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Di- and Trisubstituted γ-Lactams via Rh(II)-carbenoid Reaction of *N*-C_α-Branched, *N*-Bis(trimethylsilyl)methyl α-Diazoamides. Synthesis of (±)-α-Allokainic Acid

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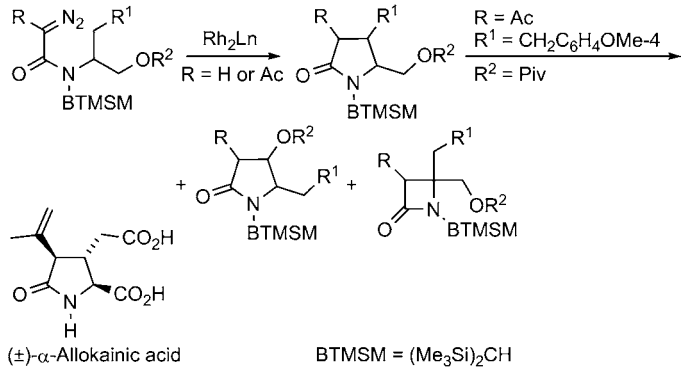
ABSTRACT



Acyclic *N*-C_α-branched, *N*-bis(trimethylsilyl)methyl (*N*-BTMSM) diazoamides undergo regio-, chemo-, and diastereoselective Rh(II)-carbenoid C−H insertion to give 4,5-disubstituted and 3,4,5-trisubstituted γ-lactams. The conformational influence of the *N*-BTMSM group and the electronic effect of the *O*-pivaloyl moiety of the C_α-oxymethylene unit are essential for the observed regioselectivity. The synthesis of α-allokainic acid demonstrates the utility of the method.

The Rh(II)-carbenoid-mediated intramolecular C−H insertion of tertiary α-diazoamides is a useful method[1] especially for the preparation of 4-substituted and 3,4-disubstituted γ-lactams. On the other hand, the Rh(II)-catalyzed reaction of diazoamides **1** (Figure 1), bearing a substituent at the *N*-C_α position (here on referred to as *N*-C_α-branched), to form 4,5-disubstituted and 3,4,5-trisubstituted γ-lactams has not been

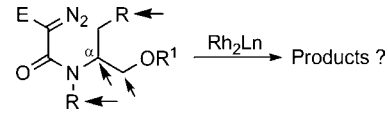


Figure 1. Potential C−H insertion sites.

(1) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis With Diazo Compounds*; Wiley-Interscience: New York, 1998. (b) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (c) Wee, A. G. H. *Curr. Org. Synth.* **2006**, *3*, 499. (d) Gois, P. M. P.; Afonso, C. A. M. *Eur. J. Org. Chem.* **2004**, 3773. (e) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (f) Merlic, C. A.; Zechman, A. L. *Synthesis* **2003**, 1137. (g) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131. (h) Chen, Z.; Chen, Z.; Jiang, Y.; Hu, W. *Synlett* **2004**, 1763. (i) Yoon, C. H.; Nagle, A.; Chen, C.; Gandhi, D.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2259. (j) Mechelke, M. F.; Meyers, A. I. *Tetrahedron Lett.* **2000**, *41*, 9377. (k) Scheidt, K. A.; Roush, W. R.; McKerrow, J. H.; Selzer, P. M.; Hansell, E.; Rosenthal, P. J. *Biorg. Med. Chem.* **1998**, *6*, 2477. (l) Langlois, N.; Radom, M.-O. *Tetrahedron Lett.* **1998**, *39*, 857. (m) Doyle, M. P.; Shanklin, M. S.; Oon, S. M.; Pho, H. Q.; van der Heide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3384. (n) Wee, A. G. H.; Liu, B. S.; McLeod, D. D. *J. Org. Chem.* **1998**, *63*, 4218.

