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A STEREOCONTROLLED SYNTHESIS OF TRANS-ALLYLIC AMINES

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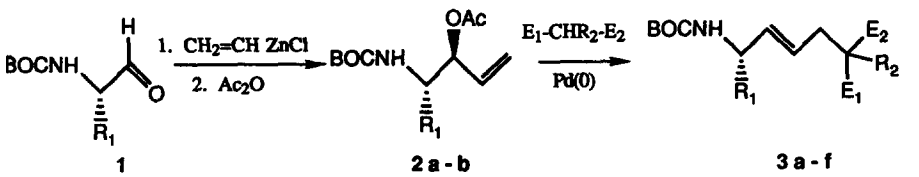
Summary: The palladium catalyzed coupling of allylic acetates with carbon nucleophiles generates urethane protected trans-allylic amines with exceptionally high stereoselectivity.

The replacement of the peptide bond with a trans carbon-carbon double bond has attracted considerable interest[1,2] in the quest for new drugs that mimic bioactive peptides. We became interested in the possibility of using chiral trans-allylic amines derived from amino acids as starting materials[3] for the synthesis of conformationally restrained dipeptide isosteres. Since the methodologies reported for transforming protected amino aldehydes[2] into the corresponding trans-alkenes require a minimum of 6 steps, we sought a more direct approach by utilizing the Trost alkylation reaction.



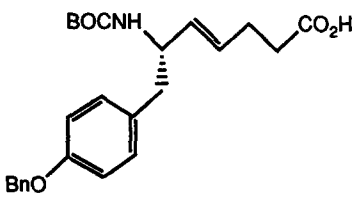
1 2a-b 3a-f

The allylic acetates **2a-b** were formed in >60% yield by addition of the BOC protected amino aldehydes **1** to excess vinylzinc chloride in THF at -30°C followed by acetylation of the resulting vinyl carbinol (Ac_2O, Et_3N, DMAP). The addition of stoichiometric ethereal zinc chloride to the vinylmagnesium bromide led to improved yields, presumably due to decreased enolization, as well as enhanced *threo* diastereoselectivity (typically 8:1).[4]

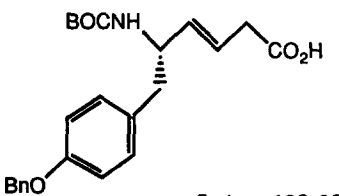
Palladium catalyzed coupling of allylic acetate **2a** with diethyl malonate ($Pd(PPh_3)_4$ cat., NaH or BSA,THF, 60°C, 2-5 h)[5] provided the desired allylic BOC-protected amine **3a** in 81% yield with remarkable 99:1 stereoselectivity.[6] Several other "soft nucleophiles" were employed in the coupling reaction with similiar success. These results are summarized in the Table below. Products **3c** and **3d** underwent efficient desulfonylation with activated Mg in methanol[7] to provide **3g** (E_1=E_2=H) and **3h** (E_1=R_2=H), respectively. Saponification of **3h** (LiOH, DME-H_2O) gave in quantitative yield Tyr-homo-Gly double bond isostere **4** which was identical in all respects with the Ireland-Claisen rearrangement[8] product of allylic acetate **2a** ($KNTMS_2$,THF; t-butyldimethylsilyl chloride, THF-HMPA, 25°C; tetra-n-butylammonium fluoride, THF, 83% recrystallized yield).[9] The product **3e** obtained from the coupling of **2a** with acetylated diethyl tartronate[10] was transformed into the protected Tyr-Gly double bond isostere **5** by a 2 step sequence ($LiBH_4$, DME; $NaIO_4$) in 62% overall yield.[11]

	R1	R2	E1	E2	Base[a]	Reaction Time[b]	Product[c]	Isolated Yield (%)	mp
2a		H	CO_2Et	CO_2Et	BSA	4.5	3a	81	68.5-69.5°C
2a		H	CO_2Et	CO_2Et	NaH	2	3a	73	
2a		H	SO_2Ph	SO_2Ph	NaH[d]	18	3b	58	61-3°C
2a		CH_2CH_2OR[e]	SO_2Ph	SO_2Ph	NaH	2.5	3c(3g)[f]	81(77)[f]	119-120.5°C
2a		CH_2CH_2OR[e]	SO_2Ph	SO_2Ph	BSA	1.5	3c	77	
2a		H	CO_2Me	SO_2Ph	BSA	4.5	3d(3h)[f]	80(61)[f]	123-124.5°C
2a		OAc[g]	CO_2Et	CO_2Et	BSA	3.5	3e	73	
2b	$CH_2CH(CH_3)_2$	H	SO_2Ph	SO_2Ph	BSA	5	3f	85	
2b		H	CO_2Et	CO_2Et	NaH	2	3g	87	

[a]BSA=bis(trimethylsilyl)acetamide [b]at reflux in THF [c]all new compounds gave satisfactory C,H,N analysis [d]DMF added for solubility [e]R=t-butyldimethylsilyl (see procedure below) [f]after desulfonylation(ref. 7); 3g (E_1=E_2=H): mp 51.5-53°C, 3h (E_2=H): mp 77-9°C. [g](ref. 10)

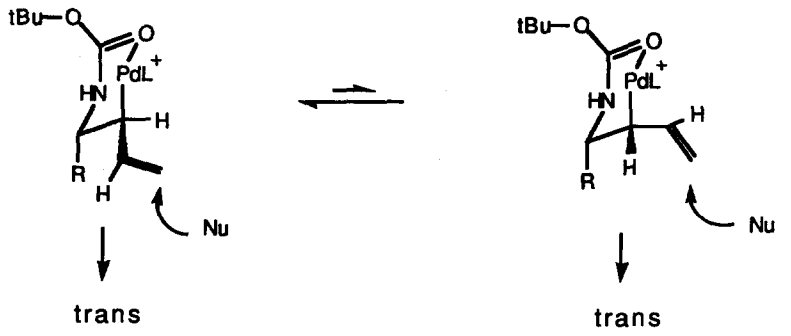


4 (mp121-2°C)



