ORGANIC LETTERS

2008
Vol. 10, No. 15
3303−3306

Enantioselective Synthesis of 3,3-Disubstituted Oxindoles through Pd-Catalyzed Cyanoamidation

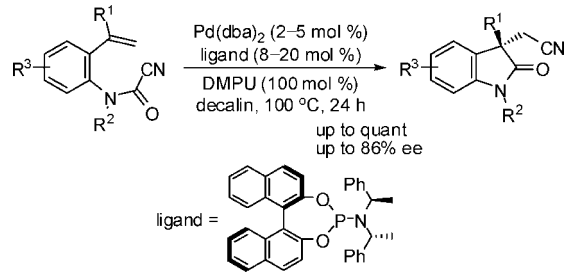
Yoshizumi Yasui, Haruhi Kamisaki, and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

takemoto@pharm.kyoto-u.ac.jp

Received May 22, 2008

ABSTRACT



The first enantioselective cyanoamidation of olefins provides quick access to a variety of 3,3-disubstituted oxindoles. The combination of $Pd(dba)_2$, an optically active phosphoramidite, and *N*,*N*-dimethylpropylene urea (DMPU) in decalin were found to be the best conditions.

Developing convenient synthetic methods for 3,3-disubstituted oxindoles may contribute to biological and pharmacological studies due to their frequent occurrence as substructures or synthetic intermediates of biologically active molecules.[1] Recent efforts have been focused on enantioselective construction of oxindoles which have a quaternary stereocenter at the 3-position.[2–9] Reported methods can be categorized in three groups according to the synthetic strategies (Figure 1). Retrosynthetic disconnection at position **a** corresponds to the enantioselective Heck reaction pioneered by Overman[2] and the domino Heck/cyanation reaction which was published recently by Zhu.[3] The same disconnection provides arylation reactions reported by Hartwig and others.[4,5] Disconnection at **b** meets O-to-C acyl migration,[6] allylic alkylation,[7] and cycloaddition[8] strategies.[9] Motivated by our interest in transition-metal-catalyzed reactions of formamide derivatives,[10–12] we planned to develop an

(1) For a review, see: (a) Galliford, C. V.; Sheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. For recent examples, see: (b) Kolackowski, M.; Nowak, M.; Pawlowski, M.; Bojarski, A. J. *J. Med. Chem.* **2006**, *49*, 6732. (c) Kato, H.; Yoshida, T.; Tokue, T.; Nojiri, Y.; Hirota, H.; Ohta, T.; Williams, R. M.; Tsukamoto, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 2254. (d) Uddin, M. K.; Reignier, S. G.; Coulter, T.; Montalbetti, C.; Grånäs, C.; Butcher, S.; Krog-Jensen, C.; Felding, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2854. (e) Stevens, F. C.; Bloomquist, W. E.; Borel, A. G.; Cohen, M. L.; Droste, C. A.; Heiman, M. L.; Kriauciunas, A.; Shall, D. J.; Tinsley, F. C.; Jesudason, C. D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6270.

(2) (a) Dounay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M *J. Am. Chem. Soc.* **2003**, *125*, 6261. For recent studies, see: (b) McDermott, M. C.; Stephenson, G. R.; Walkington, A. J *Synlett* **2007**, 51, and references cited therein.

(3) Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. *Chem. Eur. J.* **2007**, *13*, 961.

(4) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402.

(5) Kündig, E. P.; Seidel, T. M.; Jia, Y.-x.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8484.

(6) (a) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921. (b) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368.

(7) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590.

(8) Trost, B. M.; Cramer, N.; Bernsmann, H. *J. Am.Chem. Soc.* **2007**, *129*, 3086.

(9) Lipase-catalyzed desymmetrization of 3,3-bis(hydroxymethyl)oxindole has also been reported; see: Akai, S.; Tsujino, T.; Akiyama, E.; Tanimoto, K.; Naka, T.; Kita, Y. *J. Org. Chem.* **2004**, *69*, 2478.

