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The Lewis Acid-Catalyzed Nazarov Reaction of 2-(*N*-Methoxycarbonylamino)-1,4-pentadien-3-ones

Paolo Larini, Antonio Guarna, and Ernesto G. Occhiato*

Dipartimento di Chimica Organica "U. Schiff", Università di Firenze, Via della Lastruccia 13, I-50019 Sesto Fiorentino, Italy

ernesto.occhiato@unifi.it

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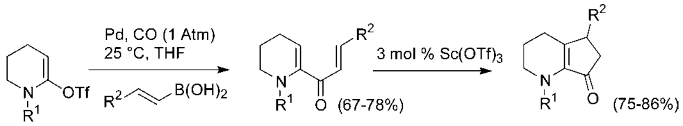
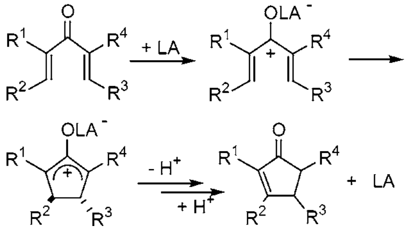
ABSTRACT



A highly efficient carbonylative Suzuki–Miyaura coupling reaction of lactam-derived vinyl triflates and alkenylboronic acids afforded 2-(*N*-methoxycarbonylamino)-1,4-pentadien-3-ones as suitable substrates for the Nazarov reaction. The most competent Lewis acids for the Nazarov reaction were Cu(OTf)$_2$ (2 mol %) and Sc(OTf)$_3$ (3 mol %) in DCE, which provided the Nazarov products in excellent yield. As both the carbonylative coupling and the subsequent Nazarov reaction were high yielding, the overall methodology is a concise and efficient route to [1]pyrindine systems.

The acid-catalyzed cyclization of a doubly α,*β*-unsaturated ketone (Scheme 1), referred to as the Nazarov reaction,[1] with its large number of variants, is a powerful method for the construction of five-membered carbocycles.[2] The Nazarov reaction has most recently been exploited for the partial or total synthesis of natural products such as terpestacin,[3] roseophilin,[4] guanacastepene A,[5] havanensin,[6] cephalotaxine,[7] cucumin H,[8] and others.[1,2] The ring closure (Scheme 1) occurs through a conrotatory electrocyclic process undergone by the 4p-electron pentadienyl cation formed, in the original version of the Nazarov reaction, upon treatment of the divinyl ketone with either a mineral or a Lewis acid. Very recently, a true catalytic variant of the original Nazarov reaction promoted by Lewis acids has been disclosed by Frontier[9] (Scheme 2, eq 1) and Trauner[10] (eq 2), who employed less

Scheme 1. The Lewis Acid-Catalyzed Nazarov Reaction



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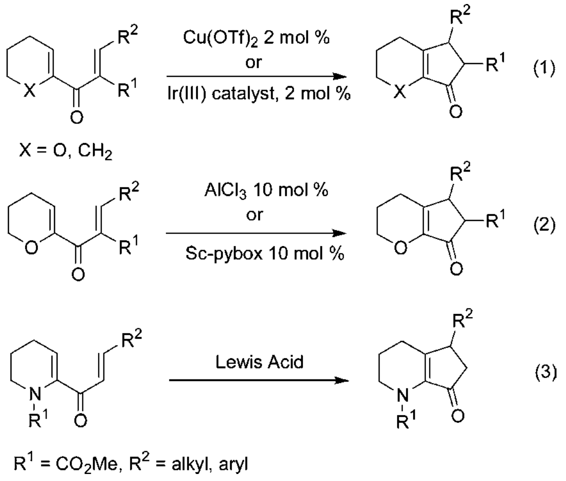
10.1021/ol053071h CCC: $33.50

Scheme 2. Lewis Acid-Catalyzed Nazarov Reactions



than 10 mol % of the catalyst [Cu(OTf)$_2$ or an Ir(III) catalyst, and AlCl$_3$, respectively] to perform the reaction.[11]

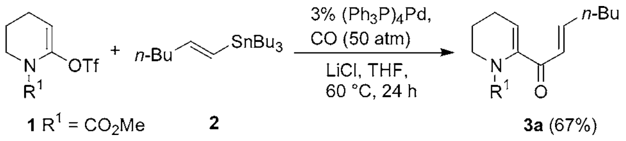
The use of chiral Lewis acids in a catalytic amount (10 mol % of a Sc-pybox) for the enantioselective Nazarov reaction has been so far reported only by Trauner (eq 2),[12] as Aggarwal[13] used 50−100 mol % of a Cu-pybox Lewis acid to efficiently promote the reaction.

