ORGANIC LETTERS

2006
Vol. 8, No. 12
2455−2458

3,3′-Oxazolidinyl-Substituted 2,2′-Biphenyldiols: Novel Tropos Ligands with a Large Induction on the Chiral Axis

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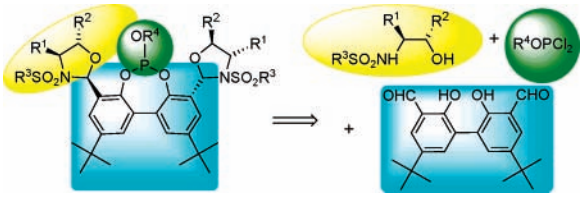
Received March 3, 2006

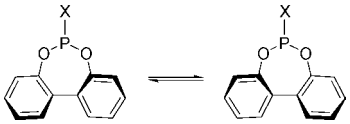
ABSTRACT



A novel type of bisphenol ligand is presented which provides high modularity. Chiral information is introduced in the 3,3′-positions as *N*-arenesulfonyl-1,3-oxazolidines inducing an unexpectedly high diastereoselectivity of up to 98:2 onto the chiral axis. The impact of each part of the molecule on the diastereomeric ratio is evaluated with extended variable-temperature (VT) NMR studies. A first example of application in asymmetric catalysis is given.

In asymmetric catalysis, enantiomerically pure BINOLs play an important role for ligand design. However, substantially less work is published using the related but flexible 2,2′-dihydroxybiphenyl as a ligand backbone.[1] In the design of such phosphite and phosphoramidite ligands, the use of chiral alcohols or amines or asymmetric activation by additional chiral ligands has been a popular approach.[2] Within these, little attention has been dedicated to the examination of asymmetric induction onto the chiral axis of the backbone,[3] whereas many researchers report rapid ring inversion of the dibenzo[*d*,*f*][1,3,2]dioxaphosphepine moiety (Scheme 1).

Scheme 1. Ring Inversion



In our laboratories, chiral *N*-arenesulfonyl-1,3-oxazolidines have played an important role as chiral auxiliaries, and we have demonstrated their utility in total synthesis.[4] Their formation from aldehydes and *N*-arenesulfonyl-2-amino-1-

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(1) For a review on atropisomerism see: Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561.

(2) See, for example: (a) Mata, Y.; Diéguez, M.; Pàmies, O.; Claver, C. *Org. Lett.* **2005**, *7*, 5597. (b) Alexakis, A.; Polet, D. *Org. Lett.* **2004**, *6*, 3529. (c) Reetz, M. T.; Li, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 2959. (d) Duursma, A.; Peña, D.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron: Asymmetry* **2005**, *16*, 1901.

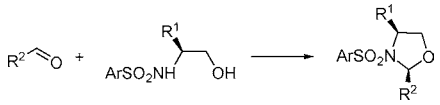
(3) See, for example: (a) Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506. (b) Shum, S. P.; Pastor, S. D.; DeBellis, A. D.; Odorisio, P. A.; Burke, L.; Clarke, F. H.; Rihs, G.; Piatek, B.; Rodebaugh, R. K. *Inorg. Chem.* **2003**, *42*, 5097. (c) Pastor, S. D.; Shum, S. P.; Rodebaugh, R. K.; DeBellis, A. D. *Helv. Chim. Acta* **1993**, *76*, 900.

(4) (a) Hoppe, I.; Hoppe, D.; Wolff, C.; Egert, E.; Herbst, R. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 67. (b) Hoppe, I.; Hoffmann, H.; Gärtner, I.; Krettek, T.; Hoppe, D. *Synthesis* **1991**, 1157. (c) Brüggemann, M.; Holst, C.; Hoppe, D. *Eur. J. Org. Chem.* **2001**, 647. (d) Winter, E.; Hoppe, D. *Tetrahedron* **1998**, *54*, 10329.