(10) For addition of cyanoformamides to alkynes and alkenes, see: (a) Kobayashi, Y.; Kamisaki, H.; Yanada, R.; Takemoto, Y. *Org. Lett.* **2006**, *8*, 2711. (b) Kobayashi, Y.; Kamisaki, H.; Takeda, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *Tetrahedron* **2007**, *63*, 2978.

(11) For amide synthesis through coupling of chloroformamides and alkylboranes, see: Yasui, Y.; Tsuchida, S.; Miyabe, H.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 5898.

10.1021/ol801168j CCC: $40.75
Published on Web 06/27/2008

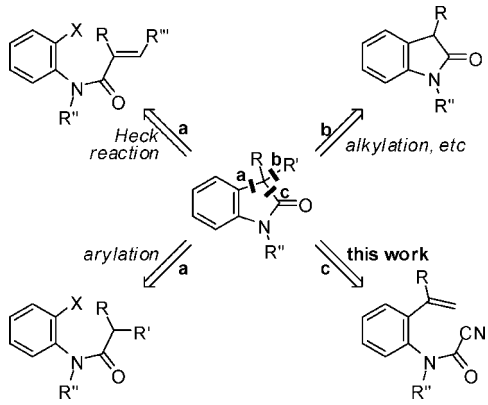


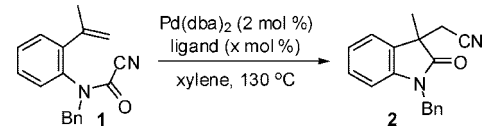
Figure 1. Strategies for enantioselective synthesis of 3,3-disubstituted oxindoles.

enantioselective intramolecular cyanoamidation of alkenyl cyanoformamides, which allows disconnection at position **c**. Our strategy will have several advantages over existing methods: (i) avoiding the use of halogens or their equivalents (vs disconnection **a**), (ii) realizing simultaneous formation of the lactam ring and a quaternary stereocenter (vs disconnection **b**), (iii) allowing use of neutral reaction conditions, and (iv) exploring the less studied utility of cyanoformamides in transition-metal-catalyzed reactions.[13,14]

Cyanoamidation is an attractive transformation that allows introduction of two carbonyl equivalents to vicinal positions of C−C multiple bonds with high atom economy. We previously found that cyanoformamides add to intramolecular triple and double bonds to give a variety of functionalized lactams in the presence of a palladium catalyst.[10,15] Herein we report the first enantioselective cyanoamidation of olefins.

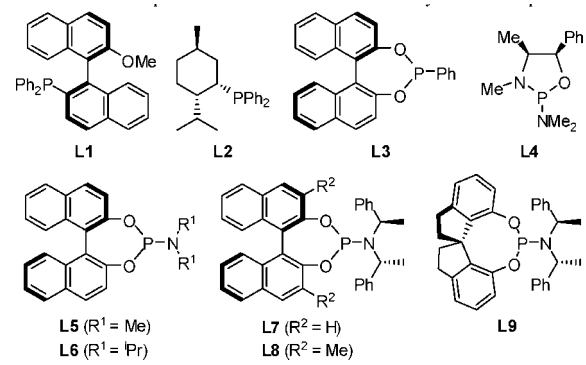
From preliminary experiments on screening achiral phosphorus ligands, it was found that monophosphorus ligands give higher conversion than bisphosphorus ligands. Based on this observation, we started this project by exploring optically active monophosphorus ligands. Therefore, cyanoformamide **1** was treated with $Pd(dba)_2$ (2 mol %) and ligands (4−8 mol %) in xylene at 130 °C (Table 1).[16] When 4 mol % of MeO-MOP (**L1**)[17] was used, the reaction finished

