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Asymmetric Iodolactamization Induced by Chiral Oxazolidine Auxiliary

Meihua Shen and Chaozhong Li*

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China

clig@mail.sioc.ac.cn

Received July 15, 2004

Asymmetric iodolactamization reactions of unsaturated amides with oxazolidines as the chiral auxiliaries were investigated. With (4*S*)-4-((2*R*)-2-butyl)-2,2-dimethyloxazolidine as the auxiliary and LiH as the base, a number of unsaturated amides underwent iodolactamization smoothly to afford the corresponding γ- and δ-lactams in 30−98% yield with de values up to 97%.

Introduction

Halocyclizations of unsaturated compounds have been well established as an indispensable tool in the synthesis of heterocyclic compounds and continue to be pursued with a growing interest in their asymmetric reactions.[1] Among them, the most widely studied type of reaction is iodolactonization. Asymmetric iodolactonization reactions have been carried out via substrate-controlled 1,3-induction[2] or with the aid of chiral auxiliaries[3] or chiral ligands such as amines.[4]

Compared to iodolactonization, iodolactamization is much less investigated. This is because the halocyclization of amides usually produces lactones rather than lactams.[1] To achieve lactamization, methods such as *N*,*O*-bis-silylation,[5] *N*-tosyl or *N*-alkoxycarbonyl substitution,[6] and use of a strong base[7] have been developed. More recently, Taguchi et al. reported the efficient iodoaminocyclization with BuLi or $LiAl(OBu^t)_4$ as the base.[8]

Whereas asymmetric iodolactonization continues to be actively pursued,[2−4] no asymmetric iodolactamization, to our surprise, has been systematically examined. Only two separate examples of substrate-controlled asymmetric iodolactamization have been reported.[9,10] Takahata et al. reported the asymmetric synthesis of statine via stereoselective iodolactamization of a chiral β-hydroxythioimidate.[9] Knapp treated 3(*S*)-hydroxy-4-pentenamide with excess $TMSOTf/Et_3N$ and iodine to generate the corresponding asymmetric γ-lactam, which served as the intermediate in the synthesis of (−)-slaframine.[10] Nevertheless, these two examples demonstrated the great potential of asymmetric iodolactamization in natural product synthesis and urged us to develop efficient and general methods for asymmetric iodolactamization. We here report the first chiral-auxiliary-induced iodolactamization leading to the asymmetric syntheses of γ- and δ-lactams.

Results and Discussion

Asymmetric oxazolidines and oxazolidinones are widely used as chiral auxiliaries in many reactions such as asymmetric free radical α-alkylation of carboxamides.[11,12] They are readily prepared from 1,2-amino alcohols, which in turn are available from the corresponding α-amino acids. Thus, we designed models **1** and **2** with oxazolidines and oxazolidinones as the chiral auxiliaries, respectively. Substrates **1** could be easily prepared in high yields in a one-pot procedure from their parent amide **3**[13] by its reaction with oxalyl chloride followed by the addition of oxazolidines.[14]

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(12) For recent examples, see: (a) Sibi, M. P.; Rheault, T. R.; Chandramouli, S. V.; Jasperse, C. P. *J. Am. Chem. Soc.* **2002**, *124*, 2924. (b) Sibi, M. P.; Liu, P.; Ji, J.; Hajra, S.; Chen, J.-x. *J. Org. Chem.* **2002**, *67*, 1738. (c) Sibi, M. P.; Chen, J.; Rheault, T. R. *Org. Lett.* **2001**, *3*, 3679.

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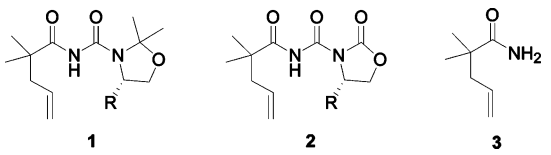
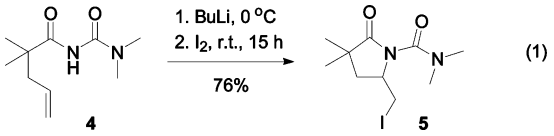
10.1021/jo0488006 CCC: $27.50
Published on Web 10/12/2004



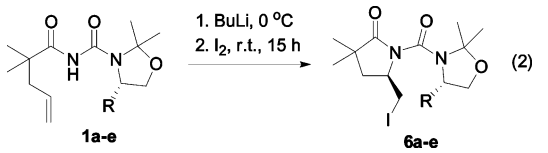
1 **2** **3**

To ensure the efficient iodolactamization for **1** and **2**, we first prepared dimethylaminocarbonyl-substituted amide **4** as the model substrate and subjected it to the reaction with iodine according to Taguchi's procedure.[8] Thus, treatment of **4** with BuLi at 0 °C followed by the addition of iodine at room temperature afforded the expected cyclization product **5** in 76% yield (eq 1).



