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Palladium Catalysis

Palladium-Catalyzed Regiodivergent Substitution of Propargylic Carbonates

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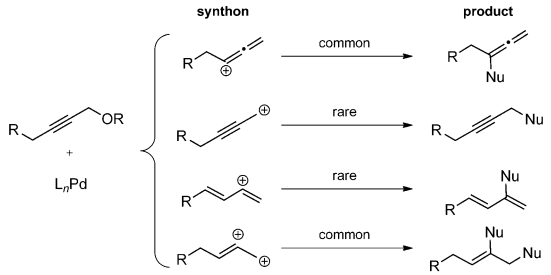
Abstract: The palladium(0)-catalyzed, ligand-controlled, regioselective addition of diaryl acetonitrile pronucleophiles to propargylic carbonates is reported. Selective formation of either terminal 1,3-dienyl or propargylated products is proposed to arise from a change in reaction mechanism controlled by the denticity of the coordinating ligand.

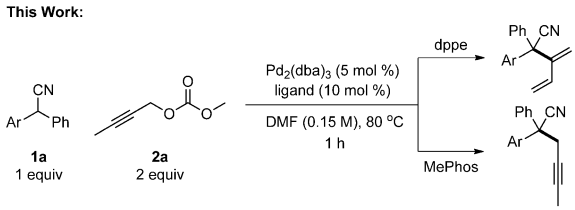
Introduction

Transition metal-catalyzed cross-coupling reactions with propargyl electrophiles offer the potential to develop regiodivergent strategies to access functionally diverse products from a single class of starting materials (Scheme 1).[1,2] However, compared to allylic analogues,[3–4] palladium-catalyzed couplings of propargyl electrophiles have received much less attention. One potential reason for the lesser development of these couplings is the greater complexity in achieving regioselective and chemoselective substitution (Scheme 1). Typically palladium-catalyzed propargylic substitutions using relatively non-stabilized carbon nucleophiles ($pK_a > 20$) yield allene products.[5] In contrast, the use of stabilized nucleophiles, such as malonates, commonly leads to bis-addition products,[6] whereas selectivity for propargylic substitution is much more rare.[7,8] Furthermore, only under select circumstances, primarily controlled through cyclization, have diene products arisen from the substitution of propargyl electrophiles.[9] Therefore, development of new methods that selectively arrive at propargyl and/or terminal dienyl functionalities from propargylic carbonates would be a significant step in overcoming current limitations in catalytic propargylic substitution chemistry.[10–12] Here, we report the palladium-catalyzed, ligand-controlled cross-coupling of propargylic carbonates with diaryl acetonitrile pronucleophiles to yield either terminal 1,3-dienyl or propargylated quaternary diarylmethane products (Scheme 2).[13]

Current synthetic methods that achieve the direct cross-coupling of butadiene synthons rely heavily on pre-formed organometallic or organoborane reagents. [14,15] Consequently, these methods lack step-economy and produce a significant amount of waste. Therefore, it would be useful to develop alternative

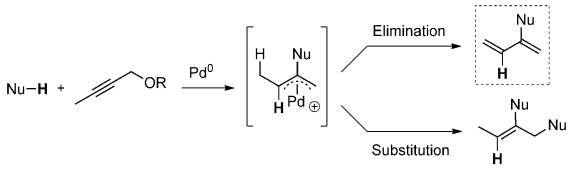


Scheme 1. Potential substitution products.



Scheme 2. Regiodivergent substitution of propargylic carbonates.

methods to cross-couple 1,3-dienyl motifs by reaction of readily available starting materials under mild reaction conditions, while minimizing overall byproduct formation. To address this need, we hypothesized that propargyl carbonates could serve as diene electrophiles if, after mono-substitution to generate a palladium π-allyl intermediate,[2b,5m,18a] elimination occurred instead of the more common attack by a second nucleophile (Scheme 3).[6] This method would provide facile access to 1,3-dienes in an atom- and step-economic fashion through the formal coupling of an electrophilic 1,3-diene synthon. To the



Scheme 3. Proposed synthetic route to 1,3-dienes.

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best of our knowledge, the use of a propargyl carbonate as a source of a butadiene electrophile for cross-coupling has not been reported.[9]

Results and Discussion

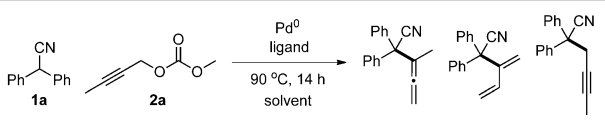
1,3-Dienylation

Given our experience with allylic alkylations of acetonitriles,[16] our optimization studies began by examining the effects of palladium catalyst, ligand, and solvent on the cross-coupling of methyl propargyl carbonate with commercially available diphenyl acetonitrile (Table 1). Initially, reaction conditions that previously provided high yields for allylation of tertiary acetonitriles with allylic alcohols were employed (entry 1).[16b] Under these conditions, GC/MS analysis revealed the formation of three isomeric products. Upon isolation and characterization of each product, it was confirmed that the major products were the 1,3-dienyl and propargyl isomers, with only minor formation of the allene. To optimize reaction conversion, we next conducted a solvent screen, which revealed that polar aprotic solvents provided optimal conversion (entries 1, 3) compared to non-polar solvents (entries 2, 17, 18). In an attempt to determine the ligand effect on product ratios, several bidentate ligands were examined (entries 4–9). Excitingly, 1,2-bis(diphenylphosphino)ethane (dppe) displayed optimal selectivity for the 1,3-diene product (entry 5). This result is in contrast with most previous accounts that report cyclization,[9] bis-addition,[6] or allenylation[5] as the major products arising from palladium-catalyzed substitution of propargylic carbonates using bidentate ligands.[1a,5m]

With the optimized reaction conditions established for the 1,3-dienylation of diphenylacetonitrile, we next evaluated the scope of α,α-diaryl acetonitrile derivatives in the substitution of methyl propargyl carbonate to synthesize 1,3-dienyl motifs (Scheme 4).[17] A variety of unsymmetric diarylacetonitrile reactants with electron-donating or -withdrawing substituents provided product in good to excellent yield (**3b**, **c**, **h**, **m**). Further, *meta*-chloro- and *para*-bromo-substituted arenes, which can be prone to other coupling reactions, were well tolerated (**3g**, **e**). Notably, a variety of substitution patterns were tolerated and even increased steric bulk at the *ortho*-position did not hinder product formation (**3c**, **f**, **h**). Basic heteroaryl moieties required reduced reaction time and, unfortunately, lead to poor isolated yields (**3i**, **j**). In contrast, the non-basic heteroaromatic 1,5-dimethyl pyrrole reactant provided product in good yield as did arene substituents that contained extended conjugation (**3d**, **f**, **k**). Lastly, styrene and benzoxazole derivatives were unsuccessful and only degradation of the starting material was observed (**3n**, **o**).

