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Dramatic Acceleration of the Pd-Catalyzed [4+2] Benzannulation Reaction of Enynes and Diynes in the Presence of Lewis Acids and Bases: Expanded Scope and New Mechanistic Insights

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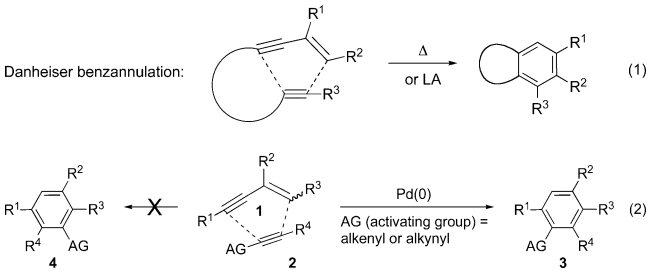
Abstract: Dramatic acceleration of the palladium catalyzed [4+2] benzannulation and sequential [2+2+2] trimerization reactions in the presence of a Lewis acid/phosphine combination or in the presence of Bronsted bases has been explored. These novel sets of conditions allowed for remarkable enhancement of reaction rates and broadening of the substrate scope and for a significant improvement of reaction yields, particularly for problematic pentasubstituted benzenes. It was found that the real nature of Lewis acid acceleration does not only lie in the isomerization of conjugated enynes but also in the direct acceleration of the [4+2] benzannulation reaction. These experimental findings, combined with the deuterium-labeling studies and DFT calculations, led to a mechanistic rationale, which (a) reasonably accounts for the observed acceleration of the reaction by Lewis acid and bases; (b) provides a viable alternative route for the ring-closing step in the mechanism of benzannulation; (c) clarifies the mechanism of hydrogen migration; and (d) for the first time provides a rationale for the origins of the remarkable stereoselectivity of the hydrogen migration during the benzannulation reaction.

Introduction

The palladium-catalyzed [4+2] benzannulation reaction of conjugated enynes and enynophiles was first reported by Yamamoto's group in 1996.[1] Since then, it has been investigated by several research groups and has become a useful synthetic method for the construction of polysubstituted benzenes.[2] One of the important features of this benzannulation reaction, which discerns it from the Danheiser benzannulation[3] (eq 1), is the requirement for an activating group (AG = alkenyl or alkynyl) in the molecule of enynophile **2** (eq 2). An activating group also exhibits an overwhelming directing effect, providing perfect regioselectivity of the cycloaddition leading to benzannulation products **3** exclusively (eq 2). Excellent functional group tolerance of the [4+2] benzannulation allowed for preparation of an array of diversely substituted arenes, such as phenols,[4] aryl ethers,[5] anilines,[6] coumaranones,[5] benzylphosphine oxides,[7] medium to large cyclophane-type structures,[8] as well as 2,6-diarylstyrenes,[9] good precursors for 4-arylphenanthrenes via a photochemical rearrangement.[10] The scope of this useful reaction has been extensively reviewed.[11]



Further elaboration of this chemistry led to the discovery of sequential trimerization of three different alkynes in the presence of Pd(0) catalyst to form up to pentasubstituted benzenes as

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(11) For reviews, see: (a) Gevorgyan, V.; Yamamoto, Y. *J. Organomet. Chem.* **1999**, *576*, 232. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (c) Saito, S.; Yamamoto, Y. Palladium-Catalyzed Benzannulation Reactions of Conjugated Enynes and Diynes. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., de Meijere, A., Eds.; Wiley: New York, 2002. (d) Rubin, M.; Sromek, A.; Gevorgyan, V. *Synlett* **2003**, 2265.

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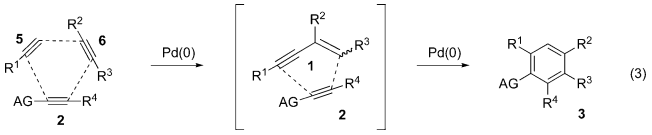
single chemo- and regioisomers (eq 3).[12] This formal [2+2+2] trimerization proceeds via reductive coupling of two similar ($R^1 = R^2$, $R^3 = H$) or different ($R^1 \neq R^2$, $R^3 = EWG$) alkynes **5** and **6** in situ furnishing requisite enyne **1**,[13] which under the same reaction conditions undergoes the [4+2] benzannulation reaction with a third alkyne component, diyne **2**, to give tetra- or pentasubstituted benzenes **3**.[12]

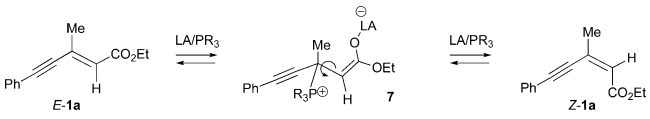


Despite remarkable selectivity and wide applicability, reactions employing di- and trisubstituted enynes usually required prolonged heating at temperatures as high as 120 °C to ensure complete conversion of starting materials.[14] As a result, the overall efficiency of the reaction in these cases was decreased, leading to only moderate yields of tetra- and pentasubstituted benzenes. Certain attempts have been made to overcome this limitation. One of the modifications involved the addition of an electron-rich phosphine ligand, such as TDMPP (TDMPP = tris(2,6-dimethoxyphenyl)phosphine), to extend the active catalyst's lifetime.[14] In the case of the [2+2+2] trimerization reaction, the most efficient protocol employed two palladium sources (Pd(II) and Pd(0) catalysts).[12] Finally, it was found that the addition of the $AlEt_2Cl/PPh_3$ combination led to a substantial acceleration of the sequential trimerization reaction. In the single reported example, a pentasubstituted benzene was obtained after 1 day at 60 °C, in contrast to the analogous reaction under Lewis acid-free conditions, which required 5 days at 100 °C for complete conversion.[12] This acceleration was attributed to the facile *E*/*Z* isomerization of trisubstituted enyne **1a**.[15] The reaction yield, however, was not improved due to the low stability of reactants under these conditions.[14]

Motivated by the importance of developing a more efficient [4+2] cyclization methodology, and intrigued by the acceleration effect observed in the presence of a Lewis acid, we performed systematic studies on the Lewis acid-assisted benzannulation reaction.

Herein, we report several important findings: (1) Pd-catalyzed benzannulation reaction performed in the presence of methylaluminoxane (MAO)/TDMPP additive resulted in dramatic acceleration of the process, as well as in significant improvement of the reaction yields; (2) the origins of Lewis acid acceleration lies not only in assisting the *E*/*Z* isomerization of enynes but, more importantly, in direct acceleration of the [4+2] benzannulation reaction; (3) addition of certain Bronsted bases causes unprecedented acceleration of the Pd-catalyzed [4+2] benzannulation reaction. The novel experimental findings combined with deuterium-labeling studies and DFT calculations resulted in a mechanistic rationale, which both reasonably explains the observed acceleration by Lewis acid and bases and also, for the first time, addresses the long held question of stereoselective hydrogen migration in the benzannulation reaction.

Table 1. Isomerization of *E*-**1a** in the Presence of Various Lewis Acids[a]



no.	Lewis acid	phosphine	time, h	*E*/*Z*	material balance, %
1	Et_2AlCl	PPh_3	0.5	1:3	75
2	$ZrBr_4$	PPh_3	5	32:1	N/D
3	$ZrCl_4$	PPh_3	15	3:1	N/D
4	$(C_6F_5)_3B$	PPh_3	15	15:1	N/D
5	Me_3Al	PPh_3	5	1:3	100
6	**Me_3Al**	**TDMPP**	**1.5**	**1:2**	**100**
7	Me_3Al	$(o\text{-Tol})_3P$	14	100:0	N/D
8	MAO[b]	PPh_3	2	1:1	80
9	**MAO[b]**	**TDMPP**	**2**	**1:1**	**94**

[a] Reaction conditions: *E*-**1a** was added to a mixture of Lewis acid (1 equiv), PPh_3 (20 mol %), and pentadecane (0.5 equiv, internal standard) at room temperature; the reaction course was monitored by GC/MS analysis. [b] Methylaluminoxane.

