Pergamon

Tetrahedron Letters 40 (1999) 2737–2740

TETRAHEDRON LETTERS

Stereoselective Grignard-type Reactions of Chiral *N,N*-Dibenzylamino Ketones

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Received 22 January 1999; accepted 10 February 1999

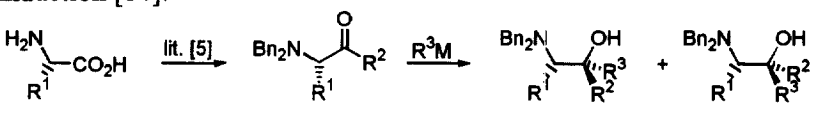
Abstract

N,N-Dibenzylamino ketones of the type $Bn_2N(R^1)CHC(O)R^2$, prepared in enantiomerically pure form from α-amino acids, undergo non-chelation controlled Grignard-type reactions with RLi, RMgX or $RCeCl_2$ without any undesired racemization.

Keywords: Amino acids and derivatives; Amino alcohols; Grignard reactions/reagents; Asymmetric induction.

N,N-Dibenzylamino aldehydes, prepared in enantiomerically pure form from α-amino acids **1** or other sources, have emerged as useful chiral building blocks in a wide variety of C-C bond forming reactions [1-3]. In most cases high levels of non-chelation control are observed. The analogous *N,N*-dibenzylamino ketones **2**, also accessible from α-amino acids **1**, undergo non-chelation controlled reduction reactions [3-12]. Such reductions are therefore stereochemically complementary to C-C bond forming reactions of the corresponding aldehydes. *N,N*-dibenzylamino ketones bearing chloromethyl moieties react with organocerium reagents to form either the corresponding rearranged azetidinols or the epoxides in a non-chelation controlled manner, depending upon the conditions used [13].

In this publication we show that *N,N*-dibenzylamino ketones **2** react with RLi, RMgX or $RCeCl_2$ to form the non-chelation controlled Grignard-type adducts **3** with a high degree of 1,2-asymmetric induction [14].



1 **2** **3** **4**

Table 1 summarizes the results of 20 reactions using 6 different ketones **2**.[1] Although the classical reagents RLi or RMgX generally display high levels of diastereoselectivity, a further

[1] General procedure for Grignard-type reaction of ketones **2**: Under an atmosphere of argon the solution of a ketone **2** [5] (1mmol) in 10 ml of diethyl ether of THF is treated dropwise with 2 mmol of RLi, RMgX or $RLi/CeCl_3$ at a temperature specified in Table 1. After the proper reaction time (Table 1), 10 ml of a sat. NH_4Cl-solution (and ether if necessary) are added and the phases separated. The aqueous phase is extracted several times with ether and the combined organic phases are washed with sat. NaCl-solution. Following drying with $MgSO_4$, the solvent is removed and the residue is chromatographed over silica gel.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00359-7

increase is possible upon transmetalation with $CeCl_3$ (Table 1, entries 2, 5). In the case of primary Grignard reagents, a side reaction (~ 30%) was observed, namely reduction brought about by β-hydride elimination (entries 10, 17, 18). This side reaction occurs with 100% non-chelation control, similar to reductions with $NaBH_4$ in methanol [5-12]. Presumably, *t*-BuMgCl would produce only reduction products. In contrast to the Grignard reagents, primary organolithium (RLi) or cerium compounds ($RLi/CeCl_3$) do not show any appreciable amounts of undesired reduction. Although optimization of all parameters was not performed, possible solvent effects were studied in several cases. Generally, the effects turned out to be small, an exception being the reaction of *n*-BuLi with ketone **2** ($R^1 = (Me)_2CHCH_2$; R^2 = Ph) which is considerably more diastereoselective in ether than in THF (entries 19, 20).

Table 1
Stereoselective Grignard-type Reactions of *N,N*-Dibenzylamino Ketones **2**

