Pergamon

Tetrahedron 55 (1999) 14685–14692

TETRAHEDRON

Use of Readily Available Chiral Compounds Related to the Betti Base in the Enantioselective Addition of Diethylzinc to Aryl Aldehydes

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Received 6 July 1999; revised 21 September 1999; accepted 7 October 1999

Abstract: Readily available members of the family of chiral non-racemic aminonaphthols related to the Betti base **1** were tested as complexing agents in the catalytic enantioselective addition of diethylzinc to aryl aldehydes. The use of these bases gave high ee values (up to >99%). The highest ee values were obtained with the tertiary aminonaphthol **2**. An important role was played by the solvent. The effect of the nature and the position of the substituents on the aromatic ring of the aldehyde was also investigated.

Keywords: asymmetric synthesis; alkylation; enantioselection; zinc and compounds.

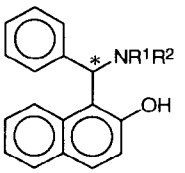
Carbonyl compounds are alkylated enantioselectively by organometallic reagents in the presence of suitable chiral complexing agents.[1-2] The first reported enantioselective alkylation of aldehydes was performed by Betti,[1-3] who reacted methylmagnesium iodide with benzaldehyde in the presence of *N,N*-dimethylbornylamine.[3-4] In recent times, enantioselective reactions of organolithium or organomagnesium compounds with aldehydes have been performed by an appropriate combination of carbonyl substrates, organometallic reagents and chiral modifiers.[1-2] However, a significant improvement has been achieved by using organozinc compounds as alkylating agents.[1, 2, 5] These reactions require a compound coordinating the metal atom to enhance its nucleophilicity, since the uncoordinated zinc compound is nearly inert. Due to the different reactivity of the complexed reagent, even a catalytic amount of the ligand can be used. Furthermore, the

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00914-X

selection of a suitable chiral non-racemic compound as a reactivity enhancer may also yield an effective enantiodifferentiation of the faces of prochiral aldehydes.

Several enantiomerically pure compounds (amino acid derivatives, terpenes, alkaloids) have been tested.[1, 2, 5] Most efforts have focused on aminoalcohols, but also β-hydroxysulfides,[6] aminothiols,[7] and oxazolidines[8] have been reported as chiral complexing agents. Aldehyde alkylations with dialkylzinc have been also performed in the presence of titanium complexes with various chiral compounds.[9-11] Despite the variety of the approaches used, the design and development of cost-effective catalysts that exhibit high reactivity and enantioselectivity is still a challenging endeavour.

Now, we wish to report a low cost, efficient and versatile solution to this problem. Our approach is based upon a family of chiral non-racemic bases whose easy preparation was recently set up in our laboratories. In particular, the 1-(α-aminobenzyl)-2-naphthol **1** (Betti base) can be obtained by a simple and straightforward condensation of 2-naphthol with benzaldehyde and ammonia[12] and resolved through its diastereoisomeric tartaric acid salts.[13] In our recent work,[14-15] we have reconsidered and improved the preparation and the resolution of the Betti base **1**, established its absolute configuration and prepared a series of chiral derivatives including compound **2**. The bases used in the present work are represented by the aminonaphthols **1-3**.

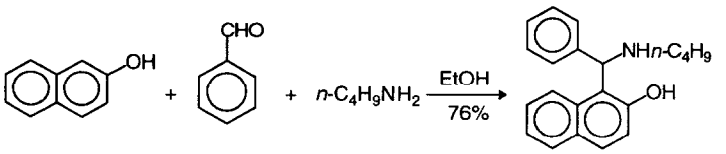


1. $R^1=R^2=H$
2. $R^1=R^2=CH_3$
3. $R^1=n\text{-}C_4H_9$; $R^2=H$

1-3

Compound **3** was obtained by Betti reaction of 2-naphthol, benzaldehyde and *n*-butylamine (Scheme 1).

