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A Thermodynamic Preference of Chiral *cis*-γ,δ-Epimino-(*E*)-α,β-Unsaturated Esters over Other Stereoisomers: Synthetically Useful Pd(0)-Catalyzed Equilibrated Reactions of Aziridines Bearing an α,β-Unsaturated Ester Group

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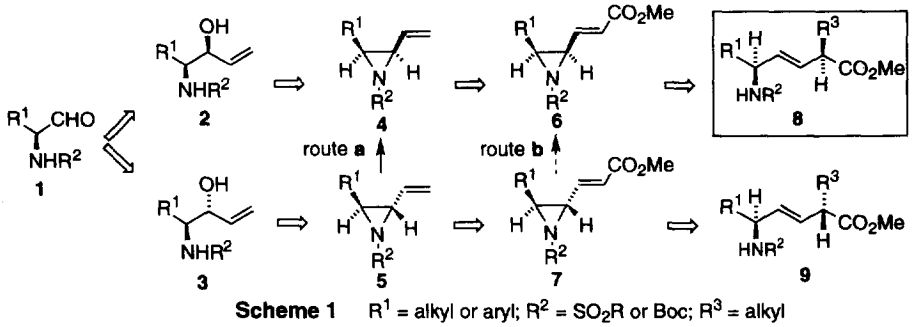
Abstract: A practical synthesis of chiral *N*-arylsulfonyl-*cis*-γ,δ-epimino-(*E*)-α,β-enoates, key intermediates for the synthesis of (*E*)-alkene dipeptide isosteres *via* Pd(0)-catalyzed equilibrated reactions, has been successfully achieved by exposing *N*-arylsulfonyl-γ,δ-epimino-α,β-unsaturated esters to a catalytic amount of $Pd(PPh_3)_4$ in THF at 0 ~ 20 °C. Copyright © 1996 Elsevier Science Ltd

Replacement of the amide bond in bioactive peptides with a *trans*-double bond has been a topic of long-standing interest in the biological,[1] theoretical,[2] and synthetic arena.[3] While many synthetic routes have been developed to construct *trans*-alkene dipeptide isosteres,[4] we [5] and Wipf [6] recently described a convenient and highly stereoselective synthesis of (*E*)-alkene dipeptide isosteres **8** and **9** *via* an organocopper-mediated S_N2' reaction of *N*-protected-γ,δ-epimino-α,β-enoates **6** and **7**, which could be derived from amino alcohols **2** and **3** *via* vinylaziridines **4** and **5**.

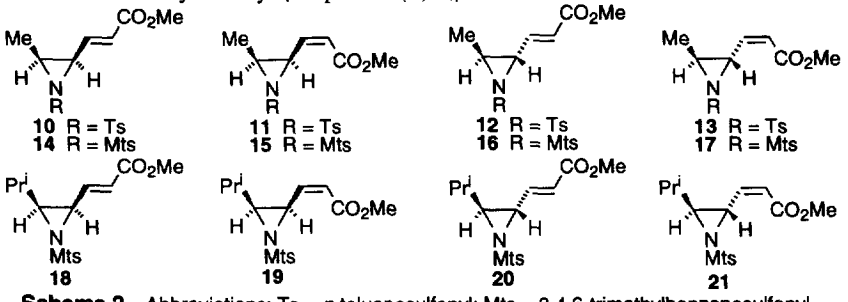
Recently, we [7] and others [8-10] have demonstrated that peptides containing *trans*-alkene dipeptide isosteres of type **8** exhibit potent biological activity. In connection with continued synthetic and biological studies, we required a reliable procedure for the synthesis of isosteres of type **8** from enoates of type **6**. However, the highly stereoselective synthesis of *syn*-amino alcohols **2** from chiral amino aldehydes **1** and hence enoates **6** has hitherto been difficult. The obstacle associated with this strategy is clearly the efficient synthesis of enoates of type **6** .