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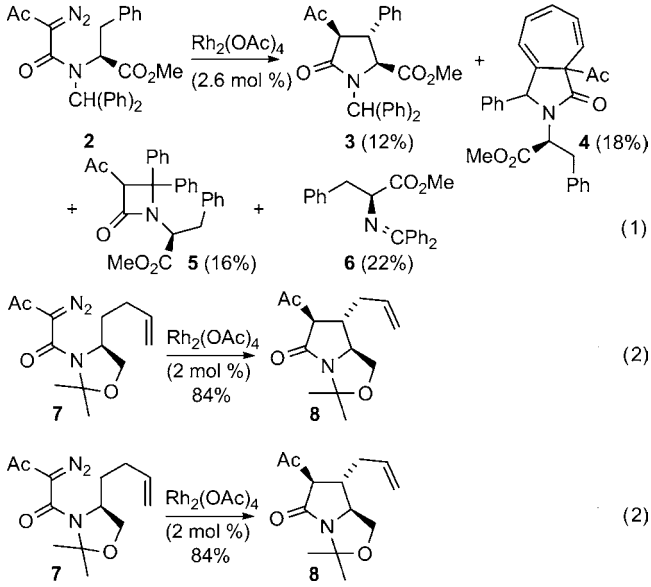
well explored. The number of potential, competitive metallocarbenoid reaction sites (indicated by →) in **1** has increased, and the control of site- and diastereoselectivity in this system poses an interesting and challenging question.

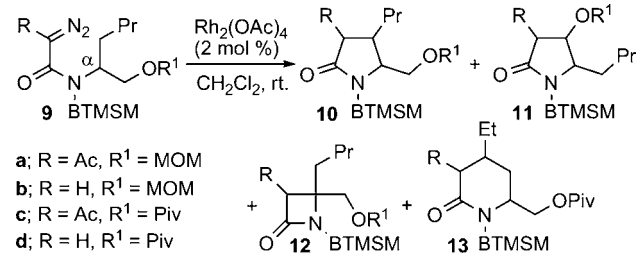


An early study, reported by Zaragoza,[2a] is the Rh(II)-catalyzed C−H insertion of α-diazoamide **2** (eq 1), which occurred with poor regio- and chemoselectivity to give only a low yield of the desired γ-lactam **3**. The products **4** and **5**, which arose from Rh(II)-carbenoid attack at the *N*-benzhydryl group, and the imine **6** were also obtained. To circumvent this difficulty, Hashimoto and co-workers resorted to the use of the 2,2-dimethyloxazolidine diazoamide (eq 1) **7**.[2b] The Rh(II)-catalyzed reaction of **7** preferentially led to the desired γ-lactam **8**, and this observation was subsequently further developed by Jung and co-workers.[2c]

We recently reported[3] that the *N*-BTMSM group is a practical, nonparticipatory N-protecting group which is effective for controlling site selectivity in Rh(II)-catalyzed reactions of tertiary α-diazoamides. We noted that the *N*-BTMSM unit has a subtle but important influence on the conformational preferences about the amide *N*-C_α σ bond in *N*-C_α-branched diazoamides.[3c] Following this cue, we initiated studies on the Rh(II)-catalyzed reaction of acyclic diazoamides of type **1** (R = BTMSM, Figure 1). We chose the oxymethylene moiety as one of the C_α-substituents as it provides flexibility for subsequent functional group manipulation in the context of synthetic applications. Herein, we report the preliminary findings of our studies and demonstrate the utility of the method in the synthesis of (±)-α-allokainic acid.

The $Rh_2(OAc)_4$-catalyzed reaction of the diazoamide[4a] **9** was first tested to assess the regioselectivity of the reaction. It is clear from Table 1 that γ-lactam formation is influenced by

Table 1. $Rh_2(OAc)_4$-Catalyzed Reaction of Diazoamide **9**



			relative yields (%)			
entry	diazo	yield (%)[a]	**10**	**11**[d]	**12**	**13**
1	**9a**	73	89[b]	0	11[e]	0
2	**9b**	82	34[c]	66	0	0
3	**9c**	88	80[b]	0	20[e]	0
4	**9d**	83	78[c]	8	8	6[f]

[a] Combined isolated yields. Relative stereochemistry: *t* = *trans*, *c* = *cis*. [b] **10a**, only *t*,*t*; **10c**, *t*,*t*:*t*,*c* = 15:1. [c] **10b**, only *t*; **10d**, *t*:*c* = 20:1. [d] **11b**, *t*:*c* = 1:1; **11d**, only *c*. [e] Inseparable *t*/*c* diastereomers: **12a**, *t*:*c* = 4:1; **12c**, *t*:*c* = 2:1. [f] Relative stereochemistry was unassigned.

