ORGANIC LETTERS

2002
Vol. 4, No. 15
2529−2532

Catalytic Asymmetric Oxidative Couplings of 2-Naphthols by Tridentate *N*-Ketopinidene-Based Vanadyl Dicarboxylates

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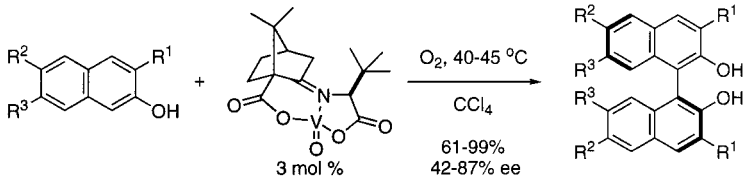
Received May 8, 2002

ABSTRACT



A series of oxovanadium(IV) complexes derived from tridentate *N*-ketopinidene-α-amino acids were synthesized. They serve as efficient catalysts for the enantioselective oxidative couplings of various 3-, 6-, or 7-substituted 2-naphthols. The best scenario involves the use of a vanadyl complex arising from L-*tert*-leucine in CCl_4. The asymmetric couplings of 2-naphthols can be conducted smoothly at 40–45 °C under a stream of gaseous oxygen, leading to 2,2′-dihydroxy-1,1′-binaphthyls in good yields (61–99%) and with enantioselectivities of up to 87%.

Axially dissymmetric 1,1′-bi-2-naphthol (BINOL) and its derivatives are important chiral auxiliaries in asymmetric syntheses and catalyses.[1] In addition, their facile conversions to the corresponding 2,2′-bis(diphenylphosphino)-1,1′-binaphthyls (BINAP) have further expanded their synthetic utilities in various domains of asymmetric catalyses.[2] In light of the comprehensive applications in asymmetric transformations, their preparation in optically pure form has remained under intense attention over the past 2 decades.[3]

In recent years, asymmetric synthesis of BINOLs by catalytic enantioselective means to complement the needs of stoichiometric resolving agents and chiral chromatography is a topic of imminent research.[4] Seminal studies of Brussee[3h,5] and Kočovský[6] on the syntheses of scalemic BINOLs involved Cu(II)−amine complex mediated oxidative couplings of 2-naphthols. However, in most instances, second-order asymmetric transformation was observed rather than asymmetric couplings. Nakajima and co-workers[7a] have demonstrated the first successful enantioselective variant by

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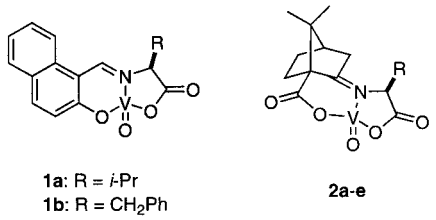
10.1021/ol026156g CCC: $22.00
Published on Web 06/26/2002

applying L-proline-derived diamine−Cu(I) complex to effect the couplings of 3-carboalkoxy-2-naphthols in up to 78% ee. Subsequent study by Kozlowski further improved the catalytic protocol to 93% ee by using Cu(I)-1,5-diazadecaline complexes.[7b] Notably, these two complexes were specifically active and enantioselective for 3-carboalkoxy-2-naphthols, presumably as a result of facile bidentate coordination of the substrates.

As part of our continuing research interests toward vanadyl complex-mediated catalysis in our laboratory,[8] we have recently developed the first successful enantioselective oxidative couplings of 2-naphthols catalyzed by *N*-salicylidene-α-amino acid based vanadyl complexes (e.g., **1a** and **1b**, Figure 1). Various 3-, 6-, and 7-substituted BINOLs



1a: R = *i*-Pr
1b: R = CH_2Ph

2a-e

Figure 1. Vanadyl complexes derived from 2-hydroxy-1-naphthaldehyde or (+)-ketopinic acid with α-amino acids.

