

Simple Silver Salts and Palladium Bis(*N*-heterocyclic carbene) Complexes As Complementary Catalysts for the Nazarov Cyclization

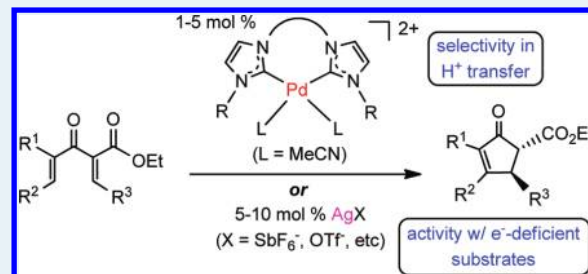
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Supporting Information

ABSTRACT: Simple silver salts and dicationic palladium bis(*N*-heterocyclic carbene) complexes were found to be effective and complementary catalysts for Nazarov cyclizations of divinyl β -keto esters. A sterically hindered palladium bis(NHC) catalyst provided remarkable endo:exo selectivity in cyclizations of cyclohexenyl β -keto esters, whereas AgSbF₆ gave improved yields with electron-deficient substrates. The high activities observed with silver salts are significant, given their widespread use as additives in catalytic Nazarov reactions.

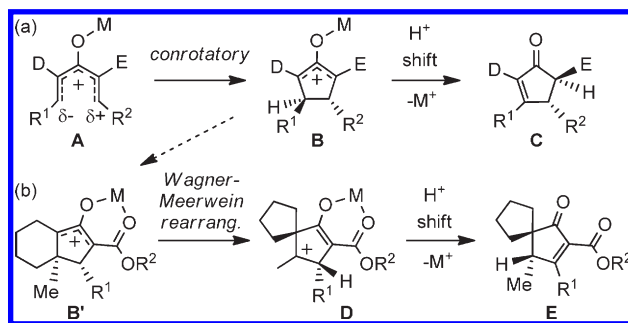
KEYWORDS: palladium catalysts, silver catalysts, catalytic electrocyclic reactions, Nazarov cyclization, *N*-heterocyclic carbene ligands



The Nazarov cyclization^{1–4} provides access to a wide range of functionalized cyclopentenone derivatives, including medicinally important natural products,^{5–8} via 4 π -electrocyclic ring closure of an oxypentadienyl cation (Scheme 1). Stoichiometric amounts of a Lewis acid promoter have historically been needed to achieve useful yields, but the introduction of polarized divinyl and aryl vinyl ketone substrates^{9,10} has allowed development in recent years¹¹ of a number of catalytic systems that effect cyclization under mild conditions. These include simple salts (e.g., triflates) of di- and trivalent metal ions^{9,10,12–14} as well as metal complexes containing chelating ligands.^{15–25} Although the conrotatory cyclization process typically ensures diastereoselectivity in the Nazarov reaction,¹⁰ achieving other types of selectivity can be a challenge due to the proton transfer step that follows electrocyclization (B \rightarrow C, Scheme 1). High enantioselectivities have been attained using chiral chelate complexes in some cases.^{15,17,19–22} Still needed, however, are catalysts that promote consistent regioselectivity when competing proton transfer steps exist as well as systems that provide high activity with electron-deficient substrates.

In several catalytic Nazarov systems, monovalent metal salt additives (e.g., Ag^I salts) have been reported to substantially affect catalytic activity. Most commonly, the role of the additive is to replace halides or triflate with noncoordinating anions,^{13,15,18,21} thereby opening substrate binding sites, enhancing the electrophilicity of the catalytic metal,²⁴ or both. Addition of stoichiometric NaBAR^F₄ (BAR^F₄[–] = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) to catalytic systems containing Ir^{III} or Pd^{II} chelate complexes has been shown to favor formation of a spirocyclic product resulting from a competing Wagner–Meerwein rearrangement in substrates with cyclic trisubstituted vinyls (B' \rightarrow E, Scheme 1),^{23,25} possibly by Na⁺ binding to free carbonyl groups that might assist in the proton transfer step leading to the Nazarov product.

