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Cationic NHC–Pd (NHC = N-heterocyclic carbene) complex-catalyzed cycloisomerization of dienes

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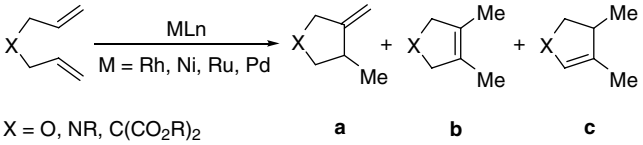
Abstract—A variety of [(NHC)Pd(η^3-allyl)]Cl (NHC = N-heterocyclic carbene) involving different allyl groups and NHC ligands were synthesized and employed for the cycloisomerization of 1,6-dienes to form cyclic compounds selectively.

Since carbocycles and heterocycles are frequently found to be a core structure of biologically active materials,[1] enormous effort has been devoted to the construction of carbocycles and heterocycles with the simple and easy way. One of the convenient ways is the transition metal catalyzed cyclization of enynes, diynes, or dienes.[2] In the case of dienes among the other derivatives, their lower complexation ability with the transition metal complex induces the poor selectivity and yield in the cycloisomerization. Therefore, many research groups have studied to enhance the reactivity of the catalytic system and expand the substrate scope. Electrophilic Sc,[3] Ti,[4] and Zr[5] complexes were found to be good for the conversion of dienes to cyclic compounds. However, the oxophilicity of these metal complexes toward the substrates, water, and air confines the substrate scope and demands vigorously anhydrous and anaerobic reaction conditions. On the other hand, late transition metal complexes (Rh,[6] Ru,[7] Ni,[8] Pd,[9] and Pt[10]) catalyze the diene cycloisomerization under less vigorous conditions. As shown in Scheme 1, late transition metal complexes can catalyze the cycloisomerization of dienes to afford three products. The ratio of three cyclized products depends on the reaction conditions as well as catalysts.

Since recent research focuses on improving the reaction efficiency and controlling regioselectivity and stereoselectivity, a range of palladium complexes have been used as a catalyst for the diene cycloisomerization due to the ease of modifying palladium complexes and their good reactivity toward this reaction.[9] As for an attempt to improve the regioselectivity and the reaction rate, Widenhoefer presents that two different cationic Pd complexes [(η^3-C_3H_5)Pd(PCy_3) (OEt_2)]$^+$[BAr_4]$^-$ [Ar = 3,5-$C_6H_3(CF_3)_2$] and [(phen)Pd(Me)(CH_3CN)]$^+$[BAr_4]$^-$ [Ar = 3,5-C_6H_3-$(CF_3)_2$], [phen = phenanthroline] catalyze the diene cycloisomerization to afford corresponding cyclized products **b** and **c** in good yields with excellent selectivities, respectively. According to Widenhoefer's report, it is speculated that the key factors affecting the reaction rate and the selectivity might be ligands around the metal center as well as the cationic character of the palladium complex.[2f,9c,d–g] Despite of recent results, the modification of ligand in cationic palladium complexes is not well established yet. In this account, we now report new catalytic systems involving various [(NHC)Pd(η^3-allyl)]Cl (NHC = N-heterocyclic carbene) for the regioselective formation of type **a** product (Scheme 1).



Scheme 1. Cycloisomerization of 1,6-dienes.

One of the noticeable properties of N-heterocyclic carbenes (NHCs) is the σ-donating power rendering different

