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

Naoyuki Shimada,

Chemistry Department, University of Hawaii at Manoa, 2545 The Mall, Honolulu, HI 96822, (USA), Fax: (+1) 808-956-5908

Craig Stewart,

Chemistry Department, University of Hawaii at Manoa, 2545 The Mall, Honolulu, HI 96822, (USA), Fax: (+1) 808-956-5908

William F. Bow,

Chemistry Department, University of Hawaii at Manoa, 2545 The Mall, Honolulu, HI 96822, (USA), Fax: (+1) 808-956-5908

Anais Jolit,

Chemistry Department, University of Hawaii at Manoa, 2545 The Mall, Honolulu, HI 96822, (USA), Fax: (+1) 808-956-5908

Kahoano Wong,

Chemistry Department, University of Hawaii at Manoa, 2545 The Mall, Honolulu, HI 96822, (USA), Fax: (+1) 808-956-5908

Zhe Zhou, and

Chemistry Department, University of Hawaii at Manoa, 2545 The Mall, Honolulu, HI 96822, (USA), Fax: (+1) 808-956-5908

Marcus A. Tius

Chemistry Department, University of Hawaii at Manoa, 2545 The Mall, Honolulu, HI 96822, (USA), Fax: (+1) 808-956-5908

The University of Hawaii Cancer Center, 677 Ala Moana Blvd, Suite 901, Honolulu, HI 96813 (USA)

Marcus A. Tius: tius@hawaii.edu

Abstract

The first Pd(0)-catalyzed Nazarov-type cyclization of diketooesters proceeds in 70% to 95% yield under strictly neutral conditions. Aryl substitution is not required so the reaction succeeds with aliphatic substrates. The mechanism appears to be novel. A single asymmetric version of this reaction is also reported.

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Correspondence to: Marcus A. Tius, tius@hawaii.edu.

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Keywords

Nazarov cyclization; homogeneous catalysis; stereoselectivity; synthetic methods; palladium

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 strong acid that limits applications to robust and unfunctionalized substrates.^[3] In recent work Trauner,^[4] Rueping^[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 Eq. (1).^[7] Exposure of diketoester **1** to organocatalyst **2** led to cyclopentenone **3** in 87% yield and in 98.5/1.5 er as a single diastereomer. The reaction was slow, likely due to product inhibition of the catalyst that can engage 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)

In earlier work we had described Pd(II)-catalyzed Nazarov-type cyclizations of α -ethoxy dienones which proceed through a palladium enolate intermediate.^[8] These Pd(II)-catalyzed cyclizations reactions are initiated through an electrophilic interaction with the metal and are suppressed in the presence of basic ligands, e.g. PPh₃. 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 in 80% yield from the treatment of **4b** with PdCl₂ or Pd(OAc)₂, respectively. However, this cyclization did not take place in the presence of PdCl₂(PPh₃)₂, thereby precluding an obvious approach to an asymmetric catalytic process. Much to our surprise, exposure of **4a** to 20 mol % Pd(PPh₃)₄ in dichloromethane at room temperature led to Nazarov product **5** in 80% yield. This Pd(0)-catalyzed reaction proceeds under strictly neutral conditions and is the first Nazarov-type cyclization that is catalyzed by a zero valent metal. The success of Pd(PPh₃)₄ as a catalyst indicates a distinct mechanism and the possibility of asymmetric catalysis through the use of chiral phosphine ligands. 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 PPh₃ 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 and 7 vs 8 and 9). In DMSO we were able to reduce the catalyst load to 0.5 mol % $\text{Pd}_2(\text{dba})_3$ (1 mol % Pd) without appreciable erosion of the rate or yield (entry 11). For less reactive substrates lacking a C6 aryl group the use of 2 mol% Pd 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).

Figure 1 summarizes our 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 through the organocatalytic process that 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 a *ca.* 1:1 mixture of diastereomers in 66% yield. Since **16** was formed through 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**. There was no evidence of the formation of **26** even after heating the solution for 24 h. Instead we observed the slow formation of tetronic acid **27**. After 24 h at 60 °C **27** was isolated as the sole reaction product (40%; 73% brsm). Reasoning that **25** might have formed but that its cyclization to **26** was slow we prepared diketoester **28** and repeated the experiment. 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. The conversion to tetronic acids **27** and **29** is plausibly 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 intermolecularly. Neither experiment provided evidence of an intermolecular reaction with styrene.