Results and Discussion

Acceleration of the [4+2] Benzannulation and Sequential [2+2+2] Trimerization Reactions by Lewis Acids. First, systematic studies on Lewis acid−phosphine-mediated isomerization of enynes have been performed. Efficiency of the new isomerization conditions were evaluated by reaction time, *E*/*Z* ratio of enyne, and material balance in comparison to that for the reported system (Table 1, entry 1). Screening various Lewis acids in combination with triphenylphosphine for the *E*/*Z* isomerization revealed that employment of Me_3Al and MAO allowed for efficient formation of the *Z*-isomer and maintained the "living" equilibrium for several hours (Table 1, entries 5, 8). The two most efficient Lewis acids were then tested against tris(*o*-tolyl)phosphine ($(o\text{-Tol})_3P$) and TDMPP, phosphines known to be optimal ligands for the benzannulation reaction.[14] Interestingly, it was found that TDMPP promoted *E*/*Z* isomerization equally well as PPh_3 (entries 6,9), whereas $(o\text{-Tol})_3P$ did not promote any reaction at all (entry 7).

The compatibility of the new isomerization conditions (Table 1, entries 6,9) with [4+2] benzannulation reaction was examined using enyne *E*-**1a** and dodecadiyne **2a** (Scheme 1). Although employment of Me_3Al as an additive proved unsuccessful, leading to fast decomposition of the starting materials, to our delight, the MAO−TDMPP combination allowed for smooth benzannulation at 80 °C, affording product **3aa** in 74% yield after 12 h (Scheme 1). This was a significant improvement compared to the Lewis acid-free conditions, which produced only 55% of **3aa** after a week of heating! Surprisingly, the experiment involving usually more reactive *Z*-**1a**[14] under these conditions provided benzene **3aa** in 63% yield only (Scheme 1).

A detailed investigation of the *E*-**1a** to *Z*-**1a** isomerization in the presence of the MAO−TDMPP system uncovered the mystery: it was found that the material balance in the isomerization remained perfect during the first hour of the reaction and then slowly decreased mainly due to the decomposition of the *Z*-enyne (Figure 1). Although the reasons for the lower stability of *Z*-**1a** in the presence of MAO are not clear, this fact plausibly accounts for the poorer yield obtained in the [4+2]

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(14) Gevorgyan, V.; Takeda, A.; Homma, M.; Sadayori, N.; Radhakrishnan, U.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 6391.
(15) As it was shown before, trisubstituted *Z*-enynes reacted much faster than their *E*-isomers, see ref 14.

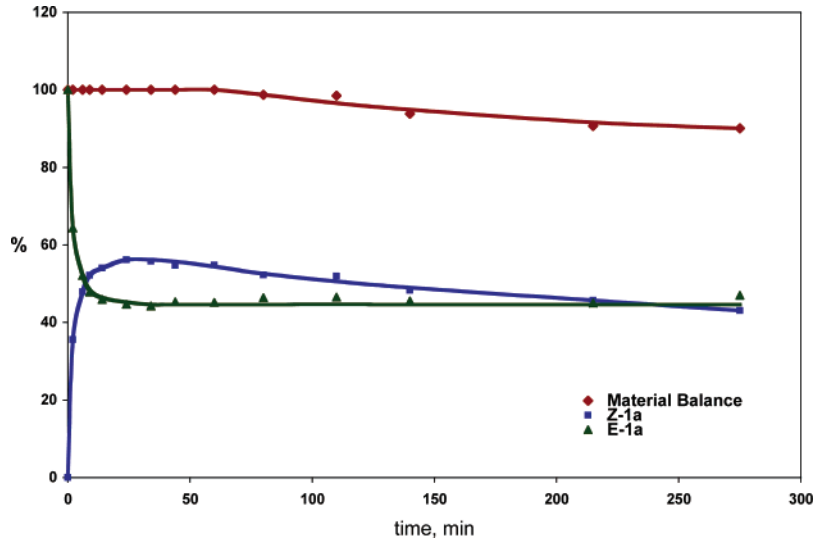
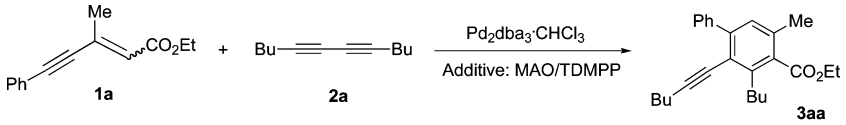


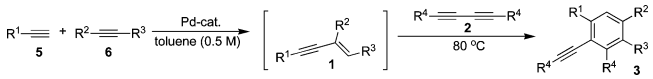
Figure 1. *E*-**1a** to *Z*-**1a** isomerization in the presence of MAO−TDMPP system.

Scheme 1



Enyne	Additive	Time/Temp.	Yield of **3aa**, %
E-**1a**	No	7 days/120 °C	55
Z-**1a**	No	6 hrs/100 °C	72
E-**1a**	Yes	12 hrs/80 °C	74
Z-**1a**	Yes	3 hrs/80 °C	63

Table 2. LA-Assisted Pd-Catalyzed [2+2+2] Trimerization of Alkynes to Pentasubstituted Benzenes



	alkynes				diyne 2							
	5	6										
no.	R^1	R^2	R^3	enyne 1[a]	R^4		time, h	ser. 1[b]	ser. 2[c]	ser. 3[d] (conds.)	product	
1	Oct	Me	COOEt	**b**	Bu	**a**	6	0	4	61 (A)	**3ba**	
2	Bu	Ph	COOEt	**c**	Ph	**b**	14	<2	<2	73 (A)	**3cb**	
3	Ph	Me	COOEt	**a**	Bu	**a**	10	0	<2	72 (A)	**3aa**	
4	Oct	Ph	COOEt	**d**	Bu	**a**	0.5	0	<2	80 (A)	**3da**	
5	Ph	Me	COOEt	**a**	Bu	**a**	18	0	<2	63 (B)	**3aa**	
6	Oct	Ph	COOEt	**d**	Bu	**a**	8	0	<2	68 (B)	**3da**	
7	Bu	Ph	COMe	**e**	Bu	**a**	3	0	<2	88 (B)	**3ea**	
8	Bu	Ph	COMe	**f**	Ph	**b**	4	0	<2	68 (B)	**3fb**	

[a] Intermediate enyne formed in situ at the first step of the sequence. [b] Series 1 NMR yields (%); conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), P(*o*-Tol)$_3$ (40 mol %). [c] Series 2 NMR yields (%); conditions: $Pd(PPh_3)_4$ (5 mol %). [d] Series 3 isolated yields (%); conditions: (A) $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol %), $Pd(OAc)_2$ (2 mol %), TDMPP (1 equiv), rt, 0.5 h; then MAO (1 equiv). (B) $Pd(OAc)_2$ (5 mol %), TDMPP (0.5 equiv), rt, 0.5 h; then MAO (0.2 equiv).

benzannulation reaction of *Z*-**1a** vs *E*-**1a** in the presence of Lewis acids (Scheme 1).

