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Meyers' bicyclic lactam formation under mild and highly stereoselective conditions

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Abstract—New and mild conditions to prepare chiral bicyclic lactams in high yields and high diastereoselectivities are reported herein. This approach based on the activation of the carboxylic acid by means of Mukaiyama's reagent is an excellent alternative to Meyers' dehydrating conditions and provide the main advantage to work at lower temperature (40 °C). Higher diastereoselectivity was obtained with 5,7-bicyclic lactams (de = 82% instead of 44% under standard dehydrating conditions).

Meyers' bicyclic lactams have proven to be helpful chiral building blocks for the stereoselective construction of optically pure nitrogen heterocycles.[1] The classical procedure used for accessing these versatile chiral bicyclic lactam templates consists of cyclodehydration of a γ-, δ- or ω-keto acid and a chiral amino alcohol by simply heating the two in toluene overnight with azeotropic removal of water (Fig. 1). These dehydrating conditions, rather drastic, may prove to be incompatible with highly functionalized substrates, limiting seriously the scope of this methodology. Taking this limitation into account, the search of further reaction conditions is highly desirable.

A survey of the literature reveals that no alternative procedures based on the activation of the carboxylic acid

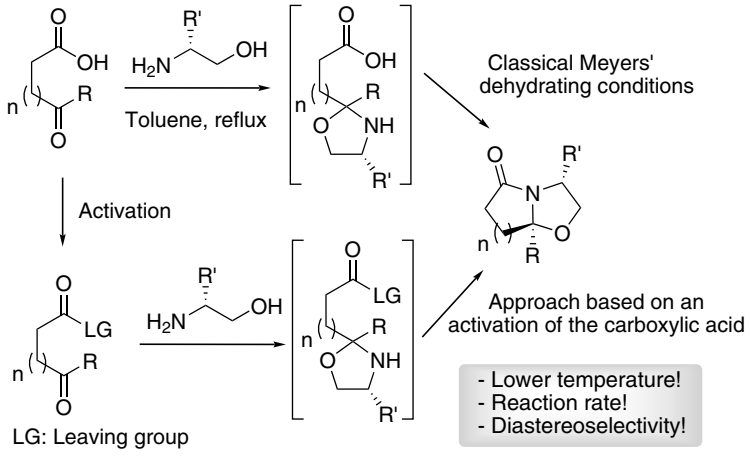

Figure 1. Meyers' bicyclic lactam formation.

Keywords: Meyers' bicyclic lactam; Thioester; Mukaiyama's reagent; (*R*)-Phenylglycinol.
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have been investigated to explore possible milder reaction conditions. In this context, we recently speculated that such an approach could provide a beneficial effect on the reaction rate and may have some influence on the diastereoselective outcome of this lactamization (Fig. 1).

The thioester group displays a good compromise between stability and reactivity so that it can be handled and purified without particular precaution, while presenting the advantage to react faster than its oxoester analogue. Accordingly, keto-thioesters appeared to be excellent candidates to lactamize under mild conditions. Thioesters have been successfully used in native peptide ligation.[2] This process, based on a preliminary transesterification step followed by a spontaneous intramolecular acyl transfer, takes advantage of this good balance between reactivity and stability of the thioester group to promote peptide bond formation under mild conditions. By analogy, this entropic activation was expected to promote the lactamization of the oxazolidine thioester intermediate under mild conditions (Fig. 2).

The required γ-keto-thioester **1b** was easily prepared in 80% yield from levulinic acid **1a** and thiophenol in the presence of 2-fluoro-1-ethylpyridinium tetrafluoroborate (FEP)[3] and diisopropylethylamine (DIEA). The reactivity of the resulting thioester **1b** was compared with that of levulinic acid **1a** during bicyclic lactam formation in the presence of (*R*)-phenylglycinol. The reaction was conducted at different temperatures, in various solvents. The results of these experiments are summarized in Table 1. The reaction rate was extremely slow at room temperature, and this with no difference between **1a** or **1b** (entries 4–6). At higher temperature (80 °C, entries 2 and 8) no difference in reactivity was observed between **1a** and **1b**. Although thioesters failed to provide any significant improvement in terms of reaction rate, this approach is still of interest because of the high stereoselectivity observed with these new cyclization precursors (Table 1).