10.1021/ol060528u CCC: $33.50
Published on Web 05/18/2006

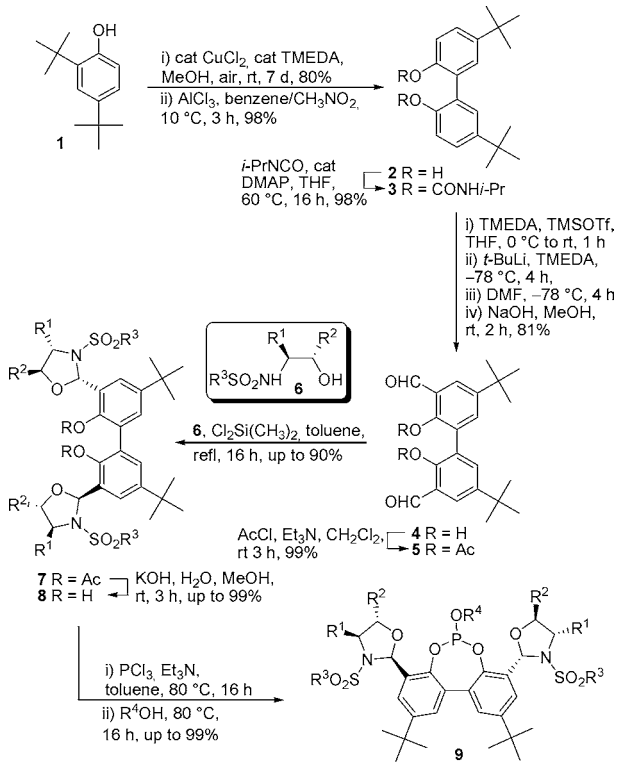
alkanols proceeds with exclusive 2,4-*cis* selectivity (Scheme 2). We decided to apply this excellent selectivity as source

Scheme 2. Formation of 2,4-*cis*-1,3-Oxazolidines



of chirality in our ligand design. The synthesis of our novel ligands is depicted in Scheme 3. Starting from phenol **1**,

Scheme 3. Synthesis of Ligands **9**[a]



[a] In a few cases, the opposite enantiomers, *ent*-**7** to *ent*-**9**, have been prepared (see Tables 1 and 2 for substituent key).

bisphenol **2** is obtained using a literature protocol[5] and is subsequently converted into the bis-carbamate **3**.

Double *ortho*-lithiation by a carefully optimized method developed in our group[6] and subsequent DMF quench and deprotection in a one-pot operation furnished bis-salicylaldehyde **4**. The key step—oxazolidine formation—turned out to be problematic. In contrast to simple benzaldehyde, a number of protocols[4] led to failure in the transformation of **4**, presumably for electronic reasons. Thus, we converted the hydroxy groups into more electron-poor acetates. Bisacetylated bisphenol **5** reacts with *N*-arenesulfonylamino alcohols **6** in the presence of dichlorodimethylsilane in refluxing toluene to give the desired bis-1,3-oxazolidines **7** in excellent yields. Finally, after hydrolysis of the acetates, the oxazolidines **8** were converted into phosphites **9** using phosphorus trichloride and alcohols.

To demonstrate the high modularity of our approach, we synthesized a number of ligands in good to excellent yields. Variations at three sites in the molecule can easily be performed: (i) a number of amino alcohols (available from cheap natural sources) can readily react with dialdehyde **5**, (ii) different arenesulfonyl groups are tolerated (Table 1), and (iii) a broad range of alcohols can be reacted to give the desired phosphites **9** (Table 2).

