ORGANIC LETTERS

1999
Vol. 1, No. 9
1487−1489

Palladium-Catalyzed Enantioselective Carbonylative Cyclization of Aryl and Alkenyl Triflates with Carbon Monoxide

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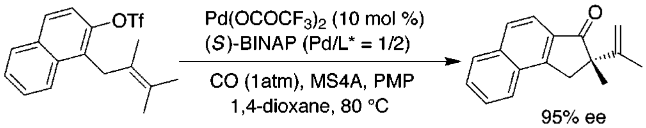
Received September 14, 1999

ABSTRACT



A catalyst system based on $Pd(OCOCF_3)_2$/(*S*)-binap has been established to effect asymmetric carbonylative cyclization of prochiral *o*-allylaryl triflates and 2-allylalkenyl triflates with carbon monoxide to produce high yields of enantiomerically enriched cyclopentenones (up to 96% ee).

Carbon monoxide has been efficiently incorporated into the synthesis of various carbonyl compounds under catalysis by transition metal complexes.[1] Over the past several years, palladium-catalyzed carbonylative cyclization with carbon monoxide has been systematically studied by Negishi and others and the carbonylative cyclization has been recognized to be a general method for the construction of cyclic ketones.[2] However, to our knowledge, few examples[3] demonstrated the application of this useful reaction to asymmetric synthesis using chiral transition metal catalysts, though asymmetric hydroformylation, hydrocarboxylation, hydroesterification, and copolymerization with prochiral olefins have been actively investigated.[4] In this Letter, we wish to report the first successful example of catalytic asymmetric carbonylative cyclization with carbon monoxide where high enantioselectivity (up to 96% ee) is attained by a fine-tuning of the catalyst systems and reaction conditions.

As a standard substrate, 1-(2,3-dimethyl-2-butenyl)-2-naphthyl triflate (**1a**) was chosen because it is readily accessible by palladium-catalyzed addition of 2-naphthol to 2,3-dimethylbutadiene[5] followed by functional group conversion from hydroxy to triflate, and this type of aryl triflate containing the tetrasubstituted double bond should retain a stereogenic carbon center after β-hydrogen elimination (Scheme 1). Negishi reported[2c] several reaction conditions for the achiral version of the carbonylative cyclization of *o*-iodoallylbenzene, typically, $PdCl_2(PPh_3)_2$, Et_3N, and 1 atm of CO, in DMF. Under the modified reaction conditions for the asymmetric reaction where $PdCl_2(PPh_3)_2$ was replaced by (*S*)-binap[6] and $Pd(OAc)_2$, the carbonylative cyclization of **1a** took place at 100 °C to give indanone derivative **2a** in 60% yield, but its enantiomeric purity was not high enough

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[1] For a review, see: Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation: Direct Synthesis of Carbonyl Compounds*; Plenum: New York, 1991.

[2] (a) Negishi, E.; Miller, J. A. *J. Am. Chem. Soc.* **1983**, *105*, 6761. (b) Tour, J. M.; Negishi, E. *J. Am. Chem. Soc.* **1985**, *107*, 8289. (c) Negishi, E.; Copéret, C.; Ma, S.; Mita, T.; Sugihara, T.; Tour, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 5904. (d) Negishi, E.; Ma, S.; Amanfu, J.; Copéret, C.; Miller, J. A.; Tour, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 5919. (e) Copéret, C.; Ma, S.; Negishi, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2125. (f) Wu, G.; Shimoyama, I.; Negishi, E. *J. Org. Chem.* **1991**, *56*, 6506. (g) Torii, S.; Okumoto, H.; Xu, L.-H. *Tetrahedron Lett.* **1990**, *31*, 7175. (h) Grigg, R.; Pratt, R. *Tetrahedron Lett.* **1997**, *38*, 4489.