As an alternative route to Meyers' methodology, it was then envisaged to have access to the desired bicyclic lactams by dehydration of the β-ketoamide-alcohol **4** intermediate (Scheme 1, route A).[4] According to Mukaiyama's procedure,[5] levulinic acid **1a** was reacted with *N*-methyl-2-chloropyridinium iodide in the presence of triethylamine in dichloromethane at reflux to generate the corresponding activated ester **3**. (*R*)-Phenylglycinol was subsequently introduced and the mixture stirred at reflux for 3 days. At this stage, we could not find in the crude reaction mixture any trace of the expected β-ketoamide-alcohol **4**, but found instead the presence of the bicyclic lactam *trans*-**2a**, which was further isolated in high yield as a single diastereoisomer (Scheme 1, route b). It should be emphasized that the same stereoselection as that expected from the classical Meyers' conditions was observed. The formation of the activated ester **3** was evidenced from a ^{1}H NMR study which allowed us to conclude that this intermediate **3** reacts with (*R*)-phenylglycinol to produce the oxazolidine intermediate **5** faster than the expected β-ketoamide-alcohol **4**. Compared with the previous cyclization conditions of levulinic acid **1a** and (*R*)-phenylglycinol (Table 1, entry 1 and 3), these new conditions proved to be superior, yielding the bicyclic lactam at lower temperature with excellent stereoselectivity (Scheme 1).

These new and mild conditions[6] were assessed in the lactamization of 2-acetyl-benzoic acid **1d** and 2-formylbenzoic acid **1c**, two cyclization precursors already subjected to lactamization in toluene under classical Dean–Stark conditions.[7] As can be appreciated from Scheme 2, we were pleased to find that the use of Mukaiyama's reagent furnished comparable results to those obtained under dehydrating conditions, giving rise to *trans*-**2c** and *trans*-**2d** in high yields and high diastereoselectivities. The relative configuration of the newly created stereogenic centre was established by comparison of ^{1}H NMR data with those previously reported by Allin

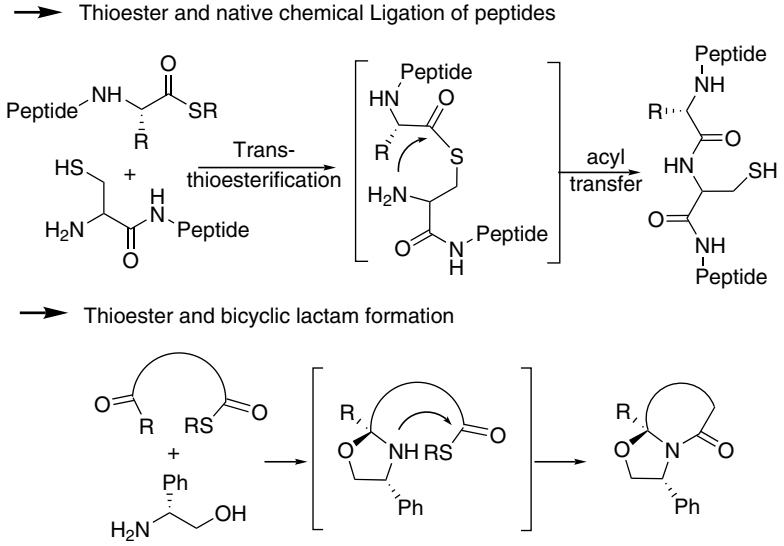
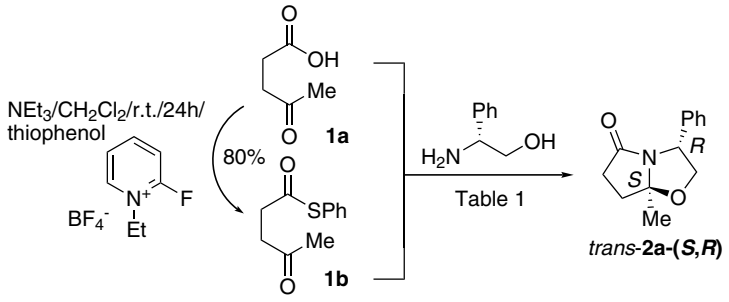
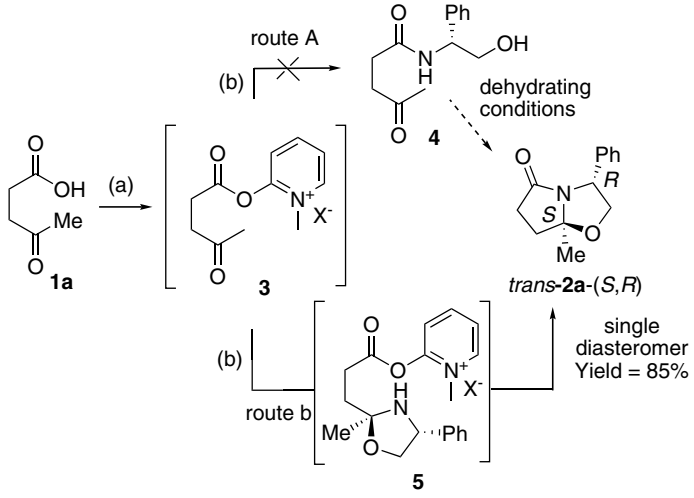