Table 1. Synthesis of 1,3-Oxazolidines **7** and **8**

entry	R^1, R^2	R^3	product **7** (% yield)	product **8** (% yield)
1	Et, H	Tol[a]	*ent*-**7a** (83)	*ent*-**8a** (99)
2	*i*-Pr, H	Tol	**7b** (90)	**8b** (99)
3	*s*-Bu, H	Tol	**7c** (90)	**8c** (95)
4	Bn, H	Tol	**7d** (84)	**8d** (94)
5	Me, Ph	As[b]	**7e** (37)	**8e** (72)
6	Et, H	Mes[c]	*ent*-**7f** (50)	*ent*-**8f** (88)

[a] Tol = 4-methylphenyl. [b] As = 4-methoxyphenyl. [c] Mes = 2,4,6-trimethylphenyl

Table 2. Synthesis of Phosphites **9**, Diastereomeric Ratio in Toluene-d_8, and Enantiomeric Excess in Model Reaction (Scheme 4)

entry	R^1, R^2	R^3	R^4	product **9** (% yield)	dr	T_C (K)	ee of **12** (%)
1	Et, H	Tol	Ph	*ent*-**9a** (86)	87:13	243	68
2	*i*-Pr, H	Tol	Ph	**9b** (90)	88:12	243	78
3	*s*-Bu, H	Tol	Ph	**9c** (69)	89:11	243	39
4	Bn, H	Tol	Ph	**9d** (98)	88:12	243	68
5	Me, Ph	As	Ph	**9e** (67)	73:27	223	2
6	Et, H	Mes	Ph	*ent*-**9f** (72)	98:2	233	9
7	Et, H	Tol	*i*-Pr	*ent*-**9g** (49)	>95:5		83
8	*i*-Pr, H	Tol	*i*-Pr	**9h** (66)	>95:5		67
9	Et, H	Tol	CH(*i*-Pr)$_2$	*ent*-**9i** (74)	95:5	243	68
10	*i*-Pr, H	Tol	CH(*i*-Pr)$_2$	**9j** (60)	94:6	253	70

As can be seen from Table 1, the formation of 1,3-oxazolidines was performed in fair to very good yields. Hydrolysis of the acetyl groups mostly occurred in excellent yield. Introduction of sterically more demanding groups (entries 5 and 6, Table 1) resulted in a decrease of the yield. In particular, the nor-pseudoephedrine-derived compounds **7e** and **8e** could only be obtained bearing the anisylsulfonyl group; other arenesulfonyl groups failed. Importantly, all oxazolidines were synthesized on a gram scale.

(5) (a) Buisman, G. J. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Tetrahedron: Asymmetry* **1993**, *4*, 1625. (b) Yamato, T.; Hasegawa, K.; Saruwatari, Y.; Doamekpor, L. *Chem. Ber.* **1993**, *126*, 1435.

(6) (a) Kauch, M.; Hoppe, D. *Can. J. Chem* **2001**, *79*, 1736. (b) Kauch, M.; Snieckus, V.; Hoppe, D. *J. Org. Chem.* **2005**, *70*, 7149.

In the final step, oxazolidines **8** were reacted with phosphorus trichloride and phenol or aliphatic alcohols, respectively (Table 2). Systematic variation of each interchangeable substituent allowed investigation of the impact of each residue on the diastereomeric ratio concerning the chiral axis (vide infra). Therefore, all oxazolidines **8** were converted into the corresponding 2-phenoxydibenzo[*d*,*f*]-[1,3,2]dioxaphosphepines **9a**−**f** (entries 1−6), and a subset was reacted with branched aliphatic alcohols to vary the steric bulk of substituent R^4 in phosphites **9**. The yields for that step range from moderate to excellent. Again, the nor-pseudoephedrine derivative afforded a lower yield. As a general trend, phenol seems to furnish higher yields.

It is worth noting that all phosphites **9** are reasonably stable toward oxidation to the corresponding phosphate and can be chromatographed on silica. However, during crystallization attempts, compound **9f** was oxidized and a single crystal of phosphate **10f** (Figure 1) was obtained; nevertheless the