With the pyrane derivatives (eqs 1−2), because of the presence of the oxygen atom in the ring, the Lewis acid is presumably bound in a bidentate fashion to the substrate, which is reputed to allow the two vinyl moieties to adopt the proper orientation for the cyclization,[9b] as well as to amplify the degree of stereocontrol in the final product formation.[12] Moreover it is also likely that the heterocycle oxygen atom accelerates the overall process by stabilizing the positive charge in the oxyallyl intermediate,[14a] as also reported with closely related substrates.[14b,c]

Due to our interest in the Nazarov reaction involving heterocyclic systems,[4a,14,15] we wanted to investigate if the reaction conditions of eqs 1 and 2 could be extended to the corresponding 2-amino-1,4-pentadien-3-ones (eq 3). This would certainly expand the scope of the Lewis acid-catalyzed Nazarov reaction, as the [1]pyrindine system that is formed is contained in a number of natural compounds,[16] and lay the basis for developing an enantioselective version of the process.[17] The presence of the electron-withdrawing N-protecting group is expected to lower the reactivity of these systems compared to the pyrane derivatives, but we know that such a protected N atom is still capable of stabilizing a positive charge in closely related substrates.[14b,c] Moreover, the N-protecting group can have a role in coordinating the Lewis acid. The methoxycarbonyl group was chosen as the N-protecting group owing to its greater stability to mineral and Lewis acids than *N*-Boc and *N*-Cbz protections.[18]

For the synthesis of the N-protected 2-amino-1,4-pentadien-3-ones **3** we relied on our experience on the coupling reactions of lactam-derived vinyl triflates **1** (Scheme 3).[19] In particular, for the rapid assembly of a model Nazarov substrate (**3a**) both Stille[20] and Suzuki−Miyaura[21] carbonylative couplings were for the first time attempted with these triflates.

Scheme 3. Carbonylative Stille Coupling



The carbonylative Stille coupling reaction of **1** with 1-hexenylstannane **2**[22] provided in our case the target compound **3a** (Scheme 3) in acceptable yield (67%) only at high CO pressure (50 atm) and temperature (60 °C), in the presence of (Ph$_3$P)$_4$Pd (3%) as the catalyst. The same reaction

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(11) PdCl$_2$(CN)$_2$ is also effective a 1−10 mol %, but the cyclization occurs through a mechanism different from the one reported in Scheme 1. (a) Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4927−4930. Examples of Lewis acid catalysis have been reported by West in interrupted Nazarov reactions. (b) Giese, S.; West, F. G. *Tetrahedron Lett.* **1998**, *39*, 8393−8396. (c) Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221−10228. (d) Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876−877. (e) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747−2750.

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(15) Prandi, C.; Deagostino, A.; Venturello, P.; Occhiato, E. G. *Org. Lett.* **2005**, *7*, 4345−4348.

(16) For example: streptazolin, streptazon C, and streptazon A, isolated from *Streptomyces viridochromogenes*, *Streptomyces luteogriseus*, and *FORM5*, Strain A1. See: (a) Drautz, H.; Zähner, H.; Kupfer, E.; Keller-Schierlein, W. *Helv. Chim. Acta* **1981**, *64*, 1752−1768. (b) Grabley, S.; Kluge, H.; Hoppe, H.-U. *Angew. Chem., Int. Ed.* **1987**, *26*, 664−665. (c) Grabley, S.; Hammann, P.; Kluge, H.; Wink, J.; Kricke, P.; Zeeck, A. *J. Antibiot.* **1991**, *44*, 797−800. (d) Puder, C.; Krastel, P.; Zeeck, A. *J. Nat. Prod.* **2000**, *63*, 1258−1260. (e) Puder, C.; Loya, S.; Hizi, A.; Zeeck, A. *J. Nat. Prod.* **2001**, *64*, 42−45. For the synthesis of streptazolin and related natural products see: (f) Trost, B. M.; Chung, C. K.; Pinkerton, A. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 4327−4329 and references therein. Pyrindicin, isolated from *Streptomyces sp. SCC 2313*. See: (g) Omura, S.; Tanaka, H.; Awaya, J.; Narimatsu, Y.; Konda, Y.; Hata, T. *Agric. Biol. Chim.* **1974**, *38*, 899−906. Abikoviromycin, isolated from *Streptomyces abikoensis*. See: (h) Gurevich, A. I.; Kolosov, M. N.; Korobko, V. G.; Onoprienko, V. V. *Tetrahedron Lett.* **1968**, *9*, 2209−2212. Proline-specific Maillard compounds: Chen, C.-W. Lu, G.; Ho, C.-T. *J. Agric. Food Chem.* **1997**, *45*, 2996−2999.