Figure 2. Thioester-assisted both ligation of peptides and bicyclic lactam formation.

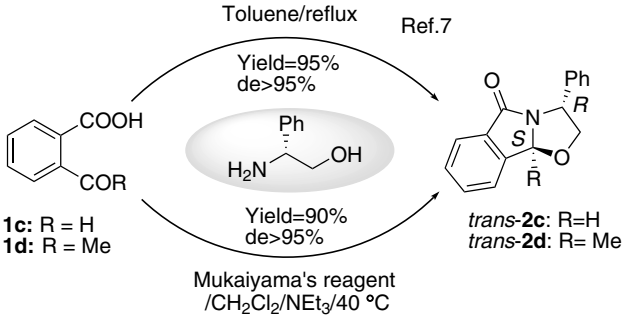
Table 1. Bicyclic lactam formation with γ-keto-thioester **1b** and levulinic acid **1a**



Entry	Sub.	*T* (°C)	Reaction time (h)	Solvent	de (%)	Conv. (%)
1	**1a**	110	24	Toluene	100	100
2	**1a**	80	72	CH_3CN	100	90
3	**1a**	40	72	CH_2Cl_2	100	40
4	**1a**	22	168	$CHCl_3$	—	—
5	**1b**	22	168	$CHCl_3$	—	—
6	**1b**	22	168	CH_3CN	—	—
7	**1b**	60	72	$CHCl_3$	100	60
8	**1b**	80	72	CH_3CN	100	90



Scheme 1. Meyers' bicyclic lactam formation by means of Mukaiyama's reagent. Reagents and conditions: (a) *N*-methyl-2-chloropyridinium iodide/NEt_3/CH_2Cl_2/15 min/reflux; (b) (*R*)-phenylglycinol/CH_2Cl_2/72 h/reflux.



Scheme 2. Bicyclic lactam formation from **1c** and **1d** under classical conditions and by means of Mukaiyama's reagent.

et al.[7] In both procedures, the same stereoselection leading to the *trans*-lactams was observed. This preliminary set of experiments showed that the same level of stereocontrol and similar yields can be achieved at much lower temperatures than those routinely reported in the literature (Scheme 2).