Next, MAO was tested as an additive in the Pd-catalyzed sequential [2+2+2] trimerization reaction between **5**, **6**, and **2** (Table 2, series 3). For a direct comparison, the same reactions were also run with two previously reported best trimerization catalyst systems[12] (Table 2, series 1,2). We were pleased to find that the new conditions for Lewis acids assistance conditions allowed for dramatic acceleration of the reaction rates compared to that under previously reported conditions, producing pentasubstituted benzenes **3** in good to high yields. In striking contrast, the known catalyst systems hardly initiated any reaction within the same time frame (Table 2, series 1,2, Figure 4). Addition of the Lewis acid also allowed for employment of a more bulky diphenyldiyne in the synthesis of pentasubstituted benzenes **3** (Table 2, entries 2,8), which failed to react under either of the previously reported conditions even at very high temperatures. Initially, the use of two different palladium sources, $Pd(OAc)_2$ and $Pd_2dba_3{\cdot}CHCl_3$, was thought to be necessary for efficient reductive coupling of two acetylenes by the former catalyst and subsequent [4+2] benzannulation step by the latter[16] (Method A, Table 2, entries 1−4). However, after careful optimization, we discovered that, in most cases, palladium acetate alone (5−10 mol %) can efficiently catalyze this reaction. Employment of this catalyst also allowed for reduced loading of the phosphine ligand and MAO (50 and 20 mol %,

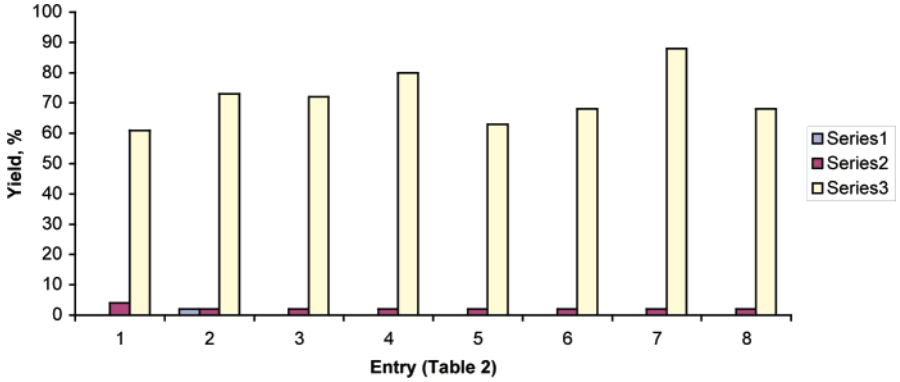


Figure 2. Comparison chart for LA-assisted Pd-catalyzed [2+2+2] trimerization of alkynes to pentasubstituted benzenes.

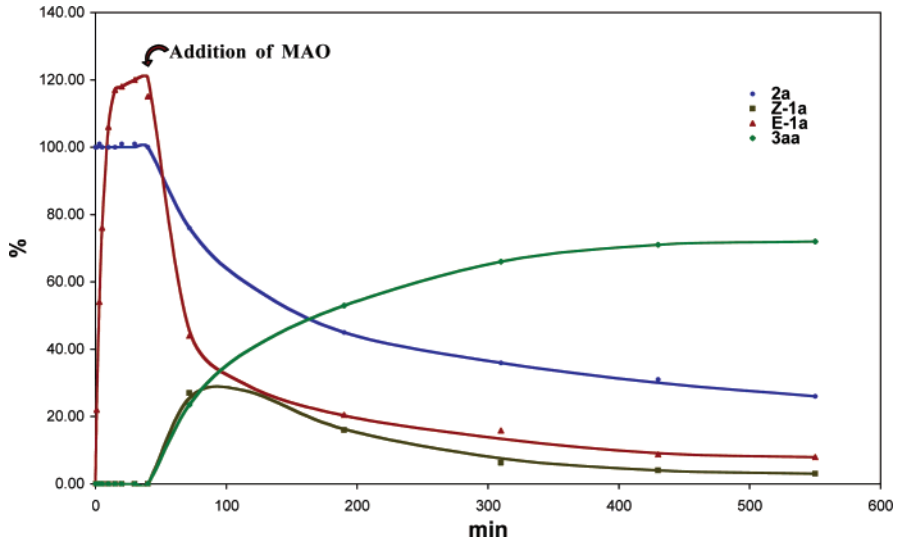


Figure 3. Kinetic profile of the sequential Pd-catalyzed [2+2+2] trimerization reaction.

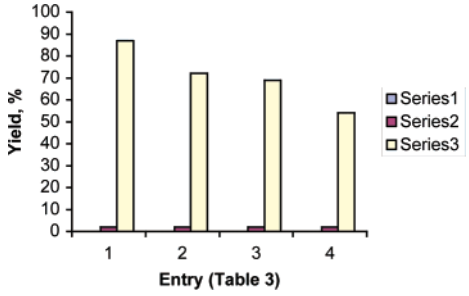


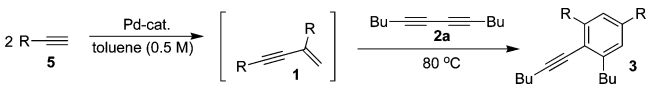
Figure 4. Comparison chart for the LA-assisted Pd-catalyzed [2+2+2] trimerization of terminal alkynes with 5,7-dodecadiyne.

respectively, Method B), which were initially used in stoichiometric amounts (Method A).

Investigation of a kinetic profile of the sequential [2+2+2] trimerization reaction has shown that at the early stage of this process, a fast formation of *E*-**1a** takes place (Figure 3).[17] Addition of MAO then triggers rapid *E*/*Z* isomerization, whereby the more reactive *Z*-enyne undergoes facile [4+2] benzannulation with the diyne **2a** to form product **3aa**.

Although at the initial stages of the project we were quite satisfied with the rationale described above for the origins of the Lewis acid acceleration effect, as we gained more unexplainable results, we began to feel that the picture is rather more complicated. For example, as mentioned earlier, the Pd-catalyzed benzannulation of *Z*-**1a** with dodecadiyne **2a** also proceeded faster in the presence of Lewis acid (Scheme 1). Intrigued by this observation, we investigated whether addition of Lewis acid would accelerate benzannulation of disubstituted enynes having no *E*/*Z* isomerization issue. To this end, we tested trimerization of terminal alkynes **5** with **2a** in the presence of MAO (Table 3, Figure 4). Remarkably, it was found that the addition of Lewis acid indeed accelerated the benzannulation, allowing reactions to take place in the span of a few hours instead of a few days!

Table 3. LA-Assisted Pd-Catalyzed [2+2+2] Trimerization of Terminal Alkynes with 5,7-Dodecadiyne

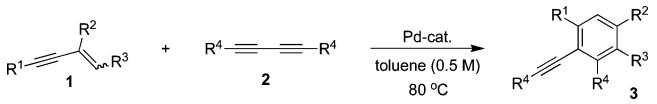


no.	alkyne 5 R	enyne 1[a]	time, h	ser. 1[b]	ser. 2[c]	ser. 3[d]	product
1	Bu	**g**	6	0	<2	87	**3ga**
2	Bn	**h**	2	0	<2	72	**3ha**
3	$Ph(CH_2)_3$	**i**	4	0	<2	69	**3ia**
4	*c*-C_3H_5	**j**	1.5	0	<2	54	**3ja**

[a] Intermediate enyne formed in situ at the first step of the sequence. [b] Series 1 NMR yields (%); conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), P(*o*-Tol)$_3$ (40 mol %). [c] Series 2 NMR yields (%); conditions: $Pd(PPh_3)_4$ (5 mol %). [d] Series 3 isolated yields (%); conditions: $Pd(OAc)_2$ (5 mol %), TDMPP (0.5 equiv), rt, 0.5 h; then MAO (0.2 equiv).

