ORGANIC LETTERS

2001
Vol. 3, No. 23
3675−3678

An Efficient Synthesis of (–)-Chloramphenicol via Asymmetric Catalytic Aziridination: A Comparison of Catalysts Prepared from Triphenylborate and Various Linear and Vaulted Biaryls

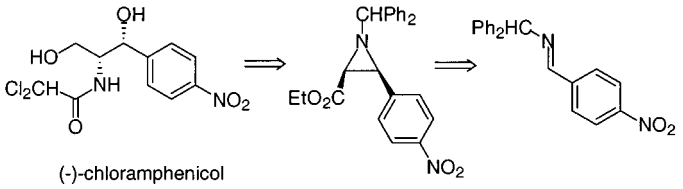
Catherine Loncaric and William D. Wulff*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

wulff@cem.msu.edu

Received August 15, 2001

ABSTRACT

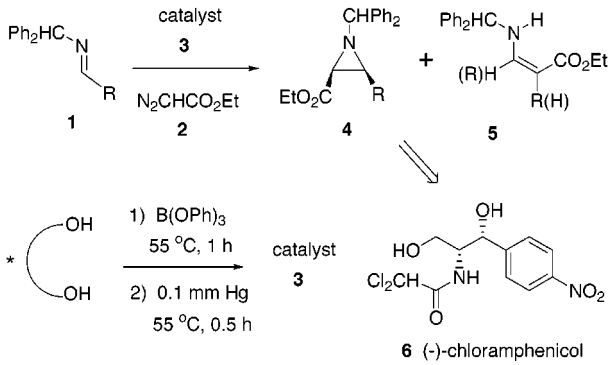


The antibiotic (–)-choramphenicol has been synthesized in only four steps from *p*-nitro-benzaldehyde in optically pure form from an asymmetric catalytic aziridination reaction with a chiral catalyst prepared from triphenylborate and the (R)-VAPOL ligand. Catalysts generated from the VAPOL and VANOL ligands give much higher asymmetric induction than do catalysts prepared from 6,6′-diphenylVAPOL, BINOL, and BANOL ligands.

One of the oldest antibacterial agents is chloroamphenicol, which was first isolated from *Streptomyces Venezuelae* in 1947.[1] This antibiotic is obtained commercially by chemical synthesis and is biological active only as its 2*R*,3*R* enantiomer. It is used clinically as a broad spectrum antibiotic and is particularly useful for the treatment of salmonella, typhi, rickettsia, and meningeal infections.[2] As a result of its link to bone marrow depression, it use is reserved for serious infections with organisms that have been demonstrated to be resistant to all other appropriate anti-microbial agents. A number of chemical syntheses of racemic chloramphenicol have been reported,[3] as well as a few in the past decade that are selective for the formation of (−)-chloramphenicol.[4] We report here an asymmetric synthesis of optically pure (−)-chloramphenicol that is the shortest of all syntheses reported to date.

The strategy for the synthesis of (−)-chlormaphenicol is outlined in Scheme 1 and features an asymmetric catalytic aziridination reaction that has recently been developed in

Scheme 1. Catalytic Asymmetric Aziridination en Route to (−)-Chloramphenicol

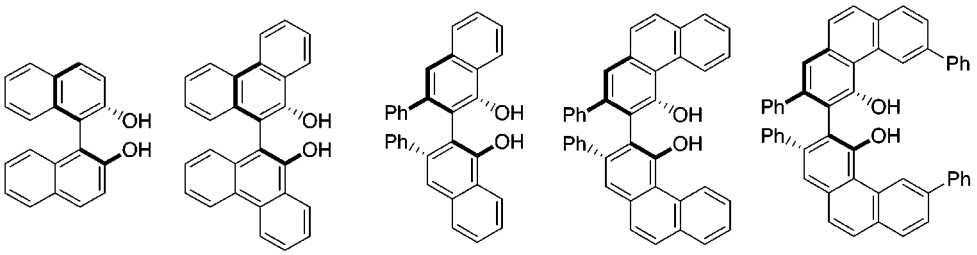


(1) Ehrlich, J.; Bartz, Q. R.; Smith, R. M.; Josylyn, D. A.; Burkholder, P. R. *Science* **1947**, *106*, 417.