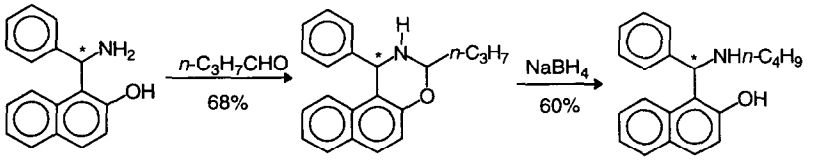
Scheme 1



3

As in the case of **2**,[14-15] the optical resolution of **3** was achieved in an easy manner, by precipitation of a single diastereoisomeric tartaric acid salt in acetone. After the work-up, the less soluble salt originated (–)-**3**. In order to establish the configuration of the produced **3**, the Betti base (*S*)-(+)-**1** was treated with *n*-butanal, yielding the oxazine (–)-**4** (a type of compound which is known to be the predominant form of a tautomeric equilibrium).[14] (–)-**4** was reduced to (+)-**3**, thus allowing us to attribute the (*S*) configuration to the compound (+)-**3** and consequently the (*R*) configuration to (–)-**3**.

Scheme 2

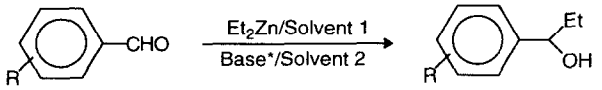


(*S*)-(+)-**1** (–)-**4** (+)-**3**

Summing up, the main distinctive features of these aminonaphthols are represented by an economical and simple synthesis (Betti reaction), involving cheap starting materials which merge to give a more complex compound without side-products, and by a subsequent expeditious procedure of resolution. Furthermore, the simplicity of the operations involved represents a good prerequisite for large scale applications.

These new chiral non-racemic aminonaphthols were applied in the enantioselective addition of diethylzinc to aryl aldehydes and the relevant results are reported in the Table. 1-Phenylpropan-1-ol was obtained with a low ee value (entry 1) by using base **1**, whereas bases **2** and **3** yielded the chiral product in 96 and 87% ee values respectively (entries 2-3). Base **2** was then chosen for further experiments (entries 4-15). The solvent had a key role in the enantioselection process (entries 2, 4-6). As expected,[1,5] toluene or hexane gave the best results. The presence of a coordinating solvent (THF, entry 4) lowered the ee values of the resulting alcohol. Temperature variations had only a small effect but confirmed the expected trend (entry 7). The use of (*S*)-**2** yielded the enantiomeric alcohol (entry 8).

Table: Diethylzinc addition to aryl aldehydes in the presence of the Betti base or related ligands.



Diethylzinc/Aryl aldehyde/Chiral complexing agent 10:7.5:1

Entry	Solvent 1[a]	Base	Solvent 2[b]	R	T (°C)	t (h)	Yield (%)[c]	ee	Config.[d]
1	toluene	(*R*)-(−)-**1**	toluene	H	rt	24	85	35[e]	(*S*)
2	toluene	(*R*)-(−)-**2**	toluene	H	rt	12	92	96[e]	(*S*)
3	toluene	(*R*)-(−)-**3**	toluene	H	rt	48	95	87[e]	(*S*)
4	hexane	(*R*)-(−)-**2**	THF	H	rt	96	40	31[e]	(*S*)
5	hexane	(*R*)-(−)-**2**	hexane	H	rt	12	72	73[e]	(*S*)
6	hexane	(*R*)-(−)-**2**	toluene	H	rt	12	78	93[e]	(*S*)
7	hexane	(*R*)-(−)-**2**	toluene	H	-10	40	63	95[e]	(*S*)
8	toluene	(*S*)-(+)-**2**	toluene	H	rt	12	93	96[e]	(*R*)
9	toluene	(*S*)-(+)-**2**	toluene	4-F	rt	24	91	92[f]	(*R*)
10	toluene	(*S*)-(+)-**2**	toluene	4-Cl	rt	24	92	94[f]	(*R*)
11	hexane	(*S*)-(+)-**2**	hexane	2-CH_3	rt	24	75	>99[e]	(*R*)
12	toluene	(*S*)-(+)-**2**	toluene	2-CH_3	rt	72	78	>99[e]	(*R*)
13	toluene	(*S*)-(+)-**2**	toluene	3-CH_3	rt	24	89	93[e]	(*R*)
14	toluene	(*S*)-(+)-**2**	toluene	4-CH_3	rt	24	94	96[f]	(*R*)
15	toluene	(*S*)-(+)-**2**	toluene	2-OCH_3	rt	24	93	96[f]	(*R*)

[a]Solvent for the diethylzinc. [b]Solvent for the other reactants. [c]Yields refer to pure isolated products. [d]Configuration of the predominant enantiomer of the product. [e]Measured by chiral HPLC (Chiralcel OD). [f]Measured by the aid of the NMR spectra of the corresponding Mosher's acid esters.