[3] Asymmetric catalytic cyclocarbonylation via a hydrido-palladium intermediate: (a) Yu, W.-Y.; Bensimon, C.; Alper, H. *Chem. Eur. J.* **1997**, *3*, 417. (b) Okuro, K.; Kai, H.; Alper, H. *Tetrahedron: Asymmetry* **1997**, *8*, 2307.

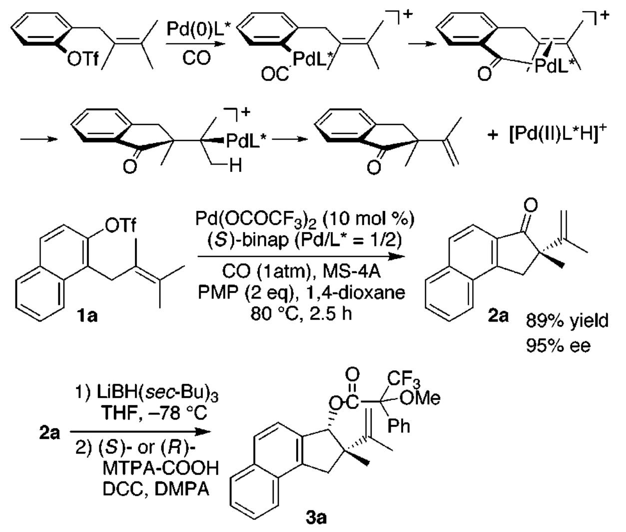
[4] Consiglio, G. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. For details, see the following. Hydroformylation: (a) Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033. (b) Sperrle, M.; Consiglio, G. *J. Am. Chem. Soc.* **1995**, *117*, 12130. Alternating carbonylative copolymerization: (c) Nozaki, K.; Sato, N. Takaya, H. *J. Am. Chem. Soc.* **1995**, *117*, 9911.

[5] Tada, Y.; Satake, A.; Shimizu, I.; Yamamoto, A. Annual Meeting of the Chemical Society of Japan, 1997, 4 F1 40.

[6] Takaya, H.; Mashima, S.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

10.1021/ol9902879 CCC: \$18.00

Scheme 1



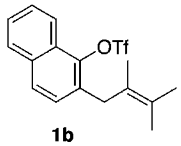
(60% ee). The asymmetric carbonylative cyclization contains many factors that can be adjusted to improve the reaction, including solvent, chiral ligand, palladium precursor, the ratio of palladium/ligand, amine, CO pressure, reaction temperature, and so on. Some of the results obtained for the reaction of **1a** under various conditions are summarized in Table 1, which contains the following significant features. (1) A bisphosphine ligand, binap or tol-binap,[6] is the chiral ligand of choice for the present asymmetric reaction. The yield of **2a** or the enantioselectivity was much lower with other ligands (entries 1−5). (2) Solvent plays an important role in enantioselectivity (entries 1 and 6−9). The enantioselectivity was higher in dioxane or benzene than in DMF, DMSO, or MeCN. (3) Chemical yields are strongly dependent on the palladium catalyst precursors (entries 10−14), the highest yield being obtained with Pd(OCOCF$_3$)$_2$. (4) Addition of MS-4A improves the chemical yield of **2a**, which prevents the formation of detriflated starting material (1-(2,3-dimethyl-2-butenyl)naphthalene) (entries 1 and 12−14). Investigations on other factors including the temperature,[7] amines,[8] the ratio of palladium/ligands,[9] and CO pressure[10] were also carried out. The best results were obtained in the reaction catalyzed by a palladium complex generated from Pd(OCOCF$_3$)$_2$ and (*S*)-binap (ligand/Pd = 2/1) in dioxane or in benzene. In the presence of 10 mol % of the palladium catalyst, 1,2,2,6,6-pentamethylpiperidine (PMP; 2 equiv to **1a**), and MS-4A (50 mg to 0.2 mmol substrate), the reaction under 1 atm of CO at 80 °C for 2.5 h gave an 89% yield of (+)-**2a** which is 95% enantiomerically pure (entry 13). The absolute configuration of **2a** was assigned to be (+)-*S* by NMR studies of the MTPA ester **3a**,[11] which was obtained through diastereoselective reduction with LiBH(*s*-Bu)$_3$.