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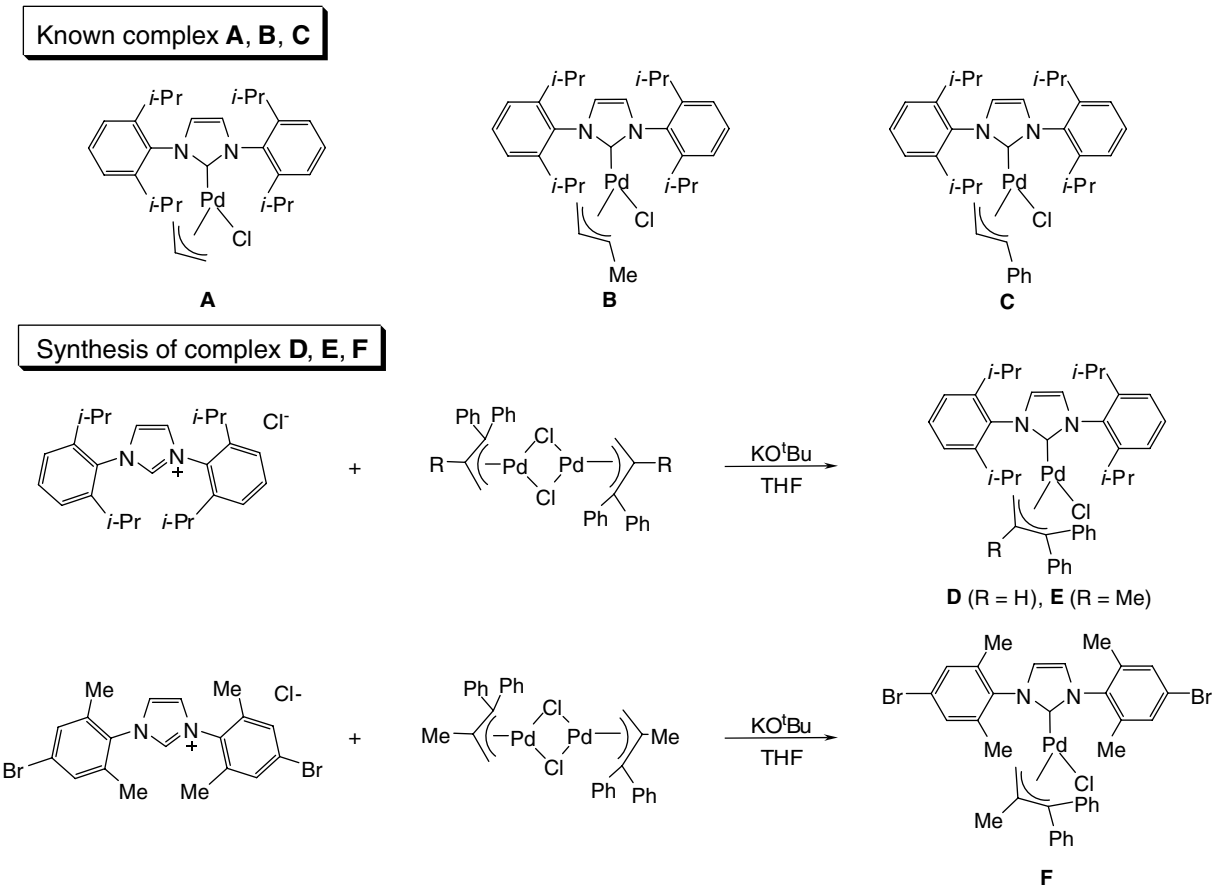


Scheme 2. [(NHC)Pd(η^3-allyl)]Cl complexes utilized in the cycloisomerization of dienes.

