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Pd-CATALYZED $S_{CN'}$ REACTIONS: STEREOSELECTIVE FORMATION OF CYCLIC CARBAMATES FROM *TERT*-BUTYLDIMETHYLSILYL CARBAMATES

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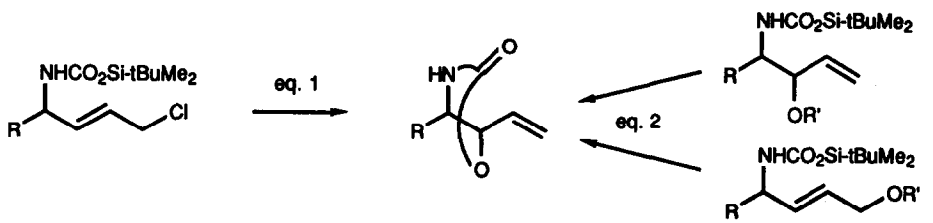
Summary: *Stereoselective formation of cyclic carbamates was achieved by the intramolecular trapping of a tert-butyldimethylsilyloxycarbonyl group with allylic esters upon activation with fluoride and cat. Pd(O). The reactive conformation is proposed to be* **D**. *The highly stereoselective reaction of 2° allylic esters allowed a detailed reaction mechanism to be proposed which accounts for the observed selectivities.*

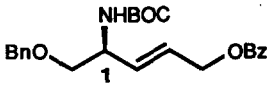
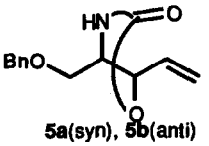
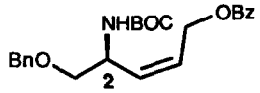
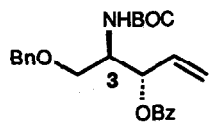
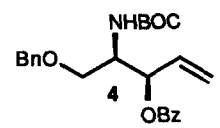
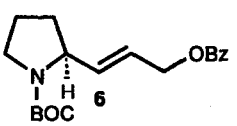
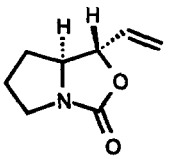
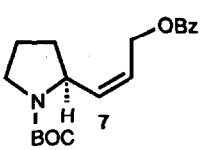
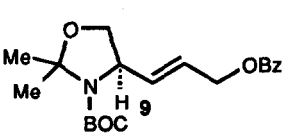
The *tert*-butyldimethylsilyloxycarbonyl group, prepared from the most common amino protecting groups Boc and Z, is an active species which is convertible into a variety of urethanes (alkyl carbamates and cyclic carbamates) by its inter- or intramolecular trapping with an electrophile.[1] In our previous studies, intramolecular reaction of this active species with allylic halides was achieved with the assistance of a AgF or AgF/Pd(II) system to provide cyclic carbamates in a stereoselective manner (eq 1).[1] To extend the scope of this method we thought of using allylic esters instead of allylic chlorides; allylic esters are easily prepared and are more stable than the corresponding allylic chlorides, are known to undergo Pd catalyzed substitution reactions,[2] and are interesting in view of stereoselectivity in the formation of corresponding cyclic carbamates (eq 2). In this communication, we describe Pd catalyzed $S_{CN'}$ type[3] cyclic carbamate formation from *tert*-butyldimethylsilyl carbamates using allylic esters as an internal electrophile.

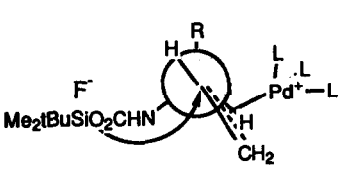
The silyl carbamates possessing an allylic ester group were prepared from their corresponding N-Boc compounds with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf)/2,6-lutidine.[1] Successive



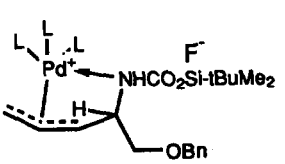
treatment of this species with 0.10 equiv of Pd(0) and 1 equiv of n-Bu_4NF in THF at room temperature gave the cyclic carbamates in fair to good yields. Several Pd catalysts and ester groups were examined in order to optimize the reaction conditions. Finally, we found that the use of tetrakis(triphenylphosphine)palladium (O) as the catalyst and benzoyl ester as the internal electrophile was best. No cyclization occurred either with fluoride but without Pd catalyst, or with Pd catalyst but without fluoride. As summarized in Table I, the yields of cyclic carbamate were dependent on the substrates, i.e., *E* allylic benzoate 1 and anti benzoate 3 both provided syn carbamate (syn/anti = 9/1) in good yields while a decrease in yields was

Table I. Cyclic carbamate formation from benzoates.