Table 1. Asymmetric Carbonylative Cyclization of **1a**^{a}

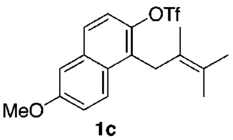
entry	solvent	ligand	Pd precursor	yield (%)^{b}	% ee^{c}
1	dioxane	(*S*)-binap	Pd(OAc)$_2$	53	93
2	dioxane	(*S*)-tol-binap	Pd(OAc)$_2$	68	96
3	dioxane	(*S*)-meo-mop	Pd(OAc)$_2$	0	
4	dioxane	(*S*,*S*)-chiraphos	Pd(OAc)$_2$	0	
5	dioxane	(*S*,*R*)-bppfa	Pd(OAc)$_2$	55	15
6	benzene	(*S*)-binap	Pd(OAc)$_2$	27	96
7	DMSO	(*S*)-binap	Pd(OAc)$_2$	68	65
8	DMF	(*S*)-binap	Pd(OAc)$_2$	60	75
9	MeCN	(*S*)-binap	Pd(OAc)$_2$	54	79
10^{d}	dioxane	(*S*)-binap	[PdCl(π-allyl)]$_2$	20	95
11^{d}	dioxane	(*S*)-binap	Pd$_2$(dba)$_3$·CHCl$_3$	22	96
12^{d}	dioxane	(*S*)-binap	Pd(OAc)$_2$	65	95
13^{d}	dioxane	(*S*)-binap	Pd(OCOCF$_3$)$_2$	89	95^{e}
14^{d,f}	dioxane	(*S*)-binap	Pd(OCOCF$_3$)$_2$	85	95

[a] The reaction was carried out with **1a** (0.2 mmol) in 1.8 mL of solvent under 1 atm of CO at 80 °C for 2.5 h. Initial conditions: Pd precursor:ligand:**1a**:PMP = 0.1:0.2:1:2. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis with a chiral stationary phase column (Daicel Chiralpak OD-H, hexane/2-propanol = 98/2). [d] In the presence of 50 mg of MS-4A. [e] $[\alpha]^{20}_{D}$ +28.3 (*c* 0.78, CHCl$_3$). [f] The reaction was performed with 5.0 mol % of catalyst for 8 h.

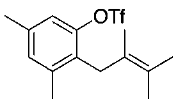
Using these optimal conditions, several aryl triflates **1b**−**1j** and alkenyl triflates **1k**−**1l** were subjected to asymmetric carbonylative cyclization. Table 2 summarizes our preliminary results of the scope of this method for synthesis of optically active cyclopentenones with a quaternary stereogenic center. It should be noted that a wide rang of aryl and alkenyl triflates are effective participants. Yields are generally



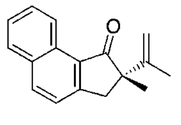
1b



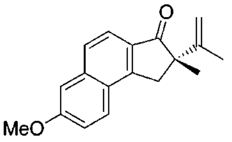
1c



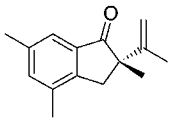
1d



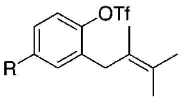
2b



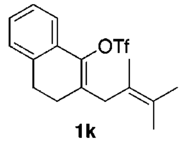
2c



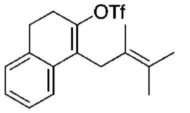
2d



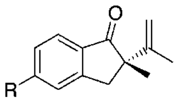
1e~1j



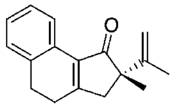
1k



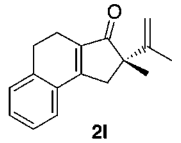
1l



2e~2j



2k



2l

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[7] The carbonylative cyclization was slower at temperatures lower than 80 °C, and the higher temperature resulted in some loss of enantioselectivity.