(17) We have already shown that with suitably substituted N-heterocycle derivatives there is an elevated control of the stereochemistry at C5. However, the possibility of organizing the absolute stereochemistry at this carbon atom by an external control is doubtlessly more attractive and general in scope. See refs 4a and 14b,c.

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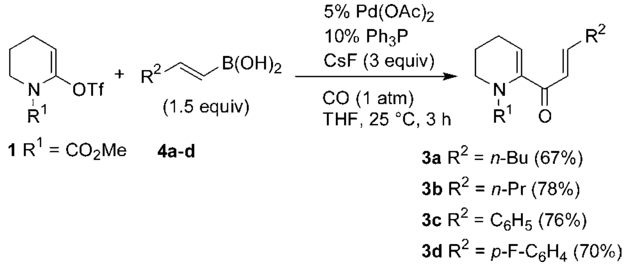
(21) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

(22) (*E*)-Tributyl-1-hexenylstannane **2** was prepared in good yield (82−86%) by Pd-catalyzed hydrostannation of 1-bromohexyne according to two different procedures: (a) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857−1867. (b) Shen, R.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650−5651.

conducted at 1 atm, with or without CuI as cocatalyst,[23] or with a different catalyst such as $Pd(OAc)_2/Ph_3P$, failed in providing higher yields, sometimes resulting either in degradation of the starting material or in the formation of the Stille product as the major component of the reaction mixture.

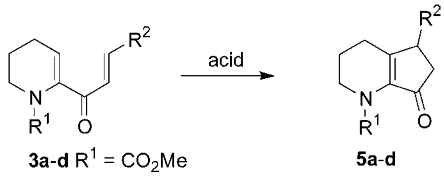
To the best of our knowledge, the carbonylative Suzuki–Miyaura coupling of vinyl triflates with alkenylboronic acids has never been reported.[24] We employed 1-pentenylboronic acid (2 equiv) and were lucky to observe the rapid formation of the desired product **3b** (R^2 = *n*-Pr, Scheme 4) at our first attempt at atmospheric pressure of CO, in the presence of 5% $Pd(OAc)_2$/10% Ph_3P as the catalyst, and CsF (3 equiv) for the boron quaternization, in THF at 60 °C. The best results were achieved by carrying out the reaction at room temperature, which avoided some degradation of the starting material (78% yield after 3 h). As expected, changing from cesium to cheaper potassium fluoride (4 equiv) decreased the yield (46% after 4 h).[25] Also, freshly prepared 1-hexenylboronic acid **4a**[26] was superior to the commercial product, perhaps because of its lower content of water.[27] The best conditions were then extended to a short series of alkenylboronic acids as reported in Scheme 4. With commercial *p*-fluorostyrylboronic acid **4d** the results of the carbonylative coupling were poorer, but they were greatly improved by slightly changing the reaction conditions (70% after chromatography, see the Supporting Information).

Scheme 4. Carbonylative Suzuki–Miyaura Coupling



The results of the Lewis acid-catalyzed Nazarov reaction of compounds **3a**–**d** are reported in Table 1.

