Recent Progress in the Enantioselective Synthesis of β-Lactams: Development of the First Catalytic Approaches

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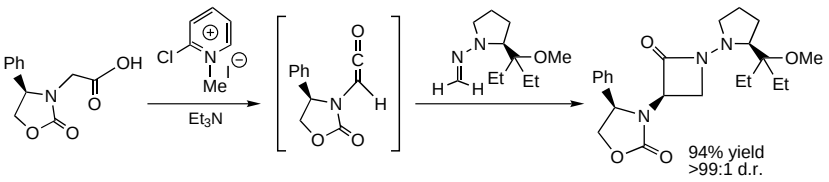
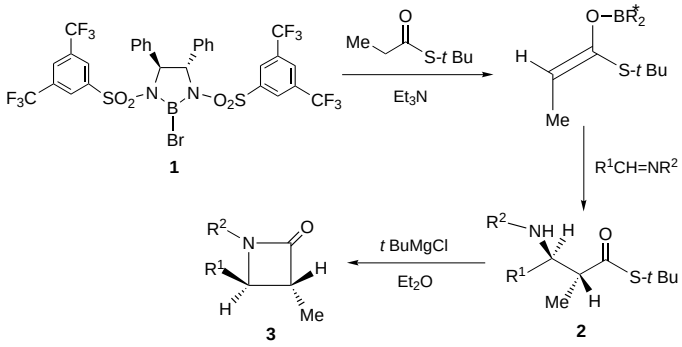
The economic importance of enantiomerically pure compounds[1] and the presence of the azetidin-2-one (β-lactam) ring in several widely used families of antibiotics, such as penicillins, cephalosporins, thienamycins, and monocyclic β-lactams (for example, monobactams),[2] coupled with the recent discoveries that β-lactams can serve as mechanism-based inhibitors of serine proteases[3] and as inhibitors of acyl-CoA cholesterol acyltransferase (ACAT),[4] which is mainly responsible for atherosclerotic coronary heart disease, have stimulated considerable research efforts toward the enantioselective synthesis of β-lactams. Additional impetus for these efforts has been provided by the introduction of the β-lactam synthon methodology, according to which enantiomerically pure β-lactams can be employed as useful intermediates for organic synthesis.[5] Up until recently, the state of the art in this endeavor consisted either of stereocontrolled ketene–imine cycloadditions (Staudinger reaction),[6] which relied on the use of chiral auxiliaries for control, or stereoselective ester enolate–imine condensations (Gilman–Speeter reaction),[7] in which either the ester or the imine component was enantiomerically pure.[8] Interestingly, in a very recent enantioselective example in which both the ketene (Evans–Sjoegren-type ketene)[6b] precursor and the imine (hydrazone in this case)[9b] were enantiomerically pure, the Staudinger reaction proceeded with almost complete diastereoselectivity (Scheme 1).[9a]



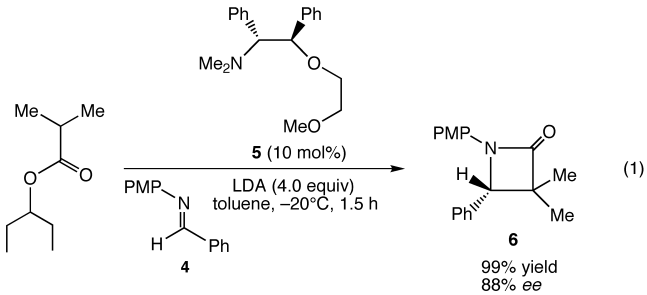
Scheme 1. Matched double diastereoselective Staudinger hydrazone cycloaddition.

The first highly enantio- and diastereoselective example of a Gilman–Speeter-type condensation involving both achiral esters and imines was reported by Corey and co-workers, who employed the chiral nonracemic organoboron Lewis acid **1** (Scheme 2) in yet another application of this useful class of reagents.[10] Treatment of the derived β-amino acid esters **2** with *tert*-butylmagnesium chloride[11] gave rise to 3,4-disubstituted β-lactams **3** (Scheme 2).[12]



Scheme 2. Nonchiral auxiliary-based enantio- and diastereoselective Gilman–Speeter reaction and β-amino ester → β-lactam ring closure.

