Highly regioselective allylation of imines with allylic barium reagents

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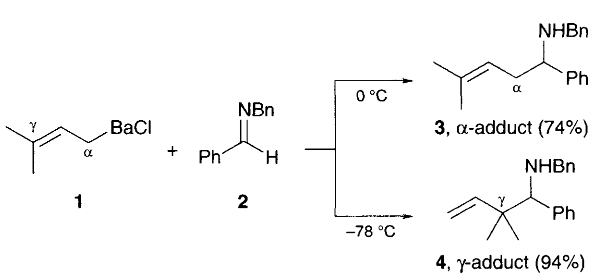
Aldimines are transformed into homoallylic amines by treatment with allylic barium reagents in which both the α- and γ-adducts are selectively obtained by simply changing the reaction temperature.

Reaction of allylic organometallic compounds with imines provides a beneficial route to homoallylic amines.[1] When γ-substituted allylic metals are employed, a linear (α-adduct) and/or branched product (γ-adduct) are obtained. Although the regioselectivity of the addition of γ-substituted allylic lithium, magnesium and zinc reagents to aldimines has been extensively studied,[2] there are no practical methods for α- and γ-selective reactions using these reactive allylic metals. Here we describe a new regioselective allylation of aldimines by allylic barium reagents in which both the α- and γ-adducts are readily obtainable by simply changing the reaction temperature.

Treatment of prenylbarium reagent **1**,[3] generated from prenyl chloride and barium in THF, with *N*-benzyl benzaldimine **2** at −78 °C afforded the γ-product **4** in 94% yield (Scheme 1). In marked contrast, the α-product **3** was obtained without contamination by the γ-isomer **4** from the same reaction carried out at 0 °C.

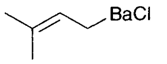
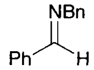
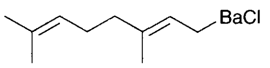
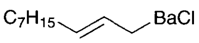
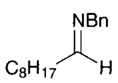
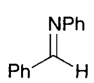
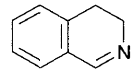
Table 1 shows the generality of the regioselective allylation of imines and shows that: (i) Reaction of γ-mono- and γ-di-substituted allylbarium reagents with **2** resulted in high product yields with remarkable regioselectivities which were temperature dependent (entries 1–6). An aliphatic imine was also successfully transformed into α- and γ-adducts in moderate yields by variation of the reaction temperature (entries 7 and 8). With *N*-phenyl benzaldimine, the corresponding α-adduct was predominantly formed even at −78 °C (entry 9). (ii) A high diastereoselectivity (95:5) was observed in the γ-allylation using a geranylbarium reagent (entry 3),[4] whereas the (*E*)-2-decenylbarium reagent provided a lower diastereoselectivity (68:32, entry 5). The double bond geometry of the allylic barium reagent was not retained[3] in the condensation reaction with imine above 0 °C (entries 4 and 6). (iii) Similar temperature dependency of the α/γ ratio was observed in the reaction of a cyclic imine with prenylbarium reagent **1** (entries 11–13). This result definitely indicated that the change of the reaction course did not arise from a *syn*/*anti* imine isomerization.[5]

The utility of allylic barium reagents for regioselective addition to imines was further demonstrated by asymmetric



Scheme 1 Regioselective addition of prenylbarium reagent **1** to imine **2**

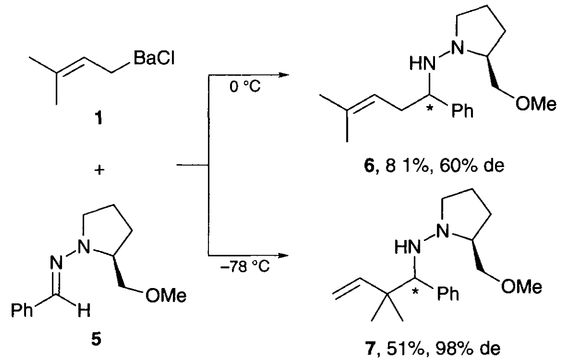
Table 1 Regioselective addition of allylic barium reagents to imine[a]

Entry	Barium reagent	Imine	Conditions		Yield (%)[b]	α:γ[c]
			T/°C	*t*/h		
1	 **1**	 **2**	−78	1	94	<1:99
2			0	1.5	74	>99:1
3		**2**	−78	1	88	<1:99[d]
4		**2**	0	2.5	78	>99:1[e]
5		**2**	−78	2.5	75	<1:99[f]
6		**2**	20	1	95	94:6[g]
7	**1**		−78	5	52	<1:99
8	**1**		0	3	42	>99:1
9	**1**		−78	1	99	98:2
10	**1**		0	2	94	80:20
11	**1**		−100	1 (min)	64	<1:99
12	**1**		−78	1	95	20:80
13	**1**		0	2	47	92:8