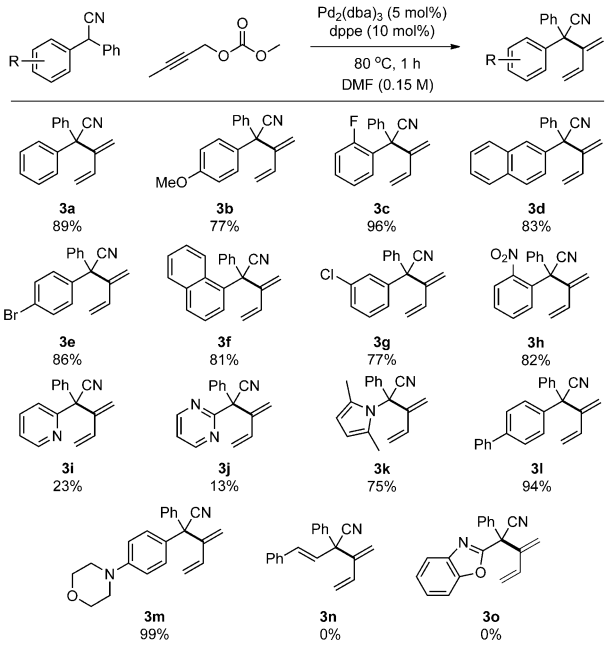
With the functional group tolerance evaluated for the acetonitrile reaction component, other propargylic carbonates were examined to see if they could be used to form substituted diene products (Table 2). It was found that nucleophilic substitution of a terminally substituted ethyl or heptyl propargylic carbonate resulted in decreased isolated yields (**4b**, **c**) compared to the model substrate **3a**. However, terminally substi-

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	Ligand	Solvent	1a	Allene	Diene	Propargyl
1	$Pd(PPh_3)_4$	–	DMSO	26	3	40	31
2	$Pd(PPh_3)_4$	–	THF	62	1	15	22
3	$Pd(PPh_3)_4$	–	DMF	3	0	55	39
4	$Pd_2(dba)_3$	dppm	CH_3CN	28	4	42	27
5	$Pd_2(dba)_3$	dppe	CH_3CN	3	0	94	3
6	$Pd_2(dba)_3$	dppp	CH_3CN	5	0	87	8
7	$Pd_2(dba)_3$	dppb	CH_3CN	2	0.2	85	13
8	$Pd_2(dba)_3$	dppf	CH_3CN	1	0.5	74	24
9	$Pd_2(dba)_3$	XantPhos	CH_3CN	1	11	7	31
10	$Pd_2(dba)_3$	*rac*-BINAP	CH_3CN	4	0.5	70	24
11[b]	$Pd_2(dba)_3$	JohnPhos	CD_3CN	45	20	2	33
12[b]	$Pd_2(dba)_3$	*t*Bu-MePhos	CD_3CN	22	29	2	47
13[b]	$Pd_2(dba)_3$	Cy-JohnPhos	CD_3CN	56	4	15	25
14[b]	$Pd_2(dba)_3$	MePhos	CD_3CN	11	3	19	67
15[c]	$Pd_2(dba)_3$	MePhos	$[D_6]$DMSO	51	5	9	35
16[b]	$Pd_2(dba)_3$	MePhos	$[D_7]$DMF	43	3	7	47
17[b]	$Pd_2(dba)_3$	MePhos	$[D_8]$toluene	87	6	0.3	6
18[b]	$Pd_2(dba)_3$	MePhos	dioxane	87	5	1	8
19	$Pd_2(dba)_3$	MePhos	DMF	10	3	6	81
20	$Pd_2(dba)_3$	dppe	DMF	3	0	95	2
21	$Pd_2(dba)_3$	MePhos	DMF	10	3	6	81
22[c]	$Pd_2(dba)_3$	dppe	DMF	9	0	91	0
23[d]	$Pd_2(dba)_3$	dppe	CH_3CN	3	0	95	2
24[e]	$Pd_2(dba)_3$	dppe	CH_3CN	1	0	98	1
25[f]	$Pd_2(dba)_3$	MePhos	DMF	1	3	6	90

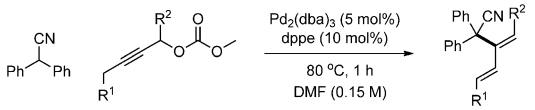
[a] Reaction condtions: diphenylacetonitrile (0.3 mmol), carbonate (0.3 mmol), catalyst (2.5 mol%), ligand (5 mol%), 0.15 M, 90 °C, 14 h; conversion (%) determined by GC/MS. [b] Diphenylacetonitrile (0.1 mmol), carbonate (0.1 mmol), reaction monitored by ^{1}H NMR spectroscopy. [c] Isolated yield 24%. [d] 0.3 M [e] 80 °C [f] 0.6 mmol carbonate.

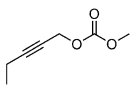
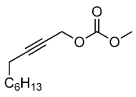
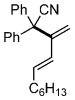
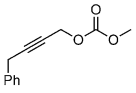
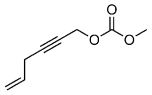
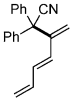
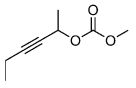
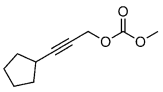


Scheme 4. Acetonitrile scope in 1,3-diene synthesis. a) nitrile (0.3 mmol), carbonate (0.6 mmol), palladium (5 mol%), dppe (10 mol%), DMF (2 mL), 80 °C, 1 h. Isolated yields are reported.

tuted benzyl propargylic carbonate produced the substituted 1,3-diene product in moderate yield (**4d**). To access more intricate triene functionalities, an allyl substituent was utilized at the terminus of the propargylic carbonate, and the resulting triene was isolated in good yield (**4e**). Unfortunately, both terminal carbocyclic substituents along with internal alkyl substituents on the propargylic carbonate significantly hindered product formation (**4f, g**).