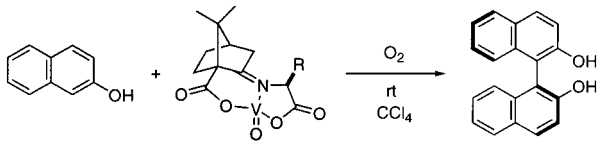
were furnished in excellent yields and with fair enantioselectivities of up to 68%.[8b,9] Notably, the preliminary searches for chiral vanadyl complexes have revealed that the carboxylate functionality in the chiral template is essential for the coupling activity.[10]

Very recently, Gong and co-workers have further extended this concept.[11] Oxovanadium(V) complexes derived from α-amino acids and a chiral salicylidene-based template, 3,3′-diformyl-2,2′-dihydroxy-1,1′-bi-2-naphthyl, could achieve a similar enantioselectivity (57% ee) in the oxidative coupling of 2-naphthol under our previously reported reaction conditions (10 mol %, 20 °C).[8b] More significantly, the enantioselectivities in the oxidative couplings of the parent, 6-bromo-, and 7-methoxy-2-naphthol were further improved to a range of 82% to 98% at a lower temperature of 0 °C.

More than 1 year ago, we identified a new category of vanadyl species, namely, vanadyl dicarboxylates, which were specifically active toward nucleophilic acyl substitution of anhydrides and oxidative couplings of 2-naphthols. We thought to examine the reactivity and enantioselectivity profiles of new chiral vanadyl dicarboxylates derived from (+)-ketopinic acid, a uniquely stable chiral β-keto acid, and α-amino acids in asymmetric oxidative couplings of 2-naphthols. Herewith, we describe the preliminary results of this work.

The targeted vanadyl dicarboxylates (**2a**−**e**) were prepared by combining vanadyl sulfate with in situ generated Schiff bases from (+)-ketopinic acid and respective α-amino acids. Mass analyses of these complexes by the FAB technique indicate that they are mainly composed of tetradentate monomers and pentadentate dimers.[12] To gain insights into their α-substituent (R) and chirality influences on enantiocontrols of the coupling processes, five natural (L-form) α-amino acids and D-valine were first examined in a model coupling of 2-naphthol. The model reactions were carried out by following a reaction protocol similar to that for catalyst **1a** or **1b** (10mol %, O_2, ambient temperature in CCl_4). It was found that the coupling rates and enantioselectivities were highly dependent on the steric bulks of R, Table 1.

Table 1. Effects of α-Amino Acids in **2** on Catalytic Asymmetric Coupling of 2-Naphthol in CCl_4



10 mol%
2a-e

S
3a

catalyst/R	time, d	yield,[a] %	ee,[b,c] %
$PhCH_2$ (**2a**)	7	96	28
i-Pr (**2b**)	10	77	52
i-Pr[d] (**2b′**)	10	69	−8
s-Bu (**2c**)	7	90	40
i-Bu (**2d**)	9	77	3
t-Bu (**2e**)	15	65	87

[a] Isolated yields after flash column purification. [b] Determined by HPLC on Chiralcel AD or OJ column. [c] Defined as (%*S* − %*R*)/(%*S* + %*R*) × 100%. [d] D-Valine was used.

In general, vanadyl complexes (**2b** and **2c**) bearing isopropyl and *sec*-butyl substituents (i.e., with 1′ branching points) led to scalemic BINOL-**3a** with enantioselectivities significantly higher (52% and 40%) than those catalyzed by **2a** and **2d** bearing 2′-branched (R = $PhCH_2$ and *i*-Bu) substituents (28% and 3% ee). More satisfactory enantioselective coupling of 2-naphthol was observed for catalyst **2e** with the sterically most demanding substituent (R = *t*-Bu), where **3a** was isolated after 15 days in 87% ee but in 65% yield. To our knowledge, this was one of the most enantio-

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(12) See the Supporting Information for details.

selective preparations of the parent BINOL by metal complex catalyzed asymmetric coupling techniques. It should be noted that the asymmetric induction (−8% ee vs 52% ee) in the coupling was reversed but to a lesser extent upon using vanadyl complex **2b′** derived from D-valine instead of L-valine.