(16) As shown before, Pd(II) sources are the most efficient catalysts for the reductive coupling of alkynes,[12,13] whereas Pd(0) sources are requisite for the second step, [4+2] benzannulation reaction.[12]
(17) A slight excess of donor and acceptor alkynes (1.2 equiv) was used.

Table 4. LA-Assisted Pd-Catalyzed [4+2] Benzannulation of Enynes with Diynes



	enyne 1				diyne 2						
no.	R^1	R^2	R^3		R^4		time, h	ser.1[a]	ser. 2[b]	ser. 3[c]	product
1	Ph	OTBS	H	**k**	Bu	**a**	6	0	76	74	**3ka**
2	Ph	Me	H	**l**	Bu	**a**	17	0	85	72	**3la**
3	Bu	Bu	H	**g**	Bu	**a**	6	0	<2	81	**3ga**
4	Hex	Me	H	**m**	Ph	**b**	18	0	4	63	**3mb**
5	Hex	Me	H	**m**	Bu	**a**	96	38	27	96	**3ma**
6	$(CH_2)_2OTBS$	Me	H	**n**	Bu	**a**	8	0	4	63	**3na**
7	Bu	Ph	H	**o**	Bu	**a**	5	0	19	63	**3oa**
8	Bu	*p*-tolyl	H	**p**	Bu	**a**	3.5	0	4	68	**3pa**
9	*c*-C_3H_5	*c*-C_3H_5	H	**j**	Bu	**a**	1.5	0	40	96	**3ja**
10	Bu	Ph	H	**o**	*p*-OMe−C_6H_4	**c**	48	0	4	49	**3oc**
11	Bu	Ph	H	**o**	Ph	**b**	5	0	49	91	**3ob**
12	Bu	Ph	H	**o**	*p*-CN−C_6H_4	**d**	8	0	60	64	**3od**
13	Pent	Ph	CO_2Et (*E*)	**q**	Bu	**a**	8	0	<2	63	**3qa**
14[d]	Ph	Me	CO_2Et (*E*)	**a**	Bu	**a**	12	0	<2	74	**3aa**
15[d]	Ph	Me	CO_2Et (*Z*)	**a**	Bu	**a**	3	0	<2	63	**3aa**

[a] Series 1 NMR yields (%); conditions: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), P(*o*-Tol)$_3$ (40 mol %). [b] Series 2 NMR yields (%); conditions: $Pd(PPh_3)_4$ (5 mol %). [c] Series 3 isolated yields (%); conditions: $Pd(OAc)_2$ (5 mol %), TDMPP (0.5 equiv), *tert*-butylacetylene[18] (TBA, 20 mol %), MAO (0.2 equiv). [d] Conditions from Scheme 1: $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), TDMPP (1 equiv), MAO (1 equiv).

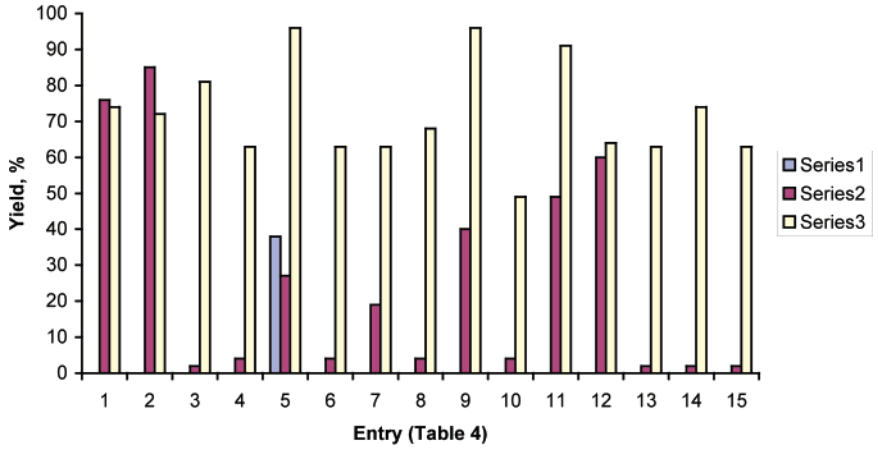


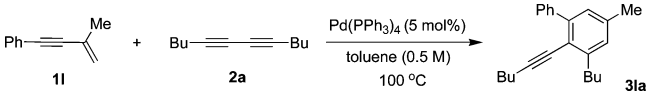
Figure 5. Comparison chart for the LA-assisted Pd-catalyzed [4+2] benzannulation of enynes with diynes.

Evidently, the Lewis acid must have another capacity in the benzannulation reaction besides simply assisting E/Z-isomerization of ester-substituted enynes!

Once it became apparent that the Lewis acid not only promotes *E/Z* isomerization but also accelerates the [4+2] benzannulation step, we examined this reaction for a series of differently substituted enynes (Table 4, Figure 5, series 3). To allow a clear-cut comparison, the same substrates were also subjected to the reaction with best reported Lewis acid-free catalyst systems[14] (series 1 and 2). It was found that a vast majority of enynes underwent benzannulation much more readily in the presence of MAO as compared to the Lewis acid-free conditions (entries 3−15). Notably, enynes possessing aryl groups at R^1 and/or R^2 reacted more readily and generally provided higher yields of products, as compared to alkyl-substituted analogues. More remarkably, cyclopropyl-substituted enyne **1j** reacted much faster than the di-*n*-butyl analogue **1g** (entry 9 vs 3), affording a very high yield of bis-cyclopropyl-substituted benzene after only 1.5 h. Apparently, the benzannulation reaction was greatly facilitated by introduction of cation-stabilizing groups in the enyne counterpart.

Acceleration of the Pd-Catalyzed [4+2] Benzannulation Reaction by Bronsted Bases. It was mentioned above that the Lewis acid-assisted benzannulation required employment of at least 0.5 equiv of basic phosphine ligand TDMPP (Tables 2−4). Naturally, we attempted to substitute the excess of expensive phosphine with alternative bases. To this end, we tested a series of different amines in the Lewis acid-assisted [4+2] benzannulation reaction. Although employment of various amine−MAO combinations did not cause any improvement, surprisingly, it was discovered that some tertiary amines alone had a notable acceleration effect on the benzannulation catalyzed by $Pd(PPh_3)_4$ (Table 5). Consequently, the accelerating effect of Bronsted bases was investigated. It was found that K_2CO_3 inhibited the reaction and secondary amines had no effect on benzannulation. In contrast, employment of 1 equiv of Et_3N indicated notable acceleration effect compared to the base-free reaction (entry 4 vs 2). Other tertiary amines tested demonstrated similar effects, leading to quantitive yields (according to NMR) after 12 h. An increase of the amine load to 2 equiv allowed for further acceleration leading to a complete reaction after only 6 h (entry 11).

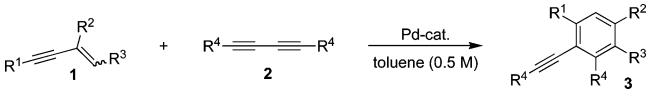
Table 5. Optimization of Base Additive in the [4+2] Benzannulation of **1l** with **2a**



no.	base (1 equiv)	time, h	NMR yield, %
1	-	6	51
2	-	12	85
3	K_2CO_3	6	19
4	*i*-Pr_2NH	12	87
5	Et_2NH	12	85
6	Et_3N	6	70
7	Et_3N	10	100
8	Pyridine	12	100
9	Et_2NMe	12	100
10	TMEDA	12	90
11	**Et_3N**[a]	**6**	**100**

[a] Two equiv of Et_3N were used.

