Enantio- and Diastereo-selective Synthesis of Amino Acids *via* the Reaction of Allylic Boron Compounds with α-Imino-esters

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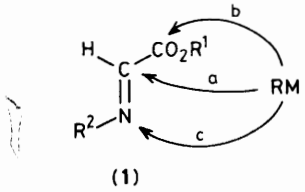
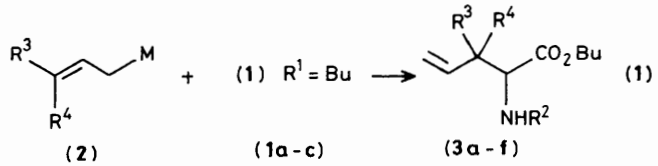
Very high enantio- and diastereo-selective syntheses of certain amino acids may be realized through the reaction of 9-allyl- and 9-but-2-enyl-9-borabicyclo[3.3.1]nonane with α-imino-esters.

Carbon–carbon bond formation *via* the reaction of the α-imino-esters (**1**) with organometallic compounds (RM) should be a highly promising reaction for the synthesis of amino acids and related compounds. However, this type of reaction has not yet been investigated widely.[1] A major problem is the regioselectivity; the nucleophile may attack three possible electrophilic centres *via* paths a, b, or c.† We report that allylic 9-borabicyclo[3.3.1]nonan-9-yl (BBN) derivatives (**2a**) react regioselectively at the imine carbon and provide the corresponding amino acid derivatives (**3**) with very high enantio- and diastereo-selectivity (up to 96% enantiomeric excess, e.e.) [equation (1)]. The results are summarized in Table 1.



(1)



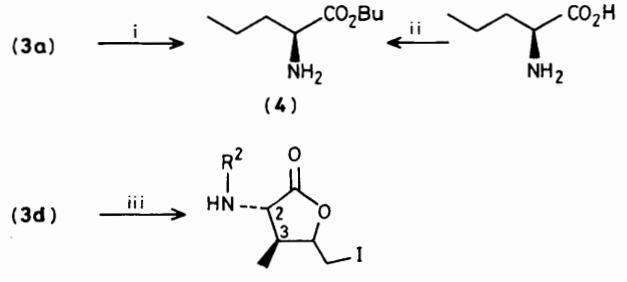
(2) (1a-c) (3a-f)

a; M = BBN
b; M = ZnBr
c; M = MgCl
d; M = $Ti(OPr^i)_3$

† Allyl-magnesium, -copper, and -titanium reagents reacted at both carbon centres (a and b). See also ref. 1.

The reaction of allyl-BBN (**2a**) with (**1a**) in which (*S*)-(−)-α-methylbenzylamine was employed as the chiral source produced (**3a**) in high chemical and optical yield (entry 1). The e.e. could be increased to 96% with (−)-1-cyclohexylethylamine (entry 4). The reaction of allyl-zinc or -magnesium reagents resulted in lower or negligible e.e.s (entries 2, 3, 5, and 7). The diastereofacial selectivity was also examined (entries 8—10). Here again, the boron reagent exhibited higher diastereoselectivity than the titanium or magnesium reagent.

The structures of compounds (**3**) were determined as shown in Scheme 1. Compound (**3a**) obtained as in entry 1 was converted into (**4**): $[\alpha]_D^{24}$ +12.6° (*c* 0.87, CH_2Cl_2), and authentic L-norvaline (*S* form) was also transformed into (**4**), with comparable $[\alpha]_D^{24}$: +10.2° (*c* 5.55, CH_2Cl_2). It should be noted that very high 1,3-asymmetric induction is realized *via* a simple chiral source, the (*S*)-amine inducing (*S*)-chirality at the imine carbon.[2] The absolute configuration of (**3b**) and (**3c**) was not determined. The iodolactonization[3] of the major isomer of (**3d**) produced (**5**) with $J_{2,3}$ 7.62 Hz (400 MHz), whereas the epimer derived from the minor isomer of (**3d**)



Scheme 1. *Reagents and conditions:* i, H_2, cat. $Pd(OH)_2$, 91%; ii, BuOH, dry HCl, 85%; iii, KOH–EtOH, then I_2–KI, 77%.

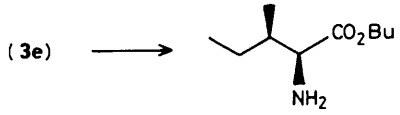
Table 1. Reaction of (**2**) with (**1**).[a]

Entry	(2)	R^3	R^4	(1)	R^2	Product, (3)	Yield, %[b]	E.e, %	*erythro*/*threo*[c]
1	(**2a**)	H	H	(**1a**)	(*S*)-(−)-CH(Ph)Me	(**3a**)	92	92	
2	(**2b**)	H	H	(**1a**)	"		94	10	
3	(**2c**)	H	H	(**1a**)	"		trace[d]	0	
4	(**2a**)	H	H	(**1b**)	(−)-CH(C_6H_{11})Me	(**3b**)	94	96	
5	(**2b**)	H	H	(**1b**)	"		53	30	
6	(**2a**)	Me	Me	(**1a**)	(*S*)-(−)-CH(Ph)Me	(**3c**)	33	54	
7	(**2b**)	Me	Me	(**1a**)	"		60	16	
8	(**2a**)	Me	H	(**1c**)	$SO_2C_6H_4Me$-*p*	(**3d**)	75		85/15
9	(**2c**)	Me	H	(**1c**)	"		78[e]		59/41
10	(**2d**)	Me	H	(**1c**)	"		75		60/40