In the hope of broadening the scope of this methodology, we then turned our attention to the construction of larger 5,7-fused bicyclic lactams. Although Meyers' methodology has been widely used in the construction of 5,5- and 5,6-fused bicyclic lactams, modest performances in terms of stereoselection and yield were obtained when extended to 5,7-fused bicyclic lactams (Fig. 3a).[8] We[9] and others[10] have recently reported a highly stereoselective access to axially chiral 5,7-fused bicyclic lactams by using Meyers' methodology. This approach offers the advantage to control in a single step a chiral centre and a biarylic chiral axis. As a result of

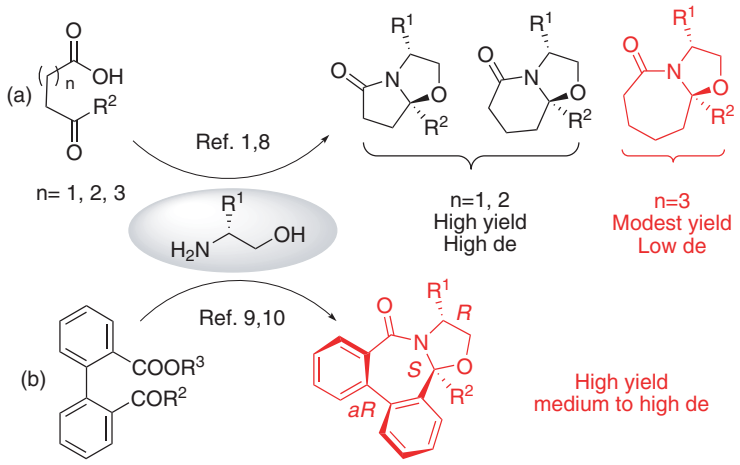
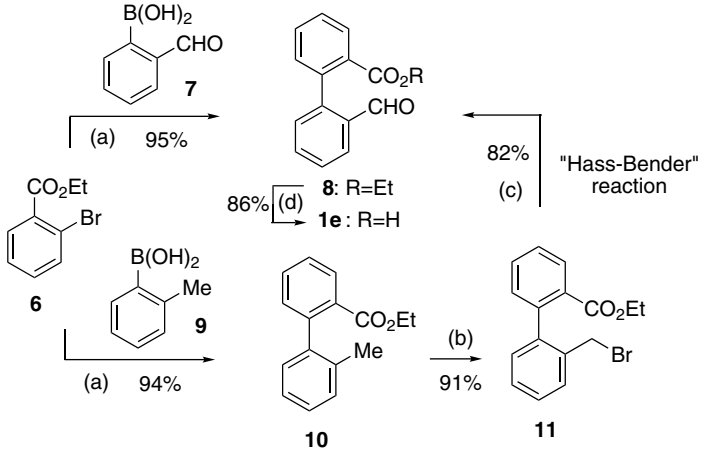


Figure 3. Scope and limitation of Meyers' methodology with: (a) aliphatic keto-carboxylic acids; (b) biaryl keto-carboxylic acids.

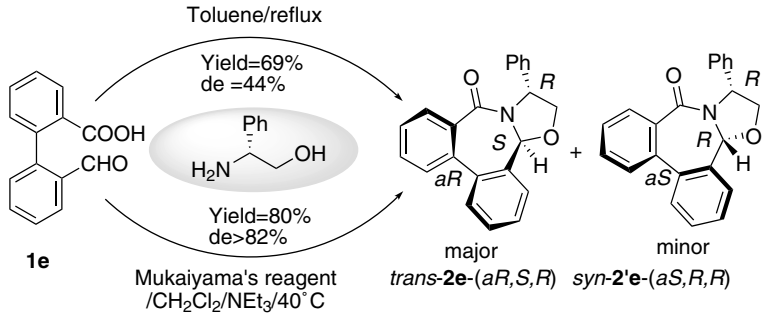
the presence of a biaryl unit, the higher stereoselectivity and reactivity observed, with this class of substrates, may be attributed to conformational restrictions during the lactamization step (Fig. 3b).