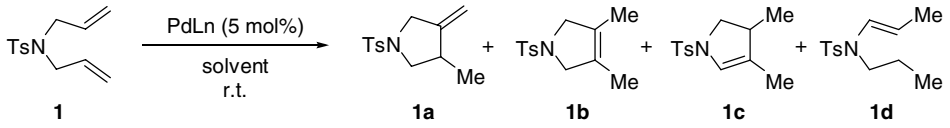
catalytic behavior of metal complexes in homogeneous catalytic transformations.[11,12] Accordingly, six (NHC)-Pd(η^3-allyl) **A**–**F** complexes possessing different allyl groups and N-heterocyclic carbenes are synthesized and used for the cycloisomerization. Complexes **A**,[13] **B**,[14] and **C**,[14] are known. The synthesis of complexes **D**,[15] **E**,[16] and **F**[17] is described in Scheme 2. The reaction of [Pd(η^3-allyl)Cl]$_2$ complex with the carbene ligand generated in situ from the imidazolium salt and KO^{t}Bu was performed in THF at ambient temperature. Resulting [(NHC)Pd(η^3-allyl)]Cl complexes are exposed to the suitable reaction conditions for the cycloisomerization. To perform an efficient and selective cycloisomerizaiton of 1,6-dienes, [(NHC)Pd(η^3-allyl)]Cl complexes and silver additives (e.g., $AgSbF_6$ and $AgClO_4$) were mixed prior to the addition of the diene assuming that highly reactive cationic NHC–Pd complexes were required for this process. In the absence of silver additives, the cyclized product was not detected.

Upon the addition of substrate **1** to the dichloromethane (CH_2Cl_2) solution of cationic NHC–Pd complexes, only cyclized product **1a** was observed along with the small amount of uncyclized product **1d** (Table 1). Neither product **1b** nor **1c** was detected under our reaction conditions.[18] This result indicates that NHC and allyl ligands on the palladium center might control the reactivity of the catalyst to form product **1a**, selectively. Different allyl moieties on the palladium center affect the yield and the reaction time (Table 1, entries 1–5). To examine the electronic effect of NHC ligands, complex **F** possessing the bromine substituted NHC ligand was used as a catalyst, rendering shorter reaction time but slightly diminished yield (Table 1, entry 9).

Based on the results of entries 1–5, and 9 in Table 1, it is noticed that complex **B**, **C**, and **E** catalyzed-cycloisomerizations show good conversion within 30 or 60 min. In further studies, the complex **E** was chosen as a catalyst for the cyclization. To increase the yield of this reaction, different silver complexes and lithium complexes were tested to form cationic NHC–Pd complexes. As indicated in entry 6 of Table 1, the reaction involving complex **E** and $AgClO_4$ provides the product in diminished yield (44%). In the case of the reaction using Li[$B(C_6F_5)_4$], no product was formed even with extended reaction time (Table 1, entry 7). In this case, changing solvents did not increase the yield (Table 1, entry 8). Thus, entry 5 of Table 1 was chosen as standard reaction conditions, which were subjected to different substrate systems.

Substrate **2** possessing a methyl substituted olefin undergoes the cyclization to provide the desired product in moderate yield.[19] Using naphthalene sulfonyl group instead of *p*-toluene sulfonyl group in the diene substrate, cyclized product **3a** was obtained in good yield (Table 2).[20] In addition to nitrogen tethered substrates,

Table 1. Cycloisomerization of substrate **1** catalyzed by cationic $[(NHC)Pd(\eta^3\text{-allyl})]^+$ complexes

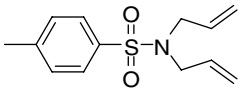
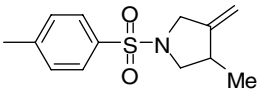
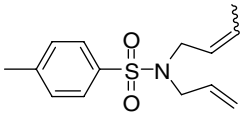
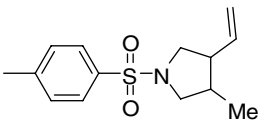
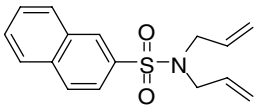
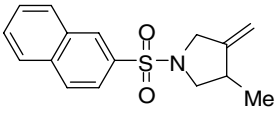