[8] Sterically bulky tertiary amines such as diisopropylethylamine and 1,2,2,6,6-pentamethylpiperidine (PMP) are effective for this reaction, while inorganic bases such as Cs$_2$CO$_3$ resulted in obvious loss of enantioselectivity.

[9] When the ratio of Ligand/Pd is less than 2, palladium black precipitates, resulting in a low conversion of triflate.

[10] This reaction is inhibited by high CO pressure.

[11] Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

Table 2. Palladium-Catalyzed Asymmetric Carbonylative Cyclization of Aryl and Alkenyl Triflates[a]

entry	substrate	product	yield (%)[b,c]	% ee[c,d]	$[\alpha]^{20}_{D}$ (c in $CHCl_3$)[c]
1	**1b**	**2b**	82	93	−3.2 (0.65)
2	**1c**	**2c**	94	96	+27.3 (1.38)
3	**1d**	**2d**	90	93	+6.9 (0.96)
4	**1e** (R = OMe)	**2e**	85 (85)	87 (91)	(+28.5 (0.79))
5	**1f** (R = Cl)	**2f**	93 (90)	85 (90)	(+24.0 (0.89))
6	**1g** (R = Me)	**2g**	90 (86)	78 (87)	(+27.6 (0.50))
7	**1h** (R = CO_2Me)	**2h**	75 (75)	77 (88)	(+31.7 (0.36))
8	**1i** (R = CN)	**2i**	73 (82)	79 (88)	(+38.3 (0.41))
9	**1j** (R = H)	**2j**	90 (87)	72 (79)	(+23.9 (0.93))
10	**1k**	**2k**	62 (64)	56 (75)	(+18.1 (0.56))
11	**1l**	**2l**	55 (65)	32 (78)	(−14.7 (1.94))

[a] The reaction was carried out with 0.2 mmol of substrate in 1.8 mL of dioxane in the presence of MS-4A (50 mg) under 1 atm of CO at 80 °C for 4 h. Initial conditions: $Pd(OCOCF_3)_2$:(*S*)-binap:triflate:PMP = 0.1:0.2:1:2. [b] Isolated yield by silica gel chromatography. [c] The data in parentheses were obtained by carrying out the same reaction with (*S*)-tol-binap in benzene for 8 h (entries 4−9) or 4 h (entries 10 and 11). Initial conditions: $Pd(OCOCF_3)_2$:(*S*)-tol-binap:triflate:PMP = 0.1:0.2:1:2. [d] Determined by HPLC analysis with chiral stationary phase columns (Diacel Chiralpak OD-H for **2b** and **2k**; AS+AS for **2c**−**j**; OJ for **2l**; hexane/2-propanol = 98/2).

high and in all cases with moderate to high enantioselectivities. Interestingly, introduction of substituents onto the para position of the phenyl ring in 2-(2,3-dimethyl-2-butenyl)phenyl triflate (**1j**) led to an increase in the enantioselectivity regardless of their electron-withdrawing or electron-donating characteristics (entries 4−9). The efficiency of this carbonylative cyclization was significantly improved by use of the (*S*)-tol-binap/benzene system instead of the (*S*)-binap/dioxane system (entries 4−9), especially for alkenyl triflates (entries 10 and 11).[12]

In summary, we have demonstrated, for the first time, that the catalytic asymmetric carbonylative cyclization which proceeds with high enantioselectivity is realized by the proper choice of reaction conditions.

Acknowledgment. This work was supported by the Research for the Future program, the Japan Society for the Promotion of Science, and a Grant-in-Aid for Scientific Research from the Ministry of Education, Japan.

Supporting Information Available: Experimental procedures, details in studies of reaction conditions, and spectroscopic and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For alkenyl triflates, the (*S*)-binap/dioxane system gave a considerable amount of 6-*endo* cyclization product. With the (*S*)-tol-binap/benzene system, the 6-*endo* cyclization was retarded to some extent, and the enantioselectivity was obviously improved.