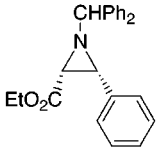
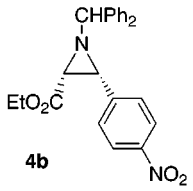
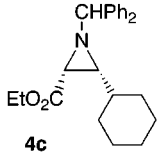
(2) *Physicians' Desk Reference*, 46th ed.; Medical Economics Data, 1992

10.1021/ol010180x CCC: $20.00
Published on Web 10/17/2001

Table 1. Asymmetric Catalytic Aziridinations with Linear and Vaulted Biaryls[a]



7 (S)-BINOL **8** (S)-BANOL **9** (S)-VANOL **10** (S)-VAPOL **11** (S)-Ph-VAPOL

entry	Imine	R	Ligand	Aziridine **4**	Time (h)	% Yield **4** [b]	cis **4** / trans **4** [c]	% ee **4** [d]	% Yield **5** [e]
1	**1a**	Ph	(S)-BINOL [f]		3	61	17 : 1	20	22
2			(S)-BANOL [g]		16	65	14 : 1	43	5
3			(S)-VANOL		0.5	85	> 50 : 1	96	4
4			(S)-VAPOL [f]		48 [h]	77	> 50 : 1	95	6
5			(R)-VAPOL		15 [i]	77	> 50 : 1	96 [j]	4
6			(S)-Ph-VAPOL	**4a**	3	80	10 : 1	50	4
7	**1b**	*p*-$NO_2C_6H_4$	(R)-BINOL		26 [k]	72	19 : 1	22 [j]	5
8			(S)-BANOL [g]		16	60	6 : 1	50	6
9			(R)-BANOL [g]		21 [i]	70	22 : 1	67 [j]	7
10			(S)-VANOL		26 [i]	77	> 50 : 1	91	< 2
11			(R)-VAPOL		21 [i]	80	30 : 1	96 [j]	7
12			(S)-Ph-VAPOL	**4b**	20 [k]	70	19 : 1	54	19
13	**1c**	Cy	(R)-BINOL		4	33 [l]	15 : 1	18 [j]	9
14			(S)-BANOL [g]		16	60	23 : 1	61	11
15			(S)-VANOL		4	83	20 : 1	87	8
16			(S)-VAPOL [f]		8	74	38 : 1	94	< 2
17			(S)-Ph-VAPOL	**4c**	16	25	5 : 1	26	3

[a] Unless otherwise specified, all reactions were run in methylene chloride (0.5 M in imine) with 10 mol % catalyst at 22 °C and with 1.1 equiv of ethyl diazoacetate. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^{1}H NMR spectrum of crude reaction mixture by the average integration of aziridine methine protons. [d] Determined by HPLC on a Chiralcel OD column. [e] Determined from ^{1}H NMR spectrum of crude reaction mixture by integration against aziridine. [f] See ref 5a. [g] BANOL ligand used was 98 % ee. [h] Reaction performed with 2 mol % catalyst. [i] In toulene at 0 °C for 5 h and then warmed to 22 °C. [j] Products is enantiomer of aziridine shown. [k] In toulene at 0 °C for 10 h and then warmed to 22 °C. [l] 50% conversion.

our laboratories.[5] Specifically, it is anticipated that the reaction of the benzhydryl imine of 4-nitrobenzaldehyde (**1**, R = 4-$NO_2C_6H_4$) with ethyl diazoacetate mediated by a catalyst generated from triphenylborate and the VAPOL ligand would give the aziridine **4**, from which a synthesis of (−)-chloroamphenicol could be fashioned. Since it has been recently found that the VAPOL and VANOL ligands give essentially the same asymmetric inductions and yields over a wide range substrates,[5a] it was decided that the asymmetric aziridination reaction should be screened with an expanded set of biaryl ligands, which are shown in Table 1. In addition to VAPOL and VANOL, these include BINOL, BANOL,[6] and 6,6′-diphenylVAPOL.[7] Catalysts prepared from this set of five ligands were used to screen the aziridination of three different imines, which were derived from benzaldehyde, cyclohexane carboxaldehyde, and 4-nitrobenzaldehyde, the latter of which is the requisite substrate for the synthesis of (−)-chloroamphenicol.

