Palladium Catalysis

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Neutral Nazarov-Type Cyclization Catalyzed by Palladium(0)**

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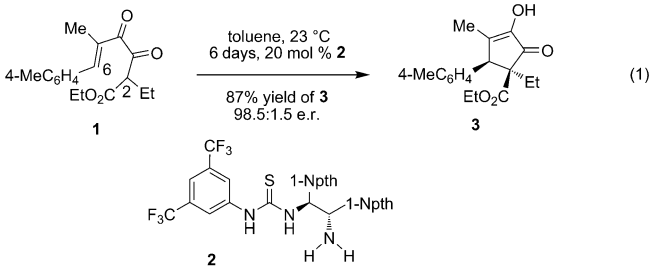
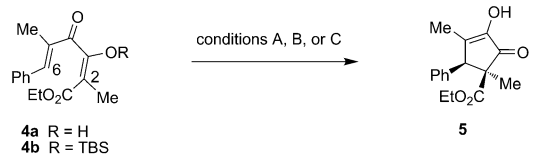
The Nazarov cyclization[1] is an attractive process for the stereocontrolled assembly of five-membered carbocycles that are a feature of many natural products.[2] The classical Nazarov reaction conditions require the use of stoichiometric or superstoichiometric amounts of strong acid that limits applications to robust and unfunctionalized substrates.[3] In recent work, Trauner and co-workers,[4] Rueping et al.,[5] and others[6] have described very mild conditions for the catalytic asymmetric Nazarov reaction. Our group developed the organocatalytic asymmetric Nazarov reaction that is shown in Equation (1).[7] Exposure of diketoester **1** to organocatalyst **2** led to cyclopentenone **3** in 87% yield and in 98.5:1.5 e.r. as a single diastereomer. The reaction was slow, most likely because of product inhibition of the catalyst, which can bind both product and starting material in a similar way through their respective keto–enol forms. The C6 aryl group in **1** was required, whereas a branched substituent at C2 was not tolerated. We sought an alternative catalytic Nazarov cyclization that would not be subject to these limitations.



1 3 2 (1)

In earlier work we described Pd^{II}-catalyzed Nazarov-type cyclizations of α-ethoxy dienones, which proceed through a palladium enolate intermediate.[8] These Pd^{II}-catalyzed cyclization reactions are initiated through an electrophilic interaction with the metal and are suppressed in the presence of basic ligands, for example, PPh_3. We postulated that silyl enol ether **4b,** which was prepared from **4a** (Scheme 1), would also undergo cyclization under Pd^{II} catalysis. The complementary polarization of carbon atoms 2 and 6 in **4a** greatly increases the reactivity, so we hoped that cyclization would not be suppressed in the presence of phosphines. This would enable the use of chiral phosphine ligands for an asymmetric catalytic cyclization. The starting materials for this study were prepared according to our published method.[7] The Nazarov product **5** was obtained in 65% or 80% yield from the treatment of **4b** with $PdCl_2$ or $Pd(OAc)_2$, respectively. However, this cyclization did not take place in the presence of $[PdCl_2(PPh_3)_2]$, thereby precluding our approach to an asymmetric catalytic process. Much to our surprise, exposure of **4a** to 20 mol% $[Pd(PPh_3)_4]$ in dichloromethane at room temperature led to Nazarov product **5** in 80% yield. This Pd^0-catalyzed reaction proceeds under strictly neutral pH conditions and is the first Nazarov-type cyclization that is catalyzed by a zero-valent metal. The success of $[Pd(PPh_3)_4]$ as a catalyst indicates a mechanism that is distinct from the Pd^{II} catalyzed reaction and suggests the possibility of asymmetric catalysis through the use of chiral phosphine ligands.



Scheme 1. Palladium-catalyzed cyclizations. Conditions: A: (**4a**) 20 mol% $[Pd(PPh_3)_4]$, 0.1 M CH_2Cl_2, room temperature, <24 h; 80% yield. B: (**4b**) 20 mol% $[PdCl_2(MeCN)_2]$, 0.1 M wet acetone, room temperature, approximately 3 d; 65% yield. C : (**4b**) 20 mol% $[Pd(OAc)_2]$, 0.1 M DMSO, room temperature, approximately 5 d; 80% yield.

First, we defined the scope of the cyclization leading to racemic products. The reaction was optimized with respect to solvent, concentration, temperature, catalyst, and catalyst load (Table 1). The cyclization was most efficient in DMF and DMSO. In the absence of added PPh_3, no reaction took place. Our initial experiments utilized a 1:4 ratio of palladium to phosphine. Decreasing the ratio to 1:2 had no effect on the yield (entries 6,7 versus 8,9). In DMSO, we were able to reduce the catalyst load to 0.5 mol% $[Pd_2(dba)_3]$ (1 mol% Pd atoms) without an appreciable decrease in the rate or yield (entry 11). For less reactive substrates that lack a C6 aryl group, the use of 2 mol% Pd atoms led to a better reaction, so we settled on the conditions that appear in entry 10 of Table 1. No reaction took place in the absence of palladium (entry 14) and only traces of product were observed in the absence of PPh_3 (entry 13).