Scheme 1. (a) Polarized Nazarov Cyclization and (b) Competing Spirocyclization Pathway



Despite AgSbF₆'s being the most widespread additive in catalytic Nazarov systems,^{15,18,24,26–30} the possibility of silver salts themselves catalyzing the Nazarov cyclization has apparently been little investigated.^{31,32} Weak background reactions (<20%) promoted by stoichiometric LiClO₄ or AgSbF₆ were reported for two specific substrates.^{13,18} Frontier and co-workers reported that catalytic amounts of AgSbF₆ promoted Nazarov cyclization of one specific pentasubstituted divinyl ketone substrate,³³ whereas stoichiometric Ag^I salts could favor the spirocycle product of the same substrate, depending on the counteranion used.³⁴ While investigating new carbene-containing metal chelate complexes as Nazarov cyclization catalysts, we discovered that simple silver salts are excellent catalysts for cyclizations of a series of β -keto esters with disubstituted vinyl groups, one of the most common substrate types. Herein, we disclose these results, which have important implications for chiral catalyst systems that use Ag salt additives.^{15,18,35}

Received: August 31, 2011

Published: September 06, 2011

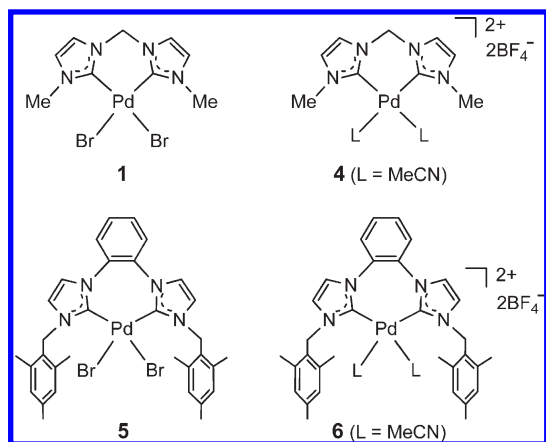
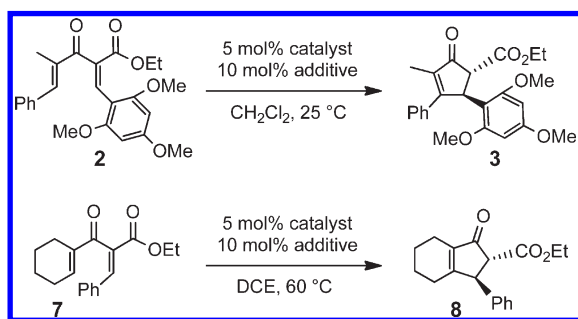


Figure 1. Bis(NHC) palladium precatalysts studied.

Table 1. Catalyst Screening



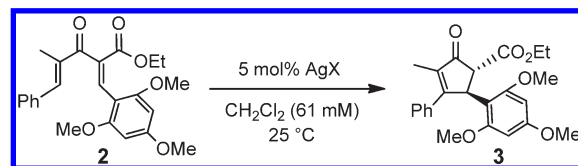
entry	sm ^a	catalyst	additive	time	% yield
1	2	1		5 d	
2	2	1	AgSbF ₆	10 min	93
3	2	1	AgBF ₄	10 min	91
4	2	1	AgBAR ₄ ^F	5 d	
5	2	4		10 min	94
6	2	5	AgSbF ₆	10 min	93
7 ^b	2	6		10 min	93
8	7	1	AgSbF ₆	2 d	88
9	7	1	AgBF ₄	4 d	78
10	7	1	AgPF ₆	4 d	8
11	7	4		4 d	67

^a Only endo products were observed for substrates 2 and 7. ^b 1 mol % 6 used.

In addition, palladium bis(*N*-heterocyclic carbene) [bis(NHC)] complexes are introduced as a new class of Nazarov cyclization catalyst that provide unprecedented endo:exo selectivity in reactions of cycloalkenyl dienones.

Although di- and tricationic diphosphine complexes of Ir^{III} are perhaps the most active Nazarov cyclization catalysts known,^{16,24} only one report of catalysis by analogous complexes of similarly electrophilic Pd^{II} has appeared.^{25,36} Our observation that cationic palladium bis(carbene) complexes can act as electrophilic catalysts for aza-Claisen rearrangements³⁷ led us to investigate the efficacy of bis(NHC) palladium catalysts in the Nazarov reaction. Initial studies focused on the known methylene-linked bis(NHC) palladium dibromide complex 1^{38,39} (Figure 1) as a precatalyst for Nazarov cyclization of β -keto ester 2. No catalysis

Table 2. Nazarov Cyclization of 2 Catalyzed By Silver Salts



entry	AgX	time	% yield of 3
1	AgSbF ₆	8 min	94
2	AgBF ₄	20 h	93
3	AgPF ₆	5 d	<2
4	AgBAR ₄ ^F	5 d	<2
5	AgOAc	4 d	92
6	AgOTf	10 min	92

occurred with 5 mol % of 1 alone, but >90% yields of the Nazarov product 3 were obtained within 10 min upon activation with 10 mol % AgSbF₆ or AgBF₄ (entries 1–3, Table 1). By contrast, AgBAR₄^F was an ineffective activator (entry 4), apparently remaining dissolved in the reaction mixture and not forming any visible AgBr. The well-defined dicationic palladium bis(NHC) acetonitrile adduct 4³⁹ provided activity similar to that of silver-activated 1 (entry 5). A new, sterically hindered, phenylene-linked bis(NHC) ligand^{40–42} was also prepared and incorporated into precatalysts 5 and 6 (Figure 1), which showed activities similar to those of 1 and 4 (entries 6, 7).

