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Palladium-Catalyzed Enantioselective Cyclization of Silyloxy-1,6-Enynes

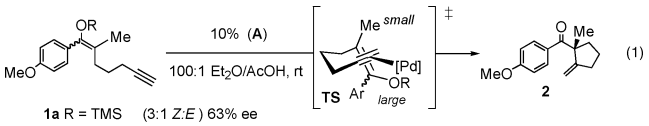
Britton K. Corkey and F. Dean Toste*

Department of Chemistry, University of California, Berkeley, California 94720

Received December 5, 2006; E-mail: fdtoste@berkeley.edu

Transition-metal-catalyzed cycloisomerization and cyclization reactions of enynes have emerged as powerful methods for the construction of hetero- and carbocyclic compounds.[1] More recently, enantioselective cycloisomerization of 1,6- and 1,7-enynes has been employed in the preparation of enantioenriched 1,4-diene containing structures.[2−4] Despite its potential utility, the related enantioselective cycloisomerization of heteroatom-substituted alkenes[5] has not been reported. Herein we report the first enantioselective cyclization reactions of 1,6-enynes containing silyloxy-substituted olefins.

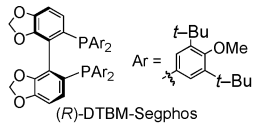
On the basis of our recent report on palladium-catalyzed enantioselective 5-exo-dig addition of 1,3-dicarbonyl compounds to alkynes,[6] we hypothesized that similar catalysts might promote the enantioselective cycloisomerization of silyl enol ethers. To this end, reaction of silyl enol ethers **1a** (3:1 *Z*:*E*) and **1b** (2:1 *Z*:*E*) catalyzed by 10 mol % of ((*R*)-DTBM-Segphos)Pd(OTf)$_2$ (**A**) cleanly afforded methylene cyclopentane **2** in 63 and 77% ee, respectively (eq 1). Furthermore, diastereomerically pure (*E*)-**1b** afforded **2** with greater enantioselectivity (81% ee) than the corresponding (*Z*)-isomer (74% ee). The enantioselectivity was further improved to 91% ee by employing *tert*-butyldimethylsilyl enol ether (*E*)-**1c**.



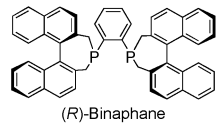
1a R = TMS (3:1 *Z*:*E*) 63% ee
b R = TES (2:1 *Z*:*E*) 77% ee; (*Z*) 74% ee; (*E*) 81% ee
c R = TBS (*Z*) 78% ee; (*E*) 91% ee
d R = TIPS (*Z*) 82% ee; (*E*) 74% ee

The fact that the silyloxy substituent and the olefin geometry impact the enantioselectivity of the reaction (eq 1) suggests that the silyl enol ether is intact during the enantiodetermining event. We envisioned two potential mechanisms consistent with this observation: (1) enantioselective addition of the enol ether to the electrophilic Pd complex and the resulting C-bonded Pd enolate[7] undergoes stereospecific[8] insertion into the pendent acetylene or (2) addition of the enol ether onto a Pd(II) activated alkyne.[9,10] Given the ease with which Pd enolates undergo protonation,[11] the observation that very little hydrolysis of the enol ether occurs during the cyclization reaction suggests these intermediates are not involved in this reaction.[12,13] Therefore, we propose that the latter mechanism is operative in the Pd-catalyzed cyclization. Additionally, the proposed transition state (**TS**)[14] for this pathway accounts for the observation that (*E*)-**1d**, in which the aryl group is placed under the forming five-membered ring in **TS**, reacted significantly slower than (*Z*)-**1d**.[15] Moreover, in **TS**, the olefin substituents are larger than the alkyl group regardless of the olefin geometry; therefore, the same enantiomer is obtained from either olefin isomer.

Initial investigation of the reaction scope indicated that *tert*-butyldimethylsilyl enol ethers derived from aryl ketones underwent efficient cyclization giving methylene cyclopentane adducts with good to excellent enantioselectivities (Table 1, entries 1−4). Notably, the potentially enolizable tertiary stereocenter in **4** was formed with good enantioselectivity (entry 2).