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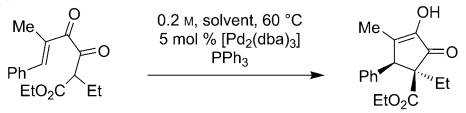
Table 1: Optimization of reaction conditions.

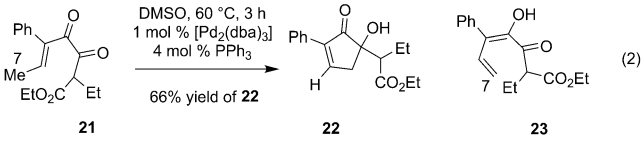


6 **7**

Entry	Solvent	Pd/P	*t* [h]	Yield [%]
1[a]	CH_2Cl_2	1:4	120	69
2	$(CH_2Cl)_2$	1:4	16	82
3	PhMe	1:4	16	85
4	THF	1:4	9	85
5	MeCN	1:4	9	86
6	DMF	1:4	7	90
7	DMSO	1:4	4	92
8	DMF	1:2	7	91
9	DMSO	1:2	4	92
10[b]	**DMSO**	**1:2**	**4.5**	**91**
11[c]	DMSO	1:2	5	91
12[a]	DMSO	1:2	40	72
13[b]	DMSO	1:0	24	trace
14	DMSO	0:1[d]	24	No rxn
15	DMSO	0:0[e]	24	No rxn

[a] 18 °C. [b] 1 mol % $[Pd_2(dba)_3]$. [c] 0.5 mol % $[Pd_2(dba)_3]$. [d] 4.0 mol % PPh_3. [e] No $[Pd_2(dba)_3]$, no PPh_3. dba = dibenzylideneacetone.

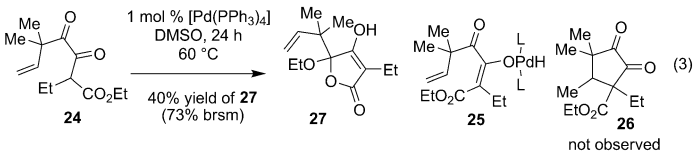
Scheme 2 summarizes the results. All products were isolated as single diastereomers in 70% to 95% yield. The formation of **8** in 82% yield is noteworthy because this product could not be prepared using the organocatalytic process, which failed for substrates bearing a branched substituent at C2.[7] The synthesis of cyclopentenones **16**–**20** in high yield demonstrates that an aryl substituent is not required for the Pd^0-catalyzed process. Cyclopentenones **16**–**20** also could not be prepared through the organocatalytic process. Diketoester **21** [Eq. (2)] led to the formation of cyclopentenone **22** as an approximately 1:1 mixture of diastereomers in 66% yield. Because **16** was formed through



21 **22** **23** (2)

the expected mode of cyclization, the presence of the C5 phenyl group must be responsible for the unexpected outcome in the case of **22**. The phenyl group may acidify the C7 methyl allowing dienol **23** to form, which can undergo ring closure to **22** either through an iso-Nazarov process or through an intramolecular aldol reaction.

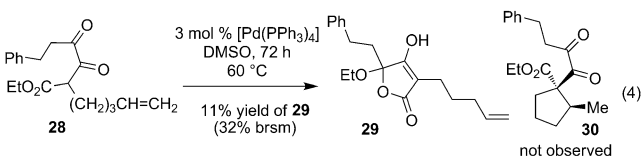
We considered that the first step of the Nazarov-type cyclization involved formation of a palladium hydride intermediate and tried to find evidence of oxidative addition of Pd^0 to the enol form of the diketoester. We first prepared diketoester **24** [Eq. (3)]. Oxidative addition of Pd^0 to the enol form of **24** might have led to **26** through hydride **25**. However, there was no evidence of the formation of **26**, even



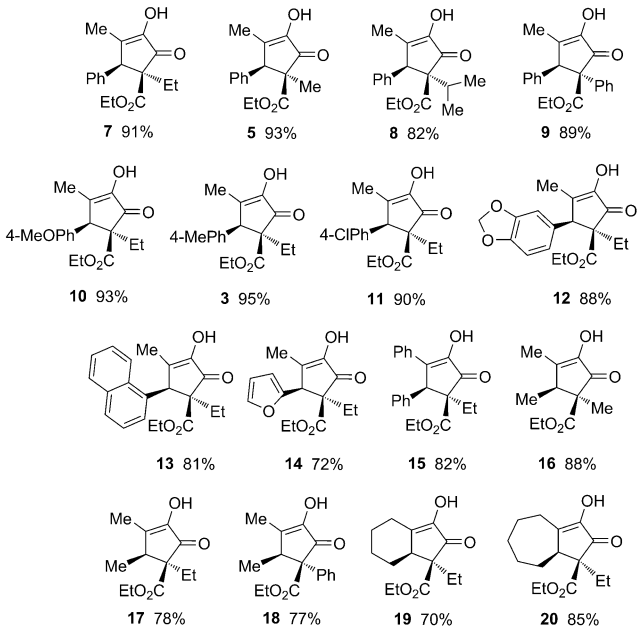
24 **27** **25** **26** (3)