The results from the screening of five different catalysts for the aziridination of imines **1a**, **1b**, and **1c** are presented in Table 1 and reveal that the VANOL and VAPOL ligands make the most effective asymmetric catalysts. Unless otherwise specified, these reactions were performed with 10 mol % catalyst in methylene chloride at room temperature. The reaction times were not optimized and should not be taken to be indicative of the relative rates of catalysts generated from different ligands. The reaction time in entry 4 is longer since this reaction was performed with only 2 mol % catalyst. Performing the reaction in toluene at 0 °C

(3) (a) Controulis, J.; Rebstock, M. C.; Crooks, H. M., Jr. *J. Am. Chem. Soc.* **1949**, *71*, 2463. (b) Long, L. M.; Troutman, H. D. *J. Am. Chem. Soc.* **1949**, *71*, 2469. (c) Long, L. M.; Troutman, H. D. *J. Am. Chem. Soc.* **1949**, *71*, 2473. (d) Ehrhart, G.; Siedel, W.; Nahm, H. *Chem. Ber.* **1957**, *90*, 2088. E. Hazra, B. G.; Pore, V. S.; Maybhate, S. P. *Synth. Commun.* **1997**, *27*, 1857.

did not enhance the asymmetric induction for the catalyst prepared from the VAPOL ligand (entries 4 and 5), but a slight increase was noted for the BANOL ligand (entries 8 and 9). The catalyst prepared from the BINOL ligand consistently gave the lowest asymmetric induction for all three of the imine substrates. Catalysts prepared from the BANOL and the Ph-VAPOL ligand gave intermediate levels of induction, whereas the VAPOL and VANOL ligands both gave rise to catalysts that gave high inductions with all three substrates. The levels of diastereoselection for the *cis*-isomer of the aziridine were also the highest for the VAPOL and VANOL derived catalysts. As was observed previously,[5b] the VAPOL and VANOL ligands gave very similar inductions for the substrates examined, which is surprising and at this point not understood.

The aziridination of the *p*-nitrobenzaldimine **1b** is the key step in the synthetic route to chloramphenicol, and thus the effect of the reaction conditions on this reaction was examined in greater detail, with particular focus on lowering the catalyst loading. The results are given in Table 2. Toluene

Table 2. Asymmetric Catalytic Aziridinations with Imine **1b**[a]

entry	mol % catalyst	$B(OPh)_3$/VAPOL	% yield **4b**[b]	*cis*-**4b**/*trans*-**4b**[c]	% ee **4b**[d]	% yield **5b**[e]
1[f]	10	3	69	19:1	80[g]	13
2[f]	10	3	81	22:1	90.3	8
3	10	3	76	28:1	83[g]	9
4	10	3	80	30:1	96	7
5	10	3	95	41:1	96[h]	3
6	10	2	88	28:1	93.5	6
7	10	1.1	86	23:1	93.4	4
8	5	3	85	40:1	92.6	<2
9	5	1.5	95	33:1	89.9	<2
10	2.5	3	85	15:1	89.6	<2
11	2.5	1.5	80	14:1	89	5
12	2.5	3	82[i]	33:1	93	

[a] Unless otherwise specified, all reactions were run at 0 °C in toulene (0.5 M in imine) with 1 mmol of imine and with 1.1 equiv of ethyl diazoacetate. Reaction times were 1−5 h with 10 mol % catalyst and 5−10 h with 1−5 mol % catalyst. Reactions run below room temperature were warmed to ambient for several hours after the indicated time. [b] Same as Table 1. [c] Same as Table 1. [d] Same as Table 1. [e] Same as Table 1. [f] In methylene chloride. [g] Reaction run at 20 °C. [h] Reaction run at −20 °C for 24 h. [i] Reaction run on 5 mmol scale.

