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Highly Enantioselective Darzens Reaction of a Camphor-Derived Sulfonium Amide to Give Glycidic Amides and Their Applications in Synthesis

Varinder K. Aggarwal,* George Hynd, Willy Picoul, and Jean-Luc Vasse

School of Chemistry, Bristol University, Cantock's Close, Bristol, BS8 1TS UK.

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Glycidic esters and amides are very important synthetic intermediates because of their rich and useful functionality. However, few methods exist for their synthesis in a concise and highly selective manner.[1] The most direct method to date is an asymmetric Darzens reaction[2] and good ee's have been achieved by employing chiral auxiliaries[3] or chiral reagents[4] although in all of these processes two separate steps are required: an aldol-type reaction followed by ring closure.[5] We now report the discovery that amide-stabilized sulfur ylides[6] bearing a readily available chiral camphor-derived moiety react with aldehydes in the presence of base to give glycidic amides directly with complete diastereocontrol and almost complete control of enantioselectivity.[7]

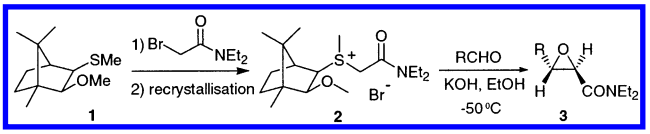
Sulfide **1**[8] was synthesized in three steps from D-camphor and subsequently alkylated with *N*,*N*-diethyl bromoacetamide to yield the salt **2** as a 10:1 mixture of diastereoisomers. Recrystallization from hexane/acetone gave diastereomerically pure **2**. Brief optimization of the reaction of the salt with benzaldehyde in the presence of base revealed that very high enantioselectivity could be achieved using KOH in ethanol at −50 °C. These conditions were applied to a range of aldehydes and found to be general for all aromatic and heteroaromatic aldehydes (Table 1, entries 1−8). Aliphatic aldehydes behaved less predictably: tertiary and monosubstituted aldehydes gave high enantioselectivities (entries 9, 11), while secondary substituted aldehyde only gave low selectivity (entry 10). In all cases complete diastereoselectivity in favor of the trans isomer was observed. Furthermore, sulfide **1** could be reisolated in essentially quantitative yield at the end of the reaction.

Efforts to understand the origin of the very high enantioselectivity have only been partially successful. It had previously been reported that the related sulfonium salt **4** reacted with aldehydes via transition state **A** to give glycidic amides in low-to-moderate enantioselectivity.[9] It was proposed that hydrogen bonding controlled the conformation of the ylide and that subsequent nonbonded interactions in **A** were responsible for enantiocontrol (Scheme 1).

However, while it is known that amide-stabilized sulfonium ylides react with aldehydes to give epoxides via betaine intermediates, we have discovered from simple crossover experiments that betaine formation is reversible.[10] Thus, enantiocontrol is achieved not in the betaine-forming step (e.g., transition state A) but in one of the subsequent steps converting the betaine into epoxide. From ab initio calculations on related compounds,[11] we found that the slowest of these steps is the C−C bond rotation, which converts the initially formed syn betaine adduct into the anti conformation. It is highly likely that the same scenario applies to the current ylide and thus conversion of **5A** to **5B** is the critical enantiodifferentiating step. It is remarkable that such high enantioselectivity can be achieved (up to 99% ee) through diastereomeric transition states (**5A**/**6A** → **5B**/**6B**) which have a high degree of conformational freedom through facile bond rotations around the C−S bonds (Scheme 2).

* To whom correspondence should be addressed. E-mail: V.Aggarwal@bristol.ac.uk.

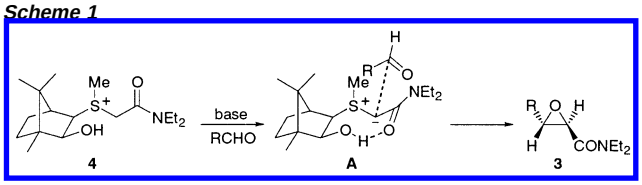
Table 1. Asymmetric Synthesis of (2*R*,3*S*)-2,3-Epoxyamides via Camphor-Derived Sulfonium Salt **2**



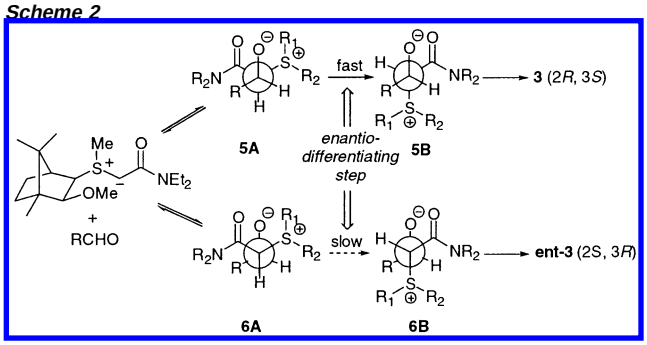
entry	R	yield (%)	ee (%)	product, configuration[c]
1	*p*-$MeOC_6H_4$	90	97	**3a**, (2*R*,3*S*)
2	Ph	93	97	**3b**, (2*R*,3*S*)
3	*p*-ClC_6H_4	87	99	**3c**, (2*R*,3*S*)
4	*p*-MeC_6H_4	88	98	**3d**, (2*R*,3*S*)
5	*p*-FC_6H_4	85	96	**3e**, (2*R*,3*S*)
6	*p*-$CF_3C_6H_4$	89	96	**3f**, (2*R*,3*S*)
7	*p*-$NO_2C_6H_4$	85	92	**3g**, (2*R*,3*S*)
8	3-pyridyl	87	95	**3h**, (2*R*,3*S*)
9[a]	dodecyl	84	63	**3i**, (2*R*,3*S*)
10[b]	*i*-propyl	79	10	**3j**,[d]
11[b]	*t*-butyl	87	93	**3k**, (2*R*,3*S*)