Table 2. Scope of substituted 1,3-dienes.



Entry	Carbonate	Product	Yield [%][b]	Diene:Propargyl[c]
4b			42	>20:1
4c			41	9:1
4d			70	>20:1
4e			74	9:1
4f			–[d]	nd
4g			51	1:1.2

[a] Reaction conditions: nitrile (0.3 mmol), carbonate (0.6 mmol), palladium (5 mol%), dppe (10 mol%), DMF (2 mL), 80 °C, 1 h, isolated yields are reported. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy; nd = not determined. [d] 14% conversion determined by GC/MS.

Fueled by the selective formation of the terminal 1,3-diene analogues, we next examined the potential pathways to dienylation. It has been reported that palladium catalysts, in the presence of bidentate ligands, favor oxidative addition to form an η^3-propargyl palladium intermediate.[18] Furthermore, outer-sphere nucleophilic attack at η^3-propargyl palladium species often occurs exclusively at the center carbon.[19] Therefore, we envisioned that 1,3-dienylation could arise through two potential mechanistic pathways (Figure 1). In both cases, initial oxidative addition of the propargylic carbonate and subsequent loss of CO_2 would yield an η^3-propargyl palladium intermediate along with methoxide. Next, deprotonation of the pronucleophile would promote nucleophilic attack at the center carbon of the palladium intermediate to generate the corresponding pallada-cyclobutene (**B**).[20] If the mechanism proceeds through

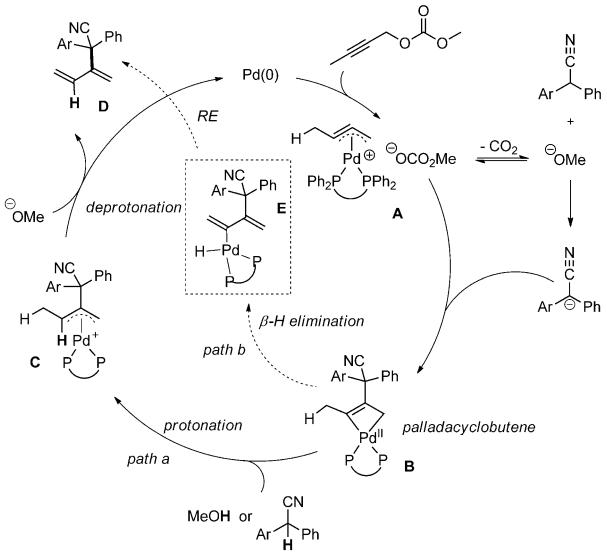


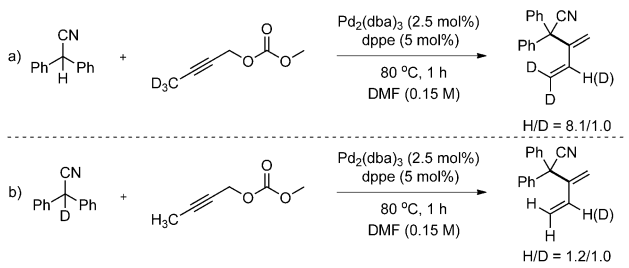
Figure 1. Potential pathways for 1,3-dienylation.

path a, protonation could occur from either methanol or nitrile, leading to π-allyl palladium intermediate **C**. Base-induced elimination would regenerate the palladium(0) catalyst and yield the 1,3-diene product.[2a,21] Alternatively, β-hydride elimination from the palladacycle **B** could produce intermediate **E**, followed by reductive elimination of the 1,3-diene product.

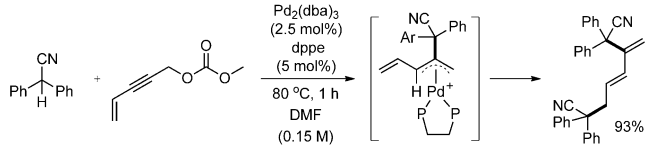
To determine which pathway is more likely, two isotopic labeling experiments were performed (Scheme 5). The terminally deuterated propargylic carbonate produced product with an 8.1:1.0 H/D ratio at the internal carbon of the diene as determined by ^{1}H NMR spectroscopy (Scheme 5a). A similar reaction coupling deuterated diphenyl acetonitrile with protio methyl propargyl carbonate resulted in an H/D ratio of 1.2:1.0 (Scheme 5b).[22] These results are inconsistent with a mechanism involving β-hydride elimination/reductive elimination. Thus, we favor *path a* involving protonation of the pallada-cyclobutene to form π-allyl palladium intermediate **C**. To trap a putative π-allyl intermediate, the palladium-catalyzed acetonitrile cross-coupling was performed with a propargylic carbonate that was unable to undergo elimination (Scheme 6). The observation of bis-substituted 1,3-diene product in 93% yield supports the kinetic feasibility of the formation of a π-allyl palladium intermediate required for *path a*.

Propargylation

As discussed previously, palladium-catalyzed substitution of methyl propargyl carbonate with α,α-diaryl acetonitrile pronucleophiles selectively forms 1,3-dienyl products in the presence of bidentate ligand dppe. During our reaction optimization studies, a change from bidentate (dppe) to monodentate (MePhos) ligand was accompanied by a switch in selectivity from the 1,3-dienyl isomer to the propargyl isomer under otherwise identical reaction conditions (Table 1). The development of palladium-catalyzed substitution of propargylic carbonates to selectively yield propargylated nucleophiles would not only



Scheme 5. Deuterium labeling studies.