subtle electronic effects from the α-substituent on the carbenoid carbon and the O-substituent of the oxymethylene group. With **9a** (entry 1), preferential C−H insertion at the butyl group to give the γ-lactam **10a** was observed, and the β-lactam **12a**, arising from insertion at the *N*-C_α−H unit, was obtained as a minor product. It is intereting to note that the γ-lactam **10a** was obtained as a single diastereomer having the C_3,C_4-*trans*; C_4,C_5-*trans* relative stereochemistry.[4b] The lactam **11a**, which could be formed via metallocarbenoid attack at the electronically activated[5a] ether C−H bond, was not detected. In accord with our previous results,[3] the *N*-BTMSM group was inert under the reaction conditions. Unexpectedly, with the unsubstituted diazoamide **9b** (entry 2), insertion at the ether C−H bond is now favored to afford γ-lactam **11b**; the γ-lactam **10b**, obtained only as the trans diastereomer, was the minor product, and the β-lactam **12b** was not detected.

To dissuade C−H insertion at the *N*-C_α-oxymethylene moiety, the *O*-MOM group was replaced with the *O*-pivaloyl (Piv) group as in diazoamides **9c**,**d**. It was reasoned that the electron-withdrawing effect of the *O*-Piv unit would deactivate the adjacent methylene C−H bonds toward metallocarbenoid insertion. Thus, reaction of **9c** gave the *trans*,*trans*-**10c** (major product) and β-lactam **12c** (minor product) as was observed for the reaction of **9a** (entry 1). Interestingly,

(2) (a) Zaragoza, F. *Tetrahedron* **1995**, *51*, 8829. (b) Anada, M.; Sugimoto, T.; Watanabe, H.; Nakajima, M.; Hashimoto, S.-H. *Heterocycles* **1999**, *50*, 969. (c) Jung, Y. C.; Yoon, C. H.; Turos, E.; Yoo, K. S.; Jung, K. W. *J. Org. Chem.* **2007**, *72*, 10114, and references cited therein.

(3) (a) Zhang, B.; Wee, A. G. H. *Chem. Commun.* **2008**, 4837. (b) Wee, A. G. H.; Duncan, S. C.; Fan, G.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 297. (c) Wee, A. G. H.; Duncan, S. C. *J. Org. Chem.* **2005**, *70*, 8372.

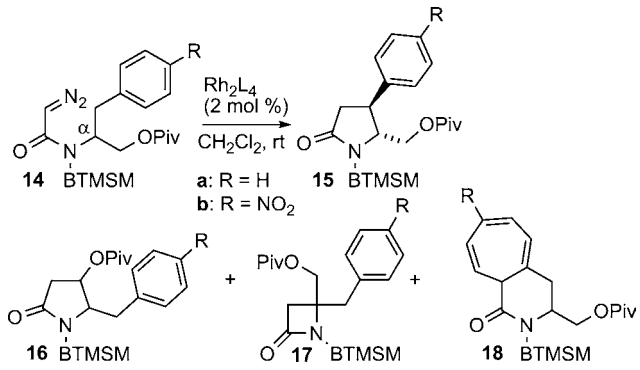
(4) (a) The preparation of the diazoamides will be presented elsewhere. (b) Only the assigned relative stereochemistries of γ-lactams **10**, **15**, and **20** are provided here. The assignment of the relative stereochemistry of γ-lactams **10**, **15**, and **20**, the regioisomeric γ-lactams **11**, **16**, and **21**, and β-lactams **12** and **28** is based on a combination of the detailed analysis of ^{1}H NMR *J* values, NOE, and X-ray crystallographic data of key products. These analyses and results will be detailed elsewhere.

(5) (a) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296. (b) Wang, J.; Chen, B.; Bao, J. *J. Org. Chem.* **1998**, *63*, 1853.

however, with **9d** C−H insertion to the butyl group to give *trans*-**10d** was now more favored over formation of γ-lactam **11d** (entries 2 and 4). The formation of **11d** and β-lactam **12d** was competitive; unexpectedly, the δ-lactam **13d** was also obtained albeit in low yield.

It is evident that the *O*-Piv group is especially useful in suppressing C−H insertion at the N−C_α-oxymethylene unit in α-unsubstituted diazoamides (**9b** vs **9d**). To further assess the influence of electronic effects on regio- and chemoselectivity, the Rh(II)-catalyzed reaction of the α-unsubstituted diazoamides carrying a *N*-C_α benzyl (**14a**) and 4-nitrobenzyl (**14b**) group was studied.