1 **1a** **1b** **1c** **1d**

Entry	PdLn	Additives	Time (min)	Solvent	Yield (**1a**) (%)
1	**A**	$AgSbF_6$ (5 mol %)	180	CH_2Cl_2	56
2	**B**	$AgSbF_6$ (5 mol %)	30	CH_2Cl_2	74
3	**C**	$AgSbF_6$ (5 mol %)	60	CH_2Cl_2	73
4	**D**	$AgSbF_6$ (5 mol %)	180	CH_2Cl_2	66
5	**E**	$AgSbF_6$ (5 mol %)	30	CH_2Cl_2	70
6	**E**	$AgClO_4$ (5 mol %)	60	CH_2Cl_2	44
7	**E**	$Li[B(C_6F_5)_4]$ (10 mol %)	60	CH_2Cl_2	—[a]
8	**E**	$Li[B(C_6F_5)_4]$ (10 mol %)	60	Chlorobenzene	—[a]
9	**F**	$AgSbF_6$ (5 mol %)	15	CH_2Cl_2	64

[a] Product **1a** was not observed.

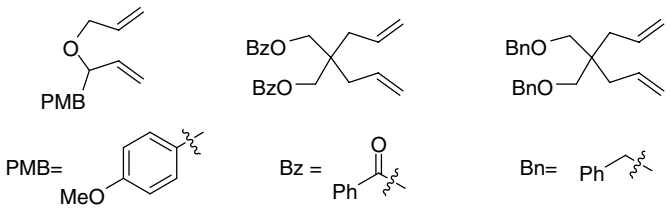
Table 2. Cycloisomerization of diene substrates catalyzed by complex **E**/$AgSbF_6$

Entry	Substrate	Product	Yield (%)
1	 **1**	 **1a**	70
2	 **2**	 **2a**	49
3	 **3**	 **3a**	72

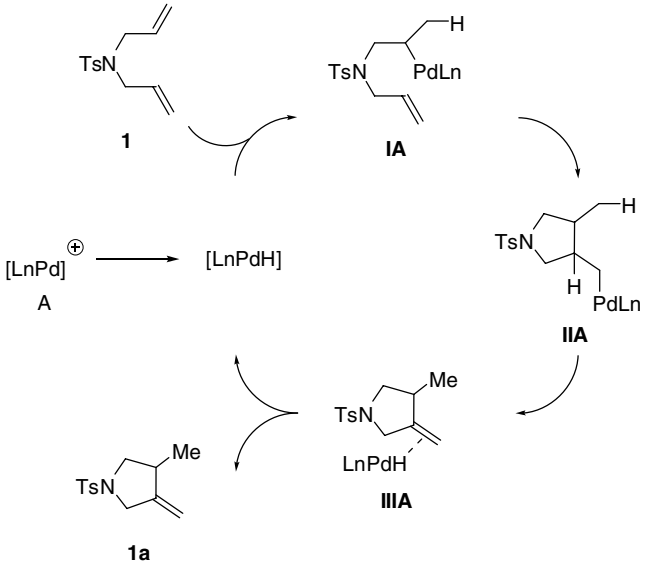
The premixed solution of $AgSbF_6$ (5 mol %) and Pd complex **E** (5 mol %) in dichloromethane (0.1 M) was added to each substrate at room temperature. The reaction was run at room temperature until the starting material was consumed.

carbon and oxygen tethered substrates were tested. Unfortunately, under our reaction conditions carbon tethered substrates did not react and were recovered at the end of the reaction. In the case of oxygen tethered substrate, starting materials were decomposed during the reaction (Scheme 3). Based on the unsuccessful results, one can speculate that the basicity of the heteroatom in the tether might be critical to perform the efficient cycloisomerization catalyzed by cationic $(NHC)Pd(\eta^3\text{-allyl})$ complexes.