The reaction was also studied with substituted aryl aldehydes. *p*-Halobenzaldehydes (entries 9-10) were alkylated with similar enantioselectivity. *o*-Tolualdehyde was converted to 1-*o*-tolyl-1-propanol (entries 11-12) in very high ee values (>99%). The reaction performed in hexane (entry 11) gave also a satisfactory yield in a shorter time than the reaction in toluene (entry 12). *m*- or *p*-tolualdehyde or *o*-anisaldehyde gave the corresponding alkylation products with high ee values (entries 13-15). In our experiments the enantioselectivity of the reaction was affected mainly by steric hindrance, whereas the electronic effects of the aryl substituents on the substrate had only a minor effect.[5] In fact, the best enantioselectivity was achieved in the synthesis of 1-*o*-tolyl-1-propanol (entries 11-12). In this respect, it is worth noting that data with a contrasting effect on the ortho-substitution have been reported.[10, 11, 16]

In conclusion, our results show the usefulness and the versatility of the aminonaphthols related to the Betti base in an important process. Indeed, an appropriate choice of ligands among the various members of the family permits to perform the addition of diethylzinc to aryl aldehydes in a highly enantioselective manner. In view of the distinctive features discussed above for these complexing agents, the process reported in the present work compares favourably with the number of similar procedures which are attracting continuous attention in the field of asymmetric synthesis. Further work is in progress in these laboratories with the aim of expanding the use of these cheap chiral compounds to other enantioselective processes.

Experimental section

Compounds **1** and **2** were prepared as previously described.[14-15]

1-(α-*N*-butylaminobenzyl)-2-naphthol (3)

Benzaldehyde (22.1 g, 0.208 mol) was added to a solution of 2-naphthol (20.0 g, 0.139 mol) in 20 ml of ethanol 95%. *n*-Butylamine (10.2 g, 0.139 mol) was added dropwise with cooling to 0°C to this solution. The mixture was stirred at rt for 6 days and the precipitate was filtered and washed with a small amount of ethanol 95%, obtaining 32.4 g (76% yield) of pure 1-(α-*N*-butylaminobenzyl)-2-naphthol **3** (white solid, mp 131-132°C).

IR (KBr) ν_{max} 3314, 3058, 2959, 2925, 2855, 1622, 1601, 1456, 1241, 1090 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.74-7.70 (m, 3 H), 7.47-7.45 (m, 2 H), 7.36-7.28 (m, 3 H), 7.26-7.22 (m, 2 H), 7.17 (d, *J*= 8.8 Hz, 1 H), 5.67 (s, 1 H), 2.86-2.80 (m, 2 H), 1.65-1.53 (m, 2 H), 1.40-1.33 (m, 2 H), 0.91 ppm (t, *J*=7.3 Hz, 3 H). At –50°C, the ^{1}H-NMR showed two additional broad signals at 14.95-14.47 ppm and 2.18-1.86 ppm. ^{13}C-NMR (125 MHz, $CDCl_3$) δ 156.87, 141.71, 132.59, 129.60, 129.07, 128.81, 128.57, 128.04, 127.72, 126.38, 122.32, 121.13, 120.13, 113.38, 64.39, 48.95, 31.65, 20.32, 13.86 ppm. Anal. Calcd for $C_{21}H_{23}NO$: C, 82.59; H, 7.59; N, 4.59. Found C, 82.70; H, 7.63; N, 4.70.