Table 2. Rh(II)-Catalyzed Reaction of Diaoamide **14**[a]



				relative yields (%)			
entry	diazo	catalyst	yields (%)[b]	**15**[c]	**16**[d]	**17**	**18**
1	**14a**	$Rh_2(cap)_4$	76	89	11	0	0
2	**14a**	$Rh_2(OAc)_4$	88	75	22	1	2
3	**14a**	$Rh_2(tfa)_4$	90	44	7	9	40
4	**14b**	$Rh_2(cap)_4$	88	72	28	0	0
5	**14b**	$Rh_2(OAc)_4$	94	72	28	0	0
6	**14b**	$Rh_2(tfa)_4$	90	77	9	11	3

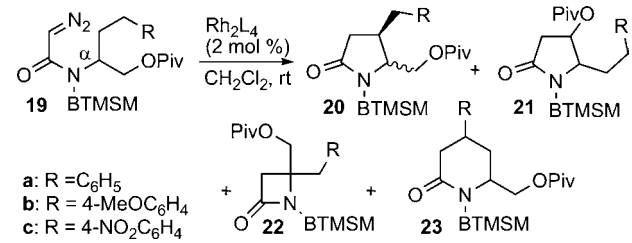
[a] Relative stereochemistry: *t* = *trans*, *c* = *cis*. [b] Combined isolated yields. [c] Only *t*-diastereomers obtained. [d] Inseparable mixture of *t*- and *c*-**16**: entry 1, *t*:*c* = 2:1; entry 2, *t*:*c* = 1:6; entry 3, *t*:*c* = 1:2.2; entry 4, *t*:*c* = 2:1; entry 5, *t*:*c* = 1:5; entry 6, only *c*-**16**.

The results in Table 2 show that Rh(II)-carbenoid C−H insertion preferentially occurred at the benzylic position to give γ-lactams **15**,[4b] and the *O*-Piv group's effectiveness in curtailing C−H insertion at the oxymethylene unit was maintained. With **14a**, the $Rh_2(cap)_4$-catalyzed reaction gave only *trans*-**15a** and **16a** (entry 1), wherein **15a** was the major product. With $Rh_2(OAc)_4$ the formation of *trans*-**15a** was still preferred over **16a**, but minor amounts of the β-lactam **17a** and the cycloheptatriene **18a** were also obtained (entry 2). It should be noted that although $Rh_2(OAc)_4$-carbenoid attack at the phenyl unit was significantly competitive in simpler *N*-BTMSM diazoamides[3c] it was not the case here. In the $Rh_2(tfa)_4$-catalyzed reaction (entry 3) almost equiamounts of *trans*-**15a** and **18a** were obtained indicating a significant erosion of chemoselectivity. However, regioselectivity was still very good as the γ-lactam **15a** was formed along with minor amounts of **16a** and **17a**. The reaction of **14b** was then explored wherein the presence of the electron-withdrawing nitro group was expected to suppress the formation of the cycloheptatriene derivative **18b** thereby improving chemoselectivity. Thus, with $Rh_2(cap)_4$ and $Rh_2(OAc)_4$ only *trans*-**15b** and **16b** were formed (entries 4 and 5), with **15b** as the preferred product. For the $Rh_2(tfa)_4$-catalyzed reaction, the formation of **18b** is markedly reduced. Although *trans*-**15b** was formed as the major product, there was a slight increase in the yields of **16b** and **17b** (entries 3 and 6).

This latter result suggests that the nitro group had not only deactivated the phenyl ring toward metallocarbenoid attack but also decreased, somewhat, the reactivity of the benzylic C−H bonds.[5b]

Next, the regioselectivity of the Rh(II)-catalyzed reaction of diazoamides **19** (Table 3) was investigated. In this system,

Table 3. Rh(II)-Catalyzed Reaction of Diazoamide **19**[f]



				relative yields (%)			
entry	diazo	catalyst	yields (%)[b]	**20**[c]	**21**[d]	**22**	**23**[e]
1	**19a**	$Rh_2(cap)_4$	87	87 (3:1)	12	0	1[f]
2	**19a**	$Rh_2(OAc)_4$	99	67 (5:1)	20	10	3[g]
3	**19a**	$Rh_2(tfa)_4$	96	70 (10:1)	10	17	3[g]
4	**19b**	$Rh_2(cap)_4$	95	85 (3:1)	8	1	6[f]
5	**19c**	$Rh_2(cap)_4$	88	82 (3:1)	18	0	0