The first example of a direct catalytic enantioselective synthesis of β-lactams was reported by Tomioka and co-workers who, by capitalizing on previously acquired knowledge on the structure of complexes and mixed aggregates between ester enolates and amide bases,[13] achieved a catalytic asymmetric Gilman–Speeter reaction [Eq. (1); LDA = lithium diisopropylamide, PMP = *p*-methoxyphenyl].[14] Specifically, the reaction of the lithium enolate of



(1)

pent-3-yl 2-methylpropanoate with imine **4** in the presence of a catalytic amount of the enantiomerically pure ether ligand **5** resulted in a ternary complex reagent (comprising an achiral

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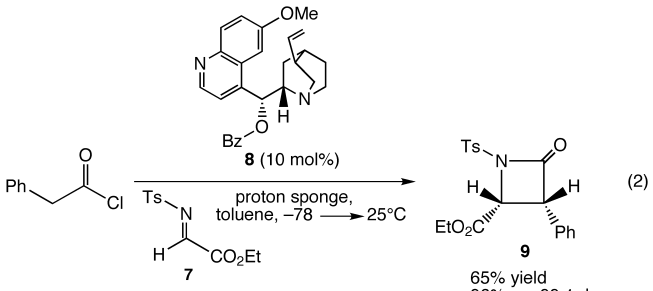
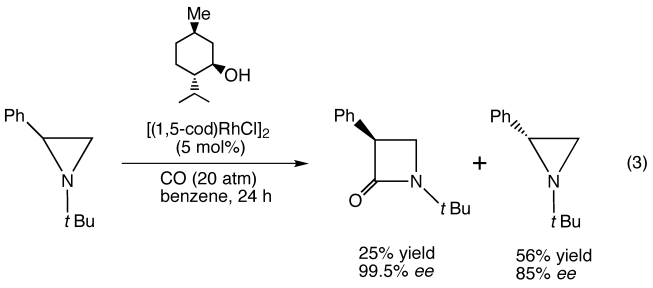
lithium amide (LDA), the ester enolate, and **5**) that afforded β-lactam **6** in high yield and enantiomeric excess (*ee*).[14]

This advance was augmented last year by Lectka and co-workers who first rendered the Staudinger reaction a catalyzed process by making the imine component non-nucleophilic by using **7** [Eq. (2); Bz = benzoyl, Ts = toluene-4-sulfonyl],[15a] and then proceeded to employ a nucleophilic catalyst such as benzoylquinine **8** and obtain *cis*-β-lactam **9** in good yield and with a high *ee* value.[15b]



(2)

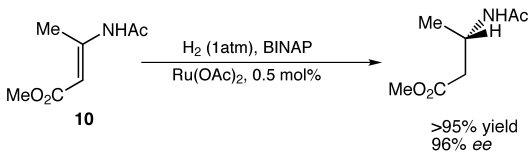
These achievements are significantly more practical and useful than an earlier approach to catalytic asymmetric synthesis of β-lactams, namely a Rh^{I}-catalyzed carbonylation and ring expansion of aziridines [Eq. (3); cod = cyclooctadiene]. This reaction does not result in the creation of a new stereogenic center and is, therefore, merely a kinetic resolution.[15c]



(3)

Since β-amino acids and their derivatives are undoubtedly very important intermediates for the synthesis of β-lactam antibiotics (Scheme 2),[11, 16] much attention has been paid to the preparation of the former compounds in optically active forms.[17]

An early approach toward the development of a catalytic enantioselective synthesis of β-amino acids was reported by Noyori and co-workers, who improved upon the original studies of Achiwa and Soga[18a] by demonstrating that BINAP-Ru^{II} metal complexes are excellent catalysts for the enantioselective hydrogenation of β-substituted (*E*)-β-(acetylamino)acrylic acids **10** [Eq. (4); Ac = acetyl, BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl].[18b] The same objective has been accomplished in three more recent approaches: two asymmetric Michael additions of azide to α,β-unsaturated carbonyl compounds catalyzed by tripeptide **11** and a chiral nonracemic [(salen)Al^{III}] (salen = *N*,*N*′-bis(salicylidene)ethylenediamine anion) complex **13** to provide β-azido amides **12** and **14**, respectively, in excellent yields [Eqs. (5) and (6); Boc = *tert*-butoxycarbonyl, Bn = benzyl, TMS = trimethylsilyl],[18c, 18d] and an enantioselective Mannich-type reaction of



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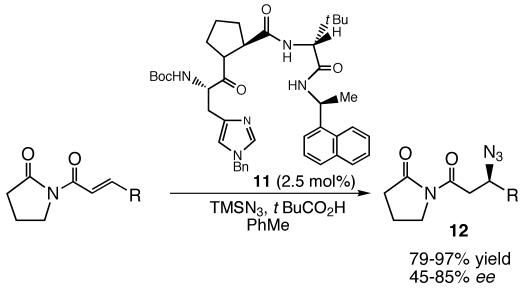