Table 1. Studies of Optically Active Ligands



entry	ligand (mol %)	time (h)	yield (%)[a]		ee (%)	config
1	**L1** (4)	0.25	quant		9	(*R*)
2	**L2** (4)	0.5	98		7	(*R*)
3	**L3** (4)	24	26	(70)	0	
4	**L4** (4)	24	4	(87)	0	
5	**L5** (4)	24	80	(16)	16	(*S*)
6	**L6** (8)	24	65	(28)	46	(*S*)
7	**L7** (4)	26	60	(32)	64	(*S*)
8	**L7** (8)	6	96		69	(*S*)
9	**L8** (8)	0.5	quant		16	(*S*)
10	**L9** (8)	0.5	97		44	(*S*)

[a] The values in parentheses shows the recovered yield of compound **1**.



in 15 min to give oxindole **2** quantitatively, but the enantioselectivity was poor (9% ee) (entry 1). NMDPP (**L2**)[18] showed a similar result (entry 2). Taking advantage of simple preparation, derivatives of phosphonic acids and phosphinic acids were tested.[19] Phosphonite **L3**[20] and phosphonic diamide **L4**[21] promoted the reaction only slightly and did not show any stereoselectivity (entries 3 and 4). However, when the reaction was performed in the presence of phosphoramidite **L5**,[22] oxindole (*S*)-**2** was obtained in 80% yield and 16% ee (entry 5). Based on this result, we started to examine the effect of substituents on phosphoramidites. Change of the dimethylamino group to a diisopropylamino group improved the selectivity to 46% ee (entry 6).[23] Moreover, use of bis[(*R*)-1-phenylethyl]amine derivative

(12) For rhodium-catalyzed hydroamidation, see: Kobayashi, Y.; Kamisaki, H.; Yanada, K.; Yanada, R.; Takemoto, Y. *Tetrahedron Lett.* **2005**, *46*, 7549.

(13) No report exists for transition-metal-catalyzed reaction of cyanoformamides except ref 10.

(14) For general reactivity of cyanoformamides, see: (a) Oku, A.; Inoue, J.; Ueda, H.; Mashio, F *Bull. Chem. Soc. Jpn.* **1977**, *50*, 549, and references cited therein. (b) Ford, R. E.; Knowles, P.; Lunt, E.; Marshall, S. M.; Penrose, A. J.; Ramsden, C. A.; Summers, A. J. H.; Walker, J. L.; Wright, D. E. *J. Med. Chem.* **1986**, *29*, 538.

(15) Related transition-metal-catalyzed insertion reactions has been reported. Carbocyanation: (a) Nakao, Y.; Hirata, Y.; Tanaka, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 385, and references cited therein. Cyanoesterification: (b) Nakao, Y.; Hirata, Y.; Hiyama, T. *J. Am. Chem. Soc.* **2006**, *128*, 7420. (c) Nishihara, Y.; Inoue, Y.; Izawa, S.; Miyasaka, M.; Tanemura, K.; Nakajima, K.; Takagi, K *Tetrahedron* **2006**, *62*, 9872. Bis(alkoxycarbonylation): (d) Liang, B.; Liu, J.; Gao, Y.-X.; Wongkhan, K.; Shu, D.-X.; Lan, Y.; Li, A.; Batsanov, A. S.; Howard, J. A. H.; Marder, T. B.; Chen, J.-H.; Yang, Z *Organometallics* **2007**, *26*, 4756, and references cited therein. (e) Aratani, T.; Tahara, K.; Takeuchi, S.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2007**, *36*, 1328.

(16) Cyanoformamides were synthesized from corresponding anilines. See the Supporting Information for details.

(17) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354.

(18) Morrison, J. D.; Burnett, R. E.; Agular, A. M.; Morrow, C. J.; Phillips, C. *J. Am. Chem. Soc.* **1971**, *93*, 1301.

(19) For a review of using phosphonic acid and phosphinic acid derivatives as a ligand for transition metal-catalyzed reactions, see: Ansell, J.; Wills, M. *Chem. Soc. Rev.* **2002**, *31*, 259.

(20) Tani, K.; Yamagata, T.; Nagata, K. *Acta Crystallogr.* **1994**, *C50*, 1274.

(21) Alexakis, A.; Mutti, S.; Normant, J. F. *J. Am. Chem. Soc.* **1991**, *113*, 6332.