[a] Relative stereochemistry: *t* = *trans*, *c* = *cis*. [b] Combined isolated yields. [c] Ratio of separable *t*-**20**/*c*-**20** in brackets. [d] Inseparable *t*-**21**/*c*-**21**. [e] Relative stereochemistry was unassigned. [f] Single diastereomer. [g] Two inseparable diastereomers.

Rh(II)-carbenoid attack at the aryl moiety is not expected on the basis of our previous studies.[3b,c] The results show that metallocarbenoid C−H insertion preferentially occurred at the phenethyl/arylethyl moiety to give γ-lactams **20** as the major product. Further, **20** was obtained as a mixture of readily separable *trans*- and *cis*-**20**, wherein the former predominated. It is also evident that product distribution was catalyst dependent. For **19a**, $Rh_2(cap)_4$ provided the best regioselectivity favoring formation of γ-lactams **20a** and **21a**; β-lactam **22a** was not detected; and δ-lactam **23a** was obtained in very minor amounts (entry 1). In comparison, $Rh_2(OAc)_4$ and $Rh_2(tfa)_4$ gave lower regioselectivity as the β-lactam **22a** was also formed in significant amounts (entries 2 and 3). The $Rh_2(cap)_4$-catalyzed reaction of **19b**,**c** revealed that the electronic effect of a *para*-substituent[5b] on the reactivity of the benzylic C−H bonds was subtle. Thus, compared to **19a**, the electron-donating 4-MeO substituent in **19b** only slightly favored the formation of the δ-lactam **23b**, whereas the electron-withdrawing 4-NO_2 group in **19c**

discouraged metallocarbenoid insertion at the benzylic position (entries 4 and 5). In this latter case, high regioselectivity, similar to that observed for **19a**, was realized (entries 1 and 5).

The utility of this method is demonstrated by the synthesis of (±)-α-allokainic acid (**24**),[2b,c,6] whose retrosynthesis (Figure 2) was guided by the above-described combined

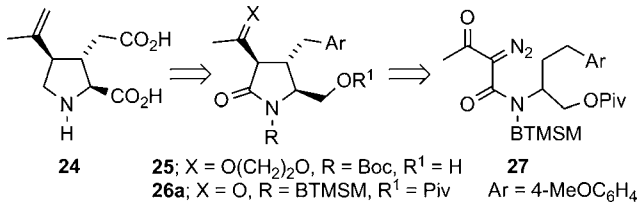
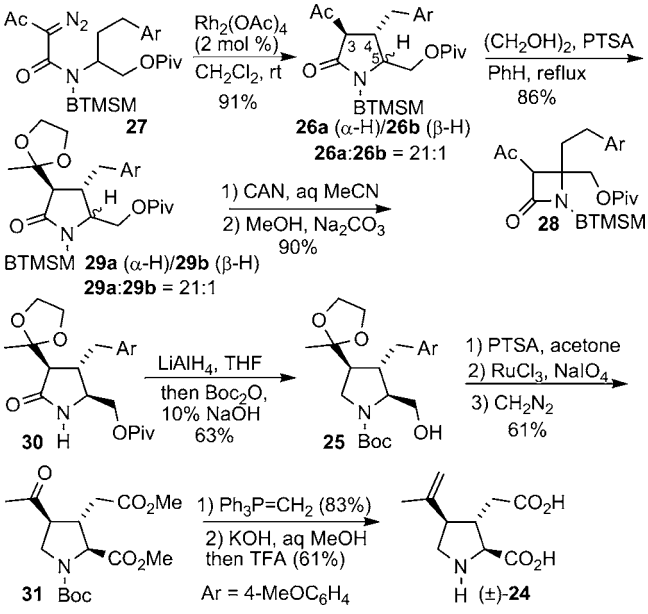


Figure 2. Retrosynthesis of **24**.

results. Compound **25** was identified as an intermediate, which can be prepared from **26a**; **26a** is to be made from diazoamide **27**.