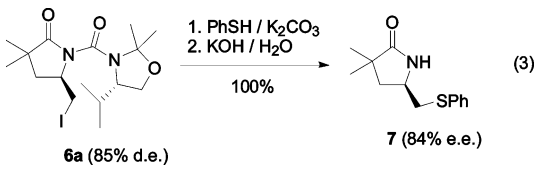
4 **5** (1)

As the yield of **5** was acceptable, we carried out the reactions of **1a**−**e** under the above experimental conditions, trying to find the best chiral auxiliary for the asymmetric induction in the cyclization products **6a**−**e** (eq 2). The results are summarized in Table 1.



1a-e **6a-e** (2)

As can be seen from Table 1, excellent diastereoselectivity was observed in the cases of **1c**−**e**. The products **6a**−**e** were converted to the corresponding phenylsulfide by reaction with PhSH/K_2CO_3 at room temperature, and HPLC analyses confirmed the de values measured by ^{1}H NMR. Furthermore, the nucleophilic substitution of **6a** (85% de) with PhSH in the presence of K_2CO_3 followed by subsequent hydrolysis with KOH afforded lactam **7** in quantitative yield with 84% ee determined by chiral HPLC (eq 3). In the meantime, the corresponding chiral 1,2-amino alcohol was recovered quantitatively. This result not only further confirmed the de values determined by ^{1}H NMR but also demonstrated the potential of the above methodology in organic synthesis. The new stereogenic center in the preferred isomers is in *R* configuration as evidenced by the X-ray structure of **6c** (see Supporting Information).



6a (85% d.e.) **7** (84% e.e.) (3)

We also prepared the corresponding oxazolidinone substrates **2** (R = Bn). However, its reaction with iodine and a base such as BuLi failed to give the expected cyclization product, and the starting material simply decomposed to the corresponding 2,2-dimethylpentenoic acid.

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TABLE 1. Synthesis of 6a−e via Iodolactamization of 1a−e with BuLi as Base

substrate	R	yield (%)[a]	de (%)[b]
1a	^{i}Pr	42	85
1b	^{t}Bu	40	75
1c	Bn	20	>99
1d	^{i}PrCH$_2$	24	>99
1e	2(*R*)-butyl	30	95

[a] Isolated yield based on **1**. [b] Determined by ^{1}H NMR of the crude product **6** and by HPLC of their phenylsulfide derivatives. See text.

TABLE 2. Effect of Base on the Cyclization of 1e

entry	base	yield (%)[a]	de (%)[b]
1	BuLi	30	95
2	LDA	38	94
3	LiAl(O^{t}Bu)$_4$	25	90
4	^{t}BuOK	37	70
5	NaH	72	70
6	LiH	67	78

[a] Isolated yield based on **1**. [b] Determined by ^{1}H NMR of the crude product **6** and by HPLC of their phenylsulfide derivatives. See text.

Compared to the substrate **4**, **1a**−**e** gave rather low yields of cyclization products. This prompted us to take measures to improve the yields of **6**. Apparently the critical factor in the reaction is the base, as also indicated by Taguchi et al.[8] We chose **1e** to optimize the reaction conditions. Thus, **1e** was treated with a base in THF at 0 °C for 1 h followed by the addition of iodine at room temperature. The results are illustrated in Table 2.

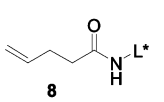
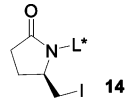
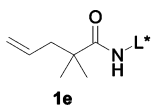
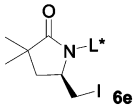
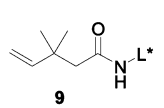
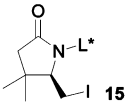
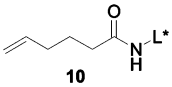
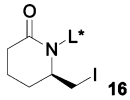
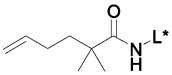
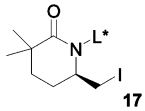
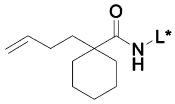
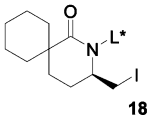
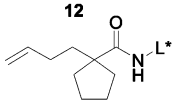
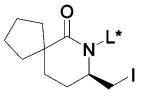
As indicated in Table 2, sodium hydride or lithium hydride gave high yields of the expected product. However, the diastereoselectivity was lowered. We suspected that the high de values in other cases (Table 1 and entries 1−3, Table 2) probably resulted from the instability of the minor isomers with high steric hindrance under those experimental conditions. The differences between metal hydrides and other bases such as BuLi might also be attributed to the steric hindrance in substrates **1**, which required the base to be of the least bulkiness.