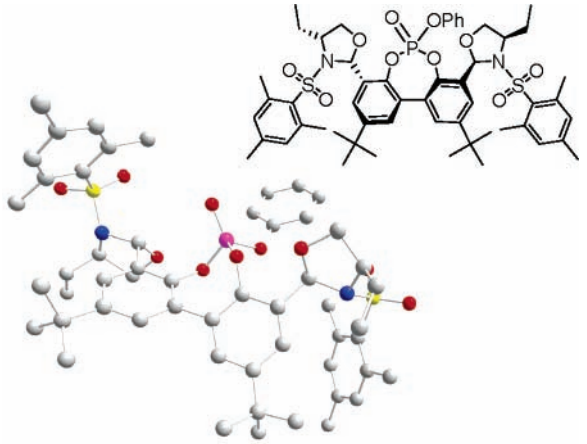


Figure 1. X-ray structure of phosphate **10f**.

desired information remains untouched: the absolute configuration of the chiral axis is (a*S*) with (2*R*,4*R*)-configured 1,3-oxazolidines. We assume that this should also be the configuration of the major isomer in solution.[7]

For the determination of diastereomeric ratios, the phosphites were subjected to VT ^{31}P NMR-spectroscopic studies. The results are shown in Table 2, and a representative plot showing coalescence and resolution of two distinct resonances is depicted in Figure 2.

The dynamic behavior found in the temperature-dependent ^{31}P NMR spectra clearly results from the interchange of both atropisomers of **9** by rotation around the chiral biaryl axis, as evidenced by two further experiments. First, irradiation experiments at low temperature showed correspondence of both signals observed. Second, the related oxazolidine **11** (Figure 3) derived from (*S*)-BINOL was synthesized similarly

(7) CD-spectroscopic and quantum chemical investigations on a related compound support this assumption; in cooperation with C. Diedrich and S. Grimme. To be published.

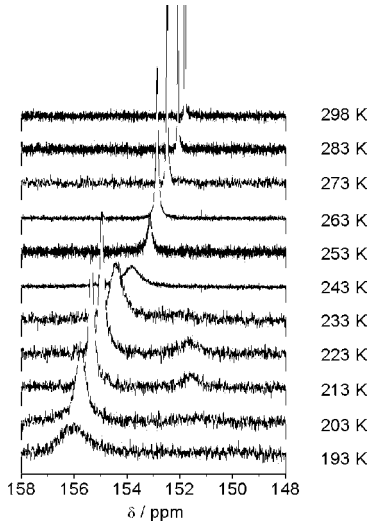


Figure 2. VT ^{31}P NMR-spectra of phosphite **9d** in toluene-d_8.

to compounds **9** in 39% overall yield. This showed no dynamic behavior in the VT NMR experiment. Hence, it can be concluded that the dynamic interconversion does not occur within the chiral 1,3-oxazolidine moieties.

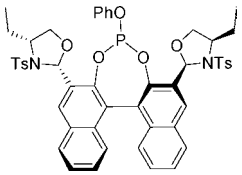


Figure 3. BINOL-derived phosphite **11**.

Most of the phosphites show coalescence around T_C = 243 K. Again, the nor-pseudoephedrine derived compound **9e** (entry 5) behaves differently with a lower temperature of coalescence at 223 K. The other exceptions, the mesitylenesulfonyl compound **9f** and the highly branched phosphite **9j** (entries 6 and 10), do not differ significantly. In nearly all cases, we observe the typical broadening of the signals which form two distinct signals upon further cooling. This is the case, even for those phosphites which display a strong difference in the population of both diastereomers (entries 6, 9, and 10). Further cooling again leads to broadening of the signals which is due to slower conformational dynamic in all parts of the molecule. In contrast, compounds **9g** and **9h** (entries 7 and 8) show slightly broadened signals around 243 K which neither become sharpened at lowered temperature nor form a second signal. We therefore cannot quote a well-defined coalescence temperature T_C. Furthermore, we expect the diasteromeric ratio to be higher than 95:5, but we cannot give exact values.