Although under classical dehydrating conditions these substrates gave fairly good results, both the reactivity and stereoselectivity were found to be profoundly influenced by various factors such as the nature of R^2 and R^3 as well as the nature of the aminoalcohol.[9,10] Of particular interest in this context is the case of 2′-formylbiphenyl-2-carboxylic acid **1e**, which has already been reported to undergo lactamization under dehydrating conditions and furnishing the corresponding lactam with only medium diastereoselectivity.[10] Accordingly, we became interested in testing our new conditions with **1e** to provide milder conditions while hoping to improve the stereoinduction of the lactamization process. Two different routes were investigated for the preparation of the required formic acid **1e**. The first route is based on a Suzuki cross-coupling reaction between the commercially available aryl bromide ester **6** and boronic acid **7**. The resulting biarylic ester **8** obtained in near quantitative yield was then hydrolyzed to furnish the desired formic acid **1e** in 86% yield. Alternatively, ester **8** could be prepared through a three-step sequence involving a preliminary Suzuki cross-coupling between boronic acid **9** and bromo ester **6**. The resultant biaryl ester **10** was subsequently converted to the corresponding bromo derivative **11** in 91% yield which was finally subjected to Hass–Bender reaction conditions to yield the corresponding aldehyde **8** in 82% yield (Scheme 3).

We next examined the lactamization of 2′-formylbiphenyl-2-carboxylic acid **1e** under classical dehydrating conditions. A solution of **1e** and (*R*)-phenylglycinol in toluene with azeotropic removal of water was stirred for 30 h. As expected, under these dehydrating conditions the lactamization proceeded in rather modest diastereoselectivity (de = 44%). The bicyclic lactam *trans*-**2e** was isolated in a satisfactory yield of 69%. In contrast, when the lactamization was carried out under activated conditions, in the presence of Mukaiyama's reagent, the bicyclic lactam *trans*-**2e** was formed in somewhat higher yield and, more interestingly, with a significant higher level of stereoinduction (de = 82%). This example demonstrated that these new lactamization conditions not only provided milder reaction condi-



Scheme 3. Reagents and conditions: (a) $Pd(PPh_3)_4$ (8%)/K_2CO_3/toluene/H_2O/reflux; (b) NBS/AIBN/CCl_4/reflux/6 h; (c) EtONa/2-nitropropane/EtOH/reflux/10 h; (d) NaOH/rt/24 h.



Scheme 4. Preparation of 5,7-fused bicyclic lactam **2e** under activated conditions by means of Mukaiyama's reagent.

tions, but also promoted higher diastereoselectivity in certain cases (Scheme 4).

In summary new and mild conditions were developed to have access to chiral bicyclic lactams in good yield and high diastereoselectivity. In a first approach, although thioesters proved to be moderately reactive, they displayed the same high level of stereoinduction as that observed with oxoester analogues, demonstrating their potential as new cyclization precursors in this stereoselective lactamization process. A second approach based on the activation of the carboxylic acid function by means of Mukaiyama's reagent revealed to be an excellent alternative to Meyers' dehydrating conditions, providing the main advantage to work at lower temperature. These new conditions are particularly attractive for cyclization precursors vulnerable to degradation. Further investigations are presently in progress to demonstrate the potential of these results in the stereoselective preparation of 5,7-fused bicyclic lactams of biological interest.

Acknowledgements

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Supplementary data

Experimental procedures for compounds **1b**,**e**, *trans*-**2a**,**c**–**e**, **8**, **10** and **11**; spectroscopic data for all compounds (including ^{1}H and ^{13}C NMR spectra). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.154.

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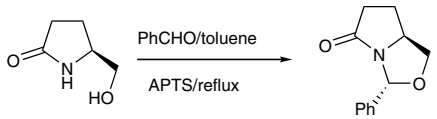

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6. *Typical procedure for the preparation of bicyclic lactams by means of Mukaiyama's reagent*. To a solution of 2-acetylbenzoic acid **1d** (1.4 g, 8.75 mmol) in CH_2Cl_2 (50 mL) was added NEt_3 (1.73 g, 17.2 mmol) and *N*-methyl-2-chloropyridinium iodide (Mukayama's reagent) (2.4 g, 9.4 mmol). The reaction mixture was heated at reflux for 15 min. (*R*)-Phenylglycinol (1.18 g, 8.6 mmol) was added and the resulting solution was stirred at reflux for a further 72 h and then cooled to room temperature. The crude was filtered, CH_2Cl_2 was evaporated and the residue was purified by flash chromatography on silica gel (AcOEt/cyclohexane: 1/1) to afford *trans*-**2d** in 90% yield (de >95%).
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