Entry	R^1	R^2	R^3-M	Solvent	Temp./Time (° C/h)	% Conversion (% Yield)[a]	**3** : **4**
1	$PhCH_2$	Me	*n*-BuLi	THF	-30→0/6	75 (46)	95 : 5
2	$PhCH_2$	Me	*n*-$BuCeCl_2$[b]	THF	-78→20/14	100 (72)	> 95 : < 5
3	$PhCH_2$	Me	PhLi	THF	-30→0/6	80 (51)	85 : 15
4	$PhCH_2$	*n*-Bu	MeLi	THF	-30→0/2	100 (84)	95 : 5
5	$PhCH_2$	*n*-Bu	$MeCeCl_2$[b]	THF	-78→20/5	100 (77)	> 95 : < 5
6	$PhCH_2$	*n*-Bu	CH_2=CHMgBr	Et_2O	0/4	100 (73)	92 : 8
7	$PhCH_2$	*n*-Bu	CH_2=$CHCH_2MgBr$	THF	0/2	100 (86)	> 95 : < 5
8	$PhCH_2$	*n*-Bu	PhLi	THF	-30→0/3.5	100 (76)	72 : 28
9	$PhCH_2$	Ph	MeLi	THF	-30→0/2	100 (81)	> 95 : < 5
10	$PhCH_2$	Ph	EtMgBr	Et_2O	0/3	100 (48)	92 : 8
11	$PhCH_2$	Ph	*n*-BuLi	THF	0/1.5	90 (69)	> 95 : < 5
12	$PhCH_2$	Ph	CH_2=$CHCH_2MgBr$	THF	-30→0/2.5	100 (89)	> 95 : < 5
13	Me_2CHCH_2	Me	*n*-BuLi	Et_2O	-30→0/5	65 (-)[c]	> 95 : < 5
14	Me_2CHCH_2	Me	PhLi	Et_2O	0/4.5	90 (65)	86 : 14
15	Me_2CHCH_2	*n*-Bu	CH_3Li	Et_2O	-30→0/2.5	100 (87)	95 : 5
16	Me_2CHCH_2	Ph	CH_3Li	Et_2O	-78→-30/2.5	100 (89)	95 : 5
17	Me_2CHCH_2	Ph	*n*-BuMgCl	THF	-30/5.5	100 (45)	> 95 : < 5
18	Me_2CHCH_2	Ph	*n*-BuMgCl	Et_2O	-30/6	100 (46)	> 95 : < 5
19	Me_2CHCH_2	Ph	*n*-BuLi	THF	-78→-30/3	100 (82)	92 : 8
20	Me_2CHCH_2	Ph	*n*-BuLi	Et_2O	-78→-30/3	100 (84)	> 95 : < 5

[a]Isolated compound in analytically pure form.

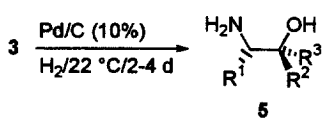
[b]Formed in situ from RLi and $CeCl_3$.

[c]Compound was not isolated in analytically pure form.

It is instructive to note that the present methodology allows for the selective production of either diastereomer **3** or **4** on an optional basis simply by choosing R^2 and R^3 properly, i.e., by permutation. Indeed, this was illustrated in several cases (e.g., entry 1 versus 4; entry 3 versus 9; entry 13 versus 15; entry 14 versus 16).

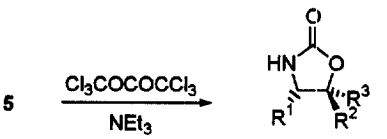
In order to explore the efficiency of deprotection and to enable configurational assignments, several of the products **3** were debenzylated by catalytic hydrogenolysis, a reaction generally performed with Pearlman catalyst $Pd(OH)_2$ [15] or Pd/C [16,17]. We first tested Pd/C (10%) in methanol [H_2 (1 bar)]. Since a smooth reaction with formation of β-amino alcohols **5** was

observed in all cases, no further optimization using Pearlman catalyst was attempted.[2]



$R^1 = PhCH_2$; $R^2 = Ph$; $R^3 = Me$: 81%
$R^1 = PhCH_2$; $R^2 = Me$; $R^3 = Ph$: 82%
$R^1 = Me_2CHCH_2$; $R^2 = Ph$; $R^3 = Me$: 84%
$R^1 = Me_2CHCH_2$; $R^2 = Me$; $R^3 = Ph$; 85%

Compounds **5** were converted into the oxazolidinones **6**, which were subjected to NOE-difference measurements proving the relative configuration. Finally, all of the compounds **5** were treated with *R*-(-)- and *S*-(+)-MTPACl [18], respectively, and the corresponding "Mosher-amides" analyzed by HPLC. Accordingly, an optical purity of > 98.5% for compounds **5** was found, demonstrating that essentially no racemization occurs during the formation or reactions of ketones **2**. In principle the enantiomeric forms of amino alcohols **3** are accessible by starting from the unnatural D-configurated amino acids **1**.



6 (~ 90%)

The direction of diastereoselectivity in the Grignard-type reactions of α-*N,N*-dibenzylamino ketones **2** corresponds to non-chelation control and stands in complete contrast to analogous reactions of the corresponding α-benzyloxy ketones which occur with chelation control [19,20]. As in the case of *N,N*-dibenzylamino aldehydes [1-3], inhibition of chelation due to steric reasons seems to pertain in reactions of **2**. The reason why a high level of stereoselectivity in favor of non-chelation control is then observed is not fully clear. Formally, the results are in line with the Felkin-Anh model [21]. However, some time ago we demonstrated by ab initio calculations that the interaction $\sigma_{C\text{-}N}$-$\pi^*_{C=O}$ in α-amino aldehydes is very small, in contrast to $\sigma_{C\text{-}O}$-$\pi^*_{C=O}$ or $\sigma_{C\text{-}Cl}$-$\pi^*_{C=O}$ in the case of α-alkoxy and α-chloro aldehydes, respectively [2]. Thus, ground state conformational effects operating in the ketones **2** may be the determining factor, although this still needs to be examined.

In summary we have demonstrated that *N,N*-dibenzylamino ketones **2**, prepared in enantiomerically pure form from α-amino acids **1**, undergo non-chelation controlled Grignard-type reactions without any appreciable racemization. The products are β-amino alcohols in which the alcohol function is tertiary. Such structural features occur in certain natural products and in some pharmaceuticals [22-28].

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