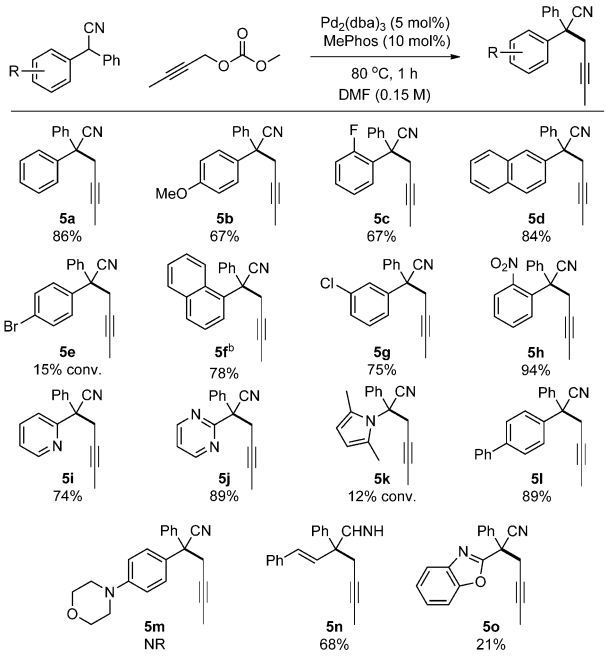


Scheme 6. Trapping of palladium π-allyl intermediate.

expand on the limited strategies known for catalytic propargylation from internal propargylic electrophiles,[23] but also allow for a regiodivergent synthesis of 1,3-dienyl and propargyl acetonitrile derivatives solely by altering the denticity of the coordinating ligand.[24]

Classically, the Nicholas reaction has been utilized as a method for propargylation utilizing propargylic alcohol reactants. Despite this, its utility has been limited by the requirement for stoichiometric organometallic reagents.[25] Recent focus on propargylation has concentrated on the development of alternative methods using catalytic transition metals. For example, propargylic alkylation using propargylic carbonates was only recently reported by Iazzetti in 2015.[7a] However, the reaction is limited to highly stabilized Meldrum's acid-like nucleophiles. Most other cases report palladium-catalyzed nucleophilic substitution of propargylic carbonates that result in cycloaddition or formation of allene derivatives.[26,5g] The method outlined here aims to expand the scope of palladium-catalyzed propargylation to weakly acidic α,α-diaryl acetonitrile motifs that give rise to functionalized quaternary diarylmethane products.

Beginning with the same optimized reaction conditions developed for the 1,3-dienylation method, we merely changed the coordinating ligand from bidentate dppe to monodentate MePhos and evaluated the scope of diarylacetonitriles that undergo propargylation (Scheme 7). Analogous to results of 1,3-diene syntheses, the propargylation of acetonitriles containing 1-naphthyl, 2-naphthyl, and *para*-substituted biphenyl derivatives provided very good yields without being influenced by steric hindrance (**5a**, **d**, **f**, **l**). When *para*-methoxy-, *ortho*-fluoro-, and *meta*-chloro-substituted phenyl rings were screened, all corresponding products were obtained in moderate to good isolated yields (**5b**, **c**, **g**). Altering the *ortho*-substituent to a nitro moiety resulted in an excellent isolated yield of 94% (**5h**). In contrast to their poor reactivity for dienylation, heterocyclic pyridine and pyrimidine derivatives were tolerated under the general reaction conditions and resulted in good isolated yields (**5i**, **j**). However, when the heterocycle was changed to a benzoxazole functionality, a dramatic decrease in yield was observed (**5o**, Scheme 7). A styrene derivative proceeded smoothly to the propargylated product albeit in slightly lower yield when compared to the polycyclic and bicyclic analogues (**5n**). Lastly, a *para*-morpholine-substituted acetonitrile failed to undergo the reaction (**5m**).



Scheme 7. Propargylation of acetonitrile derivatives. a) nitrile (0.3 mmol), carbonate (0.6 mmol), palladium (5 mol%), MePhos (10 mol%), DMF (2 mL), 80 °C, 1 h, isolated yields are reported. b) isolated with 10% allene and 7% bis-addition product.

With the propargylation of various diaryl acetonitrile substrates examined, we next sought to apply our propargylation method to substituted propargylic carbonates (Table 3). Nucleophilic substitution of terminally substituted ethyl or heptyl propargylic carbonates was well tolerated (**6b**, **c**). However, a decrease in isolated yield was observed by using a benzyl propargylic carbonate (**6d**). Gratifyingly, excellent isolated yields were obtained from propargylic carbonates that were terminally substituted by carbocycles (**6e**–**g**). Further, allyl and internally substituted methyl and ethyl propargylic carbonates resulted in moderate to high isolated yields of the propargylated products (**6h**–**k**). Unfortunately, vinyl and phenyl propargylic carbonates were not well-tolerated under the standard reaction conditions (**6l**, **m**).

Having studied the synthetic scope of the dienylation and propargylation reactions, we aimed to convert our observation of denticity-dependent regioselectivity into a more formal mechanistic hypothesis. Beginning with Pd^0 and monodentate MePhos, we propose that oxidative addition of the propargylic carbonate would initially favor a cationic η^3-propargyl palladium intermediate **E** similar to intermediate **A** in the dienylation pathway (Figure 2). Contrary to bidentate ligand dppe, which