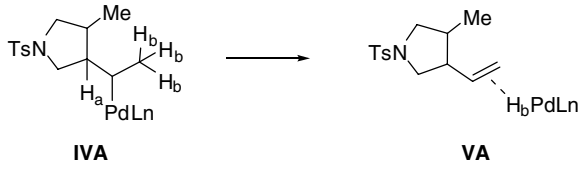
As illustrated in Scheme 4, the proposed catalytic cycle begins with the formation of a cationic palladium complex **A**.[9g] Subsequently, the palladium hydride complex can be formed through the coupling reaction of the allyl moiety and dienes, followed by β-hydride elimination as reported by Keim.[21] Once the palladium hydride complex (LnPdH) is generated, substrate **1** reacts with LnPdH through migratory insertion to afford the hydrometalated intermediate **IIA**, followed by C–C bond formation. Intermediate **IIA** undergoes β-hydride elimi-



Scheme 3. Unsuccessful substrates under the standard cycloisomerization conditions.



Scheme 4. Proposed mechanism for cationic (NHC)Pd(η^3-allyl) catalyzed cycloisomerization of dienes.



Scheme 5. β-Hydride elimination involving substrate **2**.

nation to provide the desired product **1a** along with the regeneration of LnPdH. In the case of substrate **2**, complex **IVA** undergoes β-hydride elimination with H_b in preference to H_a, which was also observed in Rh-catalyzed enyne cycloisomerization (Scheme 5).[22]

In summation, a range of [(NHC)Pd(η^3-allyl)]Cl complexes are synthesized and used as catalysts for the cycloisomerization of dienes. To find good reaction conditions, several different additives and solvents were screened. Compared to other palladium catalyzed cycloisomerization of 1,6-dienes, this protocol is highly regioselective and efficient to form cyclic compounds possessing an *exo*-methylene group. Further mechanistic studies related to this reaction and asymmetric cycloisomerization using chiral carbene ligands are underway.