Table 6. Base-Promoted Pd-Catalyzed [4+2] Benzannulation of Enynes with Diynes

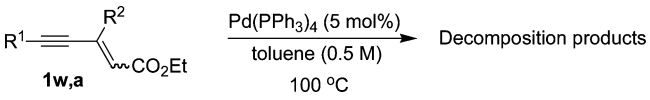


	enyne 1				diyne 2		time,				
no.	R^1	R^2	R^3		R^4		h	ser.1[a]	ser. 2[b]	ser. 3[c]	product
1	Ph	Ph	H	**r**	Bu	**a**	1	0	25	78	**3ra**
2	Ph	Ph	H	**r**	Ph	**b**	1.5	<2	<2	60	**3ra**
3	Hex	Me	H	**m**	Bu	**a**	24	0	40	70	**3ma**
4	Hex	Me	H	**m**	Ph	**b**	30	0	35	68	**3mb**
5	Ph	Me	H	**l**	Bu	**a**	5	0	62	100	**3la**
6	*c*-C_3H_5	*c*-C_3H_5	H	**j**	Bu	**a**	1	0	<2	86	**3ja**
7	Ph	Me	COOEt (*E*)	**a**	Bu	**a**	24	<2	12	70	**3aa**
8	Ph	Me	COOEt (*Z*)	**a**	Bu	**a**	5	0	35	77	**3aa**
9	Ph	Ph	COOEt (*E*)	**s**	Bu	**a**	4.5	0	44	81	**3sa**
10	Ph	Ph	COOEt (*Z*)	**s**	Bu	**a**	3	0	40	84[d]	**3sa**
11	Cyclohexene	Me	COOEt (*E*)	**t**	Bu	**a**	60	0	4	62	**3ta**
12	Cyclohexene	Me	COOEt (*Z*)	**t**	Bu	**a**	36	0	<2	75	**3ta**
13	CH_2OMe	Me	COOEt (*E*)	**u**	Bu	**a**	24	0	<2	58	**3ua**
14	CH_2OMe	Me	COOEt (*Z*)	**u**	Bu	**a**	8	0	10	66[e]	**3ua**
15	CH_2NEt_2	Me	COOEt (*Z*)	**v**	Bu	**a**	12	<2	<2	74	**3va**
16	Bu	Me	COOEt (*E*)	**w**	Bu	**a**	48	0	<2	24[f]	**3wa**
17	Bu	Me	COOEt (*Z*)	**w**	Bu	**a**	4	0	44	45[f]	**3wa**

[a] Series 1 NMR yield (%); conditions: $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %), P(*o*-Tol)$_3$ (40 mol %), 80 °C. [b] Series 2 NMR yield (%); conditions: $Pd(PPh_3)_4$ (5 mol %), 100 °C. [c] Series 3 isolated yield (%); conditions: $Pd(PPh_3)_4$ (5 mol %), Et_3N (2 equiv), 100 °C. [d] Run at 80 °C. [e] Run at 60 °C. [f] NMR yield.

Having in hand new efficient conditions for the Pd-catalyzed [4+2] benzannulation reaction of enyne **1** and diyne **2**, we investigated the generality of this method. It was found that, regardless of the substitution pattern, 1,3-disubstituted enynes reacted faster in the presence of Et_3N and provided superior yields of the corresponding benzenes (Table 6, entries 1−6, Figure 6, series 3), in striking contrast to the analogous reactions run under previously reported conditions (series 1,2). Furthermore, the addition of triethylamine allowed for broadening the scope of trisubstituted enynes that can now efficiently be employed in the [4+2] benzannulation (entries 7−17), spanning from enynes bearing bulky substituents R^1, such as cyclohexenyl groups (entries 11,12), to methoxymethyl- and aminomethyl-substituted substrates (entries 13−15).

Table 7. Stability Test for Trisubstituted Enynes *Z*-**1a**,**w**



	enyne 1					material loss[a]	
no.	R^1	R^2		config.	time, h	with Et_3N (2 equiv)	no Et_3N
1	Bu	Me	**w**	E	48	50	<5
2	Bu	Me	**w**	Z	5	50	20
3	Ph	Me	**a**	E	24	<5	<5
4	Ph	Me	**a**	Z	5	<5	<5

[a] Determined by GC/MS.

The only problem encountered with the conditions under base assistance was the somewhat poorer reaction yields obtained with trisubstituted enynes possessing an *n*-alkyl chain at the triple bond (entries 16,17). It was proposed that the decreased efficiency of the benzannulation in these cases resulted from the low stability of the starting enynes under the reaction conditions, possibly due to competing isomerization of the enyne into a cumulene analogue.[19] Indeed, control experiments performed in the absence of a diyne revealed that 4-*n*-alkyl-substituted enynes undergo substantial decomposition in the presence of amine (Table 7, entries 1,2). In contrast, enynes possessing an aryl substituent at the alkynyl position appeared to be quite stable both with and without amine present in the mixture (Table 7, entries 3,4).

Mechanistic Rationale for the Lewis Acid and Bronsted Base Acceleration in the Pd-Catalyzed Benzannulation Reaction. As mentioned in the introductory section, the Pd-catalyzed benzannulation reaction has rather unique features, which set it apart from both Danheiser benzannulation[3,20] and traditional transition metal-catalyzed [2+2+2] trimerization of

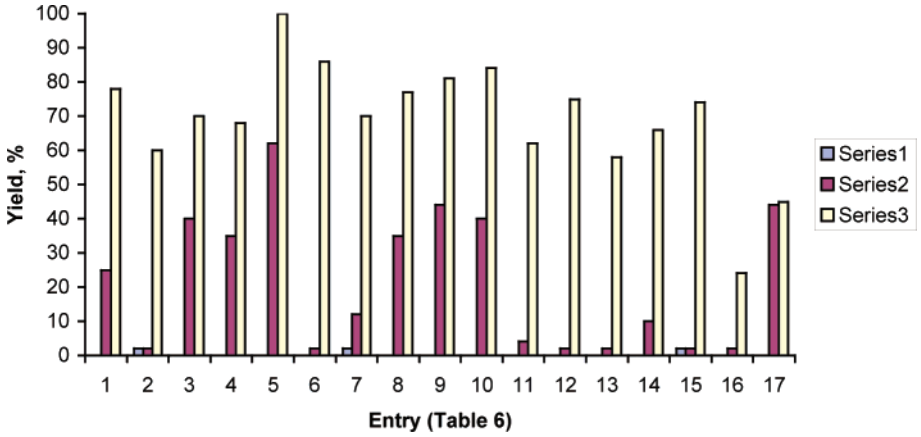
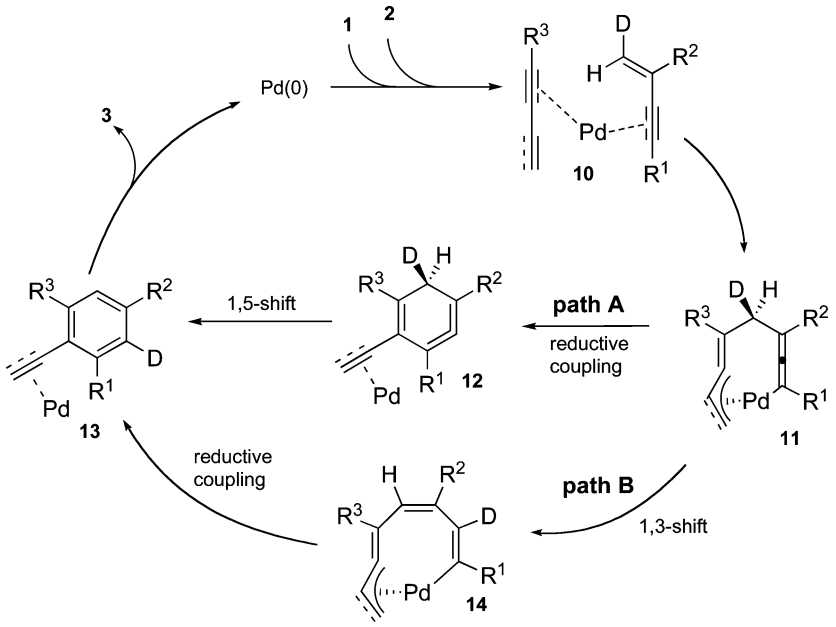