is clearly superior to methylene chloride as solvent for this reaction both in terms of asymmetric induction and in *cis*/*trans* selection (entries 2 vs 4). Because the *p*-nitro substituted imine **1b** reacts faster than the unsubstituted phenyl imine **1a**, this substrate can be aziridinated in reasonable times even at subambient temperatures and under reduced catalyst loadings. The asymmetric induction and *cis/trans* selection is higher at 0 °C than at 20 °C, and this is true for both toluene (entries 3 and 4) and methylene chloride (entries 1 and 2) as solvent. However, no increase in induction was observed when the temperature was lowered from 0 °C to −20 °C (entries 4 vs 5) despite the fact that the diastereoselection did increase. The asymmetric induction is not greatly effected by the stoichiometry of catalyst formation (entries 4, 6, and 7). The catalyst is prepared from the VAPOL ligand and triphenyl borate as indicated in Scheme 1, and the induction ranges from 93.4% to 96% ee as the equivalents of borate to VAPOL is varied from 1.1 to 3.0. There is a slight dependence in the asymmetric induction on the catalyst loading for the *p*-nitro substrate **1b** (entries 4, 8, 10, and 13), which is in contrast to the observation made for the unsubstituted phenyl substrate **1a**.[5b] The induction drops from 96% to 88.7% ee as the loading is reduced from 10 mol % to 1 mol %. However, this can be recovered to some extent by increasing the scale of the reaction. With 2.5 mol % catalyst, the induction is 89.6% ee on a 1 mmol scale and 93% ee on a 5 mmol scale (entries 10 and 12). These experiments reveal that the *cis/trans* selectivity can also be recovered with this same scale change (entries 4 vs 12). In addition to the improvement noted with the scale, it was found that the aziridine **4b** could be improved from 90% to 99% ee by a single crystallization from hexane/methylene chloride (first crop, 65% recovery).

The successful synthesis of (−)-chloramphenicol from the azirdine **4b** requires the nucleophilic ring opening of the aziridine at the benzylic position with an oxygen nucleophile with inversion of configuration. We were thus pleased to find that treatment of aziridine **4b** with 1 equiv of trifluoracetic acid in methylene chloride lead to a single diastereomer of the *β*-hydroxy amino ester **12** in 80% yield. The treatment of this aziridine with excess trifluoroacetic acid under more forcing conditions resulting in the heuristic finding that the aziridine ring is opened with inversion of configuration at the benzylic carbon and the benzhydryl protecting group on the amine is cleaved and that the amine is trifluoroacetylated. This transformation is accounted for by the sequence of events that is outlined in Scheme 2. Upon protonation, the aziridine is opened by attack of trifluoroacetate to give the intermediate **15**. Protonation of the amine function in **15** thus is envisioned to lead to the loss of the benzhydryl cation and the formation of the amino ester **17**. Finally, a trifluoroacetyl transfer from oxygen to nitrogen would lead to the observed product of this reaction. On the basis of this observation, it was thus foreseen that it may be possible to synthesize chloroamphenicol from the aziridine **4b** with simultaneous opening of the aziridine and introduction of the dichloroacetamide function by simple treatment with dichloroacetic acid.

The optimized synthesis of (−)-chloroamphenicol based on the catalytic asymmetric azirdination of imines is outlined in Scheme 3. The synthesis begins with commercially

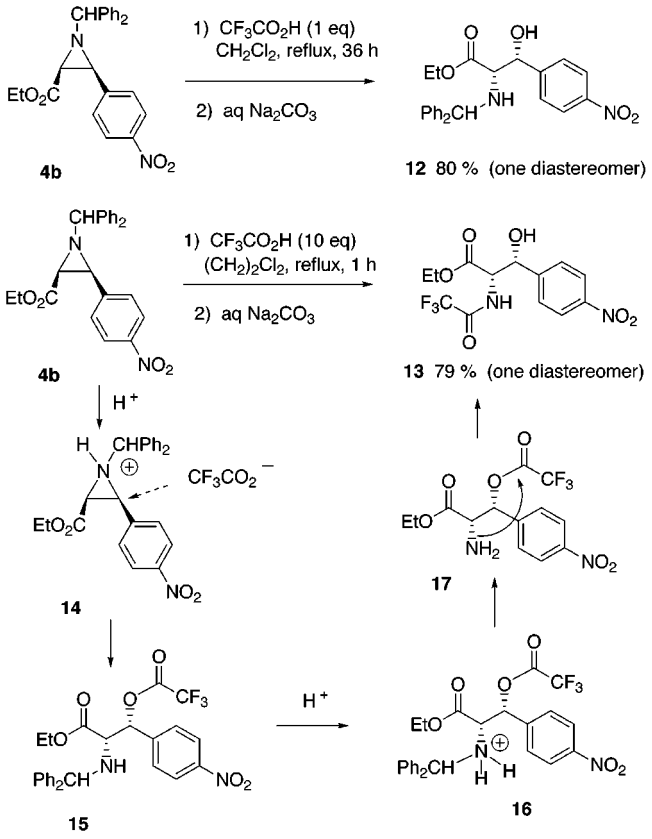
(4) (a) Cherevert, R.; Thiboutot, S. *Synthesis* **1989**, 444. (b) Rao, A. V. R.; Rao, S. P.; Bhanu, M. N. *J. Chem. Soc., Chem. Commun*. **1992**, 859. (c) Lou, B.-L.; Zhang, Y.-Z.; Dai, L.-X. *Chem. Ind*. **1993**, *7*, 249. (d) Veeresa, G.; Datta, A. *Tetrahedron Lett*. **1998**, *39*, 8503. (e) Corey, E. J.; Choi, S. *Tetrahedron Lett*. **2000**, *41*, 2765. (f) Park, J. N.; Ko, S. Y.; Koh, H. Y. *Tetrahedron Lett*. **2000**, *41*, 5553.