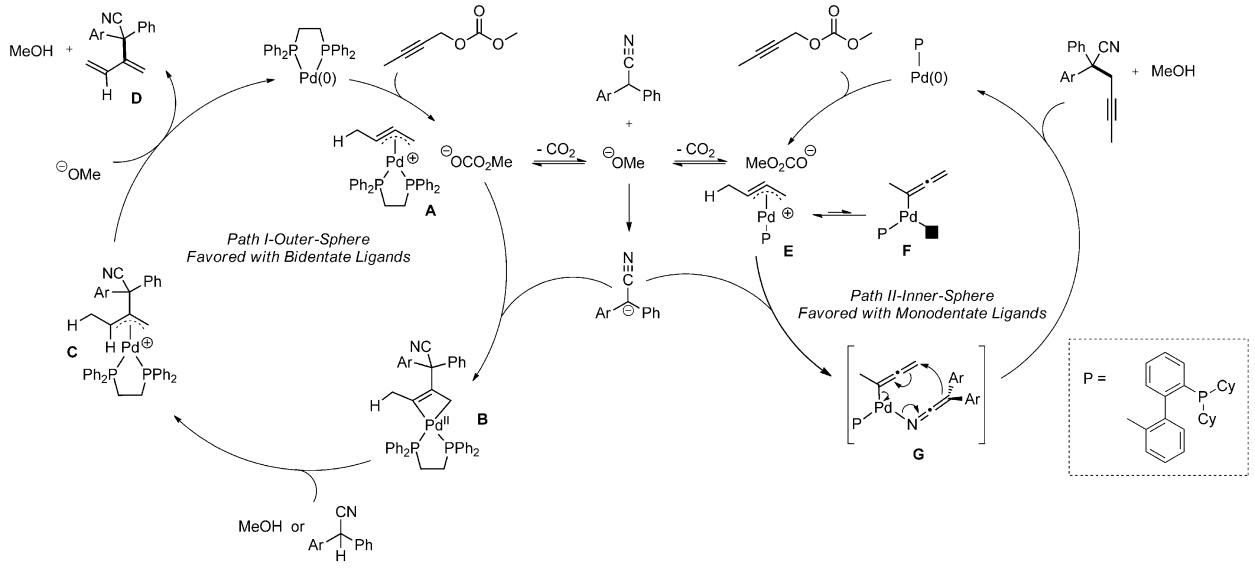
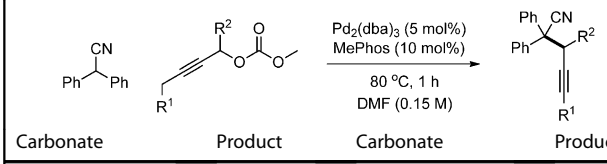
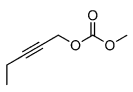
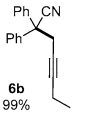
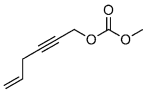
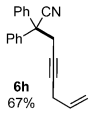
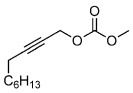
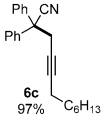
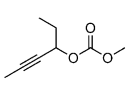
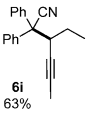
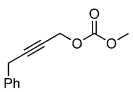
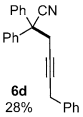
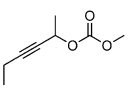
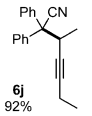
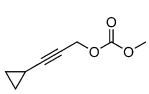
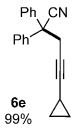
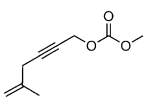
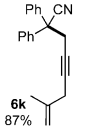
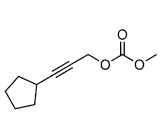
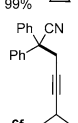
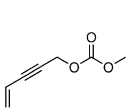
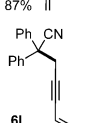
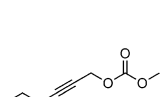
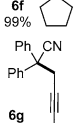
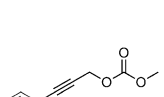
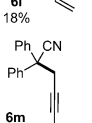


Figure 2. 1,3-Dienyl and propargyl mechanistic cycles.

Table 3. Propargylation with substituted carbonates.[a]



Carbonate	Product	Carbonate	Product
	 **6b** 99%		 **6h** 67%
	 **6c** 97%		 **6i** 63%
	 **6d** 28%		 **6j** 92%
	 **6e** 99%		 **6k** 87%
	 **6f** 99%		 **6l** 18%
	 **6g** 99%		 **6m** 18%

[a] Reaction conditions: diphenylacetonitrile (0.3 mmol), carbonate (0.6 mmol), palladium (5 mol%), MePhos (10 mol%), DMF (2 mL), 80 °C, 1 h. Isolated yields are reported.

forces outer-sphere nucleophilic attack of the activated nitrile, we propose that the mono-coordination of the MePhos ligand provides an open coordination site for binding of the activated nitrile.[16a,27] Binding of an anionic ligand has been observed to typically favor the η^1-allenyl species (in this case **G**).[2a,18,20] Subsequent inner-sphere nucleophilic attack at the terminal allenyl carbon could then occur to provide the propargylated product.[16a,27]

Conclusion

We have reported the regiodivergent synthesis of substituted 1,3-dienyl and propargyl quarternary diaryl methanes. We propose that regioselective nucleophilic substitution to palladium-bound intermediates occurs through two distinct reaction mechanisms that are controlled by the denticity of the ligand. Bidentate ligands block coordination of the nitrile nucleophile, favoring outer-sphere attack of the nucleophile, leading to dienylation. In contrast, a monodentate ligand allows coordination of the nucleophile to palladium, resulting in propargylation through an inner sphere nucleophilic attack.

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Keywords: coupling · dienylation · palladium · propargylation

[1] For select ligand-controlled regiodivergent methods, see: a) W. Su, T.-J. Gong, X. Lu, M.-Y. Xu, C.-G. Yu, Z.-Y. Xu, H.-Z. Yu, B. Xiao, Y. Fu, *Angew.*

Chem. Int. Ed. **2015**, *54*, 1812 – 1816; *Angew. Chem.* **2015**, *127*, 1832 – 1836; b) T. Rybak, D. G. Hall, *Org. Lett.* **2015**, *17*, 4156 – 4159; c) W. Ren, W. Chang, Y. Wang, J. Li, Y. Shi, *Org. Lett.* **2015**, *17*, 3544 – 3547; d) R. Sakae, K. Hirano, M. Miura, *J. Am. Chem. Soc.* **2015**, *137*, 6460 – 6463.

[2] a) M. Kalek, J. Stawinski, *Adv. Synth. Catal.* **2011**, *353*, 1741 – 1755; b) S. Ma, *Eur. J. Org. Chem.* **2004**, 1175 – 1183.

[3] For selected examples of allylic cross-coupling reactions, see: a) F. Liron, J. Oble, M. M. Lorion, G. Poli, *Eur. J. Org. Chem.* **2014**, 5863 – 5883; b) I. Shin, G. Wang, M. J. Krische, *Chem. Eur. J.* **2014**, *20*, 13382 – 13389; c) K. Hojoh, Y. Shido, K. Nagao, S. Mori, H. Ohmiya, M. Sawamura, *Tetrahedron* **2015**, *71*, 6519 – 6533; d) R. Jana, T. P. Pathak, M. S. Sigman, *Chem. Rev.* **2011**, *111*, 1417 – 1492.