Table 1. The Nazarov Reaction of Dienones **3a**–**d**[a]



entry	3	acid	equiv	conc (M)	*T* (°C)	time (h)	conv (%)[b,c]
1	**a**	TFA	neat		0	2.5	100
2	**a**	TFMSA	3	0.06	0	5	100 (83)
3	**a**	$BF_3.Et_2O$	1.5	0.02	0	18	55
4	**b**	Et_2AlCl	0.7	0.02	0	18	30
5	**b**	$SnCl_4$	0.7	0.02	0	3.5	50
6	**b**	$TiCl_4$	0.7	0.02	0	3	55 (22)
7	**a**	$FeCl_3$	0.7	0.02	0	2.5	88 (75)
8	**a**	$AlCl_3$	0.7	0.02	0	7.5	82
9	**b**	$FeCl_3$	0.1	0.2	20	23	74 (58)
10	**b**	$AlCl_3$	0.1	0.15	20	18	11
11	**b**	$Cu(OTf)_2$	0.02	0.2	55	8	92 (75)
12	**b**	$Zn(OTf)_2$	0.02	0.2	55	7	41
13	**b**	$Sc(OTf)_3$	0.03	0.2	55	3	100 (86)
14	**a**	$Yb(OTf)_3$	0.02	0.2	55	3	15
15	**c**	$Sc(OTf)_3$	0.03	0.2	55	2.5	100 (83)
16	**d**	$Sc(OTf)_3$	0.03	0.2	55	4	95 (72)

[a] Reaction carried out on 0.2–0.3 mmol of substrates in CH_2Cl_2 (entries 2–9), MeCN (entry 10), or $Cl(CH_2)_2Cl$ (entries 11–16). [b] From the ^1H NMR analysis of the crude reaction mixture. [c] The yield after chromatography is given in parentheses.

We started our study by evaluating some Brønsted acids (entries 1 and 2). Both neat TFA and triflic acid (3 equiv, in DCM) quantitatively converted **3a** into the Nazarov product **5a**. In both cases the yield was much higher than with the corresponding pyrrolidinone-derived dienones[4a,14b] reflecting the relative stability of the azabicyclic [4.3.0]nonenyl and [3.3.0]octenyl cationic intermediates. Catalytic amounts of Brønsted acids, as the Amberlyst 15 resin in chloroform, failed to give the cyclization product in accordance with our earlier observations.[14b]

A first screening of Lewis acids (entry 3–8) was carried out with 70 mol % of the catalyst but at high dilution (0.02 M) and at 0 °C. In all cases, reactions were monitored by TLC and stopped when no more conversion was observed. With the exception of the reactions carried out with $FeCl_3$ (entry 7) and $AlCl_3$ (entry 8) in no cases was the conversion appreciably higher than 50%. This could be due to degradation of the Lewis acid because of the presence of adventitious water, but a slow product-to-substrate Lewis acid exchange as the concentration of the product increases cannot be ruled out. In all cases, the N-protection was maintained in the final product. The most promising Lewis acid was $FeCl_3$, which provided in 2.5 h the Nazarov product **5a** in 75% yield (after chromatography) (entry 7). The same reaction was carried out with 10 mol % of $FeCl_3$ at low (0.04 M) and high (0.2 M) concentration at 20 °C. In the latter case the reaction did not proceed further after 23 h (74% conversion) and the product was obtained in 58% yield (entry 9). We wanted to try also $AlCl_3$ in 10 mol % which was the best catalyst with 2-alkoxy-1,4-pentadien-3-ones as **6** (Figure 1; this gave the Nazarov product in 92% after 50 min),[10] but to our surprise

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[23] Mazzola, R. D., Jr.; Giese, S.; Benson, C. L.; West, F. G. *J. Org. Chem.* **2004**, *69*, 220–223.

[24] Actually, we are aware of no examples of carbonylative Suzuki–Miyaura couplings of alkenylboronic acids, with the exception of a carbonylative reaction of a styrylboronic acid with a diazonium salt. The carbonylative coupling of 9-alkyl-9-BBN, arylboronic acids, and heteroarylboronic acids is instead well-known, and usually requires high temperature and CO pressure. (a) Andrus, M. B.; Ma, Y.; Zang, Y.; Song, C. *Tetrahedron Lett.* **2002**, *43*, 9137–9140 and references therein. (b) See ref 21.