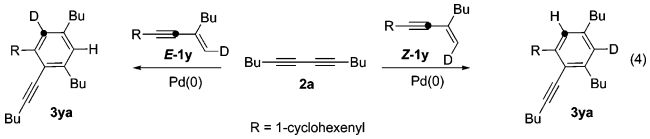
Figure 6. Comparison chart for the base-promoted Pd-catalyzed [4+2] benzannulation of enynes with diynes.

Scheme 2



alkynes.[21,22,23] Thus, attempts to invoke mechanistic pathways analogous to those proposed for the latter transformations failed to explain (a) the exclusive formation of a single regioisomer **3** over **4** (eq 2) and (b) the requirement for the activating group in the coupling partner **2**. Consequently, at early stages of this chemistry, we have proposed the following mechanistic rationale, which reasonably addressed the above issues (Scheme 2).[14] According to this mechanism, triple bonds of reactants **1** and **2** coordinate to palladium to form a bis-alkynylpalladium complex **10**, which via metallacycloaddition is transformed into the key intermediate **11**. This species undergoes reductive elimination to form strained cyclohexatriene **12**, which via a subsequent [1,5]-hydride shift[3a] affords intermediate **13** (Scheme 2, **path A**). Alternatively, a formal 1,3-hydrogen migration in **11** transforms it into palladaheptatriene **14**, which upon reductive elimination and dissociation furnishes reaction product **3** (Scheme 2, **path B**).[14]

The major flaw of **path A** was the inexplicable stereoselectivity of hydrogen migration observed in the benzannulation of monodeuterated enynes *E*- and *Z*-**1y**, which showed the exclusive migration of deuterium from the *E*-position (sp-carbon atom, to which migration occurs is marked for clarity, eq 4).[14] Indeed, in this case, neither a [1,5]-hydride shift[3a] nor a series of [1,2] shifts[20] in the rather planar **12**[24] should exhibit stereochemical preference. Furthermore, it was shown that partial scrambling (ca. 10%) occurs in the benzannulation reaction performed with 1,1-dideutero-enyne **1**, which is inconsistent with a pure sigmatropic hydride shift.[14]



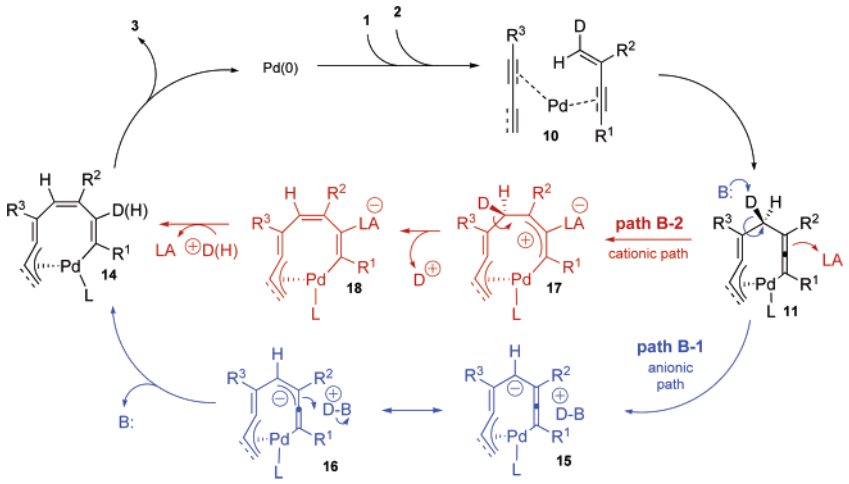
(4)

Thus, we were eager to clarify whether there is a route under general **path B**, which could account for the exceptional selectivity of the hydrogen migration in **11**. We rationalized that potentially, the apparent 1,3-hydrogen migration may proceed via two routes: (1) deprotonation/protonation sequence (**path B-1**) and (2) an electrophilic **path B-2** (Scheme 3). The anionic **path B-1**[25] presumes deprotonation/protonation sequence **11**→**15**/**16**→**14**. This path is strongly supported by the significant acceleration observed in the presence of Bronsted bases and also by the fact that a geminal EWG, which facilitates deprotonation, is well tolerated at that position.[12,14] The prototropic rearrangement[26] (**path B-2**) is consistent with the discovered Lewis acid acceleration effect. It operates via electrophilic attack of proton (or Lewis acid) at the sp carbon of allene **11** to form **17**. Formation of intermediate **17** is in accord with our observation that cation-stabilizing groups at R^1 and R^2 greatly facilitate the reaction (vide supra). Subsequent deprotonation followed by a replacement of the Lewis acid by a proton (unless LA = H^+) leads to the same palladaheptatriene **14**.

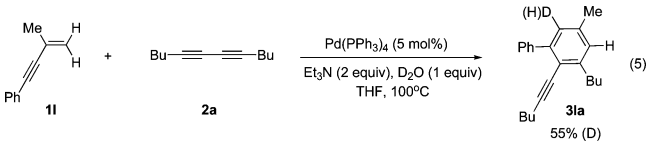
To gain additional support for the possible ionic motif of the formal 1,3-hydrogen migration, we performed an experiment in which protio enyne **1l** was subjected to the reaction with **2a** in the presence of NEt_3/D_2O mixture (eq 5). As a result, benzene **3la** was obtained with 55% D incorporation at the C-3 position,

(18) *tert*-Butylacetylene was added as "dummy" alkyne to assist the reduction of Pd(II) to Pd(0).
(19) Ogasawara, M.; Hayashi, T. Transition Metal-Catalyzed Synthesis of Allenes. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004.
(20) For a discussion on Danheiser benzannulation, see: Rodriguez, D.; Navarro-Vazquez, A.; Castedo, L.; Dominguez, D.; Saa, C. *J. Org. Chem.* **2003**, *68*, 1938, and references therein.
(21) Ozerov, O. V.; Patrick, B. O. Ladipo, F. T. *J. Am. Chem. Soc.* **2000**, *122*, 6423.
(22) For a review, see: (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. See also: (b) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **2001**, *123*, 9324. For the discussion on the mechanism of the transition metal-catalyzed [2+2+2] trimerization reaction, see: (c) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (d) Hardesty, J. H.; Koerner, J. B.; Albright, T. A.; Lee, G.−Y. *J. Am. Chem. Soc.* **1999**, *121*, 6055.
(23) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **1999**, *121*, 11093.
(24) Angus, R. O., Jr.; Schmidt, M. W.; Johnson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 532.
(25) For anionic isomerization in allylic system, see: Huenig, S.; Klaunzer, N.; Schlund, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1281.
(26) For allylic prototropic rearrangements catalyzed by Lewis acid, see: Cameron, G. S.; Stimson, V. R. *Aust. J. Chem.* **1977**, *30*, 923.