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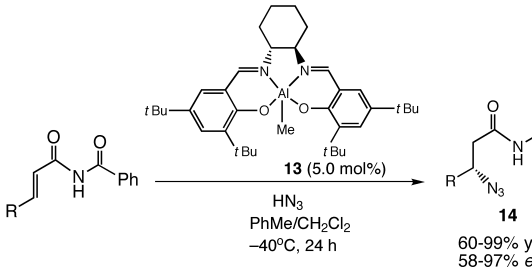
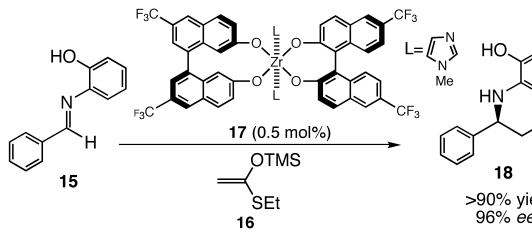


(6)

2-aminophenol-derived aldimine **15** with silylketene thioacetal **16** using a novel enantiomerically pure zirconium catalyst **17** to furnish β-amino thioester **18** quantitatively [Eq. (7)].[18e]



(7)

Finally, in related developments, a catalytic asymmetric conjugate addition of *O*-benzylhydroxylamine to unsaturated amides [Eq. (8)] and a catalytic asymmetric acyl halide – aldehyde cyclocondensation [Eq. (9); DIEA = diisopropylethylamine] were reported by the research groups of Sibi and Nelson, respectively, as additional strategies for enantioselective β-amino acid synthesis.[19] Thus, Michael addition of *O*-benzylhydroxylamine to the pyrazole-derived α,β-unsaturated amides **19** in the presence of a chiral nonracemic Lewis acid prepared from $MgBr_2 \cdot OEt_2$ and bisoxazoline **20** yielded β-amino amides **21** of satisfactory enantiomeric purity [Eq. (8)].[19a] On the other hand, ring-opening of the

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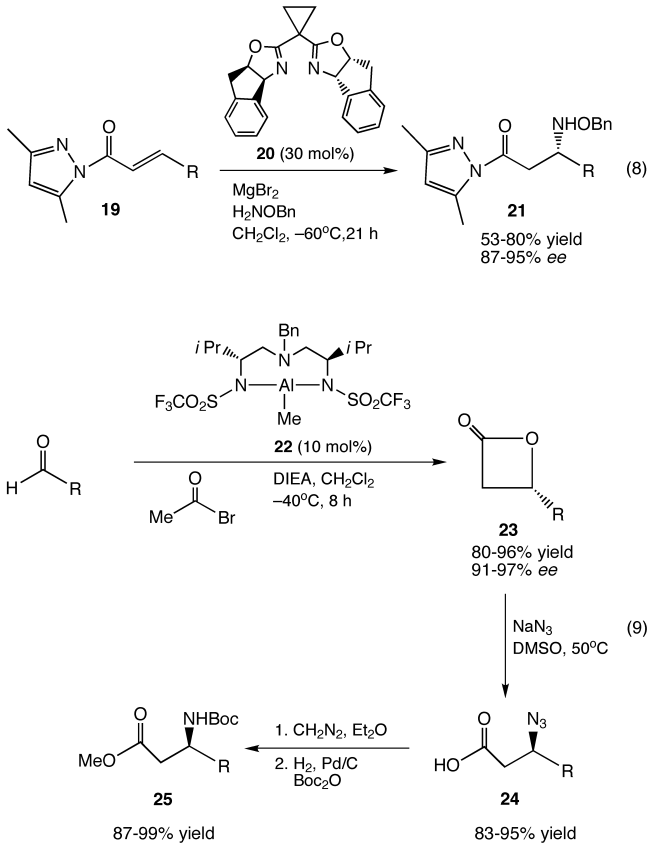

β-lactones **23** obtained from the acyl halide-cyclocondensation catalyzed by the Al^{III}-triamine complex **22** gave rise to β-azido acids **24** which were in turn converted into their corresponding *N*-Boc-protected β-amino acid derivatives **25** by using standard procedures [Eq. (9)].[19b]

Upon consideration of the acyl halide – imine **7** and the acyl halide – aldehyde cyclocondensations described in Equations (2) and (9), respectively, it becomes very tempting to speculate on the outcome, as far as the development of a novel catalytic asymmetric synthesis of β-lactams is concerned, of the Staudinger cycloaddition of **7** catalyzed by an enantiomerically pure Lewis acid such as **22** [Eq. (9)] or **1** (Scheme 2) and promoted by an appropriate base for efficient in situ ketene generation.[15b, 19b]

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