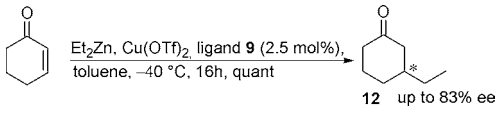
We first examined the impact of substituent R^1 on the diasteromeric ratio (entries 1−4, Table 2). Increasing the size

of R^1 slightly enhances the energy difference between both configurations, whereas introduction of aromatic side groups in **9d** has no influence. We then turned our attention on the effect of further substitution of the 1,3-oxazolidine moiety (entry 5). It is necessary that substituents at carbons 4 and 5 of the heterocycle are in a *trans* relationship.[8] However, this variation only led to dramaticly less selectivity in combination with a lowered rotational barrier as can be seen from the lower coalescence temperature of **9e**. To our delight, increasing the steric bulk of the arenesulfonyl group shows substantial impact on the diastereoselectivity; a ratio of 98:2 is observed in *ent*-**9f**.

We finally varied the size of the substituent at the phosphorus atom (entries 7−10). On going from flat phenol to branched alcohols we expected stronger steric interaction of the heterocycles with the residue at the P-atom. Introduction of an isopropoxy group led to the described behavior of compound **9g** in the VT NMR spectra (vide supra). With this strongly enhanced selectivity of more than 95:5 in hand, we hoped that an even more branched substituent (compound **9i**) would lead to higher selectivity and clear spectra. In contrast, we obtained spectra with a more developed coalescence phenomenon (more equal populations of the interchanging signals furnishes more broadened signals at T_C) and a selectivity below our expectations of 95:5. We therefore further investigated this behavior by slightly increasing the size of the alkyl residues R^1 in the heterocycles. Isopropoxy compound **9h** (entry 8) showed spectra comparable to phosphite **9g**. Finally, the highly branched phosphite **9j** again displayed a decrease in selectivity. Interestingly, the ratio of 94:6 is slightly lower than that of compound **9i** bearing a sterically less demanding alkyl group R^1. This makes us assume that in phosphites **9i** and **9j** the molecule might be somewhat sterically overcrowded, leading to a decrease in selectivity.

To demonstrate the potential use of our novel bisphenol compounds as ligands in asymmetric catalysis, we applied them in the copper-mediated Michael-type addition of diethylzinc to 2-cyclohexenone (Scheme 4).[9]

Scheme 4. Michael Addition of Diethylzinc to 2-Cyclohexenone



The enantioselectivities obtained are found in Table 2. In general, (2*R*,4*R*)-configured ligands furnish (*R*)-**12**.[10] On one hand, ligand **9g**, which displays one of the best ratios concerning the chiral axis, delivers the best result in the model reaction, but on the other hand, there is no general trend between the diastereoselectivity within the free ligand and the ee in the Michael product **12**. Nevertheless, these results demonstrate the potential that lies within our highly modular ligands.

In conclusion, we presented the synthesis of novel and highly modular (four variable sites) bisphenol-based ligands. All synthetic steps proceed in good to excellent yield and can be performed on a gram scale. To the best of our knowledge, this is the first bisphenol-based phosphorus ligand reported that bears the chiral information at the 3,3′-positions. The 1,3-oxazolidinyl substituents are relatively far away from the chiral biaryl axis and have an unexpectedly high impact on the diastereomeric ratio. The selectivity of up to 98:2 for this type of compounds is the best so far reported. The strong influence of the arenesulfonyl group on the diastereomeric ratio renders the free hydroxy oxazolidines **8** an interesting subject of research suitable for the use as diol ligands, complementing BINOL compounds. This project is currently under way, as well as further investigations in the field of phosphites **9**.

Acknowledgment. Generous support by the Fonds der Chemischen Industrie is gratefully acknowledged.

Supporting Information Available: Representative procedures, spectral data of new compounds, and crystallographic data (CIF) for compound **10f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) In our work using chiral *N*-arenesulfonyl-1,3-oxazolidines as chiral auxiliaries, nor-pseudoephedrine derivatives often provided superior selectivity; see, for example: Brüggemann, M.; Fröhlich, R.; Wibbeling, B.; Holst, C.; Hoppe, D. *Tetrahedron* **2002**, *58*, 321.

(9) For reviews on copper-catalyzed Michael additions, see: (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171.

(10) The absolute configuration of **12** was determined by derivatization: Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2431.