[4] For selected reviews on nucleophilic reactions with allyl carbonates, see: a) J. Tsuji, I. Minami, *Acc. Chem. Res.* **1987**, *20*, 140 – 145; b) M. Moreno-Mañas, R. Pleixats in *Handbook of Organopalladium Chemistry for Organic Synthesis*. (Ed.: Ei-ichi Negishi), Wiley, Hoboken, **2002**, pp. 1707 – 1767; c) J. D. Weaver, A. Recio III, A. J. Grenning, J. A. Tunge, *Chem. Rev.* **2011**, *111*, 1846 – 1913; d) S. Arseniyadis, J. Fournier, S. Thangavelu, O. Lozano, S. Prevost, A. Archambeau, C. Menozzi, J. Cossy, *Synlett* **2013**, *24*, 2350 – 2364; e) M. Riemer, *Synlett* **2014**, *25*, 1041 – 1042.

[5] For reports of allene syntheses from palladium-catalyzed reactions with propargyl carbonates, see: a) W. Shu, G. Jia, S. Ma, *Org. Lett.* **2009**, *11*, 117 – 120; b) W. Shu, S. Ma, *Tetrahedron* **2010**, *66*, 2869 – 2874; c) M. Kalek, T. Johansson, M. Jezowska, J. Stawinski, *Org. Lett.* **2010**, *12*, 4702 – 4704; d) G. Chen, Y. Zhang, C. Fu, S. Ma, *Tetrahedron* **2011**, *67*, 2332 – 2337; e) J. Ye, S. Li, S. Ma, *Org. Lett.* **2012**, *14*, 2312 – 2315; f) Y. Wang, W. Zhang, S. Ma, *J. Am. Chem. Soc.* **2013**, *135*, 11517 – 11520; g) M. Yoshida, S. Ohno, K. Namba, *Angew. Chem. Int. Ed.* **2013**, *52*, 13597 – 13600; *Angew. Chem.* **2013**, *125*, 13842 – 13845; h) J. Ye, S. Ma, *Acc. Chem. Res.* **2014**, *47*, 989 – 1000. **Cu:** i) H. Ito, Y. Sasaki, M. Sawamura, *J. Am. Chem. Soc.* **2008**, *130*, 15774 – 15775; j) C. Zhong, Y. Sasaki, H. Ito, M. Sawamura, *Chem. Commun.* **2009**, *39*, 5850 – 5860; k) C. Deutsch, B. H. Lipshutz, N. Krause, *Org. Lett.* **2009**, *11*, 5010 – 5012. **Rh:** l) H. Ohmiya, H. Ito, M. Sawamura, *Org. Lett.* **2009**, *11*, 5618 – 5620. For a review, see: m) J. Tsuji, T. Mandai, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2589 – 2612; *Angew. Chem.* **1995**, *107*, 2830 – 2854.

[6] For selected examples of dinucleophilic substitution of propargylic carbonates, see: a) L.-N. Guo, X.-H. Duan, H.-P. Bi, X.-Y. Liu, Y.-M. Liang, *J. Org. Chem.* **2007**, *72*, 1538 – 1540; b) Z.-H. Ren, Z.-H. Guan, Y.-M. Liang, *J. Org. Chem.* **2009**, *74*, 3145 – 3147; c) H.-P. Bi, L.-N. Guo, F.-R. Gou, X.-H. Duan, X.-Y. Liu, Y.-M. Liang, *J. Org. Chem.* **2008**, *73*, 4713 – 4716; d) M. Yoshida, T. Nakagawa, K. Kinoshita, K. Shishido, *J. Org. Chem.* **2013**, *78*, 1687 – 1692; e) A. E. Nibbs, T. D. Montgomery, Y. Zhu, V. H. Rawal, *J. Org. Chem.* **2015**, *80*, 4928 – 4941. For a review, see: f) M. Yoshida, *Chem. Pharm. Bull.* **2012**, *60*, 285 – 299.

[7] For propargylation of carbon nucleophiles, see: a) I. Ambrogio, S. Cacchi, G. Fabrizi, A. Goggiamani, A. Iazzetti, *Eur. J. Org. Chem.* **2015**, 3147 – 3151; b) A. Millán, L. Álvarez de Cienfuegos, A. Martín-Lasanta, A. G. Campaña, J. M. Cuerva, *Adv. Synth. Catal.* **2011**, *353*, 73 – 78; c) T. Hirashita, Y. Suzuki, H. Tsuji, Y. Sato, K. Naito, S. Araki, *Eur. J. Org. Chem.* **2012**, 5668 – 5672; d) M. Ikeda, Y. Miyake, Y. Nishibayashi, *Chem. Eur. J.* **2012**, *18*, 3321 – 3328; e) W. Shao, H. Li, C. Liu, C.-J. Liu, S.-L. You, *Angew. Chem. Int. Ed.* **2015**, *54*, 7684 – 7687; *Angew. Chem.* **2015**, *127*, 7794 – 7797; f) Y. Imada, M. Yuasa, I. Nakamura, S.-I. Murahashi, *J. Org. Chem.* **1994**, *59*, 2282 – 2284; g) E. Bustelo, P. H. Dixneuf, *Adv. Synth. Catal.* **2007**, *349*, 933 – 942.

[8] For palladium-catalyzed substitutions on propargylic carbonates, see: a) J. Tsuji, T. Mandai in *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: F. Diedrich, P. J. Stange), Wiley-VCH, Weinheim, **1998**, pp. 455; b) J. Tsuji, *Palladium Reagents and Catalysis: New Prospectives for the 21 st Century*, Wiley, Chichester, **2004**, pp. 543.

[9] a) T. Nemoto, Z. Zhao, T. Yokosaka, Y. Suzuki, R. Wu, Y. Hamada, *Angew. Chem. Int. Ed.* **2013**, *52*, 2217; *Angew. Chem.* **2013**, *125*, 2273; b) H. Weinstabl, T. Gaich, J. Mulzer, *Org. Lett.* **2012**, *14*, 2834 – 2837; c) Y. Inada, Y. Nishibayashi, S. Uemura, *Angew. Chem. Int. Ed.* **2005**, *44*, 7715 – 7717; *Angew. Chem.* **2005**, *117*, 7893 – 7895; d) Y. Kozawa, M. Mori, *J. Org. Chem.* **2003**, *68*, 8068 – 8074; e) I. Ambrogio, S. Cacchi, F. Gabrizi, A. Prastaro, *Tetrahedron* **2009**, *65*, 8916 – 8929; f) D. S. B. Daniels, A. S. Jones, A. L. Thompson, R. S. Paton, E. A. Anderson, *Angew. Chem. Int. Ed.* **2014**, *53*, 1915 – 1920; *Angew. Chem.* **2014**, *126*, 1946 – 1951.