Scheme 1 R^1 = alkyl or aryl; R^2 = SO_2R or Boc; R^3 = alkyl

Taking advantage of recent results we obtained in Pd(0)-catalyzed isomerizations of *N*-alkylsulfonyl- or arylsulfonyl-3-alkyl-2-vinylaziridines of type **5** to compounds of type **4** (route **a** in Scheme 1),[11] we decided to investigate equilibration reactions of various α,β-enoates with $Pd(PPh_3)_4$ (route **b** in Scheme 1). If successful, this sequence would be a valuable addition to the arsenal of reliable synthetic routes, since *anti*-amino alcohols of type **3**, and hence enoates of type **7**, could be converted into desired isosteres **8** *via* enoates **6**. We are aware of no successful examples of synthetically useful equilibration in these systems, although 2-alkenylaziridines are

known to undergo Pd(0)-catalyzed carbonylations affording β-lactams,[12] and Pd(0)-formic acid mediated reductive cleavage, yielding alkene isosteres.[13] We now describe a study involving the palladium(0)-catalyzed equilibration of a series of *N*-arylsulfonyl-γ,δ-epimino-(*E*)-α,β-enoates.



Scheme 2 Abbreviations: Ts = *p*-toluenesulfonyl; Mts = 2,4,6-trimethylbenzenesulfonyl

The requisite diastereoisomerically pure substrates shown in Scheme 2 for the present experiments were readily prepared in acceptable overall yields from either (*S*)-α-amino acids or optically active 2,3-epoxy alcohols by standard methods.[14] Exposure of the γ,δ-epimino-α,β-enoate **12** to a catalytic amount of $Pd(PPh_3)_4$ in dry THF at 15 °C for 15 h yielded an 85.09 : 5.12 : 9.79 : < 0.01 mixture of **10**, **11**, **12**, and **13** (entry 3, Table 1), in which the new isomer **10** predominated. Within the limits of experimental error, essentially identical results were obtained following treatment of isomeric enoates **10**, **11**, and **13** under the same reaction conditions (entries 1, 2, and 4, Table 1). The optical activity of **10** was the same before and after $Pd(PPh_3)_4$ equilibrated reaction. Tetrahydrofuran is the best choice among reaction solvents. Higher reaction temperatures (> 30 °C) sometimes decreased the combined isolated yields of equilibrated products presumably due to competing decomposition.

This Pd(0)-catalyzed reaction was successfully carried out on other α,β-enoates through the judicious choice of reaction conditions. The desired *cis*-(*E*)-product **14** was obtained with a selectivity as high as ca. 9:1 [**14**:(**15**+**16**+**17**)] when a catalytic amount of $Pd(PPh_3)_4$ (2 mol%) was employed in the equilibrated reaction of **15**, **16**, or **17** (entries 6-8, Table 1). Similarly, $Pd(PPh_3)_4$-catalyzed reactions of **19**, **20**, or **21** provided ca. 94:0.5:5.5:< 0.001 mixtures of four stereoisomers **18**, **19**, **20**, and **21** in which the desired isomer **18** predominated over other stereoisomers **19**, **20**, and **21** (entries 10-12, Table 1).

Table 1. $Pd(PPh_3)_4$-catalyzed equilibration reactions of *N*-arylsulfonyl-γ,δ-epimino-α,β-enoates [a]