Although the results with 2 did not suggest any interference from the silver salt additives, cyclizations of the less reactive substrate 7, which required extended heating at 60 °C, showed a marked dependence on the identity of the silver salt. With precatalyst 1 and activation by AgSbF₆, the maximum yield of cyclized product 8 was obtained in 2 days (entry 8). With AgBF₄ activation, 4 days was needed for complete substrate consumption and attainment of comparable yields, whereas use of AgPF₆ resulted in little product formation after 4 days (entries 9, 10). In addition, catalysis with the preformed dication 4 was slower than when 1 was used in combination with AgSbF₆ (entry 11). Although these results might be plausibly attributed to a counteranion effect,⁴³ we chose to investigate whether Ag^I salts alone were competent to catalyze Nazarov cyclizations.

Given that Togni and co-workers reported only low yields of 3 at long reaction times upon treating substrate 2 with 1 equiv of AgSbF₆,¹⁸ we were surprised to find that cyclization occurred rapidly and with high yield when 5 mol % AgSbF₆ was used (Table 2, entry 1). We confirmed that only traces of 2 (<2%) are formed when stoichiometric AgSbF₆ is used. Reasons for the discrepant result at high AgSbF₆ loading might include inhibition of H⁺ transfer due to binding of free carbonyl groups by silver^{23,25} or competing reaction pathways.³³ A survey of other Ag^I salts revealed that catalytic activity did not correlate simply with the presence of a noncoordinating anion, as shown by the slow cyclization with AgBF₄ and the lack of reaction with AgPF₆ (entries 2, 3). These results suggest that the size of the noncoordinating anion strongly influences the reaction, perhaps through ion pairing with the cationic oxypentadienyl or oxallyl intermediates (A, B, Scheme 1). The documented ability of acetate and BAR₄^F to bind Ag^I in a bridging⁴⁴ or η^2, η^2 -chelating⁴⁵ mode, respectively, may account for the poor activity of salts of these anions (entries 4, 5). However, AgOTf afforded activity comparable to that of AgSbF₆, despite the known

Table 3. Scope of Nazarov Reactions Catalyzed by AgSbF₆^a

entry	Substrate ^b	time	Products (% yield)
1 ^c		1 h	10 (84)
2		11 h	12 (89)
3 ^c		0.5 h	14 (48)
			15 (46)
4		1 h	17 (52)
			18 (41)
5		40 h	8 (83) ^e
6		40 h	20 (52)
			21 (41)
7		5 d	23 (89) ^e

^a Conditions (except as noted): 10 mol % AgSbF₆, DCE (61 mM), 60 °C. ^b PMP = 4-methoxyphenyl; PNP = 4-nitrophenyl; TMP = 2,4,6-trimethoxyphenyl. ^c 5 mol % AgSbF₆, CH₂Cl₂ (61 mM), 25 °C. ^d Mixture of E/Z (1:4.5). ^e Traces (<5%) of carboxylic acid resulting from hydrolysis of the ester product were observed.

propensity of triflate to weakly coordinate Ag^I.⁴⁶ Overall, the results indicate that a balance of multiple anion effects is necessary to achieve catalysis with Ag^I salts.

The scope of Nazarov cyclizations catalyzed by AgSbF₆ was examined with a series of β-keto esters containing aryl or vinyl substituents adjacent to the ester and either 2-methyl-2-styryl or cyclohexenyl as the second vinyl moiety (Table 3). Decreasing the electron-donating character of the aryl substituents substantially slowed catalytic rates, as observed in several other systems,^{10,18,25} necessitating the use of higher temperature and longer reaction times in most cases. Nevertheless, good to high yields were obtained for all substrates studied. The respectable yields of products **12** and **23** are noteworthy, given that only a few examples of effective catalytic Nazarov cyclizations of dienones with *p*-nitrophenyl substituents have been reported.^{10,18,23} Similarly to other catalyst systems,^{10,16,34} reactions of some cyclohexenyl β-keto esters gave rise to

Table 4. Scope of Nazarov Reactions Catalyzed by **6**^a

entry	substrate	time	products (% yield)
1	9	1 h	10 (91)
2	11	5 d	12 (48)
3 ^b	13	0.5 h	14 (64), 15 (30)
4	16	1 h	17 (59), 18 (31)
5	7	40 h	8 (86)
6	19	40 h	20 (83)
7	22	5 d	23 (53)

^a Conditions (except as noted): 5 mol % **6**, DCE (61 mM), 60 °C.