[10] a) T.-Y. Chen, R. Tsutsumi, T. P. Montgomery, I. Volchkov, M. J. Krische, *J. Am. Chem. Soc.* **2015**, *137*, 1798 – 1801; b) B. C. Lainhart, E. Alexanian, *Org. Lett.* **2015**, *17*, 1284 – 1287; c) Y. Ebe, M. Hatano, T. Nishimura, *Adv. Synth. Catal.* **2015**, *357*, 1425 – 1436; d) A. Eske, B. Goldfuss, A. G. Griesbeck, A. de Kiff, M. Kleczka, M. Leven, J.-M. Neudörfl, M. Vollmer, *J. Org. Chem.* **2014**, *79*, 1818 – 1829.

[11] a) X. Xia, P. H. Toy, *Synlett* **2014**, *25*, 2787 – 2790; b) Z. Tian, P. Sun, Y. Yan, Z. Wu, Q. Zheng, S. Zhou, H. Zhang, F. Yu, X. Jia, D. Chen, A. Mándi, T. Kurtán, W. Liu, *Nat. Chem. Biol.* **2015**, *11*, 1769; c) L. Minuti, E. Ballerini, A. Barattucci, P. M. Bonaccorsi, M. L. Di Gioia, A. Leggio, C. Siciliano, A. Temperini, *Tetrahedron* **2015**, *71*, 3253 – 3262; d) C. Sabot, D. Bérard, S. Canesi, *Org. Lett.* **2008**, *10*, 4629 – 4632; e) Y.-J. Jian, Y. Wu, *Org. Biomol. Chem.* **2010**, *8*, 811 – 821; f) S. Yokoshima, *Chem. Pharm. Bull.* **2013**, *61*, 251 – 257; g) S. Yu, S. Ma, *Chem. Commun.* **2011**, *47*, 5384 – 5418.

[12] a) L. Zhu, J. Xiao, J. Shi, J. Wang, S. Lv, Y. Xu, Y. Luo, Y. Xiao, S. Wang, Q. Meng, X. Li, D. Li, *Nano Res.* **2015**, *8*, 1116 – 1127; b) S. E. Parker, J. Börgel, T. Ritter, *J. Am. Chem. Soc.* **2014**, *136*, 4857 – 4860.

[13] a) I. M. Yonova, A. G. Johnson, C. A. Osborne, C. E. Moore, N. S. Morrissette, E. R. Jarvo, *Angew. Chem. Int. Ed.* **2014**, *53*, 2422 – 2427; *Angew. Chem.* **2014**, *126*, 2454 – 2459; b) S. Mondal, G. Panda, *RSC Adv.* **2014**, *4*, 28317 – 28358; c) M. D. Cullen, T. Sarkar, E. Hamel, T. L. Hartman, K. M. Watson, R. W. Buckheit Jr., C. Pannecouque, E. D. Clercq, M. Cushman, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 469 – 473; d) S.-C. Sha, J. Zhang, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2013**, *135*, 17602 – 17609; e) Q. Hu, L. Yin, C. Jagusch, U. E. Hille, R. W. Hartmann, *J. Med. Chem.* **2010**, *53*, 5049 – 5053; f) S. Messaoudi, A. Hamze, O. Provot, B. Tréguier, J. R. De Losada, J. Bignon, J.-M. Liu, J. Wdzieczak-Bakala, S. Thoret, J. Dubois, M. Alami, *ChemMedChem* **2011**, *6*, 488 – 497; g) T. P. Pathak, K. M. Gligorich, B. E. Welm, M. S. Sigman, *J. Am. Chem. Soc.* **2010**, *132*, 7870 – 7871; h) C. Tsutsui, Y. Yamada, M. Ando, D. Toyama, J.-l. Wu, L. Wang, S. Taketani, T. Kataoka, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4084 – 4089.

[14] For selected examples of organometallic reagents, see Grignard reagents: a) A. D. Payne, G. Bojase, M. N. Paddon-Row, M. S. Sherburn, *Angew. Chem. Int. Ed.* **2009**, *48*, 4836 – 4839; *Angew. Chem.* **2009**, *121*, 4930 – 4933; b) S. Nunomoto, Y. Kawakami, Y. Yamashita, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2831 – 2832; organozinc: c) P. Villiers, N. Vicart, Y. Ramondenc, G. Plé, *Eur. J. Org. Chem.* **2001**, 561 – 574; organocuprates: d) P. Kraft, K. Popaj, *Eur. J. Org. Chem.* **2008**, 261 – 268; e) K. J. Shea, P. Q. Pham, *Tetrahedron Lett.* **1983**, *24*, 1003 – 1006; organostanne: f) M. Luo, Y. Iwabuchi, S. Hatakeyama, *Synlett* **1999**, 1109 – 1112; organosilane: T. Takeda, A. Mori, T. Fujii, A. Tsubouchi, *Tetrahedron* **2014**, *70*, 5776 – 5786.

[15] a) For organoborane reagents, see: Y. Huang, X. Yang, Z. Lv, C. Cai, C. Kai, Y. Pei, Y. Feng, *Angew. Chem. Int. Ed.* **2015**, *54*, 7299 – 7302; *Angew. Chem.* **2015**, *127*, 7407 – 7410; b) L. Wang, M. E. Welker, *J. Org. Chem.* **2012**, *77*, 8280 – 8286; c) E. G. Occhiato, C. Prandi, A. Ferrali, A. Guarna, P. Venturello, *J. Org. Chem.* **2003**, *68*, 9728 – 9741.

[16] a) A. Recio, J. A. Tunge, *Org. Lett.* **2009**, *11*, 5630 – 5633; b) S. B. Lang, T. M. Locascio, J. A. Tunge, *Org. Lett.* **2014**, *16*, 4308 – 4311; c) T. Maji, K. Ramakumar, J. A. Tunge, *Chem. Commun.* **2014**, *50*, 14045 – 14048; d) Y. Ariyarathna, J. A. Tunge, *Chem. Commun.* **2014**, *50*, 14049 – 14052.

