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Catalytic Enantioselective Conia-Ene Reaction

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The Michael addition of compounds containing active methylenes to a π-acceptor provides an attractive method for the stereoselective construction of all carbon quaternary centers.[1] Recently, significant progress has been made in the development of enantioselective intermolecular addition of prochiral nucleophiles to olefinic π-acceptors.[2] On the other hand, enantioselective intramolecular Michael addition of pronucleophiles is rare.[3] The related addition to the π-bond of an unactivated alkyne offers the advantage that the product contains an alkene that can be further functionalized and that the noncatalyzed reaction proceeds only at elevated temperatures; however, enantioselective α-vinylation[4] by addition to alkynes is extremely rare.[5]

We recently reported a gold(I)-catalyzed intramolecular addition of β-ketoesters to alkynes.[6] This catalyst system provided the basis for our initial studies on the development of a transition metal-catalyzed enantioselective Conia-ene reaction. To this end, treatment of β-ketoester **1** with 5% of cationic chiral gold complexes **2** or **3** resulted in the expected product **4** in good yield. Unfortunately, no enantioselectivity was observed in the product of either reaction (Table 1, entries 1−2).

We rationalized that lack of enantioselectivity derived from the poor transmission of the ligand chirality as a consequence of the linear geometry of the gold(I) complexes. We therefore examined electrophilic late metal catalysts containing bidentate chiral ligands. While chiral Cu(II), Ni(II), and Pt(II) complexes gave poor selectivity,[7−9] treatment of β-ketoester **1** with a catalytic amount of cationic BINAP−Pd(II)[2a] complex generated the Conia-ene adduct **4** in low yield and with moderate enantiomeric excess (68% ee). Examination of various cationic chiral bisphosphine−palladium(II) complexes revealed that the bis(triflate)−Pd(II) complex derived from DTBM-SEGPHOS[10] (**5**; Figure 1) produced Conia-ene product **4** in 81% ee albeit in only 18% yield (entry 3).[11]

In contrast to previous reports of palladium-catalyzed addition of β-ketoester to alkynes under basic conditions,[12] addition of an amine base completely inhibited our enantioselective Conia-ene reaction (entry 4). On the other hand, a stoichiometric amount of acid increased the yield of **4** dramatically, with no deterioration of ee (entries 5,6); however, the reaction required 72 h to reach completion. While the use of $Yb(OTf)_3$ as a cocatalyst dramatically increased the rate of consumption of **1** at the expense of yield of **4** (entry 7), the combination of a protic and Lewis acid produced the desired rate enhancement without deterioration in the yield or enantioselectivity of the palladium-catalyzed reaction (entries 8,9).[9,13] Finally, switching the solvent from methylene chloride to diethyl ether and lowering the reaction concentration to 0.02 M allowed for the preparation of **4** in 84% yield and 89% ee (entry 10).

A wide range of β-dicarbonyl compounds undergo the Pd(II)/Yb(III)-catalyzed enantioselective Conia-ene reaction (Table 2).[14] For example, replacing isopropyl ester of **1** with ethyl (**6**) or allyl esters (**8**) produced methylenecyclopentenes **7** and **9** with 89% ee and 90% ee, respectively (entries 2,3). Surprisingly, *tert*-butyl ester analogue **10** cyclized to give **11** with significantly lower enantioselectivity (entry 4). Substitution of the aromatic ring with an ortho methyl group produced an enhancement in the enantiomeric excess to 93% and 94% (entries 5 and 7); however, Pd(II)/Yb(III)-catalyzed reaction of *o*-iodoaryl ketone **14** furnished **15** with 85% ee (entry 6). While introduction of an electron donating substituent at the para position only moderately influenced the enantioselectivity of the reaction (entry 8), the presence of an electron-withdrawing para nitro group produced a notable decrease in the selectivity of the cyclization (entry 9). Larger aryl ketones, such as 1-naphthyl (**22**) and 2-naphthyl (**24**) ketones participate equally well in the enantioselective Conia-ene (entries 10, 11). On the other hand, the use of aliphatic ketone **26** afforded **27** with only 44% ee (entry 12). β-Diketone substrates **28** and **30** underwent cyclization with diminished enantioselectivity to give **29** and **31**, respectively (entries 12 and 13).

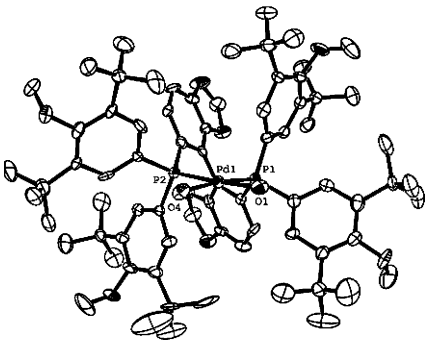
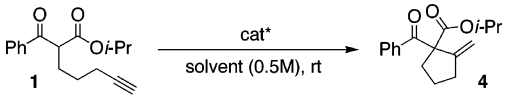
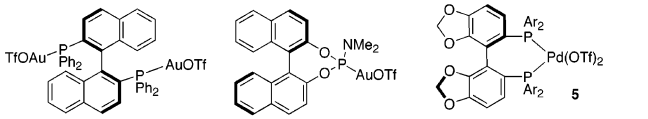


Figure 1. ORTEP of (DTBM-SEGPHOS)Pd(OTf)$_2$. Viewed down the C_2 axis of the molecule. Thermal ellipsoids shown at 50% probability. Hydrogens and triflate ligands (except Pd−O) omitted for clarity.