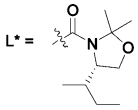
We also tested the effect of Lewis acids in the above reaction with NaH as the base. Unfortunately, it turned out that the addition of Lewis acids screened did not help improve the diastereoselectivity. For example, with the presence of Ti(O^{i}Pr)$_4$ (1 equiv), the iodolactamization of **1e** afforded **6e** in 60% yield with a 71% de. With the addition of $MgBr_2 \cdot OEt_2$ (2 equiv), **1e** was partially decomposed. After the usual workup, only 48% of the starting material was recovered and no expected cyclization product could be isolated. Other Lewis acids such as Zn(OTf)$_2$ showed no effect on the outcome of iodolactamization of **1e** or led to the decomposition of **1e**.

With LiH or NaH as the base, we rechecked the effect of R groups in **1** on the asymmetric induction. However, for **1c** (R = Bn) and **1d** (R = ^{i}PrCH$_2$), no significant improvement in the yields of cyclization could be observed, probably because they were more bulky in structure than **1e**. As a comparison, the iodolactamization of **4** afforded **5** in 98% yield with LiH as the base.

It is worth mentioning here that we also explored extensively the possible 5-exo amidyl radical cyclization

TABLE 3. Iodolactamization of 1e and 8−13

entry	substrate	product[a]	yield (%)[b]	d.e. (%)
1	 **8**	 **14**	60	59[c]
2	 **1e**	 **6e**	67	78[c]
3	 **9**	 **15**	30	91[c]
4	 **10**	 **16**	50	76[d]
5	 **11**	 **17**	95	84[d]
6	 **12**	 **18**	98	85[d]
7	 **13**	 **19**	90	97[d]

L* = 

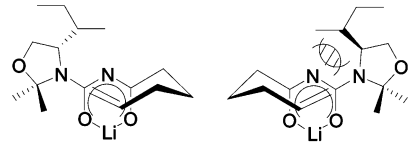
[a] [b] Isolated yield. [c] Determined by ^{1}H NMR (300 MHz) of the crude product. [d] Determined by HPLC.

reactions[15,16] of **1** under various experimental conditions (^{t}BuOCl/I_2,[17] PhI(OAc)$_2$/I_2/^{t}BuOH,[18] etc.). Unfortunately, our attempt failed and only iodolactonization occurred in most cases.

On the basis of the above efforts, we concluded that the optimized condition for the asymmetric iodolactamization was to use 2(*S*)-butyl-substituted oxazolidine (as in **1e**) as the chiral auxiliary and to use NaH or LiH as the base. Thus, we carried out the iodolactamization reactions of unsaturated amides **8**−**13** with LiH as the base. The results are summarized in Table 3.

As indicated in Table 3, both γ-lactams and δ-lactams could be achieved in this manner. For substrates **9** and **10** with no substitution at α-carbonyl position, the cyclization yields were moderate. On the other hand, with α-disubstituted hexenamides **11**−**13**, the iodolactamization products **17**−**19** were obtained in excellent yields (90−98%). Good to excellent diastereoselectivities (59−97% de) were observed. The best asymmetric induction was observed in the case of **13** with a cyclopentyl substitution, probably as a result of its relatively rigid conformation.

The above selectivity is possibly rationalized by the transition state conformations **A** and **B**. In the chairlike transition state model **A**, the olefinic moiety and the *sec*-butyl group lie at the opposite faces of the imide plane to avoid steric repulsion, whereas the two groups are at the same face in model **B**. Therefore, model **A** should be more favorable than **B**. Thus, the new chiral center formed is preferentially in the *R* configuration.



A **B**

Conclusion

We have demonstrated for the first time a relatively efficient model for chiral-auxiliary-induced asymmetric iodolactamization. With LiH as the base and the appropriate oxazolidine as the chiral auxiliary, both γ- and δ-lactams can be achieved in high yield with good to excellent diastereoselectivity. Moreover, the cyclization products could undergo further transformations and subsequent hydrolysis without loss of diastereoselectivity, thus making the above strategy of important application in organic synthesis.

Experimental Section

Preparation of 1e. Typical Procedure. Oxalyl chloride (1.45 mL, 17 mmol) in ethylene dichloride (5 mL) was added to 2,2-dimethyl-4-pentenamide (1.52 g, 12 mmol) in ethylene dichloride (30 mL) at 0 °C. The solution was allowed to warm to room temperature and then refluxed with stirring for 24 h. The resulting mixture was concentrated under reduced pressure to leave the residue as 2,2-dimethyl-pent-4-enoyl isocyanate, which was directly used without further purification.

