Investigation of the Diastereoselectivity During the Addition of an Enantiomerically Pure (2-Lithiophenyl)acetaldehyde Acetal to Various Imines[1]

Bernhard Wünsch* and Sven Nerdinger
Pharmazeutisches Institut der Universität Freiburg, Hermann-Herder-Str. 9, D-79104 Freiburg i. Br., Germany

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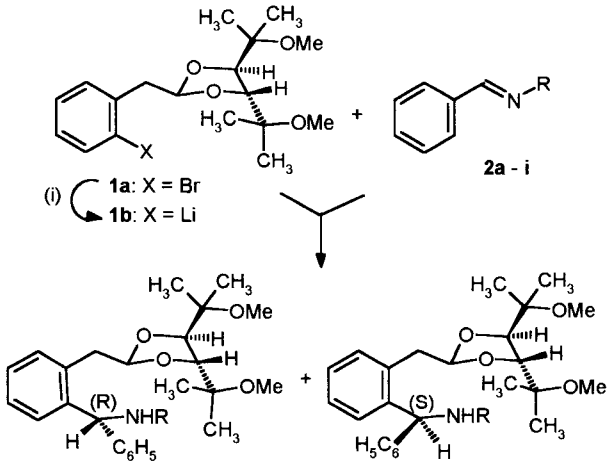
The diastereoselectivity during the addition of the homochiral (2-lithiophenyl)acetaldehyde acetal **1b** to various imine components was investigated. The diastereoselectivity could be raised to 84.2% de by addition of **1b** to benzylidenanisidine **2h**. Removal of the tosyl and the *p*-methoxyphenyl protective groups of **3c**, **4c** and **3h/4h** succeeded with sodium in liquid ammonia and ammonium cerium(IV) nitrate, respectively, to yield the enantiopure benzhydrylamines **5** and **6**.

Recently, we described an asymmetric synthesis of the pharmacologically important[2] (*S*)- and (*R*)-configured 1-phenyl-1,2,3,4-tetrahydroisoquinolines. The key step in this synthesis is the diastereoselective addition of homochiral phenylacetaldehyde acetals to acylimines.[1,3] However, only unsatisfactory diastereoselectivities were obtained during these additions, and, moreover, the very reactive and thus unstable acylimines had to be freshly prepared for each reaction.[4] Therefore, we looked for alternative imine components, which should be more stable and provide higher diastereoselectivities. These studies were performed with the sterically demanding bis(2-methoxypropan-2-yl) substituted 1,3-dioxolane **1a**, which was obtained by transacetalization of the 2-(2-bromophenyl)acetaldehyde dimethyl acetal with the (*R,R*)-configured 2,5-dimethoxy-2,5-dimethylhexane-3,4-diol.[5]

The first investigated imine component was the stable, moisture and air insensitive, crystalline tosylimine **2c**, which is easily available by condensation of *p*-toluenesulfonamide with benzaldehyde or benzaldehyde diethyl acetal.[6] The sulfonylimine **2c** and the acylimines **2a,b** are comparable in their activation of the imine moiety, but differ in their structural features. With n-butyllithium at -100 °C the bromine atom of the aryl bromide **1a** was exchanged for a lithium atom. Subsequently, the tosylimine **2c** was reacted at -100 °C with the thus generated aryllithium intermediate **1b** to provide the sulfonamides **3c/4c** in 62 % yield (entry 3). The diastereomeric ratio **3c** : **4c** was determined by integration of the separated phenyl-C*H* signals in the ^{1}H NMR spectrum and confirmed by HPLC analysis (**3c** : **4c** = 60.9 : 39.1). In comparison with the additions of **1b** to the acylimines **2a,b** (entries 1,2) only a slight improvement of the diastereomeric ratio was obtained with the sulfonylimine **2c**.

Next, we investigated the addition of **1b** to the less electrophilic N-benzylimines **2d - f** bearing tetrahedral, rotatable, and facile cleavable substituents at the nitrogen atom. Within 6 h at -100 °C the aryllithium intermediate **1b** did not react with the N-tritylimine **2d** to yield the expected addition products. Even raising the reaction temperature to +25 °C, elongation of the reaction time to 18 h and diminution of the large triphenylmethyl substituent (**2d**) to the smaller diphenylmethyl (**2e**) or benzyl group (**2f**) did not lead to any addition products (entries 4 - 6). The same result was obtained with sterically less demanding



(i) n-BuLi, -100 °C, THF, 15 min, then addition of **2**, reaction at -85 to -100 °C