[a] −30 °C. [b] −20 °C. [c] The absolute configuration of **3b** and **3c** have been determined by comparison of HPLC elution orders and by comparison of $[\alpha]_D$ with the lit.,[9] respectively. All others are given by analogy. [d] The absolute configuration was not determined.

Scheme 1



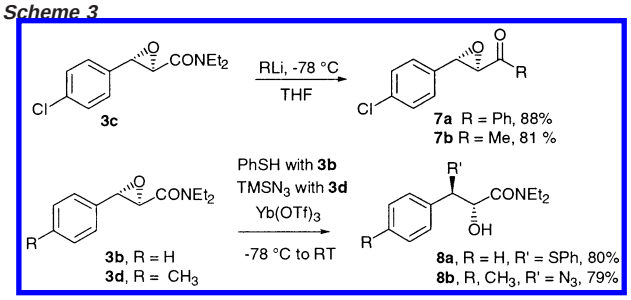
Scheme 2



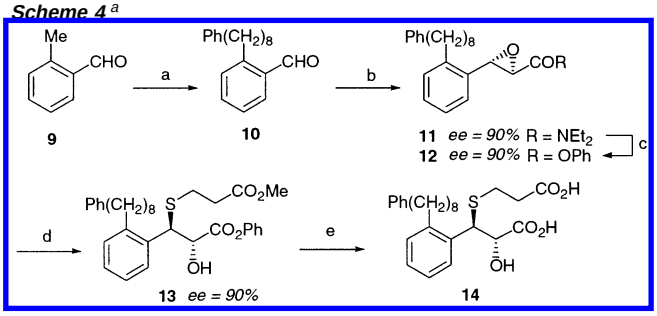
Further studies revealed that both the temperature and diastereomeric purity of the salt influenced enantioselectivity (see Supporting Information for full details). We studied the latter issue in further detail, and from analysis of the stereochemical outcome of different diastereomeric mixtures, we determined that the pure minor diastereomer **2′** gave the same major enantiomer but with reduced selectivity (54% ee) compared to the major diastereomer **2**.[12]

10.1021/ja0272540 CCC: $22.00

Scheme 3



Scheme 4 [a]



[a] Conditions: a) see ref 16, 90%; b) **2**, KOH, MeOH, −30 °C, 24 h, 77%; c) (i) PhLi, THF, −78 °C, 84%, (ii) *m*CPBA, CH_2Cl_2, Δ, 68%; d) HS-$(CH_2)_2$-CO_2Me, $Yb(OTf)_3$, CH_2Cl_2, −78 °C to rt, 64%, e) NaOH, MeOH, H_2O, rt, 16 h, 81%.

Our new methodology allows access to a range of potential building blocks through further selective transformations. The epoxyamides can be converted directly into epoxyketones by treatment with organolithium reagents with complete chemoselectivity (Scheme 3).[13] Epoxides can also be ring-opened by nucleophiles, and we had initially assumed that ring-opening would occur regioselectively at the benzylic position. However, reaction of thiophenol with **3b** in different solvents with different bases furnished a 1:1 mixture of regioisomers. Sharpless has described the use of Ti(O-*i*-Pr)$_4$ for C_3 selective ring-opening of glycidic esters and secondary amides,[14] but this method also gave a 1:1 mixture of regioisomers. Finally, we discovered that $Yb(OTf)_3$ catalyzed the ring-opening with complete regioselectivity for the C_3 position with both S and N nucleophiles (Scheme 3).

The usefulness of the new process is exemplified in a short synthesis of SK&F 104353 **14**, a leukotriene D_4 antagonist in the potential treatment of bronchial asthma (Scheme 4).[15] We were delighted to find that ylide reaction with the sterically hindered aldehyde **10**[16] furnished the glycidic amide **11** in 90% ee. Although we were able to regioselectively open the epoxide with the required thiol, we found it difficult to hydrolyze the amide in the presence of the remaining functionality. However, we were able to convert the epoxyamide into the corresponding epoxyester using a two-step sequence involving addition of phenyllithium followed by Baeyer−Villiger oxidation. Regioselective ring-opening of the epoxyester with the required thiol and subsequent hydrolysis gave the target molecule.

In summary, we have described a completely diastereoselective, highly enantioselective and practical synthesis of glycidic amides and applied this new methodology to an asymmetric synthesis of SK&F 104353. Although the origin of the enantioselectivity is not completely understood, we have identified the enantiodifferentiating step of the process. We are currently exploring the precise origin of the enantiocontrol and new alternative methods for amide hydrolysis to further expand the scope of this work.

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Supporting Information Available: Full experimental details, optimization results, and analytical data (including chiral HPLC data of **3a**−**3k** and **9**) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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