To (4*S*)-4-((2*R*)-2-butyl)-2,2-dimethyloxazolidine[19] (1.57 g, 10 mmol) in dry dichloromethane (30 mL) was added the above isocyanate (1.53 g, 10 mmol) in dry dichloromethane (10 mL), and the resulting solution was stirred for 4 h at room temperature. After removal of the solvent, the crude product was purified by column chromatography on silica gel with hexane−acetone (20:1) as the eluent to give the pure **1e** as a colorless oil: yield 2.52 g (85%); $[\alpha]^{25}_D = +24.7$ (*c* 1.00, CH_3COCH_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76−0.83 (6H, m), 0.90−1.05 (1H, m), 1.14 (6H, s), 1.21−1.33 (1H, m), 1.49 (3H, s), 1.59 (3H, s), 1.62−1.71 (1H, m), 2.18−2.32 (2H, m), 3.76−3.80 (2H, m), 3.89−3.95 (1H, m), 5.00−5.05 (2H, m), 5.63−5.75 (1H, m), 8.50 (1H, br); ^{13}C NMR ($CDCl_3$) δ 21.6, 23.1, 23.6, 24.5, 24.6, 25.6, 26.7, 42.6, 43.0, 44.2, 56.4, 67.1, 95.0, 118.6, 133.5, 150.1, 176.3; EIMS *m/z* (rel intensity) 295 ($M^+ - CH_3$, 4), 252 (7), 237 (6), 210 (21), 169 (10), 142 (100), 100 (24), 83

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(65). Anal. Calcd for $C_{17}H_{30}N_2O_3$: C, 65.77; H, 9.74; N, 9.02. Found: C, 65.64; H, 9.70; N, 8.97.

Typical Procedure for Iodolactamization Reactions. To a solution of **1e** (124 mg, 0.4 mmol) in dry THF (10 mL) was added LiH (98%, 9.73 mg, 1.2 mmol) at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 20 min, allowed to warm to room temperature, and stirred for an additional 20 min. Iodine (305 mg, 1.2 mmol) was added, and the resulting mixture was stirred at room temperature for 15 h. Aqueous $NaHSO_3$ solution (10 mL) was then added with care. The two layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (2 × 10 mL) and then dried over anhydrous $MgSO_4$. After removal of the solvent, the crude product was purified by column chromatography on silica gel with hexane−acetone (20:1) as the eluent to give **6e** as a white solid: yield 117 mg (67%). Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79−0.86 (6H, m), 1.02−1.22 (2H, m), 1.12 (3H, s), 1.15 (3H, s), 1.40−1.49 (1H, m), 1.46 (3H, s), 1.64 (3H, s), 1.67−1.74 (1H, m), 2.26−2.32 (1H, m), 2.82−2.89 (1H, m), 3.49 (1H, dd, J = 3.4, 9.2 Hz), 3.77−3.82 (1H, m), 3.87−3.96 (1H, m), 4.16−4.27 (2H, m); ^{13}C NMR ($CDCl_3$) δ 6.7, 12.2, 14.5, 23.3, 24.2, 25.5, 25.7, 27.0, 37.2, 41.5, 41.9, 55.2, 60.2, 64.1, 96.0, 150.7, 180.1. Minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79−0.86 (6H, m), 1.02−1.22 (2H, m), 1.10 (3H, s), 1.17 (3H, s), 1.50 (3H, s), 1.62 (3H, s), 1.67−1.74 (1H, m), 1.94−2.13 (1H, m), 3.18−3.25 (1H, m), 3.47−3.51 (1H, m), 3.73−3.78 (1H, m), 3.87−3.96 (2H, m), 4.04−4.09 (1H, m); ^{13}C NMR ($CDCl_3$) δ 6.7, 12.2, 14.3, 23.3, 24.2, 25.5, 26.0, 26.5, 37.2, 41.4, 41.9, 57.3, 60.2, 64.7, 95.8, 152.2, 179.5. EIMS *m/z* (rel intensity) 421 ($M^+ - CH_3$, 33), 379 (28), 350 (100), 297 (69), 280 (70), 254 (65), 209 (33), 83 (81); HRMS calcd for $C_{16}H_{26}IN_2O_3$ ($M^+ - CH_3$) 421.1055, found 421.1022.

Acknowledgment. This project was supported by the National Natural Science Foundation of China, by the Shanghai Municipal Scientific Committee, and by the Chinese Academy of Sciences.

Supporting Information Available: Synthesis and characterization of compounds **1a**−**d**, **4**, **5**, **6a**−**d**, and **7**−**19** and X-ray crystal structure of **6c** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0488006