The synthesis started with the $Rh_2(OAc)_4$-catalyzed reaction of **27**[7a] (Scheme 1), which efficiently (91%) gave a 3.8:1

Scheme 1. Synthesis of **24**



ratio of the readily separable trisubstituted γ-lactam **26** and the β-lactam **28**; however, each of these lactams was obtained as an inseparable mixture of two diastereomers. Ketalization of γ-lactam **26** afforded an 86% yield of the ketal **29** as an oil. Gratifyingly, the ketal diastereomers were amenable to separation by chromatography, which provided a 21:1 ratio (based on isolated yields) of **29a**:**29b**. The major diastereomer **29a** was N-deprotected[3b,c] to give a 90% yield of crystalline **30**. At this juncture, a single-crystal X-ray analysis was performed on **30**,[7b] which helped to establish its relative stereochemistry as C_3,C_4-*trans*; C_4,C_5-*trans*. For the minor diastereomer **29b**, NOE experiments gave, upon irradiation of H-5, an 8.7% enhancement of H-4, but none for H-3. This led us to assign the C_3,C_4-*trans*; C_4,C_5-*cis* relative stereochemistry to **29b**. The combined data also allowed the assignment of the relative stereochemistry for the major diastereomers **26a** and **29a** as C_3,C_4-*trans*; C_4,C_5-*trans* and for the minor diastereomers **26b** as C_3,C_4-*trans*; C_4,C_5-*cis*.

Compound **30** was then treated with $LiAlH_4$ in refluxing THF to reduce the lactam carbonyl unit and effect O-depivaloylation to obtain the corresponding pyrrolidine alcohol, which without isolation was converted to *N*-Boc carbamate **25** in 63% yield (over two steps). The 4-methoxyphenyl group in **25** was to serve as a carboxylic acid equivalent. Thus, acid-catalyzed hydrolysis of the ketal unit followed by RuO_4 oxidation[8] of the primary alcohol and 4-methoxyphenyl groups provided the crude diacid, which was immediately methylated (CH_2N_2) to give **31**[9] in 61% overall yield (three steps). Subsequent Wittig methylenation of **31** installed the isopropenyl group, followed by base hydrolysis and then *N*-Boc deprotection using TFA to yield (±)-α-allokainic acid (**24**). Purification (Dowex 50W-H^+) gave (±)-**24** in 61% yield, which showed melting point and spectroscopic data in agreement with reported data.[2b,6e,f]

In summary, intramolecular Rh(II)-carbenoid-mediated C−H insertion of acyclic *N*-C_α-branched *N*-BTMSM diazoamides proceeded efficiently with good to excellent regio-, chemo-, and diastereoselectivity to give highly functionalized di- and trisubstituted γ-lactams. The high regioselectivity realized in γ-lactam formation arises from (i) the conformational effect of the *N*-BTMSM group on the amide N−C(O) unit and N−C_α σ bond and (ii) the electronic effect of the OPiv unit of the oxymethylene group. The utility of the method was demonstrated by the total synthesis of (±)-α-allokainic acid (**24**).

Acknowledgment. We thank the Natural Sciences and Engineering Research Council, Canada, and the University of Regina for financial support. We thank Dr. B. Sterenberg of this department for help with X-ray data.

Supporting Information Available: Spectroscopic data and copies of spectra of key compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) (a) Cook, G. R.; Sun, L. *Org. Lett.* **2004**, *6*, 2481. (b) Ma, D.; Wu, W.; Deng, P. *Tetrahedron Lett.* **2001**, *42*, 6929. (c) Chevliakov, M. V.; Montgomery, J. *Angew. Chem., Int. Ed.* **1998**, *37*, 3144. (d) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Aoe, K.; Hiramatsu, H.; Naito, T. *Heterocycles* **1997**, *46*, 321. (e) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418. (f) Oppolzer, W.; Andres, H. *Tetrahedron Lett.* **1978**, 3397.

(7) (a) The $Rh_2(cap)_4$-catalyzed reaction proceeded only in refluxing CH_2Cl_2. The ratio of γ-lactam **26**:β-lactam **28** was 11.5:1, but the diastereoselectivity realized for **26** was lower; **26a**:**26b** = 4:1. (b) See Supporting Information.

(8) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(9) For (2*S*,3*S*,4*R*)-**31**, see: Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J. *J. Org. Chem.* **2001**, *66*, 2588.