Acknowledgements

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15. Synthesis of **D**: Bis-2,6-diisopropylimidazolium salt (0.30 g, 0.63 mmol) and potassium *tert*-butoxide (78 mg, 0.70 mmol) in 20 mL of tetrahydrofuran were stirred at room temperature for 4 h. Compound **4** in 10 mL of tetrahydrofuran was added to the reaction mixture and the resulting solution was stirred overnight at room temperature. After the solvent was evaporated, the product was separated by column chromatography on a silica gel column eluting with hexane and ethyl acetate (v/v, 7:3). Yield: 0.38 g (94%). ^{1}H NMR ($CDCl_3$): δ 7.42 (m, 2H), 7.11 (m, 16H), 5.01 (dd, $J = 7.4$ Hz, 1H), 3.03 (sep, $J = 6.6$ Hz, 2H), 2.92 (sep, $J = 6.6$ Hz, 2H), 2.89 (d, $J = 6.9$ Hz, 1H), 2.12 (d, $J = 12.3$ Hz, 1H), 1.40 (d, $J = 6.6$ Hz, 12H), 1.17 (d, $J = 6.6$ Hz, 12H), 1.08 (d, $J = 6.7$ Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 184.9, 145.9, 145.8, 143.4, 138.4, 136.0, 130.7, 129.7, 128.6, 128.2, 127.6, 126.7, 126.5, 124.1, 123.7, 123.6, 108.2, 108.0, 46.4, 28.6, 28.5, 26.4, 26.1, 22.8, 22.1. HRMS (M^+) calcd: 687.2930, obsd: 687.2926. $(C_{42}H_{49}N_2PdCl)_n(723.74)_n$: calcd: C, 69.70; H, 6.82; N, 3.87. Found: C, 69.88; H, 6.66; N, 3.80.
16. Synthesis of **E**: The procedure of the synthesis of **E** was in the same manner as the synthesis of **D**. Yield: 93%; ^{1}H NMR ($CDCl_3$): δ 7.32 (m, 6H), 7.11 (m, 10H), 6.87 (t, $J = 7.4$ Hz, 2H), 3.17 (sep, $J = 6.4$ Hz, 2H), 2.74 (sep, $J = 6.4$ Hz, 2H), 2.66 (s, 1H), 2.18 (s, 1H), 1.43 (d, $J = 6.6$ Hz, 12H), 1.24 (d, $J = 7.2$ Hz, 12H), 1.20 (s, 3H), 0.95 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 186.2, 146.1, 146.0, 142.4, 142.2, 136.3, 130.9, 130.6, 129.6, 128.1, 127.1, 126.1, 125.8, 124.1, 123.8, 123.7, 120.7, 105.8, 49.3, 28.7, 28.4, 27.0, 25.7, 23.1, 21.6, 21.2. HRMS (M^+) calcd: 701.3086, obsd: 701.3088. $(C_{43}H_{51}N_2PdCl)_n(737.76)_n$: calcd: C, 70.01; H, 6.97; N, 3.80. Found: C, 70.46; H, 6.93; N, 3.56.
17. Synthesis of **F**: The procedure of the synthesis of **F** was in the same manner as the synthesis of **D**. Yield: 89%; ^{1}H NMR ($CDCl_3$): δ 7.12 (m, 2H), 7.02 (m, 4H), 6.97 (m, 10H), 2.71 (d, $J = 1.5$ Hz, 1H), 2.11 (s, 6H), 2.03 (d, $J = 1.5$ Hz, 1H), 2.00 (s, 6H), 1.42 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 183.9, 141.8, 141.5, 137.7, 137.3, 131.2, 131.0, 130.8, 130.1, 127.8, 127.2, 126.4, 126.2, 122.8, 122.6, 119.8, 107.8, 49.2, 21.5, 18.5, 18.2. HRMS (M^+) calcd: 745.0045, obsd: 745.0046. $(C_{33}H_{33}N_2Br_2PdCl)_n(783.34)_n$: calcd: C, 53.67; H, 4.25; N, 3.58. Found: C, 53.48; H, 4.34; N, 3.26.
18. In Ref. 9e, $[(\eta^3\text{-}C_3H_5)Pd(MeCN)2]^+[OTf]^-$ catalyzed cycloisomerizations provide the product **a** at the initial stage. However, products **b** and **c** were also observed during the course of the reaction via Pd-catalyzed isomerization.
19. Reference for compound **2a** Oppolzer, W.; Schröder, F. *Tetrahedron Lett.* **1994**, *35*, 7939.
20. Compound **3a**: $AgSbF_6$ (8.59 mg, 0.025 mmol) and Pd complex **E** (18.45 mg, 0.025 mmol) in dichloromethane (3 mL) were stirred at room temperature for 1 h. *N*,*N*-Diallylnaphthalene-2-sulfonamide (143.7 mg, 0.5 mmol) was added to this mixture and the resulting solution was stirred at room temperature for another 10 min. The solvent was removed with a rotary evaporator to produce a residue, which was purified by column chromatography on a silica gel eluting with hexane and ethyl acetate (v/v, 100:3). Yield: 103.8 mg (72%); ^{1}H NMR ($CDCl_3$): δ 8.38 (s, 1H), 7.96 (d, $J = 8.8$ Hz, 2H), 7.90 (d, $J = 7.6$ Hz, 1H), 7.80 (d, $J = 6.8$ Hz, 1H), 7.61 (t, $J = 6.8$ Hz, 2H), 4.84 (d, $J = 6.9$ Hz, 2H), 4.02 (d, $J = 13.6$ Hz, 1H), 3.81 (d, $J = 14$ Hz, 1H), 3.81 (dt, $J = 9.2$, 2.0 Hz, 1H), 2.76 (dt, $J = 8.8$, 2.0 Hz, 1H), 2.69 (m, 1H), 1.019 (d, $J = 6.4$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 149.2, 135.03, 133.2, 132.3, 129.3, 128.1, 127.7, 123.2, 106.4, 55.5, 52.6, 37.9, 16.4. HRMS $[M+H]^+$ calcd: 288.10, obsd: 288.11. FTIR(NaCl): 2960, 2920, 2870, 1340, 1160 cm^{-1}.
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