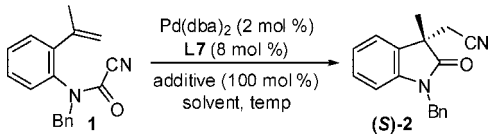
(22) Hulst, R.; de Vries, N. K.; Feringa, B. L. *Tetrahedron: Asymmetry* **1994**, *5*, 699.

(23) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **1996**, *35*, 2374.

L7[24] led to 60% yield and 64% ee (entry 7). Finally, by increasing the amount of **L7** from 4 mol % to 8 mol %, 96% yield and 69% ee was achieved (entry 8). Reactions in the presence of **L8** and **L9** provided higher yields but lower selectivities (entries 9 and 10).

The effect of solvent and additives was examined for the reaction catalyzed by $Pd(dba)_2$ (2 mol %) and **L7** (8 mol %) (Table 2). When *N*-methyl-2-pyrrolidone (NMP) was used as solvent, to our surprise, the reaction was complete in 15 min at 130 °C, but the selectivity dropped to 56% ee (entry 2). On the other hand, the reaction in decalin provided poor conversion but higher selectivity (entry 3). Therefore, we planned to add polar additives such as NMP to the reaction in decalin. When 100 mol % of NMP was added, oxindole (*S*)-**2** was obtained quantitatively and the selectivity reached 78% ee. It was possible to reduce the reaction temperature to 100 °C when polar additives were present. At the end, the best conditions were determined to be the addition of *N*,*N*-dimethylpropylene urea (DMPU) in decalin at 100 °C, which gave quantitative yield and 81% ee (entry 6).

Table 2. Effect of Solvent and Additive

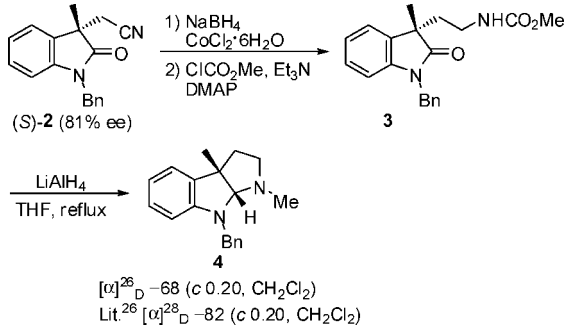


entry	solvent	additive	*T* (°C)	time (h)	yield[a] (%)	ee (%)
1	xylene		130	6	96	69
2	NMP		130	0.25	97	56
3	decalin		130	24	83 (10)	74
4	decalin	NMP	130	7	quant	78
5	decalin	NMP	100	24	85 (15)	80
6	decalin	DMPU	100	24	quant	81

[a] The values in parentheses show the recovered yield of compound **1**.

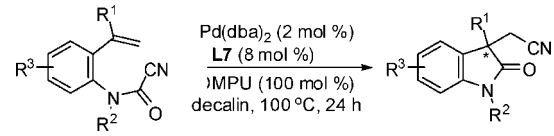
The absolute configuration of the major enantiomer of oxindole **2** obtained from the reaction using **L7** was determined by converting **2** to known pyrroloindole **4** (Scheme 1). Selective reduction of the cyano group[25] followed by methoxycarbonylation and reductive cyclization gave pyrroloindole **4**. Comparison of the optical rotation of **4** with that reported in the literature showed that oxindole **2** has the *S*-configuration.[26]

Scheme 1. Determination of Absolute Configuration



A variety of 3,3-disubstituted oxindoles were synthesized through enantioselective cyanoamidation (Table 3). *N*-Methylcyanoformamide **5** underwent cyclization in 88% yield and 75% ee (entry 1). The substituent on the vinyl group can accommodate a simple alkyl group as well as a

Table 3. Enantioselective Intramolecular Cyanoamidation



entry	substrate	product	yield[a]/ee (%)
1	**5**	**6**	88/75
2	**7**	**8**	quant./72
3	**9**	**10**	72/68
4	**11**	**12**	94/74
5	**13**	**14**	quant./82
6	**15**	**16**	43(46)/78
7[b]			94/78
8[b]	**17**	**18**	91/82
9[c]	**19**	**20**	44(53)/86

[a] The values in parentheses show the recovered yield of starting materials. [b] $Pd(dba)_2$ (5 mol %) and **L7** (20 mol %) were used. [c] $Pd(dba)_2$ (5 mol %) and **L7** (10 mol %) were used.