Entry	substrate	$Pd(PPh_3)_4$ mol %	condition		Product ratio *cis*-(*E*) : *cis*-(*Z*) : *trans*-(*E*) : *trans*-(*Z*)	Combined isolated yield
1	**10**	2	15 °C	15 h	**10** : **11** : **12** : **13** = ***85.74*** : 5.02 : 9.24 : < 0.01	93%
2	**11**	2	15 °C	15 h	**10** : **11** : **12** : **13** = ***87.00*** : 4.70 : 8.30 : < 0.01	86%
3	**12**	2	15 °C	15 h	**10** : **11** : **12** : **13** = ***85.09*** : 5.12 : 9.79 : < 0.01	84%
4	**13**	2	15 °C	15 h	**10** : **11** : **12** : **13** = ***87.86*** : 5.70 : 6.44 : < 0.01	88%
5	**14**	2	20 °C	15 h	**14** : **15** : **16** : **17** = ***90.40*** : 3.89 : 5.71 : < 0.001	87%
6	**15**	2	20 °C	15 h	**14** : **15** : **16** : **17** = ***91.23*** : 3.17 : 5.60 : < 0.001	90%
7	**16**	2	20 °C	15 h	**14** : **15** : **16** : **17** = ***90.91*** : 3.57 : 5.52 : < 0.001	96%
8	**17**	2	20 °C	15 h	**14** : **15** : **16** : **17** = ***90.54*** : 3.85 : 5.61 : < 0.001	96%
9	**18**	4	0 °C	24 h	**18** : **19** : **20** : **21** = ***94.13*** : 0.43 : 5.44 : < 0.001	97%
10	**19**	4	0 °C	24 h	**18** : **19** : **20** : **21** = ***94.12*** : 0.51 : 5.47 : < 0.001	98%
11	**20**	2	0 °C	24 h	**18** : **19** : **20** : **21** = ***94.03*** : 0.50 : 5.47 : < 0.001	97%
12	**21**	2	0 °C	24 h	**18** : **19** : **20** : **21** = ***94.06*** : 0.56 : 5.38 : < 0.001	96%

[a] All reactions were carried out in dry THF (ca. 0.05 molar solution) under slight positive argon pressure. Product ratios were determined by reverse phase HPLC.

From the above results, it is evident that palladium(0)-catalyzed reactions led to equilibrium ratios of the all possible stereoisomers, which are functions of their relative stabilities. Clearly the thermodynamic stabilities of the *trans*-(*Z*)-isomers **13**, **17**, and **21** are lower than those of the corresponding *cis*-(*E*)-isomers **10**, **14**, and **18**. In addition, it is apparent from entries (5-8) and (9-12) in Table 1, that the greater steric bulk of the nitrogen protecting group (Mts) and the alkyl group (*iso*-Pr) on the aziridine ring tended to afford considerably higher ratios of the desired *N*-arylsulfonyl-*cis*-γ,δ-epimino-(*E*)-α,β-enoates.

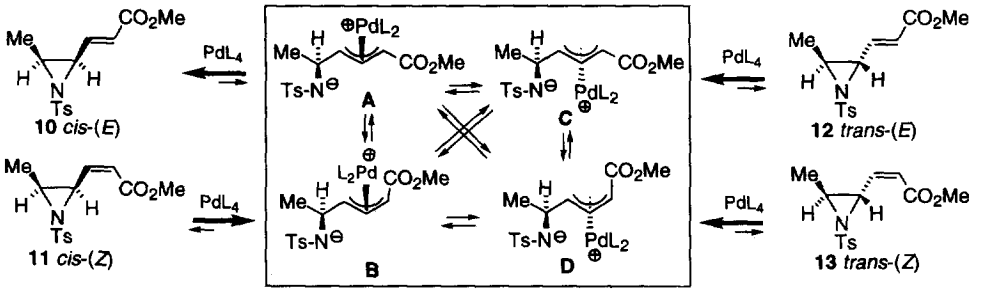
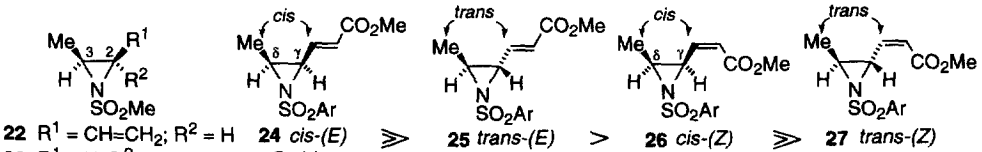