To improve the coupling yields with intact enantioselection in the test reaction by **2e**,[13] we further examined a couple of key factors such as O_2 pressure and temperature in rate controls. The coupling rate was greatly enhanced by more than 6 times (from 15 days to 60 and 52 h, respectively) under an oxygen pressure of 75 and 130 psi, respectively. However, a significant drop in ee by 26% and 33%, respectively, for BINOL-**3a** was observed (entries 1−3, Table 2).

Table 2. Effects of Pressure, Temperature, and Catalyst Loading on Catalytic Asymmetric Coupling of 2-Naphthol by **2e**

entry	loading/T	time/pressure	yield,[a] %	ee,[b] %
1	**10 mol %/rt**	**15 d/- - -**	**65**	**87**
2	10 mol %/rt	2.5 d/75 psi	88	61
3	10 mol %/rt	2.2 d/130 psi	80	54
4	10 mol %/40 °C	10 d/- - -	71	83
5	**10 mol %/45 °C**	**7 d/- - -**	**95**	**81**
6	10 mol %/50 °C	3 d/- - -	99	62
7	10 mol %/70 °C	2 d/- - -	99	61
8	**5 mol %/45 °C**	**7 d/- - -**	**99**	**83**
9	5 mol %/45 °C	11 d/30 psi	97	64
10	**3 mol %[c]/45 °C**	**7 d/- - -**	**99**	**84**
11	2 mol %/45 °C	7 d/- - -	87	76
12	1 mol %/45 °C	9 d/- - -	83	62

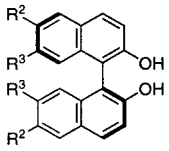
[a] Isolated yields after flash column purification. [b] Determined by HPLC on Chiralcel AD or OJ column. [c] A salt free catalyst was employed.

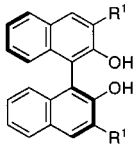
A similar trend was observed by conducting the coupling at 70 °C (entry 7). Further trials at different elevated temperatures (entries 4−7) led to an optimal working temperature range of 40−45 °C, where virtually quantitative formation of **3a** can be achieved in 81% ee in 7 days (entry 5). In addition, the catalyst loading can be reduced down to 3 mol % (entries 8−12, Table 2) without compromising yields and enantioselectivities in the model coupling reaction.

With the optimized catalytic protocol in hand, we further explored its generality toward substrate scope. As shown in Table 3, moderate to good enantioselectivities (42−87% ee) were achieved for asymmetric couplings of 2-naphthols with varying C(3), C(6), or C(7) appendages. For comparison, the best results obtained earlier from our catalysts[8b] or very recently from Gong's are included in parentheses. In all cases except 6,6′-dibromo- and 7,7′-dimethoxy-BINOL, **3b** and **3e** (entries 2 and 5), good improvement in enantiomeric excesses

(13) Among five different solvent classes (chloroalkanes, ethers, nitriles, nitroalkanes, alcohols, and arenes) screened, better asymmetric inductions were observed for the coupling reactions conducted in CCl_4 (87% ee) and toluene (53% ee) albeit still with moderate yields (65−67%) at ambient temperature. As to co-oxidant effects, the reaction was complete in 40 h at 0 °C with trityl hydroperoxide and BINOL-**3a** was isolated in 80% with significant drop in ee by 17%.