Scheme 3



thus confirming the above hypothesis.[27] Apparently, both anionic and cationic pathways can operate under the "neutral conditions" (i.e. in the absence of Lewis acid or base), because the phosphine ligands present are somewhat basic and eventual proton sources always exist in the reaction mixture. The extent to which one pathway dominates over the other can be affected by the substitution pattern of substrates and the nature of the catalyst system employed.



Next, to clarify the stereochemical preference of the hydrogen migration, we analyzed the proposed intermediates in **paths B-1** and **B-2** from the standpoint of potential differences in deprotonation aptitude between *Z* and *E* hydrogens. We reasoned that abstraction of either *Z* or *E* proton from **11** in **path B-1** should provide the same flat anionic species **15**, which already lost the stereochemical information due to strong conjugation. Indeed, our DFT calculations (B3LYP LANL2DZ) confirmed the conjugation and completely flat geometry of anion **15** (Figure 7).[28]

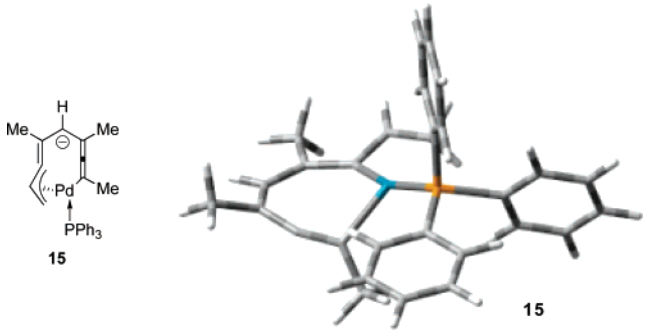


Figure 7. Optimized geometry of intermediate **15**.

Consequently, the enthalpies of abstraction of either *E* or *Z* protons would be identical; therefore, the observed selectivity cannot be explained on the basis of thermodynamic factors and most likely arise from the difference in kinetic acidity between H^E and H^Z (Scheme 2). Indeed, it is reasonable to propose that palladacyclic intermediate **11** still preserves the stereochemical information, creating a different steric environment for the former *E* and *Z* hydrogen atoms, thus altering their propensity toward deprotonation. To validate these assumptions, we performed computational studies. We considered two potential structures for palladacyclic intermediate **11**, 16-electron η^1- and η^3-complexes **11a** and **11b**, and looked at the relative steric surroundings for the *E* and *Z* hydrogen atoms in the optimized geometries for both putative intermediates (Figure 8).[28] As it can be seen from the optimized structures, the former *Z* hydrogen atom is significantly more sterically hindered in both **11a** and **11b** complexes. Thus, in **11a**, H^Z is blocked from potential approach by a base by one of the aryl rings of the phosphine ligand and a substituent at C-2 (i.e., R^2) of the former enyne. Similarly, in η^3-complex **11b**, pseudoequatorial H^Z is clamped by the two substituents at the adjacent carbon atoms, which makes pseudoaxial H^E much more accessible for the base. Although it is not clear whether deprotonation occurs at **11a** and/or **11b**,[29] on the basis of the analysis provided above, in either palladacycle, H^E is expected to be more accessible for deprotonation, explaining the observed stereochemical preference in hydrogen migration.

Geometries of the analogous mono and bisphosphine cationic intermediate complexes **17a,b** (**pathway B-2**) were also examined with respect to relative propensity of H^E and H^Z toward deprotonation (Figure 9).[28] Optimization of cation **17b** revealed that the empty *p*-orbital of the carbocation is nearly orthogonal (ca. 80°) to the C−H^Z bond, whereas the corresponding angle with the C−H^E bond is a factor of 2 smaller (ca. 40°). Accordingly, more efficient hyperconjugation of the *p*-orbital of the carbocation with the σ*-orbital of C−H^E would make this bond significantly weaker and, thus, more prone to deprotonation.

(27) Analogously, partial incorporation of electrophilic entities into the benzene ring was observed in various types of benzannulation reactions. See ref 2b, 3a, 20.

(28) Geometry optimization was performed employing B3LYP in LANL2DZ basis. See Supporting Information for details.

(29) Comparison of the ground-state energy values obtained for mono- and bisphosphine intermediates **11a** and **11b** (i.e., **11a** vs **11b** + PPh_3) revealed that the former complex is 1.7 kcal/mol more stable than the latter. This relatively insignificant difference does not allow for unambiguous assignment of either form **11a** or **11b** to the intermediate **11**, which most likely exists in equilibrium between these two forms, which is affected by the temperature and effective concentration of phosphine ligands in the reaction mixture.

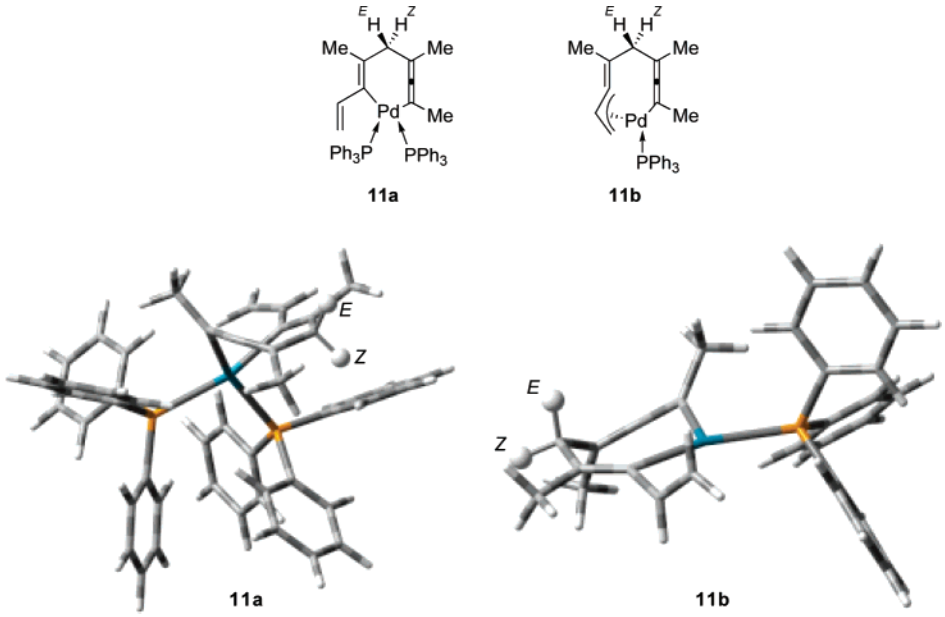


Figure 8. Optimized geometries of intermediates **11a** and **11b**.