(2)

(3)

(4)

Since 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 valent metals might also catalyze the cyclization. In fact 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 % Pd₂(dba)₃ and a small excess of phosphoramidite **31**^[11] leads to **7** in 80.5/19.5 er. Significantly, the cyclization is complete within a few hours at room temperature.^[12]

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 conditions and has a much broader scope than the organocatalyzed process of Eq. (1). Aryl substitution at C6 is not required so the reaction succeeds with aliphatic substrates, including ones that fail to cyclize in the presence of organocatalyst **2** (e.g. **8**, and **16–20**). The mechanism appears to be novel, and 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.

(5)

Experimental Section

A solution of diketoester **6** (58 mg, 0.20 mmol), Pd₂(dba)₃•CHCl₃ (2 mg, 2.0 μmol, 1 mol %) and PPh₃ (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. Na₂SO₄). Evaporation and column chromatography (silica gel, 15% EtOAc in hexanes) produced **7** as a clear oil (53 mg, 91% yield): ¹H NMR (300 MHz, CDCl₃) δ 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 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 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; IR (neat, cm⁻¹) 3342, 1731, 1713, 1660, 1242, 1079; HRMS (EI⁺) calculated for C₁₇H₂₀O₄ (M⁺): 288.1362, found 288.1364; EI⁺ *m/z* (%): 288 (M⁺, 100), 242 (23), 215 (35), 145 (61), 143 (75), 115 (54).