after heating the solution for 24 h. Instead we detected the slow formation of tetronic acid **27**. After 24 h at 60 °C **27** was isolated as the sole reaction product (40%; 73% based on recovered starting material (brsm)). Reasoning that **25** might have formed but that its cyclization to **26** was slow, we prepared diketoester **28** and repeated the experiment [Eq. (4)]. Once again we observed only the slow formation of tetronic acid **29** (11%; 32% brsm after 72 h at 60 °C) with no evidence for the formation of **30**. Control experiments showed that tetronic acid formation was not palladium catalyzed. It is plausible that the conversion to tetronic acids **27** and **29** is initiated by nucleophilic attack of a ketone carbonyl oxygen atom onto the ester carbonyl carbon atom. The experiments with **24** and **28** were repeated in the presence of 10 equiv styrene in an attempt to trap the palladium hydride through an intermolecular process. Neither experiment provided evidence of an intermolecular reaction with styrene.

Because our results to date have not provided evidence for a Pd^0–Pd^{II} catalytic cycle proceeding by means of a metal hydride intermediate, the mechanism for the Nazarov-type cyclization remains unknown. We considered that other zero

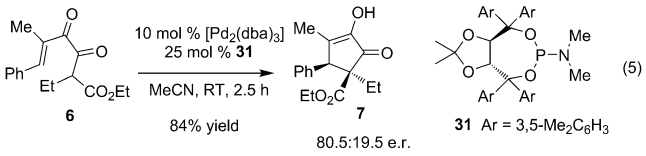


28 **29** **30** (4)



Scheme 2. Examples of the Pd^0-catalyzed Nazarov cyclization with yields.

valent metals might also catalyze the cyclization. In fact, bis(1,5-cyclooctadiene)nickel(0) [$Ni(cod)_2$] also catalyzes the conversion of **6** to **7**.[9] Unlike the Pd^{II}-catalyzed Nazarov cyclizations that are suppressed by basic phosphine ligands, the Pd^0-catalyzed cyclization is amenable to asymmetric catalysis by phosphines and phosphoramidites.[10] For example, exposure of **6** in dry acetonitrile to 10 mol% [$Pd_2(dba)_3$] and a small excess of phosphoramidite **31**[11] leads to **7** in 80.5:19.5 e.r. [Eq. 5]. Significantly, the cyclization is complete within a few hours at room temperature. [12]



(5)

In conclusion, we have described the first Pd^0-catalyzed Nazarov-type cyclization of diketoesters. The reaction proceeds in good to excellent yields for a variety of substrates under strictly neutral pH conditions and has a much broader scope than the organocatalyzed process of Equation (1). Aryl substitution at C6 is not required, so the reaction succeeds with aliphatic substrates, including those that fail to cyclize in the presence of organocatalyst **2** (e.g. **8**, and **16**–**20**). The mechanism may not involve a pentadienyl cation intermediate, even though the reaction leads to the same products as a Nazarov cyclization. Early indications suggest that the asymmetric version of this process will also be successful.

Experimental Section

A solution of diketoester **6** (58 mg, 0.20 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (2 mg, 2.0 μmol, 1 mol%), and PPh_3 (2 mg, 8.0 μmol, 4 mol%) in dry DMSO (1.0 mL, 0.2 M) was stirred at 60 °C. After 4.5 h, the reaction mixture was poured into water (5 mL) and extracted with ether (3 × 10 mL). The combined ether extracts were washed with water, brine, and dried (anh. Na_2SO_4). Evaporation and column chromatography (silica gel, 15% EtOAc in hexanes) produced **7** as a clear oil (53 mg, 91% yield): ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.26$–7.27 (m, 3H), 7.08–7.11 (m, 2H), 3.73 (s, 1H), 3.53 (dq, $J = 10.8$, 7.2 Hz, 1H), 3.42 (dq, $J = 10.8$, 7.2 Hz, 1H), 2.23 (dq, $J = 14.8$, 7.4 Hz, 1H), 2.20 (dq, $J = 14.8$, 7.4 Hz, 1H), 1.90 (s, 3H), 0.92 (t, $J = 7.4$ Hz, 3H), 0.85 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 199.8$, 169.8, 149.6, 142.8, 136.9, 129.3, 128.1, 127.6, 62.4, 60.8, 55.7, 28.4, 13.4, 12.8, 8.3 ppm; IR (neat): $\tilde{\nu} = 3342$, 1731, 1713, 1660, 1242, 1079 cm^{-1}; MS (EI^+): m/z (%): 288 [M^+, 100], 242 (23), 215 (35), 145 (61), 143 (75), 115 (54); HRMS (EI^+): m/z calcd for $C_{17}H_{20}O_4$: 288.1362 [M^+]; found 288.1364.

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[9] In the presence of approximately 23 mol% [$Ni(cod)_2$], **6** was converted into **7** in 58% yield (86% brsm, not optimized) after 24 h at room temperature. See the Supporting Information for the reaction conditions.

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[12] Efforts to improve the enantioselectivity of this reaction are underway.