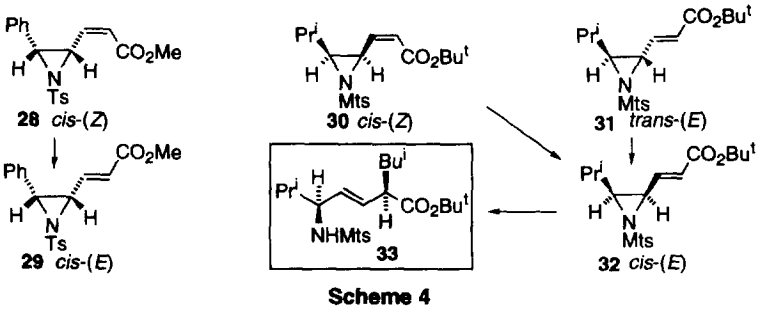
Figure 1

The stereochemical outcomes of the palladium-catalyzed isomerizations disclosed above can be rationalized by assuming the well-known π–σ–π interconversions[15] of π-allyl palladium complexes **A**, **B**, **C**, and **D** generated by oxidative addition of *N*-arylsulfonyl-γ,δ-epimino-α,β-enoates **10**, **11**, **12**, and **13** to the Pd(0) complexes as shown in Figure 1.



Scheme 3

What is the origin of the thermodynamic preference of *cis*-(*E*)-enoates over other stereoisomers? Previous work in this laboratory has shown that 2,3-*cis*-vinylaziridine **22** is 6 KJ/mol more thermodynamically stable than its 2,3-*trans*-stereoisomer **23**.[11] Steric interaction between the alkyl group at the C-3 position and the vinyl group at the C-2 position in compound **22** would be of less importance. In the present study, although the basis for the thermodynamic preference of *cis*-(*E*)-enoate **24** over its *trans*-(*E*)-isomer **25** is not clear, we speculate that the origin of this energy difference might lie in a steric and/or electronic repulsive interaction between the *N*-arylsulfonyl group and the unsaturated ester group. The thermodynamic preference of **26** over **27** may be explained in the same way.



Scheme 4

The above reactions did work in practice. Thus, chiral *cis*-(*Z*)-enoate **28** bearing a phenyl group can be converted into diastereomerically pure *cis*-(*E*)-enoate **29** in the following manner. Exposure of **28** to

$Pd(PPh_3)_4$ (4 mol%) in dry THF at 20 °C for 18 h was followed by filtration through a short pad of silica gel with *n*-hexane-EtOAc (1:1). Concentration under reduced pressure gave a crystalline residue. Recrystallization from MeOH gave essentially pure *cis-(E)*-enoate **29** as silky needles in 75% yield. The mother liquor was concentrated to a semisolid, which was again treated with $Pd(PPh_3)_4$ (4 mol%) in dry THF. Work-up as described above gave additional **29** in 6% yield. The total yield of **29** amounted to 81%. In the same manner, both *cis-(Z)*- and *trans-(E)*-enoates **30** and **31** were converted into the desired enoate **32** with *cis-(E)*-stereochemistry in 83.6 and 86.7% isolated yields. Space restrictions prevent detailed descriptions of all results, however, it is apparent that the Pd(0)-catalyzed reactions give very satisfactory results. Finally, reaction of **32** with *iso*-BuCu(CN)MgCl in THF at - 78 °C for 30 min gave the required isostere **33** in 95% isolated yield as a single isomer. Further details on the scope and limitation of this technology will be reported in a full paper.

In summary, it was shown that palladium-catalyzed equilibrated reactions of various γ,δ-epimino-α,β-enoates afford mixtures of four possible stereoisomers in which the desired *cis-(E)*-isomers predominated over other stereoisomers. This new methodology could lead to a series of diastereomerically pure *cis*-γ,δ-epimino-*(E)*-α,β-enoates which could be utilized in the stereoselective synthesis of *(E)*-alkene dipeptide isosteres.

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