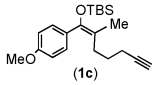
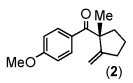
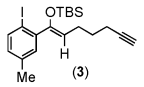
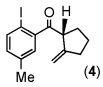
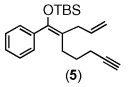
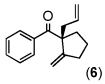
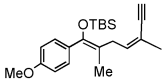
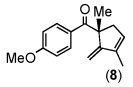
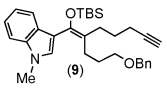
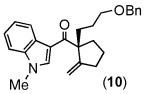
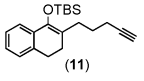
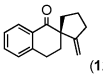
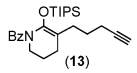
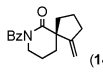
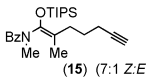
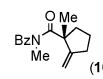
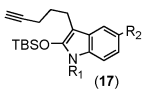
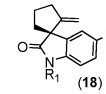
((*R*)-DTBM-Segphos)Pd(OTf$_2$) **A**



((*R*)-Binaphane)Pd(OH$_2$)$_2$(OTf$_2$) **B**

While the use of ((*R*)-DTBM-Segphos)Pd(OTf)$_2$ as a catalyst provided modest enantioselectivities when non-aryl-substituted enol ethers were employed, we were pleased to find that ((*R*)-Binaphane)-Pd(OH$_2$)$_2$(OTf)$_2$ (**B**)[16] is a highly active and selective catalyst for the cyclization of a greater range of substrates (Table 1, entries 5−10). For example, cyclization of indolyl enol ether **9** catalyzed by 10 mol % of **A** cleanly afforded **10** but with only 7% ee, whereas the same reaction catalyzed by 5% **B** gave ketone **10** in 89% ee (entry 5). Moreover, whereas reactions with catalyst **A** usually required 10% loading and several hours to complete, reactions catalyzed by 5% **B** generally took place in minutes. Most notably,

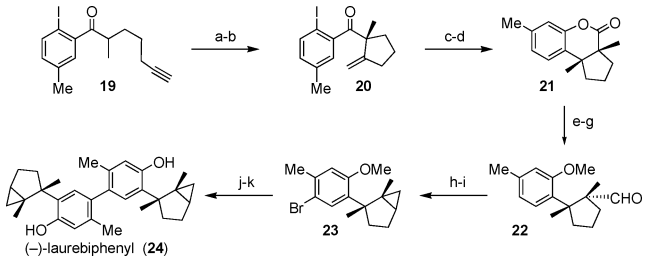
Table 1. Enantioselective Pd-Catalyzed Cyclization[a]

Entry	Substrate	Conditions, Time	Product	Yield (ee)
1	 (**1c**)	**A**, 12 h	 (**2**)	93% (91% ee)
2	 (**3**)	**A**, 6 h	 (**4**)	86% (85% ee)[b]
3	 (**5**)	**A**, 12 h	 (**6**)	92% (88% ee)
4	 (**7**)	**A**, 12 h	 (**8**)	70% (73% ee)
5	 (**9**)	**B**, 30 min	 (**10**)	83% (89% ee)[c]
6	 (**11**)	**B**, 30 min	 (**12**)	91% (87% ee)
7	 (**13**)	**B**, 20 min	 (**14**)	80% (98% ee)
8	 (**15**) (7:1 *Z*:*E*)	**B**, 2 h	 (**16**)	79% (80% ee)
9	 (**17**)	**a** R_1 =Bz, R_2 = H	**B**, 20 min	83% (91% ee)
10		**b** R_1 =Ac, R_2 = OAc	**B**, 30 min	67% (82% ee)
			 (**18**)	

[a] Conditions A: 10% **A**, rt, 0.02 M 100:1 Et$_2$O/AcOH; B: 5% **B**, rt, 0.02 M 100:1 Et$_2$O/AcOH. [b] Conditions: 10% **A**, 0 °C, 0.02 M 100:1 Et$_2$O/AcOH. [c] Conditions: 5% **B**, rt, 0.02 M 100:1 dichloromethane/AcOH as solvent. Enol ethers shown are the major isomer obtained from the corresponding ketone (see Supporting Information).