References

1. Reviews of the Nazarov reaction: Shimada N, Stewart C, Tius MA. *Tetrahedron*. 2011; 67:5851–5870. [PubMed: 21857751] Nakanishi W, West FG. *Curr. Op. Drug Disc. Dev.* 2009; 12:732–751. Grant TN, Rieder CJ, West FG. *J. Chem. Soc., Chem. Comm.* 2009; 45:5676–5688. Frontier AJ, Collison C. *Tetrahedron*. 2005; 61:7577–7606. Pellissier H. *Tetrahedron*. 2005; 61:6479–6517. Tius MA. *Eur. J. Org. Chem.* 2005:2193–2206.
2. a) Churrua F, Fouteris M, Ishikawa Y, Rekowski MW, Hounsou C, Surrey T, Giannis A. *Org. Lett.* 2010; 12:2096–2099. [PubMed: 20387880] b) Gao S, Wang Q, Huang LJ-S, Lum L, Chen C. *J. Am. Chem. Soc.* 2010; 132:371–383. [PubMed: 20000429] c) Williams DR, Robinson LA, Nevill CR, Reddy JP. *Angew. Chem. Int. Ed.* 2007; 46:915–918. d) Harrington PE, Tius MA. *J. Am. Chem. Soc.* 2001; 123:8509–8514. [PubMed: 11525658] e) Vaidya T, Eisenberg R, Frontier AJ. *Chem. Cat. Chem.* 2011; 3:1531–1548.
3. Recent examples of catalytic Nazarov reactions: Brooks JL, Caruana PA, Frontier AJ. *J. Am. Chem. Soc.* 2011; 133:12454–12457. [PubMed: 21780785] Krafft ME, Vidhani DV, Cran JW, Manoharan M. *J. Chem. Soc., Chem. Commun.* 2011; 47:6707–6709. Murugan K, Srimurugan S, Chen C. *J. Chem. Soc., Chem. Commun.* 2010; 46:1127–1129. Zhang J, Vaidya T, Brennessel WW, Frontier AJ, Eisenberg R. *Organometallics*. 2010; 29:3341–3349. Wender PA, Stemmler RT, Sirois LE. *J. Am. Chem. Soc.* 2010; 132:2532–2533. [PubMed: 20141136] Vaidya T, Atesin AC, Herrick IR, Frontier AJ, Eisenberg R. *Angew. Chem., Int. Ed.* 2010; 49:3363–3366. Rieder CJ, Winberg KJ, West FG. *J. Am. Chem. Soc.* 2009; 131:7504–7505. [PubMed: 19435345] Cordier P, Aubert C, Malacria M, Lacôte E, Gandon V. *Angew. Chem., Int. Ed.* 2009; 48:8757–8760. Barbero M, Cadamuro S, Deagostino A, Dughera S, Larini P, Occhiato EG, Prandi C, Tabasso S, Vulcano R, Venturello P. *Synthesis*. 2009:2260–2266. Lemiere G, Gandon V, Cariou K, Hours A, Fukuyama T, Dhimane A-L, Fensterbank L, Malacria, M M. *J. Am. Chem. Soc.* 2009; 131:2993–3006. [PubMed: 19209868] Bitar AY, Frontier AJ. *Org. Lett.* 2009; 11:49–52. [PubMed: 19053717]
4. a) Liang G, Trauner D. *J. Am. Chem. Soc.* 2004; 126:9544–9545. [PubMed: 15291550] b) Liang G, Gradl SN, Trauner D. *Org. Lett.* 2003; 5:4931–4934. [PubMed: 14682732]
5. a) Rueping M, Ieawsuwan W, Antonchick AP, Nachtsheim BJ. *Angew. Chem., Int. Ed.* 2007; 46:2097–2100. b) Rueping M, Ieawsuwan W. *Adv. Synth. Catal.* 2009; 351:78–84. c) Rueping M, Ieawsuwan W. *J. Chem. Soc., Chem. Commun.* 2011; 47:11450–11452.
6. a) Shimada N, Ashburn BO, Basak AK, Bow WF, Vicic DA, Tius MA. *J. Chem. Soc., Chem. Commun.* 2010; 46:3774–3775. b) Kawatsura M, Kajita K, Hayase S, Itoh T. *Synlett*. 2010:1243–1246. c) Cao P, Deng C, Zhou Y-Y, Sun X-L, Zheng J-C, Xie Z, Tang Y. *Angew. Chem., Int. Ed.* 2010; 49:4463–4466. d) Yaji K, Shindo M. *Synlett*. 2009:2524–2528. e) Kokubo M, Kobayashi S. *Chem. Asian J.* 2009; 4:526–528. [PubMed: 19212964] f) Walz I, Togni A. *J. Chem. Soc., Chem. Commun.* 2008:4315–4317. g) Nie J, Zhu H-W, Cui H-F, Hua M-Q, Ma J-A. *Org. Lett.* 2007; 9:3053–3056. [PubMed: 17629286] h) Huang J, Frontier AJ. *J. Am. Chem. Soc.* 2007; 129:8060–8061. [PubMed: 17555319]
7. Basak AK, Shimada N, Bow WF, Vicic DA, Tius MA. *J. Am. Chem. Soc.* 2010; 132:8266–8267. [PubMed: 20507121]
8. Bee C, Leclerc E, Tius MA. *Org. Lett.* 2003; 5:4927–4930. [PubMed: 14682731]
9. In the presence of ca. 23 mol % Ni(COD)₂ **6** was converted to **7** in 58% yield (86% brsm, not optimized) after 24 h at rt. See the S.I. for the reaction conditions.
10. Teichert JF, Feringa BL. *Angew. Chem., Int. Ed.* 2010; 49:2486–2528.
11. Boele MDK, Kamer PCJ, Lutz M, Spek AL, de Vries JG, van Leeuwen PWNM, van Strijdonck GPF. *Chem. Eur. J.* 2004; 10:6232–6246. [PubMed: 15515069]
12. Efforts to improve the enantioselectivity of this reaction are underway.

Figure 1.
Examples of the Pd(0)-catalyzed Nazarov cyclization (yield)

Scheme 1.

Pd-catalyzed cyclizations. Conditions A: (**4a**) 20 mol % Pd(PPh₃)₄, 0.1 M CH₂Cl₂, rt, <24 h; 80% yield. Conditions B : (**4b**) 20 mol % PdCl₂(MeCN)₂, 0.1 M wet acetone, rt, ca. 3 d; 65% yield. Conditions C : (**4b**) 20 mol % Pd(OAc)₂, 0.1 M DMSO, rt, ca. 5 d; 80% yield.

Table 1

Optimization of Reaction Conditions

6		7		
Entry	Solvent	Pd/P	Time [h]	Yield [%]
1 ^[a]	CH ₂ Cl ₂	1:4	120	69
2	(CH ₂ Cl) 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	^[e]	24	No rxn

^[a] 18 °C.^[b] 1 mol % Pd₂(dba)₃^[c] 0.5 mol % Pd₂(dba)₃.^[d] 4.0 mol % PPh₃.^[e] No Pd₂(dba)₃, no PPh₃.