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A Trialkylphosphine-Derived Palladacycle as a Catalyst in the Selective Cross-Dimerization of Terminal Arylacetylenes with Terminal Propargyl Alcohols and Amides

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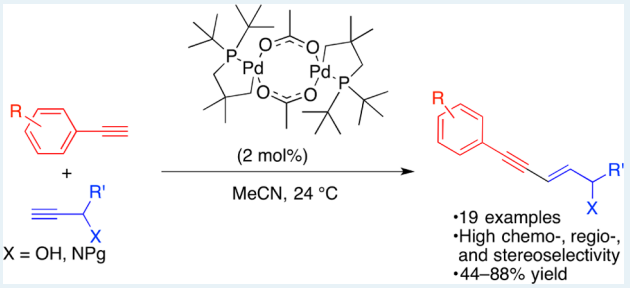
Supporting Information

ABSTRACT: A method for the selective cross-dimerization of terminal aryl alkynes with propargyl alcohols to afford linear (*E*)-enynol products is reported. The complex [Pd(μ-κ^2-*O*,*O*-OAc)(κ^2-*C*,*P*-(*t*-Bu)$_2$PCH$_2$C(Me)$_2$CH$_2$)]$_2$ selectively affords (*E*)-5-aryl-2-en-4-yn-1-ol products in good yields under mild conditions with high chemo-, regio-, and stereoselectivity. In contrast, previously reported examples of this reaction afford the branched 4-aryl-2-hydroxymethanol-1-buten-3-yne. Propargyl amides are also selectively cross-dimerized, but with lower regioselectivity for the linear enyne. The method has been applied to the synthesis of (*E*)-5-phenyl-2-penten-4-yn-1ol, which is a precursor to type 2 diabetes drug candidate NNC 61-4655, in 72% yield from phenylacetylene and propargyl alcohol. The palladacycle precatalyst reacts with aryl alkynes to afford the first example of a dimeric palladacycle complex with a μ-κ^2-C^1,C^1-bound acetylide ligand. This complex is observed during the catalytic reaction and is a competent precatalyst.

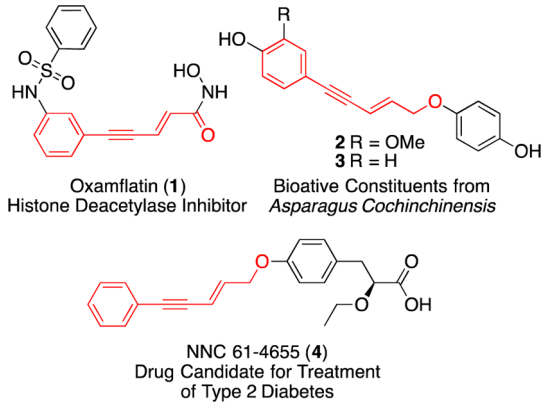


KEYWORDS: *palladacycle, alkyne dimerization, hydroalkynylation, enyne, μ-acetylide complex*

INTRODUCTION

Linear *trans*-enynes are an important motif found in a number of biologically active compounds and natural products, including oxamflatin (**1**),[1] bioactive constituents isolated from *Asparagus Cochinchinensis* (**2** and **3**),[2] and diabetes treatment candidate NNC 61-4655 (**4**) (Chart 1).[3] Notably, each of these examples contains an oxygen functionality in the allylic position. 2-En-4-yn-1-ols and related compounds are useful precursors in a variety of synthetic methods.[4] Conjugated linear enynes are commonly synthesized via Sonogashira reactions of vinyl halides,[5] olefination of conjugated ynals,[3,4,6] or the elimination of propargyl alcohols.[7]

Chart 1. Biologically Active Compounds Containing a Linear Enyne Motif



The selective catalytic dimerization of terminal alkynes is an efficient method for the formation of enyne structures.[8] Homodimerization of alkynes to form enynes can result in the formation of either linear (*E*/*Z*-**5**) or branched (**6**) enynes (Scheme 1) depending on the choice of catalyst. Selectively producing a single product becomes even more challenging when coupling two different alkynes. In this case, the catalyst must selectively produce a single product from 12 possible stereoisomers and constitutional isomers through precise control of chemoselectivity, regioselectivity, and stereoselectivity.

Although a number of methods have been published for the homodimerization of alkynes to give either linear (**5**) or branched (**6**) enyne products, far fewer methods are known for the cross-dimerization of two different terminal alkynes. Silyl alkynes are selectively coupled with alkyl and aryl alkynes to give *E* or *Z* head-to-head enynes (*E*/*Z*-**7**, $R^1 = R_3Si$)[9] or head-to-tail enynes (**8**, $R^1 = R_3Si$)[10] depending on the choice of

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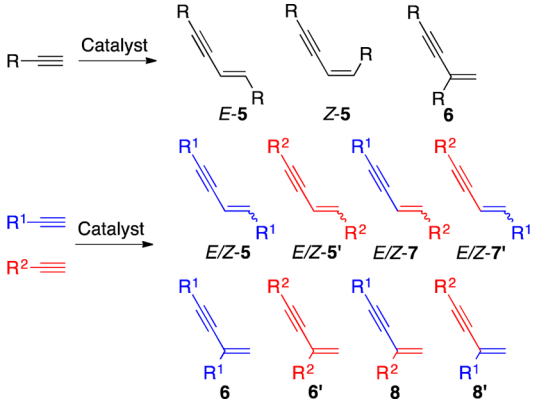
Scheme 1. Possible Enyne Isomers in Alkyne Dimerization Reactions