Table 3. Effects of Substrates on the Catalytic Asymmetric Couplings Mediated by **2e**[a]





(*S*)-**3a**: $R^2 = R^3 = H$ (*S*)-**3b**: $R^2 = Br$, $R^3 = H$ (*S*)-**3c**: $R^2 = OMe$, $R^3 = H$ (*S*)-**3d**: $R^2 = OCH_2Ph$, $R^3 = H$ (*S*)-**3e**: $R^2 = H$, $R^3 = OMe$ (*S*)-**3f**: $R^2 = H$, $R^3 = OCH_2Ph$ (*S*)-**3g**: $R^1 = CPh_2(OH)$

entry	time, d	product	yield,[b] %	ee,[c] %
1	7	**3a**	99 (95[d])	84 (83)
2	8	**3b**	86 (99)	42 (88)
3	8	**3c**	99 (100)	64 (39)
4	10[e]	**3d**	95 (- - -)	59 (- - -)
5	8	**3e**	99 (88)	85 (98)
6	7	**3f**	96 (- - -)	87 (- - -)
7	10[e]	**3g**	61 (98)	76 (35)

[a] All reactions were carried out with 3 mol % of salt-free catalyst **2e** at 40−45 °C. [b] Isolated yields after flash column purification. [c] Determined by HPLC analysis on Chiralpak AD or AS or Chiralcel OD column. [d] The numbers in parentheses correspond to the most selective results reported in refs 8b and 11. [e] Carried out in toluene.

of the coupling products by 25−41% was attained when catalyst **2e** was employed.

Among three substrate classes examined, poorer asymmetric inductions were observed in the couplings of 6-substituted-2-naphthols (42−64% ee, entries 2−4), where the electron-withdrawing 6-Br case led to the least enantioselectivity (42% ee).[14] So far, more promising enantioselective substrates for the couplings were 7-methoxy- and 7-benzyloxy-2-naphthol. BINOL-**3e** and -**3f** were furnished in 85% and 87% ee, respectively, and in essentially quantitative yields in 8 days (entries 5 and 6). In comparison with Gong's results, BINOL-**3e** provided by our catalytic system (85% ee) exhibits lower enantioselectivity by 13%, although with slightly higher chemical yield (by 11%, entry 5).

In comparison, the coupling reactions of 3-substituted-2-naphthols were either far less enantioselective (e.g., ca. 10% ee for $R^1 = CH_2OAc$ and OCH_2Ph) or inactive (e.g., $R^1 =$ Br, CO_2R). The only example with a satisfactory level of enantioselectivity is 3-(1-hydroxy-1,1-diphenylmethyl)-2-naphthol. After 10 days of reaction in toluene, its coupling product **3g** was obtained in 76% ee with 61% yield. Notably, the X-ray crystallographic analysis of this potentially useful new chiral auxiliary **3g** shows delicate topological C_2 symmetry around the four phenyl units.[12]

In conclusion, we have presented a new catalytic asymmetric oxidative coupling protocol for 2-naphthols by chiral vanadyl dicarboxylates. When combined with vanadyl sulfate, they can be readily prepared from ketopinic acid and α-amino acids. The couplings proceed smoothly at 40−45

(14) As a detour to solve this problem, **3b** may also be prepared directly from **3a** by double bromination: Castro, P. P.; Diederich, F. *Tetrahedron Lett.* **1991**, *32*, 6277.

°C under O_2 with 3 mol % of catalyst loading, leading to various BINOLs with good to high enantioselectivities of up to 87%. To our knowledge, Gong's and our new catalytic systems represent one of the best enantioselective couplings of 2-naphthols to date and complement the systems developed by Nakajima and Kozlowski.[7] In addition, the conceptually new catalytic system of the stable, chiral β-keto acid based vanadyl dicarboxylates might open a new entry to search for better catalysts in order to achieve even higher levels of asymmetric oxidative couplings of 2-naphthols, as well as other domains of asymmetric catalysis. The ready availability for either antipodes of ketopinic acid and α-amino acids, as well as easy catalyst preparation and product purification, augur well for their potential applications in organic synthesis and practical uses.

Acknowledgment. We are grateful to the National Science Council of the Republic of China for a generous support of this research.

Supporting Information Available: Optimal procedures for the preparation of catalyst **2e** and for its mediated coupling of 2-naphthol and full spectroscopic characterization of **3a**−**g** in PDF format; X-ray data for **3g** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026156G