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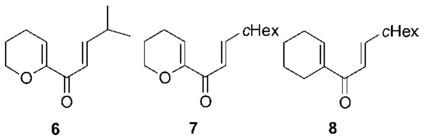
[27] The water present in mixture with *trans*-1-hexenylboronic acid can interfere with the catalytic cycle by hydrolyzing the acyl–palladium intermediate complex.



6 7 8

Figure 1. 2-Alkoxy-1,4-pentadien-3-ones.

$AlCl_3$ gave very poor results (entry 10). Al^{3+} is a harder cation than Fe^{3+}, which could result in a stronger O−Al bond[28] in the Nazarov product and thus in a slower turnover. The presence of the *N*-CO_2Me protecting group could further favor the Al^{3+} coordination in the final product, which could contribute to the sensible difference in reactivity between **3b** and **6** under the same conditions.

1,4-Pentadien-3-ones **7** and **8** (Figure 1) have been reported to react successfully to form the corresponding Nazarov products in the presence of 2 mol % of $Cu(OTf)_2$ in DCE at 55 °C.[9a,b] Because of the presence of the 2-oxygen atom, dienone **7** was more reactive than **8** under these conditions (60% yield after 0.5 h, and 37% yield after 4 h, respectively). Based on our reasoning on the effect of N-protection we expected something between these results with substrate **3b**. In fact, after 4 h the conversion into **5b** was higher than 50% and after 8 h the reaction was almost complete (92% conversion, 75% yield after chromatography, entry 11). Of the fourth period transition metal Lewis acids, however, $Sc(OTf)_3$ (3 mol %) was the best one (entry 13), as the substrate was quantitatively converted into **5b** after 3 h at 55 °C (86% yield after chromatography).

Of the lanthanide Lewis acids we tried the $Yb(OTf)_3$ (2 mol %), as Yb^{3+} is the smallest and the hardest cation of the series, and therefore the closest to the highly efficient Sc^{3+}.[29] However, the results were poor, as after 3 h at 55 °C the conversion was only 15% (entry 14), which could simply reflect the lower Lewis acidity of $Yb(OTf)_3$ compared to $Sc(OTf)_3$.[30]

Finally the best conditions [$Sc(OTf)_3$ (3 mol %)] were applied to substrates **3c**,**d** possessing a distal aromatic moiety (entries 15 and 16). Notwithstanding the presence of the aromatic ring that could stabilize the positive charge of the pentadienyl cation, with **3c** the reaction was as fast as that with **3b**. Also, the *p*-F group in **3d** had no particular effect on the rate of the process (reaction almost complete in 4 h, entry 16). Under these reaction conditions, therefore, there seems not to be dependence of the reaction rate on the electrocyclization step, as was also recently observed by Frontier.[9c]

In conclusion, we have for the first time carried out a very efficient carbonylative Suzuki−Miyaura coupling reaction using alkenylboronic acids as the nucleophiles, which provided 2-(*N*-methoxycarbonylamino)-1,4-pentadien-3-ones as useful substrates for the Lewis acid-catalyzed Nazarov reaction. To this aim, the most competent Lewis acids were $Cu(OTf)_2$ (2 mol %) and $Sc(OTf)_3$ (3 mol %) in DCE, which provided the Nazarov product in high yield. Despite the electron withdrawing N-protecting group, the reactivity of 2-amino-1,4-pentadien-3-ones was comparable or just slightly lower than that of the corresponding 2-alkoxy-1,4-pentadien-3-ones. As both the carbonylative coupling and the subsequent Nazarov reaction were high yielding, the overall methodology is a concise and efficient route to cyclopenta-fused N-heterocycles. The use of chiral Lewis acids for the enantioselective Nazarov reaction of 2-(*N*-methoxycarbonylamino)-1,4-pentadien-3-ones is currently being investigated in our laboratory.

Acknowledgment. We thank MIUR and University of Florence for financial support, Cassa di Risparmio di Firenze for granting a 400 MHz NMR spectrometer, and Maurizio Passaponti and Brunella Innocenti for technical support.

Supporting Information Available: Full experimental details and spectroscopic data; ^1H NMR spectra of compounds **3a**−**d** and **5a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[30] Kobayashi, S.; Manabe, K. *Pure Appl. Chem.* **2000**, *72*, 1373−1380.