(24) Badalassi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Arnold, A.; Feringa, B. L. *Tetrahedron Lett.* **1998**, *39*, 7795.

(25) (a) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, 4555. (b) Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 6801.

(26) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043.

siloxymethyl group (entries 2 and 3). Especially, resulting oxindole **10**, which has distinct functional groups on both side chains, seems to be a promising synthetic intermediate for more complicated derivatives. The reaction has high tolerance toward substitutions on the aromatic ring. Cyanoformamides which have a methyl or chloro substituent on the aromatic ring gave the corresponding lactams in high yield and good selectivity (entries 4 and 5). A strange behavior was observed when methoxy-substituted cyanoformamide **15** was subjected to the reaction. Using 2 mol % of $Pd(dba)_2$ and 8 mol % of **L7** led to incomplete reaction after 24 h (entry 6). However, by increasing the palladium catalyst to 5 mol % and the ligand to 20 mol %, the desired oxindole **16** was obtained in 94% and 78% ee (entry 7). Dimethoxy derivative **17** also required an increased amount of catalyst, but the reaction proceeded smoothly (entry 8). Unfortunately, cyclization of cyanoformamide **19** which has a methyl substituent ortho to the propenyl group did not go to completion, even with high catalyst loading (entry 9).

Though there is not much information for the reaction mechanism, we believe that the reaction proceeds through oxidative addition of the CO−CN bond to palladium(0), followed by amidopalladation and reductive elimination (Figure 2).[27] We propose that the oxidative addition into the CO−CN bond forms intermediate **C** prior to the insertion. Other pathways through five coordinated complex **E** or cationic complex **F**, which are frequently proposed in enantioselective Heck reactions,[28] are unlikely since the reaction was catalyzed effectively by large unidentate ligands and not by bidentate ligands.

In conclusion, the synthesis of 3,3-disubstituted oxindoles through enantioselective cyanoamidation has been developed. A suitable combination of optically active ligand and Lewis basic additives enables excellent yield and good to high enantioselectivity. Broad substrate scope and neutral reaction conditions may meet further applications in pharmacological and biological studies.

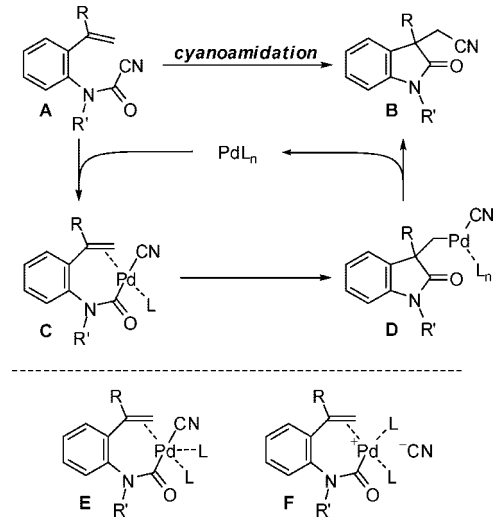


Figure 2. Plausible mechanism for cyanoamidation.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research (B) (Y.T.) and for Young Scientists (Start-up) (Y.Y.), Scientific Research on Priority Areas: Creation of Biologically Functional Molecules, and "Targeted Proteins Research Program" from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and 21st Century COE Program "Knowledge Information Infrastructure for Genome Science".

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

OL801168J

(27) The corresponding pathway through cyanopalladation was excluded through previous studies; see ref 10b.

(28) For similar discussion on enantioselective Heck reaction, see: Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.