5 (mp 129-30.5°C)

While a general preference for trans-alkenes was observed in earlier reports, this degree of stereoselectivity is unusual for the intermolecular variant of the Trost alkylation reaction. One attractive explanation of the observed stereoselectivity involves the participation of the BOC-urethane in the formation of the predominant π-allyl palladium intermediate. The fluxional σ- and π-allyl forms of the η^3-allyl complex may be stabilized in a chair-like conformation as depicted below for the σ-allyl complex. Of the 4 possible η^3-allyl conformers these two isomers would be energetically favored due to decreased steric interactions of the terminal vinyl protons. Thus, both the pseudoaxial and pseudoequatorial isomers would lead to the trans product.



Preparation of the allylic acetates (2): The following procedure for the preparation of **2a** is typical: To a stirred 1M solution of $ZnCl_2$ in ether (160 mL) was added 400 mL of THF. The solution was cooled to 0°C (internal temp.) and 240 mL of 1M vinylmagnesium bromide in THF was added. After 30 min, the suspension was cooled to -30°C and a solution of 20g (56 mmol) of N-tert-butoxycarbonyl-O-benzyl-L-tyrosinal[12] in 300 mL of THF was added over 20 min, keeping the internal temperature at -30°C ± 5°C. The mixture was allowed to warm to 0°C over 1.5 h, then cooled to -30°C, cautiously quenched with 1L of 5% aqueous citric acid, and diluted with 2L of ether. The organic layer was washed with 600 mL of water, 600 mL of sat'd $NaHCO_3$ and dried over $MgSO_4$. Purification on silica gel, eluting with 8:2 CH_2Cl_2:ethyl acetate gave 13.7 g (62.7%) of the *threo*-allylic alcohol as a white solid. Acetylation with Ac_2O and Et_3N (1.1 equiv of each) in the presence of DMAP (0.1 equiv) in CH_2Cl_2 gave acetate **2a** in quantitative yield: mp 73-4°C, C,H,N.

Preparation of the BOC protected trans-allylic amines: The procedure for the preparation of **3c** is typical: A solution of 150 mg(0.37 mmol) of allylic acetate **2a**, 21 mg(0.02 mmol) of $(\Phi_3P)_4Pd$ and 10 mg(0.04 mmol) of Φ_3P in 5 mL of THF was added to a mixture of 255 mg(0.56 mmol) of bis-sulfone **6** and 115 mg(0.57 mmol) of bis(trimethylsilyl)acetamide [or 22 mg(0.56 mmol) of 60% NaH] in 4 mL of THF. The resulting mixture was stirred under reflux for 1.5 hrs (until complete by TLC), then concentrated to dryness and purified by chromatography on silica gel with 3:1 hexanes:ethyl acetate. After drying 230 mg (77%) of **3c** was obtained as a colorless solid : mp 119-120.5°C; C,H,N.

Preparation of 1-t-butyldimethylsilyloxy-3,3-bis(phenylsulfonyl)propane (6): A mixture of the sodium salt of bis(phenylsulfonyl)methane (60 mmol, from 17.7 g of bis-sulfone and 2.4g of 60% NaH) and 20g (70 mmol) of 2-t-butyldimethylsilyloxyethyl iodide[14] in 200 mL of 1:1 THF:DMF was heated to reflux for 48 hrs. After cooling, the mixture was diluted with 300 mL of ether and 100 mL of 5% aqueous citric acid. The organic layer was washed with 3 X 300 mL of H_2O, sat'd NaCl and dried over $MgSO_4$. Chromatography on silica gel (3:1 ethyl acetate:hexanes) gave 18.7g (71%) of **6** as a white crystalline solid: mp 87.5-89.5°C; C,H,N.

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11. A solution of the triester **3e** (0.5g) in 10 mL of DME was added to 5 mL of commercial 2M $LiBH_4$ in THF. After 20h the reaction was quenched with aqueous 5% citric acid and product isolated by ethyl acetate extraction. The crude product was allowed to react with 0.8g of $NaIO_4$ in 30 mL of 1:1 dioxane: H_2O for 1.5 h. The product **5** was isolated by ethyl acetate extraction and purified by silica gel chromatography (2% MeOH/ $CHCl_3$): (220 mg), mp 129-30.5°C, $[\alpha]_D^{25}$=-4.5° (c=0.5, MeOH); C,H,N.
12. Prepared using the procedure of Goel et. al. (ref. 13), with the following modifications: For the preparation of the N-methoxy-N-methyl amide, isobutyl chloroformate is substituted for the methyl chloroformate and the reaction time for mixed anhydride formation is increased from 2 min at -12°C to 30 min at 0°C. The product was obtained in 93% yield after filtration through a pad of silica gel eluting with ethyl acetate (BOC-(O-benzyl)-L-tyrosine N-methyl-O-methylcarboxamide): mp 107-8°C, $[\alpha]_D$25= +5.60 (c=1.745, MeOH), C,H,N. Also, for the preparation of N-BOC-(O-benzyl)-L-tyrosinal, the N-methyl-O-methylcarboxamide was dissolved in THF (O.2M) for addition to the ethereal $LiAlH_4$. The aldehyde was obtained as a white crystalline solid in quantitative yield: mp 98-9°C; $[\alpha]_D^{25}$=-27.4° (c=1.6, MeOH).
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