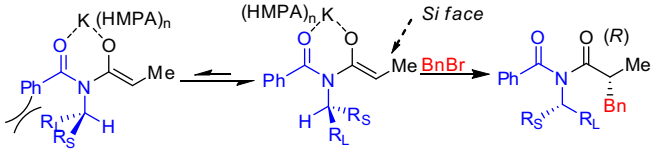


Figure 4. Selectivity in the alkylation reaction.

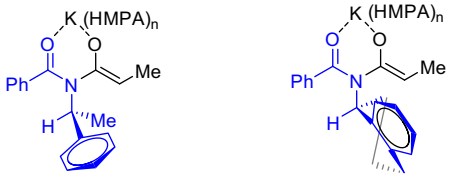


Figure 5. Comparison between enolates of imides **2** and **11**.

conformer minimizes this steric interaction leaving the large group blocking the *Re* face of the enolate so the addition occurs from the *Si* face of the enolate (Fig. 4).

In the case of imide **2** it is clear that the phenyl is the large group, whereas in the imide **11** with the tetrahydronaphtyl group the methylene of the cyclohexene is the small group and the large group is the phenyl ring. The difference in selectivity between these groups can be accounted to the spatial distribution of the phenyl ring; while in the enolate of **2** the aromatic ring is parallel to the C*–H bond, in the enolate of imide **11** the phenyl is perpendicular to the C*–H bond because of the half chair conformation of the cyclohexene ring[14] (Fig. 5).

We believe that this auxiliary could be a good contribution to the current auxiliaries because of the almost trivial synthesis, modular design, and the compatibility with other reactions that employ Evans auxiliaries.

In conclusion, we have shown that it is possible to achieve good selectivities with an acyclic chiral auxiliary. This auxiliary is easy to obtain and modify because of its modular structure and the alkylation proceeds with good selectivity. The factors responsible for the good selectivity observed in the alkylation reactions are the chelate structure with the carbonyl of the auxiliary and the allylic 1,3-strain of the amide that restrict the conformation between the stereocenter of the auxiliary and the nitrogen.

Acknowledgments

We thank DGAPA-UNAM for financial support (IB201312-RR281312) and CONACyT fellowship (510789). We would also like to thank L. Velasco, F. Pérez, E. García, C. Marquez, M.A. Peña, I. Chávez, E. Huerta, B. Quiroz, H. Ríos, R. Gaviño, R. Patiño, A. Toscano, and S. Hernández for technical support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.148.

References and notes

1. (a) Gnas, Y.; Glorius, F. *Synthesis* **2006**, 1899–1930; (b) Evans, D. A.; Helmchen, G.; Rüping, M. In *Asymmetric Synthesis the Essentials*; Christmann, M., Bräse, S., Eds., 2nd ed.; Wiley-VCH: Weinheim, 2007; pp 3–9.
2. (a) Enders, D.; Wortmann, L.; Peters, R. *Acc. Chem. Res.* **2000**, *33*, 157–169; (b) Meyers, A. I. *J. Org. Chem.* **2005**, *70*, 6137–6151; (c) Schöllkopf, U. *Tetrahedron* **1983**, *39*, 2085–2091; (d) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969–2004; (e) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243–1250; (f) Juaristi, E.; Quintana, D.; Balderas, M.; García-Pérez, E. *Tetrahedron: Asymmetry* **1996**, *7*, 2233–2246; (g) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908–6909.
3. (a) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361–9362; (b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511; (c) Myers, A. G.; Yang, B. H. *Org. Synth.* **2000**, *77*, 22–25; (d) Hugelshofer, C. L.; Mellem, K. T.; Myers, A. G. *Org. Lett.* **2013**, *15*, 3134–3137.
4. (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129; (b) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23–32; (c) Evans, D. A.; Kim, A. S. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. O., Ed.; John Wiley & Sons: New York, 1995; Vol. 1, p 345; (d) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta* **1997**, *30*, 3–12; (e) Shamszad, M.; Crimmins, M. T. In *Comprehensive Chirality*; Carreira, E. M., Yamamoto, H., Eds.; Elsevier: Amsterdam, 2012; pp 19–41 (http://www.sciencedirect.com/science/article/pii/B9780080951676003025); (f) Heravi, M. H.; Zadsirjan, V. *Tetrahedron: Asymmetry* **2013**, *24*, 1149–1188.
5. (a) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894–902; (b) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127–1130.
6. (a) Barluenga, J.; Suero, M. G.; de la Campa, R.; Flores, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 9720–9724; (b) Kerr, D. J.; Miletic, M.; Chaplin, J. H.; White, J. M.; Flynn, B. L. *Org. Lett.* **2012**, *14*, 1732–1735; (c) Minko, Y.; Pasco, M.; Lercher, L.; Botoshansky, M.; Marek, I. *Nature* **2012**, *490*, 522–526.
7. It is noteworthy the chemistry of ynamides and allenamides with Evans auxiliaries: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064–5106; (b) Lu, T.; Lu, Z.; Ma, Z.-X.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2013**, *113*, 4862–4904.
8. Bandala, Y.; Juaristi, E. *Aldrichim. Acta* **2010**, *43*, 65–78.
9. With CCDC deposition number 953129.
10. (a) Normant, H. *Angew. Chem. Int. Ed. Eng.* **1967**, *6*, 1046–1067; (b) Reichardt, C.; Welton, T. *Solvents and Solvent Effects in Organic Chemistry*, 4th ed.; Wiley-VCH: Weinheim, 2011.
11. In a scale up reaction with 3 mmol of imide a 98% yield and 96:4 dr was obtained. It can also be changed the HMPA to the nontoxic DMPU obtaining a 96:4 dr.
12. There was no racemization in the hydrolysis. The enantiomeric purity was evaluated by coupling the acid with (*S*)-1-naphthylethylamine and contrasted with the coupled product of the racemic acid.
13. (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860; (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124–1134; (c) Hernández-Rodríguez, M.; Melgar-Fernández, R.; Juaristi, E. *J. Phys. Org. Chem.* **2005**, *18*, 792–799.
14. This half chair conformation can be seen in the urea of the tetrahydronaphtylamine With CCDC 921521 reported in: Trejo-Huizar, K. E.; Peña-González, M. A.; Hernández-Rodríguez, M. *New J. Chem.* **2013**, *37*, 2610–2613. and contrasted with the urea of the phenylethylamine CCDC 263119 reported in Ref. 12.