Table 1. Results of the addition of **1b** to the imines **2**

Entry	Imine 2	R	Diastereomeric ratio[a]	Yield[b]
1	**2a**	$CO_2CH_2C_6H_5$	**3a** : **4a** = 51 49	63 %[1,3]
2	**2b**	$COC(CH_3)_3$	**3b** : **4b** = 55 : 45	66 %[1,3]
3	**2c**	$SO_2C_6H_4CH_3$	**3c** : **4c** = 61 : 39	62 %
4	**2d**	$C(C_6H_5)_3$	no addition	0 %
5	**2e**	$CH(C_6H_5)_2$	no addition	0 %
6	**2f**	$CH_2C_6H_5$	no addition	0 %
7	**2g**	C_6H_5	**3g** : **4g** = 91 : 9	75 %
8	**2h**	$C_6H_4OCH_3$	**3h** : **4h** = 91 : 9	38 %
9	**2h**	$C_6H_4OCH_3$	**3h** : **4h** = 92.1 : 7.9[c]	67 %[d]
10	**2i**	$N(CH_3)C_6H_5$	no addition	0 %

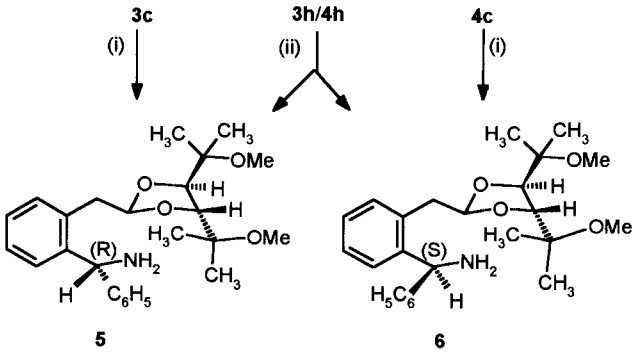
[a] Determined by ^{1}H NMR spectroscopy
[b] Isolated yield after 4 h at -100 °C
[c] Determined by HPLC analysis
[d] Isolated yield after 2 h at -100 °C and 2 h at 0 °C

phenylacetaldehyde acetals **1** substituted with methoxymethyl or methyl residues instead of 2-methoxypropan-2-yl groups in the dioxolane ring.

An unexpected enhancement of the diastereoselectivity was observed after addition of **1b** to benzylidenaniline **2g**. According to the ^{1}H NMR spectrum the ratio of the diastereomeric addition products **3g** : **4g** was 91 : 9 (entry 7). Moreover, the 75% yield of **3g/4g** exceeded the yields of the sulfonylimine and acylimine addition products. However, the separation of the diastereomeric addition products **3g** and **4g** proved to be very problematic even by HPLC analysis, and, additionally, the phenyl residue attached to the nitrogen atom of **3g/4g** could not be cleaved.

Therefore, the methoxy derivative of **2g**, the benzylidenanisidine **2h**,[7] was employed as imine component. The electron releasing 4-methoxy substituent of **2h** reduced the electrophilicity of the imine C=N double bond, which led to a decreased yield (38%, entry 8). However, modification of the reaction conditions - stirring 2 h at -100 °C and 2 h at 0 °C instead of 4 h at -100 °C - enhanced the yield of **3h/4h** to 67% without changing the diastereomeric ratio of 91 : 9, determined by ^{1}H NMR spectroscopy. A HPLC analysis specified the ratio of **3h** : **4h** to 92.1 : 7.9 (entry 9).

A further optimization of the diastereoselectivity should be achieved with the hydrazone **2i**, which also exists in a planar geometry. However, even at room temperature the aryllithium intermediate **1b** did not react with the hydrazone **2i** to afford the expected addition products; this is presumably due to the low reactivity of **2i** (entry 10).



(i) Na, NH_3 liquid, -78 °C, 45 min
(ii) $(NH_4)_2Ce(NO_3)_6$, CH_3CN/H_2O (9:1), 20 °C, 3 h

The reductive cleavage of the N-protective group of the chromatographically separated sulfonamides **3c** and **4c** succeeded with sodium metal in liquid ammonia at -78 °C[8] to furnish the diastereomerically and enantiomerically pure primary amines **5** and **6**, respectively. The *p*-methoxyphenyl residue of **3h/4h** (92 : 8) was oxidatively cleaved with ammonium cerium(IV) nitrate[9] to yield a 92 : 8 diastereomeric mixture of **5** and **6**. A further purification of this mixture was performed via the chromatographically separable sulfonamides **3c** and **4c**.

The thus available primary benzhydrylamines **5** and **6** bearing a protected formylmethyl substituent in one ortho position represent versatile building blocks for the synthesis of enantiopure 1-aryl azaheterocycles, e.g. tetrahydroisoquinolines or tetrahydro-2-benzazepines.

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