(2*R*,3*R*)-Tartaric acid (3.30 g, 22 mmol) in 70 ml of acetone was added to racemic **3** (6.72 g, 22 mmol) in acetone (120 ml). After 12 h, the mixture was filtered and the less soluble salt was washed with acetone and then twice with ethanol at rt yielding 4.70 g of one of the diastereomeric salts (47% of the total amount). The salt was suspended in water (10 ml/g salt) and a 2 M Na_2CO_3 solution was added (10 ml/g salt) to this suspension. After 15

minutes, the mixture was extracted with ethyl acetate, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give (–)-**3** (95% yield), $[\alpha]_D$= – 212 (c=0.5, ethanol). The enantiomeric purity was tested by chiral HPLC (Chiralcel OD, hexane/*i*-propanol 90/10, flow rate 0.9 ml/min) and was found to be >99%. Due to difficulties in the purification, it is not considered convenient to obtain the enantiomeric (+)-**3** by working up the solution containing the most soluble diastereomeric salt. The transformation of (*S*)-(+)-**1** into (+)-**3** should be preferred. Such a transformation is described below.

1-Phenyl-3-*n*-propyl-2,3-dihydro-1H-naphth[1,2-*e*][1,3]oxazine (main form) (4).

A solution of *n*-butanal (0.144 g, 2 mmol) in 1 ml of ethanol 95% was added dropwise to a solution of (+)-**1** (0.499 g, 2 mmol) in 12 ml of ethanol 95%. The mixture was stirred for 24 h at rt and then it was cooled to 0°C. The precipitate was filtered and washed with a small amount of ethanol 95% (0.413 g, 68% yield). (–)-**4**, white solid, mp= 97-98°C, $[\alpha]_D$= –15.2 (c=1.5, dichloromethane). IR (KBr) ν_{max} 3333, 3065, 2959, 2922, 2872, 1623, 1599, 1467, 1235, 1064 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ, 7.75-7.67 (m, 2 H), 7.37-7.20 (m, 8 H), 7.09 (d, *J*=8.9 Hz, 1 H), 5.51 (s, 1 H), 4.65 (t, *J*= 5.7 Hz, 1 H), 2.01-1.84 (broad m, 1 H), 1.80-1.63 (m, 2 H), 1.50-1.44 (m, 2 H), 0.88 ppm (t, *J*=7.4 Hz, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 152.66, 143.02, 131.71, 129.24, 129.04, 128.61, 128.43, 128.17, 127.14, 126.47, 123.04, 122.82, 119.22, 114.27, 82.04, 53.76, 37.29, 17.72, 13.87 ppm. Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found C, 83.09; H, 6.78; N, 4.59.

Synthesis of (+)-3 from (–)-4.

A large excess of $NaBH_4$ (0.144 g, 3.8 mmol) was added to a solution of (–)-**4** (0.115 g, 0.38 mmol) in 6 ml of methanol. The mixture was stirred for 6 h. The usual work-up yielded (+)-**3** (0.070 g, 60 %yield), $[\alpha]_D$= + 210 (c=0.35, ethanol). As in the case of (–)-**3**, the enantiomeric purity (>99%) was measured by chiral HPLC.

Reactions of diethylzinc with aryl aldehydes. General procedure. 9.1 ml of a 1.1 M solution of diethylzinc were added to 1 mmol of the chiral complexing agent in 5 ml of the specified solvent (see Table). After 30 min, 7.5 mmol of aryl aldehyde in 5 ml of the specified solvent were added and the reaction mixture was stirred for the time reported in the Table. The usual work-up and purification led to the 1-aryl-1-propanol.

Determination of the ee values. The ee values of the resulting products were measured by HPLC or NMR (see Table). HPLC measurements were performed with a Chiralcel OD column, eluents hexane/*i*-propanol in the range 90/10-97/3, flow rate 0.7 ml/min, separation factors α = 1.3-1.4. When HPLC separations were not satisfactory, the chiral alcohols were treated with (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, deriving from the (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid) according to the reported procedure.[17] The ee of the alcohols were inferred from the de of the resulting Mosher's acid esters. In particular, in the ^{1}H-NMR spectra the differences in chemical shifts among the signals related to the diastereomeric methoxy groups were in the range 0.06-0.11 ppm.

(*R*)-1-Phenyl-1-propanol (Kugelrohr oven temp. 150°C, 26 mbar) $[\alpha]_D$ = + 44.0 (c=5, chloroform) for a 96% ee. lit.[7] $[\alpha]_D$= +46 (c=5.2, chloroform).

(*R*)-1-*p*-Fluorophenyl-1-propanol (Kugelrohr oven temp. 115°C, 4 mbar) $[\alpha]_D$ = +38.0 (c=3.2, chloroform) for a 92% ee. lit.[7] $[\alpha]_D$ = + 51.2 (c=2.5, chloroform).