^b 1 mol % **6**, CH₂Cl₂ (61 mM), 25 °C.

approximately 1:1 mixtures of products with the double bond in either the endo or exo position as a consequence of competing H⁺ elimination events (entries 3, 4, 6). Stereoconvergent formation of only the trans diastereomers of each product was observed, as is common for this type of Nazarov substrate.¹⁰

Complex **6** was selected for further study of catalysis by a palladium bis(NHC) complex because it was thought that the phenylene bridge should reduce the ligand donor ability and thus increase metal electrophilicity compared with methylene bridged complex **4**. This was confirmed by comparing the $\Delta\nu^{\text{MeNC}}$ values of bis(methylisocyanide) adducts of **6** (115 cm⁻¹) and **4** (109 cm⁻¹).⁴⁷ With substrates **2** and **13** bearing trimethoxyphenyl substituents, activity comparable to that seen with 5 mol % AgSbF₆ was achieved using only 1 mol % of **6**. Less reactive substrates required 5 mol % **6** and heating at 60 °C for maximum yields (Table 4). Only moderate yields were obtained with nitroaryl-substituted **11** and **22** (entries 2, 7). A remarkable feature of catalyst **6** was its substantial selectivity for the endo product with cyclohexenyl substrates. Endo:exo ratios of ~2:1 were obtained for **13** and **16**, whereas only endo product was detected for **19**, in contrast to the lack of selectivity with AgSbF₆. We attribute this selectivity to a steric influence of the bulky trimethylbenzyl ligand substituents on the H⁺ transfer step. To our knowledge, **6** is the first catalyst demonstrated to give consistent endo:exo selectivity in Nazarov cyclizations of cyclohexenyl dienones. Preliminary experiments indicate that a significant counteranion effect also operates for the palladium bis(NHC) catalysts (e.g., conversion of **7** to **8** occurs in 90% yield within 3 h using 5 mol % **5** + 10 mol % AgSbF₆, versus 40 h for catalyst **6**), providing a topic for future extensions of this work.

In summary, simple Ag^I salts and dicationic palladium bis(NHC) complexes represent two new classes of Nazarov cyclization catalysts that are complementary in several respects. Silver salts are inexpensive and provide good yields for difficult Nazarov substrates with electron-deficient aromatic groups, whereas the palladium catalysts show reduced substrate scope but provide higher endo:exo selectivity in cyclizations of cyclohexenyl-substituted β-keto esters. Furthermore, AgSbF₆ shows sufficient activity with less reactive substrates (e.g., **7**) that it may contribute significantly to catalytic turnover when used in excess as an additive with other metal catalysts. This is an important consideration for development of enantioselective Nazarov cyclization catalysts and is in agreement with previous reports of reduced enantioselectivity in the presence of AgSbF₆.^{15,21,35}

■ ASSOCIATED CONTENT

S Supporting Information. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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■ ACKNOWLEDGMENT

This research was supported by the National Science Foundation (CAREER Award CHE-0645438). We thank Gianna Bell-Eunice for assistance with NMR characterization.