[a] Allylation was carried out using an allylic barium reagent (3 equiv.) and imine (1 equiv.) in THF. [b] Isolated yield. [c] Determined by 300 MHz ^{1}H NMR analysis. [d] The diastereoisomeric ratio of the γ-product was 95:5. [e] The *E*:*Z* ratio of the α-product was determined to be 85:15 by HPLC analysis. [f] The diastereoisomeric ratio of the γ-product was 68:32. [g] The *E*:*Z* ratio of the α-product was determined to be 67:33 by HPLC analysis.

allylations with an optically active imine. Treatment of the SAMP-hydrazone **5**[6] with prenylbarium reagent **1** in THF at 0 °C almost exclusively afforded the α-allylated hydrazine **6** with 60% de (Scheme 2) [SAMP = (*S*)-(−)-1-amino-2-methoxymethylpyrrolidine]. When the reaction was carried out at −78 °C, the γ-adduct **7** was obtained as the major product in 98% de.

We assumed that this striking regiochemical outcome was due to the reversibility in the reaction of allylic barium reagents with aldimines.[7] The temperature dependence of the α/γ ratio in the reaction of benzaldimine **2** with prenylmetal reagents (Li,† Mg‡ and Ba) was clearly demonstrated from the following experiment: the imine **2** was first treated with prenylmetal reagent at −78 °C for 1 h to complete the formation of the γ-adduct **4**.§ The reaction mixture was then slowly warmed to 20 °C. Sampling was carried out during this warming period at 15–20 °C intervals.¶ The α/γ ratio was measured by analysing the samples which were immediately quenched with sat. aq. $NaHCO_3$ (Fig. 1). With the barium reagent, the formation of α-adduct **3** was observed at 0 °C and predominated (α/γ = 93/7) at 20 °C. No α-adduct **3** of the magnesium reagent was obtained even at 20 °C.



Scheme 2 Diastereo- and regio-selective addition of prenylbarium reagent **1** to SAMP-hydrazone **5**

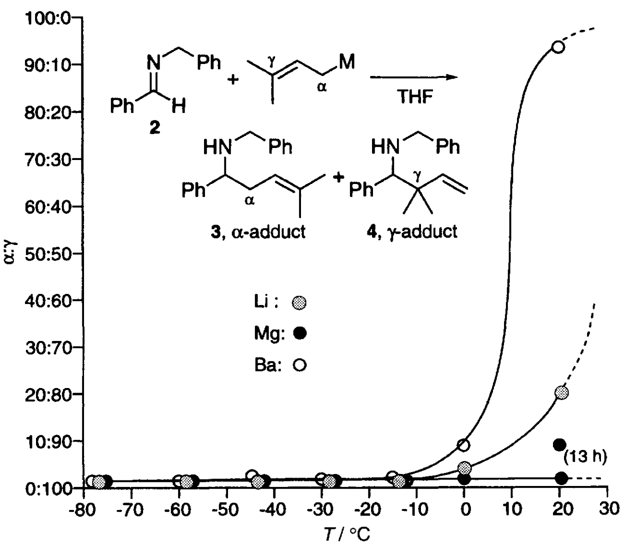


Fig. 1 Temperature dependence of α:γ in the reaction of *N*-benzyl benzaldimine **2** with prenylmetal reagents (Li, Mg and Ba)

These results show that the γ-adduct **4** is kinetically produced and gradually isomerizes to the thermodynamically stable α-adduct **3** at higher temperatures. This might be at least part of the reason for the high α-selectivity obtained with the reaction of allylic barium reagents with imines at 0 °C.

Financial support from the Ministry of Education, Science and Culture of the Japanese Government and the Asahi Glass Foundation is gratefully acknowledged.

Footnotes

† Prepared from prenyl chloride and lithium biphenylide.[7]

‡ Prepared from prenyl chloride and Rieke-Mg.[8]

§ Yields of the γ-adduct obtained by the reaction of the imine **2** with prenylmetal reagents in THF at −78 °C for 1 h were, for M = Li, 75% and for M = Mg, 85%.

¶ A digital thermometer (Model HH81, OMEGA Engineering, Inc.) was used to measure the internal reaction temperatures.

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Received, 19th September 1995; Com. 5/06161J