(*R*)-1-*p*-Chlorophenyl-1-propanol (Kugelrohr oven temp. 115°C, 4 mbar) $[\alpha]_D$ = +24.8 (c=1.5, benzene) for a 94% ee. lit.[7] $[\alpha]_D$ = + 28 (c=5, benzene).

(*R*)-1-*o*-Tolyl-1-propanol (Kugelrohr oven temp. 130°C, 6 mbar) $[\alpha]_D$ = +58.5 (c=2, benzene). lit.[8] $[\alpha]_D$ = –56.18 (c=4, benzene) for the (*S*)-configuration and for a 97%ee.

(*R*)-1-*m*-Tolyl-1-propanol (Kugelrohr oven temp. 115°C, 4 mbar) $[\alpha]_D$ = +42.2 (c=1.1, benzene) for a 93% ee. lit.[18] $[\alpha]_D$ = + 32.29 (benzene) for a 72% ee.

(*R*)-1-*p*-Tolyl-1-propanol (Kugelrohr oven temp. 110°C, 6 mbar) $[\alpha]_D$ = +39.2 (c=5, benzene) for a 96% ee. lit.[8] $[\alpha]_D$ = –37.31 (c=5, benzene) for the (*S*)-configuration and for a 98% ee.

(*R*)-1-*o*-Anisyl-1-propanol (Kugelrohr oven temp. 130°C, 4 mbar) $[\alpha]_D$ = +50.1 (c=3, toluene) for a 96% ee. lit.[7] $[\alpha]_D$ = + 53.3 (c=3, toluene).

Acknowledgement. This work was financially supported in part by Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome (National Project

"Stereoselezione in Sintesi Organica. Metodologie e Applicazioni") and by University of Bari.

References and notes

(1) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49-69.

(2) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994.

(3) Betti, M.; Lucchi, E. *Boll. Sci. Fac. Chim. Ind. Bologna* **1940**, *1-2*, 2-5. *Chem. Abstr.* **1940**, *34*, 2354. Although the result was questioned[4], the original claim remained valid, at least conceptually.

(4) Tarbell, D.S.; Paulson, M.C. *J. Am. Chem. Soc.* **1942**, *64*, 2842-2844.

(5) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833-856.

(6) Hulst, R.; Heres, H.; Fitzpatrick, K.; Peper, N.C.M.W.; Kellogg, R.M. *Tetrahedron: Asymmetry*, **1996**, *7*, 2755-2760.

(7) Kang, J.; Lee, J.W.; Kim, J.I. *J. Chem. Soc. Chem. Commun.* **1994**, 2009-2010.

(8) Prasad, H.R.K.; Joshi, N.N. *J. Org. Chem.* **1997**, *62*, 3770-3771.

(9) Seebach, D.; Beck, A. K.; Schimdt, B.; Wang, Y.M. *Tetrahedron* **1994**, *50*, 4363-4384.

(10) Zhang, F.-Y.; Yip, C.-W.; Cao, R.; Chan, A.S.C. *Tetrahedron: Asymmetry* **1997**, *8*, 585-589.

(11) Hwang, C.-D.; Uang, B.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 3979-3984.

(12) Betti, M. *Organic Syntheses Coll.* **1941**, *1*, 381-383.

(13) Betti, M. *Gazz. Chim. Ital.* **1906**, *36 I*, 388-401.

(14) Cardellicchio, C.; Ciccarella, G.; Naso, F.; Schingaro, E.; Scordari, F. *Tetrahedron: Asymmetry* **1998**, *9*, 3667-3675.

(15) Cardellicchio, C.; Ciccarella, G.; Naso, F. Italian Patent MI 98 A 000159 (1/28/1998).

(16) Ishizaki, M.; Fujita, K.; Shimamoto, M.; Hoshino, O. *Tetrahedron: Asymmetry* **1994**, *5*, 411-424.

(17) Dale, J.A.; Dule, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543-2549.

(18) Chaloner, P.A.; Langadianou, E.; Perera, S.A.R. *J. Chem. Soc. Perkin Trans. I*, **1991**, 2731-2735.