■ REFERENCES

- (1) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React. (N.Y.)* **1994**, *45*, 1–158.
- (2) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193–2206.
- (3) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577–7606.
- (4) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479–6517.
- (5) Bitar, A. Y.; Frontier, A. J. *Org. Lett.* **2009**, *11*, 49–52.
- (6) Malona, J. A.; Cariou, K.; Frontier, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 7560–7561.
- (7) Marcus, A. P.; Sarpong, R. *Org. Lett.* **2010**, *12*, 4560–4563.
- (8) Cai, Z.; Harmata, M. *Org. Lett.* **2010**, *12*, 5668–5670.
- (9) He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278–14279.
- (10) He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003–1011.
- (11) For an example of a highly active Brønsted acid catalyst for the Nazarov cyclization, see: Murugan, K.; Srimurugan, S.; Chen, C. *Chem. Commun.* **2010**, 46, 1127–1129.
- (12) Liang, G.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931–4934.
- (13) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661–5664.
- (14) Nie, J.; Zhu, H.-W.; Cui, H.-F.; Hua, M.-Q.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 3053–3056.
- (15) Aggarwal, V. K.; Belfield, A. J. *Org. Lett.* **2003**, *5*, 5075–5078.
- (16) Janka, M.; He, W.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2004**, *126*, 6864–6865.
- (17) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544–9545.
- (18) Walz, I.; Bertogg, A.; Togni, A. *Eur. J. Org. Chem.* **2007**, 2650–2658.
- (19) Walz, I.; Togni, A. *Chem. Commun.* **2008**, 4315–4317.
- (20) Yaji, K.; Shindo, M. *Synlett* **2009**, 2524–2528.
- (21) 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.
- (22) Kawatsura, M.; Kajita, K.; Hayase, S.; Itoh, T. *Synlett* **2010**, 1243–1246.
- (23) Atesin, A. C.; Zhang, J.; Vaidya, T.; Brennessel, W. W.; Frontier, A. J.; Eisenberg, R. *Inorg. Chem.* **2010**, *49*, 4331–4342.
- (24) Vaidya, T.; Atesin, A. C.; Herrick, I. R.; Frontier, A. J.; Eisenberg, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 3363–3366.
- (25) Zhang, J.; Vaidya, T.; Brennessel, W. W.; Frontier, A. J.; Eisenberg, R. *Organometallics* **2010**, *29*, 3341–3349.
- (26) Several tandem reactions involving a Nazarov-type step and using (phosphine)AuCl catalysts with added AgSbF₆ have been reported (see refs 27–30).
- (27) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442–1443.
- (28) Jin, T.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 3137–3139.
- (29) Lin, C.-C.; Teng, T.-M.; Tsai, C.-C.; Liao, H.-Y.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**, *130*, 16417–16423.
- (30) Lemièrre, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993–3006.
- (31) Negative controls with AgSbF₆ were reported for Nazarov cyclizations of polarized aryl vinyl ketones (ref 24) and a tandem 3,3-rearrangement/Nazarov process (ref 27); catalysis by AgSbF₆ with poor selectivity was reported for a related tandem reaction (ref 29, Supporting Information Table S1).
- (32) For an example of AgOTf catalysis of a related electrocyclic reaction, see: Cordier, P.; Aubert, C.; Malacria, M.; Lacôte, E.; Gandon, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8757–8760.
- (33) Huang, J.; Frontier, A. J. *J. Am. Chem. Soc.* **2007**, *129*, 8060–8061.
- (34) Huang, J.; Lebœuf, D.; Frontier, A. J. *J. Am. Chem. Soc.* **2011**, *133*, 6307–6317.
- (35) See the Supporting Information of ref 21 (Table S1, entry 10).
- (36) Catalysis of the Nazarov cyclization by Pd(OAc)₂ or PdCl₂(MeCN)₂ has been reported. See: Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4927–4930.
- (37) Wanniarachchi, Y. A.; Kogiso, Y.; Slaughter, L. M. *Organometallics* **2008**, *27*, 21–24.
- (38) Herrmann, W. A.; Elison, M.; Fischer, J.; Kocher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371–2374.
- (39) Gardiner, M. G.; Herrmann, W. A.; Reisinger, C.-P.; Schwarz, J.; Spiegler, M. *J. Organomet. Chem.* **1999**, *572*, 239–247.
- (40) Only one phenylene-bridged bis(NHC) ligand has been previously reported (refs 41,42).
- (41) Tubaro, C.; Biffis, A.; Gonzato, C.; Zecca, M.; Basata, M. *J. Mol. Catal. A: Chem.* **2006**, *248*, 93–98.
- (42) Canac, Y.; Lepetit, C.; Abdalilah, M.; Duhayon, C.; Chauvin, R. *J. Am. Chem. Soc.* **2008**, *130*, 8406–8413.
- (43) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798–800.
- (44) Olson, L. P.; Whitcomb, D. R.; Rajeswaran, M.; Blanton, T. N.; Stwertka, B. J. *Chem. Mater.* **2006**, *18*, 1667–1674.
- (45) Powell, J.; Lough, A.; Saeed, T. *J. Chem. Soc., Dalton Trans.* **1997**, 4137–4138.
- (46) James, S. L.; Mingos, D. M. P.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **1998**, 2323–2324.
- (47) $\Delta\nu^{\text{MeNC}} = [\nu\text{NC (avg) of coordinated MeNC}] - [\nu\text{NC of free MeNC}]$; see ref 37.