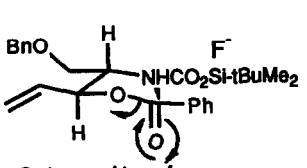
entry	allyl benzoate	products	yield (syn/anti)
1.		 **5a**(syn), **5b**(anti)	78%(9/1)
2.		**5a,5b**	25%(15/1)
3.		**5a, 5b**	70%(9/1)
4.		**5a,5b**	11%(9/1)
5.		 **8a**-syn(trans), **8b**-anti(cis)	76%(3/2) syn(trans)/anti(cis)
6.		**8a, 8b**	64%(3/2) syn(trans)/anti(cis)
7.		—	0%



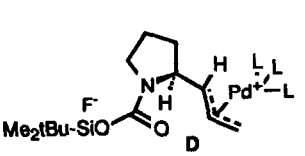
A: transition state



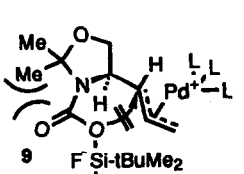
B: internal Lewis acid delivery



C: benzoyl transfer



D

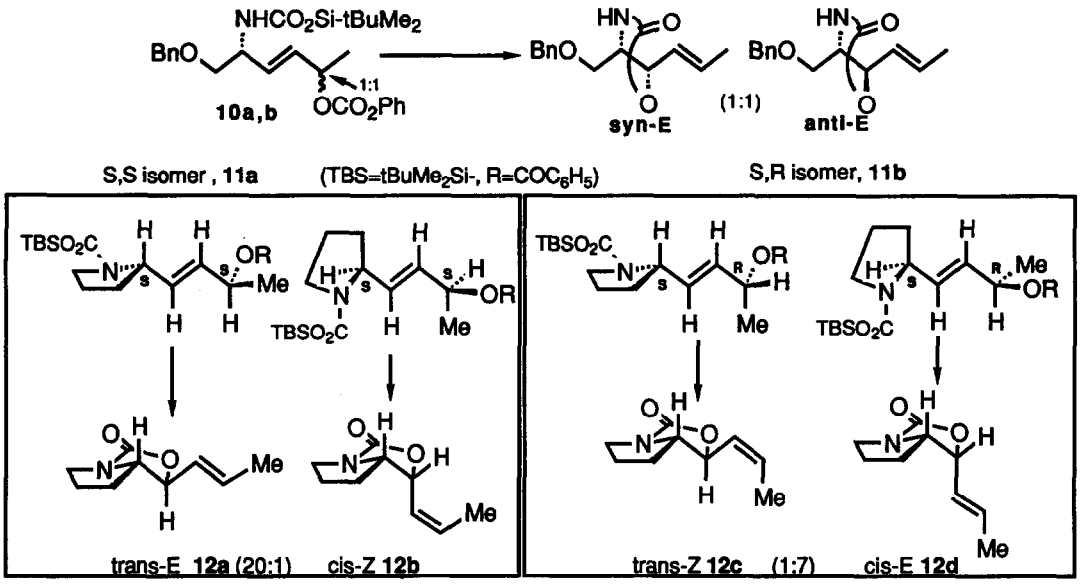


decarboxylation

observed in the case of the *Z* benzoate **2** and syn benzoate **4**. The stereoselectivity of the products was in accord with that of the allylic chlorides as previously reported (eq 1). The major product **5a** could be produced from the transition state structure **A** in a S_{cN}' manner. In the case of the *Z* allylic benzoate (entry 2), internal delivery of Lewis acid[2] due to the proximity of the cationic palladium species to the amino group may accelerate the desilylation followed by decarboxylation to give free amine as the major product (**B**). In entry 4, the major product was the benzoyl amide in which benzoyl transfer to the amino group is the major process due to neighboring group participation of the amino group (**C**).

On the other hand, the benzoates of both *E*-**6** and *Z*-**7** gave in good yields a mixture of syn and anti carbamates (**8a** and **8b**).[4] However, the stereoselectivity of the products decreased (syn(trans)-**8a**/anti(cis)-**8b** = 3/2, respectively) probably due to the reduced steric bulkiness of the R group in transition state **A** (comformationally constrained $-CH_2-$ in a five membered ring versus freely rotating $-CH_2OR$). It is noted that treatment of the cyclic analog **9** does not provide any cyclic carbamate but gives decarboxylated free amine, exclusively. This result suggests that to attack the intermediary palladium π-allyl complex the conformation of the silyloxycarbonyl group is (**D**); for the case of **9** the bulky dimethyl group on the five membered ring prevents the silyloxycarbonyl group from having the appropriate conformation, thus leading only to decarboxylation.