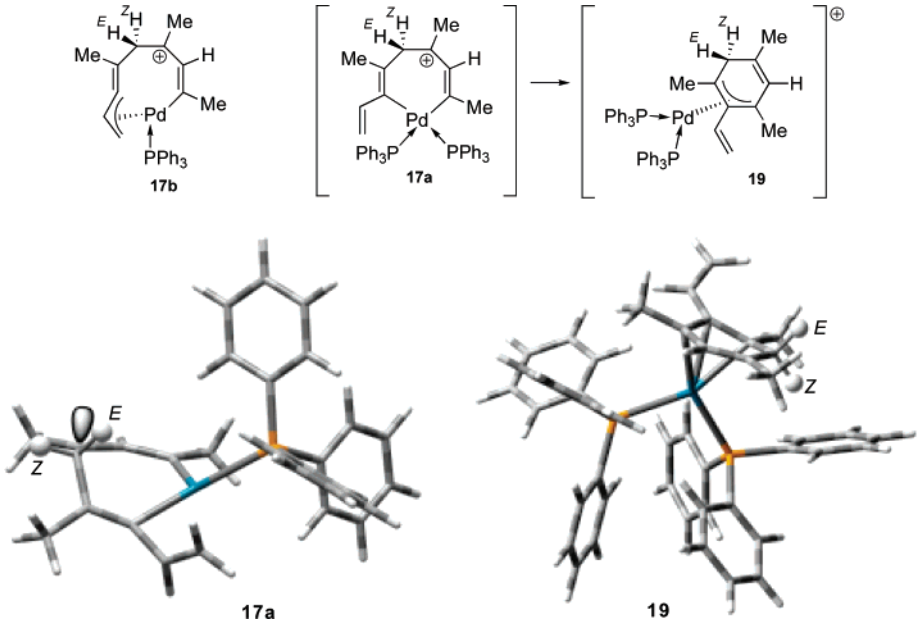
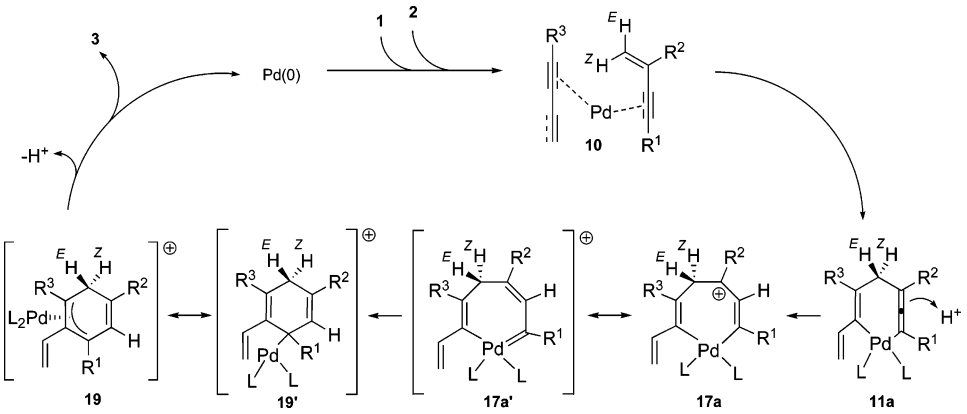


Figure 9. Optimized geometries of intermediates **17a** and **19**.

Unexpectedly, attempts to find a global minimum for bisphosphine complex **17a** failed, and geometry optimization resulted in a cationic η^3-cyclohexadienylpalladium species **19** (Figure 9). The transformation of **17a** into **19** can be rationalized as a migratory insertion of the carbene into the metal−carbon bond (or 1,2-migration), a process that has numerous literature precedents.[30] The cationic complex **17a** can also be represented as another resonance form **17a′**, with a vinyl group and a carbene ligand on palladium (Scheme 4). Two bulky, electron-rich phosphine ligands would provide sufficient electronic stabilization for the resonance form **17a′** and, simultaneously, create significant steric constraints to trigger 1,2-migration (the situation that is not realized in the monophosphine complex **17b** due to the presence of only one phosphine ligand). The obtained nearly planar cationic complex **19**, in contrast to **17b**, does not have any thermodynamic preferences toward abstraction of either *E* or *Z* protons (Figure 9). However, similarly to **11a**, kinetic acidity should be significantly higher for the sterically less encumbered H^E in **19**. Upon phosphine- or external base-assisted deprotonation, **19** would be transformed into benzannulation product **3** and the released Pd(0) species would return to the catalytic cycle (Scheme 4). An attractive feature of this mechanistic rationale is that, in contrast to the previously proposed mechanisms, it provides a viable alternative route for the ring-closing step via a very facile protonation[31] of the strained allenic

(30) For representative examples, see: (a) Hoover, J. F.; Stryker, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 464. (b) O'Connor, J. M.; Pu, L.; Woolard, S.; Chadha, R. K. *J. Am. Chem. Soc.* **1990**, *112*, 6731. (c) Trace, R. L.; Sanchez, J.; Yang, J.; Yin, J.; Jones, W. M. *Organometallics* **1992**, *11*, 1440. (d) Bergamini, P.; Costa, E. *Organometallics* **1994**, *13*, 1058. (e) Nakazawa, H.; Yamaguchi, Y.; Mizuta, T.; Ichimura, S.; Miyoshi, K. *Organometallics* **1995**, *14*, 4635. (f) McGuinness, D. S.; Saendig, N.; Yates, B. F.; Cavell, K. J. *J. Am. Chem. Soc.* **2001**, *123*, 4029.

Scheme 4



species **11**, followed by spontaneous, sterically driven migratory insertion to form **19**, thus avoiding the arguable[32] metallaheptatriene intermediate **14** (Schemes 2,3).

Overall, several important implications arise from these mechanistic studies. The stereochemical information is translated from enyne **1** to the key intermediate **11**, and, thus, the former *E* and *Z* hydrogens in **11** appear in different steric environments. The 1,3-migration of hydrogen has significant ionic nature and can potentially proceed via a deprotonation/protonation sequence (**path B-1**), or via a cationic pathway (**B-2**) depending on the substitution pattern of substrates, the catalyst combination, and the presence of acidic or basic additives in the reaction mixture. Migration of the *E* hydrogen atom is more favorable than that of the *Z* hydrogen regardless of the pathway, as H^Z is significantly more hindered by the vicinal substituents and by the aryl rings of the phosphine ligands. Formation of the six-membered ring of the product can potentially occur not only via the reductive elimination of palladium from the palladaheptatriene species **14** (Scheme 3) but also via the protonated intermediate **17a′** that, upon 1,2-migration of an alkenyl group from palladium to a carbene ligand, can produce η^3-cyclohexadienylpalladium species **19**, which, after loss of a proton, affords the benzene derivative **3** (Scheme 4).

Conclusions

In summary, a dramatic acceleration of the Pd-catalyzed benzannulation reaction was achieved in the presence of MAO−TDMPP additives. It was also found that tertiary amines exhibit even more pronounced accelerating effects on this reaction. These novel sets of conditions not only significantly facilitated the Pd-catalyzed [4+2] benzannulation reaction but also improved the yields and, most remarkably, widened the scope of tetra- and pentasubstituted benzenes which can now efficiently be obtained by this methodology. A detailed investigation of the observed effects suggested that the real nature of the acceleration lies not only in assisting the *E*/*Z* isomerization of starting enynes but also in promoting one of the key steps of the [4+2] benzannulation, the formal 1,3-hydrogen migration. The proposed new mechanistic rationale for the first time reasonably accounts for the origins of highly stereoselective formal 1,3-migration involved in the benzannulation step.

Acknowledgment. Financial support by the National Science Foundation (CHE 0354613) is gratefully acknowledged.

Supporting Information Available: Full experimental details, Cartesian coordinates of B3LYP/LANL2DZ-optimized geometries for reactive intermediates **11a**,**b**, **15**, **17b**, **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA060085P

(31) Nikitina, A. F.; Sheridan, R. S. *Org. Lett.* **2005**, *7*, 4467.
(32) Involvement of a metalloheptatriene intermediate in transition metal-catalyzed [2+2+2] cyclotrimerization of alkynes is still under debate. See: (a) Bianchini, C.; Caulton, K. G.; Chardon, C.; Eisenstein, O.; Folting, K.; Johnson, T. J.; Meli, A.; Peruzzini, M.; Rauscher, D. J.; Streib, W. E.; Vizza, F. *J. Am. Chem. Soc.* **1991**, *113*, 5127. (b) Hardesty, J. H.; Koerner, J. B.; Albrignt, T. A.; Lee, G.-Y. *J. Am. Chem. Soc.* **1999**, *121*, 6055.