[a] All reactions were carried out on a 1 mmol scale under N_2. To a dry tetrahydrofuran (THF) solution of (**1**) cooled at −78 °C was added (**2**) (1.1 equiv.) and the resulting mixture was warmed to room temperature over a period of 12 h. The reaction was quenched with water except for the reaction of (**2a**), in which a few drops of conc. HCl were added at 0 °C to hydrolyse the B–N bond; ethanolamine was then added to remove the BBN moiety. The product was isolated through a short column of silica gel (hexane–Et_2O, 10 : 1). [b] Isolated yield. [c] Determined by 400 MHz ^1H and ^{13}C n.m.r. spectra. The diastereoselectivity was determined by h.p.l.c. [d] A major product was the di-allylated tertiary alcohol formed *via* path b. [e] Only small amounts of the diallylated by-product were detected. Therefore, the regioselectivity is highly dependent upon R^2, R^3, and R^4.

(**2a**), R^3 = Me, R^4 = H + (**1a**) → (**3e**), R^2 = (*S*)-(−)-CH(Ph)Me, R^3 = Me, R^4 = H Isomer ratio, 93 : 3 : 3 : 1

(**2a**), R^3 = Me, R^4 = H + (**1b**) → (**3f**), R^2 = (−)-CH(C_6H_{11})Me, R^3 = Me, R^4 = H Isomer ratio, 85 : 6 : 6 : 3



(**6**)

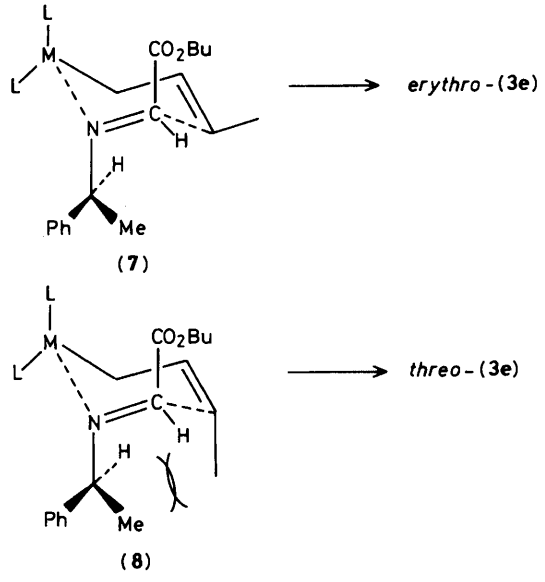
Scheme 2

exhibited $J_{2,3}$ 5.19 Hz. From these data, the structure of (**5**) could not be determined unambiguously. However, the *erythro* diastereoselectivity in entries 8—10 was strongly supported by previous observations[2,4] and the experiment shown below.

We next examined the reaction of but-2-enyl-BBN (**2a**), R^3 = Me, R^4 = H with (**1a**) and (**1b**) to discover whether two chiral centres can be created with high enantio- and diastereoselectivity. As shown in Scheme 2, the reaction with (**1a**) produced (**3e**) almost quantitatively, with an isomer ratio of 93 : 3 : 3 : 1 (400 MHz ^1H n.m.r.). The relative stereochemistry was assigned by the iodocyclization reaction described above, and the absolute stereochemistry was determined by transformation into L-alloisoleucine butyl ester (**6**): $[\alpha]_D^{23}$ +13.5° (*c* 7.35, $CHCl_3$). An authentic sample prepared from L-alloisoleucine (Serva) had $[\alpha]_D^{23}$ +12.0° (*c* 8.50, $CHCl_3$).

Other but-2-enylorganometallic derivatives, such as those of Ti and Mg, were also examined. However, four isomers of (**3e**) were obtained in almost equal proportions. The reaction of the BBN reagent (**2a**), R^3 = Me, R^4 = H with (**1b**) produced (**3f**) in which the ratio of isomers was 85 : 6 : 6 : 3. The relative and absolute configuration of (**3f**) was not determined.

The high enantio- and diastereo-selectivity *via* but-2-enyl-BBN can be explained as shown in Scheme 3. As previously reported,[2] the boron reagent attacks from the *si* face of (**1a**) owing to the steric and stereoelectronic effect of the imine and BBN groups. The transition state (**8**) leading to *threo*-(**3e**) is highly destabilized in comparison to (**7**), leading to *erythro*-(**3e**). Normally, the *erythro*-selectivity in the reaction of but-2-enyl-BBN with an imine such as *N*-butylidene-n-propylamine or *N*-benzylidene-n-propylamine is in the range 75—85%.[5] In the present reaction, the *erythro*-selectivity is greater than 93%. Therefore, the α-methylbenzylamine group dictates not only the enantioselectivity but also enhances diastereoselectivity. In conclusion, the present development provides a new method for very high enantio- and diastereoselective syntheses of amino acids and related compounds *via* C–C bond formation.



Scheme 3

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5 Unpublished results.