10.1021/ja068723r CCC: $37.00

Scheme 1. Total Synthesis of (−)-Laurebiphenyl[a]



[a] Reagents and conditions: (a) TEA, TBS-OTf, CH_2Cl_2, 72% *Z*, 19% *E*; (b) 10% **A**, Et_2O, HOAc, rt, 96% yield, 95% ee (91% recovered catalyst after recrystallization); (c) 10% $Pd(OAc)_2$, 22% PPh_3, HCO_2H, TEA, DMF, 80 °C, 96%; (d) $CF_3C(O)OOH$, BF_3•Et_2O, CH_2Cl_2, −10°C, 48% (59% brsm); (e) LAH, THF; (f) K_2CO_3, MeI, DMF; (g) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, 81% over three steps; (h) $TsNHNH_2$, HCl, MeOH, 73% (84% brsm); (i) NaH, *o*-dichlorobenzene, 160 °C, 2 min; then Br_2, CH_2Cl_2, 68%; (j) *t*-BuLi, 0.5 equiv of CuCN, tetramethylquinone, Et_2O, −78 °C to rt, 51%; (k) NaH, EtSH, DMF, 150 °C, 70%.

the Pd-catalyzed cyclizations to form amides **14** and **16** represent rare examples of enantioselective catalysis employing *O*-silyl ketene aminals.[17] Catalyst **B** also allows for the enantioselective preparation of spiro-stereocenters (entries 6, 7, 9, and 10). For example, reaction of 2-silyloxy indole **17a** afforded spiro-oxindole **18a** in 83% yield and 91% ee (entry 9).

The utility of the Pd-catalyzed method for enantioselective formation of all carbon quaternary centers is illustrated in the total synthesis of (−)-laurebiphenyl (**24**), a rare example of a dimeric cyclolaurane-type sesquiterpene (Scheme 1). Originally isolated from *Laurencia nidifica*, laurebiphenyl (**24**) was recently shown to possess moderate cytotoxicity against a variety of cell lines.[18] Conversion of ketone **19**[19] to the corresponding (*Z*)-enol ether in 72% yield sets the stage for the Pd-catalyzed enantioselective cyclization. Treatment of the enol ether with 10% **A** resulted in clean conversion to cyclopentane **20** in 95% ee and 96% yield. Upon completion of the reaction, the Pd catalyst can be recovered, recrystallized (91% yield), and reused without any loss of activity (see Supporting Information).

Ketone **20** was subjected to a reductive Heck cyclization followed by Baeyer−Villager oxidation to afford lactone **21**, which was converted to aldehyde **22** in three steps. Conversion of aldehyde **22** to the corresponding tosyl hydrazone, followed by diazo decomposition, gave the crude cyclopropane product, which was immediately brominated to give **23**.[20] Ullman coupling of aryl bromide **23** forged the biaryl bond, and subsequent demethylation furnished (−)-laurebiphenyl (**24**).[21]

In conclusion, the first enantioselective Pd-catalyzed addition of silyl enol ethers and silyl ketene aminals onto alkynes has been developed. The reaction provides rapid access to highly functionalized enantioenriched methylene cyclopentane adducts, as exemplified by its application to the preparation of (−)-laurebiphenyl. In a broader sense, the reactions reported herein significantly extend the scope of Pd-catalyzed enantioselective enyne cyclization reactions to include heteroatom and tetrasubstituted olefins.

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Supporting Information Available: Experimental procedures, compound characterization data (PDF), and X-ray structure data for catalyst **B** and compound **23** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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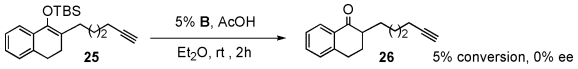
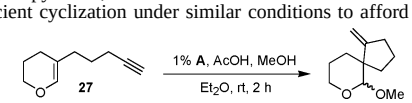
(12) In contrast to reported Pd-catalyzed enantioselective protonolysis of TMS-enol ethers,[7b] racemic ketone **26** was formed in 5% conversion from the hydrolysis of TBS-enol ether **25**.



(13) Dihydropyran **27**, from which Pd enolate formation is unlikely, undergoes efficient cyclization under similar conditions to afford spiro-bicycle **28**.



(14) This proposed transition resembles that calculated for the Pt-catalyzed cyclization of enol ether with alkynes.[5h]

(15) Pd-catalyzed reactions of (*Z*)-**1b**, **1c**, and **1d** all required 6−8 h to reach completion. In contrast, (*E*)-**1d** reached 50% conversion after 8 h.

(16) See the Supporting Information for an X-ray structure of complex **B**.

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(19) Ketone **19** was prepared in four steps from 2-iodo-5-methylbenzoic acid (see Supporting Information).

(20) The absolute stereochemistry of bromide **23** was determined by X-ray crystallography (see Supporting Information).

(21) The optical rotation of synthetic **24** ($[\alpha]_D = -14.5°$) is opposite that of the natural product ($[\alpha]_D = +15.2°$).

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