[17] Note that extended reaction time resulted in degradation of the 1,3-diene products.

[18] a) C.-C. Su, J.-T. Chen, G.-H. Lee, Y. Wang, *J. Am. Chem. Soc.* **1994**, *116*, 4999 – 5000; b) K. Tsutsumi, T. Yabukami, K. Fujimoto, T. Kawase, T. Morimoto, K. Kakiuchi, *Organometallics* **2003**, *22*, 2996 – 2999; c) K. Tsutsumi, S. Ogoshi, S. Nishiguchi, H. Kurosawa, *J. Am. Chem. Soc.* **1998**, *120*, 1938 – 1939; d) K. Tsutsumi, K. Kawase, K. Kakiuchi, S. Ogoshi, Y. Okada, H. Kurosawa, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687 – 2692.

[19] a) P. W. Blosser, D. G. Schimpff, J. C. Gallucci, A. Wojcicki, *Organometallics* **1993**, *12*, 1993 – 1995; b) H. Kurosawa, S. Ogoshi, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 973 – 984; c) K. Tsutsumi, S. Ogoshi, K. Kakiuchi, S. Nishiguchi, H. Kurosawa, *Inorg. Chim. Acta* **1999**, *296*, 37 – 44; d) T.-M. Huang, J.-T. Chen, G.-H. Lee, Y. Wang, *J. Am. Chem. Soc.* **1993**, *115*, 1170 – 1171.

[20] a) C. P. Casey, J. R. Nash, C. S. Yi, A. D. Selmeczy, S. Chung, D. R. Powell, R. K. Hayashi, *J. Am. Chem. Soc.* **1998**, *120*, 722 – 733; b) J.-R. Labrosse, P. Lhoste, F. Delbecq, D. Sinou, *Eur. J. Org. Chem.* **2003**, 2813 – 2822.

[21] a) Y. Xia, Y. Xia, Z. Liu, Y. Zhang, Z. Wang, *J. Org. Chem.* **2014**, *79*, 7711 – 7717; b) C. Fu, S. Ma, *Org. Lett.* **2005**, *7*, 1707 – 1709; c) C. S. Hampton, M. Harmata, *Org. Lett.* **2014**, *16*, 1256 – 1259.

[22] The differing ratios result from a primary kinetic isotope effect for protonation combined with the competitive protonation from nitrile and liberated methanol.

[23] a) E. Nakamura, T. Hatakeyama, S. Ito, K. Ishizuka, L. Ilies, M. Nakamura, in *Organic Reactions, Vol. 83 (*Ed.: S. E. Denmark), Wiley, Hoboken, **2014**, pp. 25 – 31; b) U. Schneider, S. Kobayashi, *Acc. Chem. Res.* **2012**, *45*, 1331 – 1344; c) M. Bandini, P. G. Cozzi, P. Melchiorre, R. Tino, A. Umani-Ronchi, *Tetrahedron: Asymmetry* **2001**, *12*, 1063 – 1069; d) P. H. Lee, E. Shim, K. Lee, D. Seomoon, S. Kim, *Bull. Korean Chem. Soc.* **2005**, *26*, 157 – 160.

[24] For several examples of regiodivergent reactions with propargyl electrophiles see ref. [9d] and a) S. Ma, G. Wang, *Angew. Chem. Int. Ed.* **2003**, *42*, 4215 – 44217; *Angew. Chem.* **2003**, *115*, 4347 – 4349; b) H. Ohmiya, M. Yang, Y. Yamauchi, Y. Ohtsuka, M. Sawamura, *Org. Lett.* **2010**, *12*, 1796 – 1799.

[25] R. F. Lockwood, K. M. Nicholas, *Tetrahedron Lett.* **1977**, *18*, 4163 – 4166.

[26] For reports of palladium-catalyzed cyclizations with propargyl carbonates, see: a) I. Ambrogio, S. Cacchi, G. Fabrizi, *Tetrahedron Lett.* **2007**, *48*, 7721 – 7725; b) M. Yoshida, M. Higuchi, K. Shishido, *Tetrahedron Lett.* **2008**, *49*, 1678 – 1681; c) Z.-H. Ren, Z.-H. Guan, Y.-M. Liang, *J. Org. Chem.* **2009**, *74*, 3145 – 3147; d) Z.-H. Guan, Z.-H. Ren, L.-B. Zhao, Y.-M. Liang, *Org. Biomol. Chem.* **2008**, *6*, 1040 – 1045; e) M. Yoshida, M. Higuchi, K. Shishido, *Org. Lett.* **2009**, *11*, 4752 – 4755; f) M. Yoshida, M. Higuchi, K. Shishido, *Tetrahedron* **2010**, *66*, 2675 – 2682; g) R.-D. Gao, C. Liu, L.-X. Dai, W. Zhang, S.-L. You, *Org. Lett.* **2014**, *16*, 3919; h) T. D. Montgomery, A. E. Nibbs, Y. Zhu, V. H. Rawal, *Org. Lett.* **2014**, *16*, 3480 – 3483.

[27] a) M. J. Ardolino, J. P. Morkin, *J. Am. Chem. Soc.* **2012**, *134*, 8770; b) A. Recio, III, J. D. Heinzman, J. A. Tunge, *Chem. Commun.* **2012**, *48*, 142 – 144.

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FULL PAPER

Palladium Catalysis

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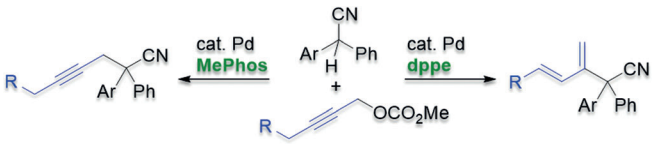
Palladium-Catalyzed Regiodivergent Substitution of Propargylic Carbonates



Regiodivergent coupling of propargyl carbonates allows their use to form quaternary diarylmethanes that are either propargylated or dienylated. The latter case represents the first example of the use of propargyl carbonates as inexpensive, readily available synthetic equivalents of dienyl cations.