The use of secondary allylic esters is of interest since now there are 4 possible products considering both the ring stereochemistry [syn(trans)/anti(cis)] and double bond geometry (*E*/*Z*). The phenylcarbamates (in this case the benzoates were unreactive), obtained as an inseparable mixture of (S,S)-**10a** and (S,R)-**10b** (1/1),[5] were treated in the same manner as above to give as the main products a 1:1 mixture of syn and anti *E* cyclic carbamates in 50% yield (with a small amount of *Z* olefin). The increased formation of the anti-diastereomer is unusual in this series of substrates and suggests that there is an additional control element in this case. A 1:1 mixture of the proline derivatives (S,S)-**11a** and (S,R)-**11b** behaved in a similar manner yielding a 1:1 mixture of the syn and anti *E* cyclic carbamates in 74% yield (with a small amount of *Z* isomer).[6] At this point the mechanism was unclear since the N-carboxylate could attack the π-allyl palladium complex from either the backside (net retention) or frontside (net inversion).[7] To clarify this point each proline derivative (S,S)-**11a** and (S,R)-**11b** was examined as the stereochemically pure substrate.[6] From the (S,S)-**11a**, trans-*E* product **12a** was produced, highly stereoselectively (20:1), while (S,R)-**11b** gave the cis-*E* adduct **12d** as the major product (cis-*E*/trans-*Z* = 7/1). Formation of the trans adduct from the (S,S) isomer and primarily the cis adduct from the (S,R) isomer suggests the mechanism of these transformation to be (1) the leaving group and the silyloxyl group are placed on the same side of the olefin in the ground state conformation; the major or exclusive isomer is produced from the conformation with the least $A^{1,3}$ strain;[8] (2) palladium (0) attacks from the back side of the leaving group, and (3) attack of the N-carboxylate ion species to the π-allyl palladium complex to give the cyclic carbamate in a S_{cN}' manner. These results provide strong evidence for the S_{cN}' mechanism of the present transformations as well as a stereoselective method for the synthesis of either 1,2-syn or anti amino hydroxyl system.[9,10]



References and Footnotes:

1. (a) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870.
   (b) Sakaitani, M.; Ohfune, Y. *J. Am Chem. Soc.* **1990**, *112*, 1150.
2. Trost, B. M.; Verhoeven, T. R. *Comprehensive Organometallic Chemistry*; Sir Wilkinson, G; Stone, F. G. A.; Abel, E. W., Eds.; Pergamon Press, Oxford, 1982; pp.799.
3. Stork, G.; Schoofs, A. R. *J. Am. Chem. Soc.* **1979**, *101*, 5081.
4. The stereochemistry was determined by comparison with literature examples. See: Parker, K. A.; O'Fee, R. *J. Am. Chem. Soc.* **1983**, *105*, 654.
5. These were synthesized either by $NaBH_4$ reduction of the corresponding α,β-unsaturated ketone, or by MeLi addition to the α,β-unsaturated aldehyde, followed by esterification with $ClCO_2Ph$.
6. The 1:1 mixture of **11a** and **11b** was synthesized by $NaBH_4$ reduction of the corresponding α,β-unsaturated ketone followed by esterification with PhCOOH. The pure diastereomers **11a** and **11b** were obtained by HPLC separation of the alcohols (ODS column, 3:2/MeOH:H_2O, RI detector, 1 mL/min., retention time for S,R alcohol = 46.9 min., S,S alcohol=49.4 min.) followed by esterification.

   The assignment of the stereochemistry of the secondary esters was made as follows: Compound **11b** was cleaved with O_3 and reduced with $NaBH_4$ to give the 1,2 alcohol benzoate which was treated with $tBuMe_2SiCl$ in the usual way to yield the 1,2 silyl ether benzoate. This was correlated with authentic material prepared as follows: (S)-(+)-1,2-propandiol was treated first with 1 equiv of $tBuMe_2SiCl$ and then with BzCl. The authentic material had the same optical rotation as the material derived from compound **11b**, $[\alpha]_D^{24}$ +11.8° (c 1.75, $CHCl_3$).
7. Backside attack is usually favored in *inter*molecular reactions, but for *intra*molecular reactions little is known. See footnote 2.
8. Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
9. Jurczak, J.; Gołębiowski, A. *Chem. Rev.* **1989**, *89*, 149.
10. Representative experimental: To the silylcarbamate (prepared from 81 μmol **1** as described[1]) was added 0.40 mL freshly distilled THF, 100 μL 1 N Bu_4NF in THF (1.2 eq.) and 9 mg $Pd(Ph_3P)_4$ (0.1 eq.) under Argon. After 1 hr. at r.t., the reaction was quenched with saturated aqueous $NaHCO_3$, extracted with Et_20(4x), dried($MgSO_4$), filtered, and stripped. ^1H NMR (360 MHz) of the crude reaction mixture showed a 9:1 mixture of trans:cis cyclic carbamates (integration of the nitrogen methine: trans d 3.79(m), cis d 4.05(m)). Flash chromatography (10% EtOAc:Et_2O) provided the pure carbamates (77% yield from **1**), identical to authentic samples.[1]

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