Table 1. Enantioselective Conia-Ene Reaction



entry	cat.	additive	solvent	time (h)	yield (%)	ee (%)
1	2	−	CH_2Cl_2	8	85	0
2	3	−	CH_2Cl_2	8	80	0
3	5	−	CH_2Cl_2	72	18	81
4	5	Et_3N (100%)	CH_2Cl_2	72	0	-
5	5	PPTS (100%)	CH_2Cl_2	72	60	81
6	5	AcOH (100%)	CH_2Cl_2	72	81	81
7	5	$Yb(OTf)_3$ (20%)	CH_2Cl_2	3	15	80
8	5	AcOH (500%), $Yb(OTf)_3$ (20%)	CH_2Cl_2	3	81	80
9	5	AcOH (500%), $Yb(OTf)_3$ (20%)	Et_2O	2	83	82
10	5	AcOH (1000%), $Yb(OTf)_3$ (20%)	Et_2O (0.02 M)	12	84	89



Ar = 3,5-di(*tert*-butyl)-4-methoxyphenyl: (*R*)-DTBM-SEGPHOS

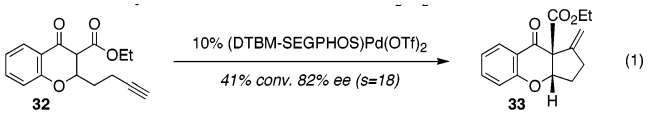
10.1021/ja055059q CCC: $30.25

Table 2. Pd(II)-Catalyzed Enantioselective Conia-ene Reaction[a]

entry	substrate	time (h)	product	yield (%)	ee (%)
1	R = *i*-Pr (**1**)	24	(**4**)	84	89
2	R = Et (**6**)	12	(**7**)	86	89
3	R = allyl (**8**)	12	(**9**)	80	90
4	R = t-Bu (**10**)	30	(**11**)	94	80
5	X = Me R = Et (**12**)	12	(**13**)	80	93
6	X = I R = Et (**14**)	12	(**15**)	95	85
7	X = Me R = allyl (**16**)	12	(**17**)	81	94
8	X = OMe (**18**)	36	(**19**)	81	86
9	X = NO_2 (**20**)	24	(**21**)	73	79
10	(**22**)	8	(**23**)	70	89
11	(**24**)	24	(**25**)	82	87
12	(**26**)	6	(**27**)	97	44
13	(**28**)	3	(**29**)	90	70[b]
14	(**30**)	12	(**31**)	79	74

[a] Reaction conditions: 10 mol % **5**, 20% $Yb(OTf)_3$, 10 equiv of AcOH, 0.02 M in diethyl ether, rt. [b] Run in 0.5 M CH_2Cl_2

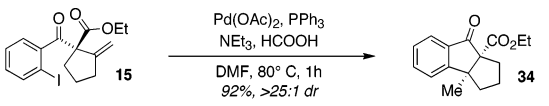
The reaction also proceeds well with cyclic ketones allowing for the enantioselective synthesis of polycycles through a kinetic resolution. For example, ketone **32** underwent palladium-catalyzed cyclization to afford **33** in 82% ee at 41% conversion ($s = 18$) (eq 1). Notably, in this case the reaction proceeded well in the absence



(1)

of $Yb(OTf)_3$. A mechanistic hypothesis involving generation of a palladium enolate[2a] of the β-dicarbonyl nucleophile that undergoes Lewis acid (or Brønsted acid in the case of eq 1)-promoted addition to the alkyne is envisioned.[15,16]

In conclusion, we have developed the first enantioselective intramolecular Conia-ene reaction of β-dicarbonyl compounds and alkynes. The Pd(II)/Yb(III) dual catalyst system allows for the asymmetric synthesis of all-carbon quaternary centers and generates a product containing an alkene that can be further manipulated. For example, Conia-ene adduct **15** was employed in an intramolecular reductive-Heck cyclization to produce tricyclic ketone **34**[17] (eq 2). Further applications of this Pd(II)/Yb(III) dual catalyst system for enantioselective synthesis will be reported in due course.



(2)

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Supporting Information Available: Experimental procedures, compound characterization data; X-ray structure data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) (PyBOX)Copper(II) triflate failed to catalyze the reaction even in the presence of a cationic gold(I) cocatalyst.[8] Both cationic BINAP−nickel-(II)[8] (<5% ee) and BINAP−platinum(II) (18% ee) complexes promoted the reaction; however, the enantioselectivity was poor.

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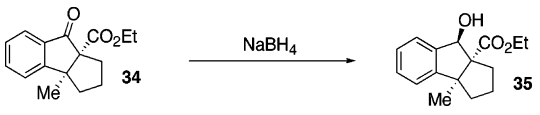
(14) The corresponding 5-*endo-dig* carbocyclization[6b] required prolonged reaction times (7 days) and gave racemic products.

(15) In accord with a mechanism involving trans addition to the alkyne, cyclization of a deutero-acetylene resulted in isolation of the adduct in which deuterium was only incorporated cis to the ketoester; however, this experiment was complicated by deuterium exchange of acetylenic proton.

(16) A mechanism involving alkyne activation by Pd(II) was excluded in isomerization of 1,6-enynes catalyzed by related cationic bis(phosphine)-palladium(II) complexes: Mikami, K.; Hatano, M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5767.

(17) The absolute stereochemistry of **34** was assigned using the mandelate method on alcohol **35** (see Supporting Information). The stereochemistry of remaining ketoesters was assigned by analogy and is consistent with the stereochemistry predicted by the Sodeoka model.[2a]



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