(5) (a) Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518. (b) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc*. **1999**, *121*, 5099.

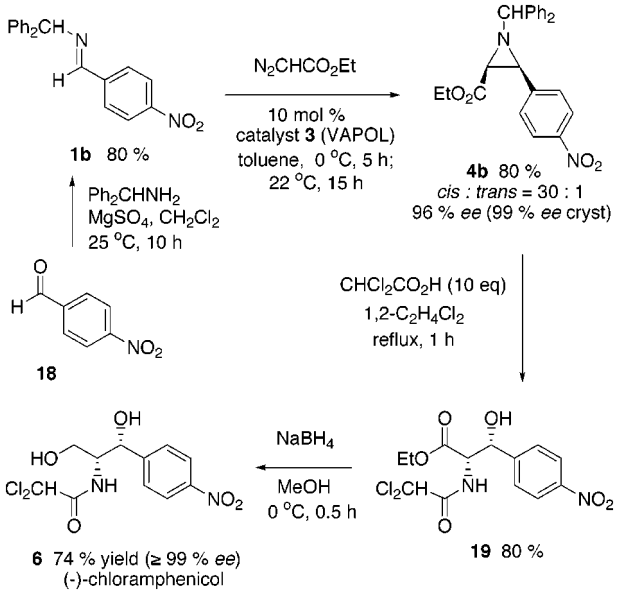
(6) Yamanoto, K.; Fukushima, H.; Nakazaki, M. *J. Chem. Soc., Chem. Commun*. **1984**, 1490. (b) Toda, F.; Tanaka, K.; Nassimbeni, L.; Niven, M. *Chem. Lett*. **1988**, *8*, 1371. (c) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem*. **1988**, *60*, 1597.

(7) Heller, D. P.; Wulff, W. D. Unpublished results.

Scheme 2



Scheme 3



available *p*-nitrobenzaldehyde and its conversion to its corresponding benzhydryl imine **1b**, which is obtained in 80% yield after crystallization from ethanol. The aziridination is carried out with 10 mol % of the catalyst prepared from the VAPOL ligand in toluene at 0 °C to give the aziridine **4b** in 80% yield, 96% ee, and with a 30:1 *cis*/*trans* selectivity. The enantiomeric purity of this aziridine could be improved to 99% ee with a single crystallization from hexane/methylene chloride (84% yield, first crop). As anticipated by the above observations, treatment of the optically pure aziridine with 10 equiv of dichloroacetic acid in refluxing 1,2-dichloroethane for 1 h gave the hydroxy acetamide **19** in 80% yield as a single diastereomer. Completion of the synthesis was accomplished by reduction of the ethyl ester with sodium borohydride, which gave (−)-chloroamphenicol in 74% yield and in greater than 99% enantiomeric excess. The rotation measured on the synthetic (−)-chloroamphenicol ($[\alpha]_D = -25.4°$, $c = 1$, EtOAc) compares favorably with previously reported values ($[\alpha]_D = -25.5°$, $c = 1$, EtOAc).[8] The synthesis of enantiomerically pure (−)-chloroamphenicol is thus achieved in four steps from commercially available starting materials in 38% overall yield.

The results of this study serve to solidify the utility of VANOL and VAPOL derived catalysts in asymmetric catalytic aziridination reactions. Further studies on the scope and mechanism of this reaction will be reported in due course, as well as the applications of this process in organic synthesis.

Acknowledgment. This work was supported by the National Institutes of Health.

Supporting Information Available: Full experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010180X

(8) Bartz, Q. R. *J. Biol. Chem.* **1948**, *172*, 445.