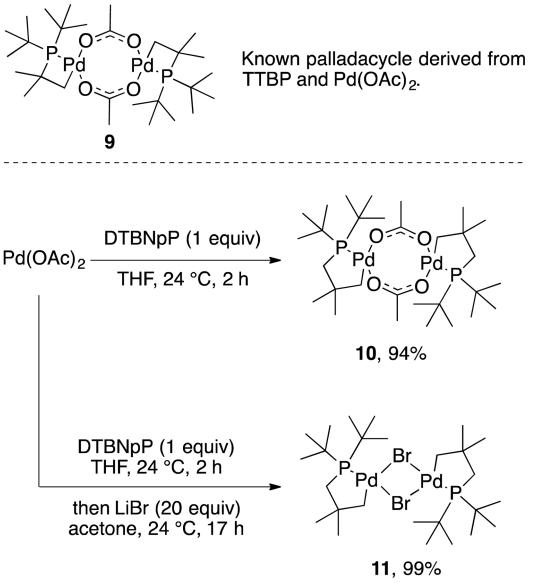
catalyst. Oshovsky and de Bruin reported a Ti(III) metallocene catalyst for the selective addition of aryl alkynes across alkyl alkynes to give head-to-tail enyne products (**8**, R^1 = aryl, R^2 = alkyl).[11] Propargyl alcohols and amines provide high selectivity in cross-dimerization reactions to give type **8** enynes, where R^2 is the $-CH_2X$ group (X = OH, NHR), using both Ti(III)[11] and late transition metals.[12] There are no examples of cross-dimerization of alkynes with propargyl alcohols or amines to afford linear type **7** enynes relevant to the structures in Chart 1. Herein, we report the first example of a catalyst that cross-dimerizes aryl acetylenes with propargyl alcohols or amides to afford linear 2-en-4-yn-1-ols and 2-en-4-yn-1-yl amides (*E*-**7**) with high selectivity under mild conditions.

RESULTS

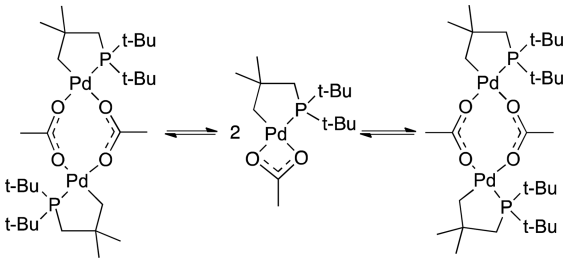
DTBNpP-Derived Palladacycle. During our investigations of the use of neopentyl phosphine ligands in Heck couplings an unknown broad peak in the phosphorus NMR spectra at 94 ppm was often observed in the reaction mixture when di-*tert*-butylneopentylphosphine (DTBNpP) was used as a ligand.[13] We hypothesized that this species could be a cyclometalated complex on the basis of the known ability of neopentylphosphines to form metallacyclic compounds.[14] Platinum[15] and iridium[16] metallacycles derived from neopentylphosphines have been reported. Surprising, no neopentylphosphine-derived palladacycles have been reported. In contrast, the palladacycle derived from tri-*tert*-butylphosphine (TTBP) is known.[17]

The DTBNpP-derived palladacycle **10** (Scheme 2) was prepared using conditions reported by Stambuli and co-workers[17a] for palladacycle **9** derived from TTBP and $Pd(OAc)_2$ (Scheme 2). Mixing $Pd(OAc)_2$, with 1 equiv of DTBNpP in THF at ambient temperature produced the cyclometalated dimer **10** in 94% yield as an air-stable material giving a broad ^{31}P NMR resonance at 94 ppm. The fluxional nature of acetate-bridged phosphapalladacycles has been previously noted.[18] At low temperature, the broad feature at 94 ppm resolves into three resonances at 98, 94.5, and 90 ppm (Figure S1 in the Supporting Information). These species likely correspond to cis and trans isomers of the dimer plus a monomeric palladacycle with a κ^2-*O*,*O*-bound acetate (Scheme 3). Since the potential cyclometalated complex formed in the Heck couplings of aryl bromides would have bromide as ligands rather than acetate, the bromide dimer **11** was prepared. Treatment of crude product **10** with 20 equiv of lithium bromide in acetone afforded dimer **11** in 99% yield in a one-pot

Scheme 2. Palladacycles Derived from Bulky Electron-Rich Phosphines

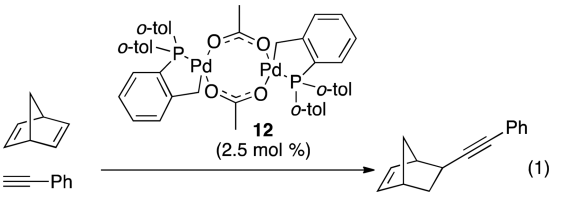


Scheme 3. Proposed Solution Equilibrium of Complex 10



reaction. The peak in the ^{31}P NMR spectrum for **11** matched that observed in the Heck coupling reaction mixtures.

Despite the fact that **9** has found limited use as an active catalyst in organic synthesis,[17b,19] palladacycles are widely used as both precatalysts and active catalysts in organic synthesis.[20] Due to the ease of synthesis and stability of complex **10**, uses in palladium(II) catalysis were explored. A 2006 report by Tenaglia and co-workers on the Herrmann–Beller palladacycle (**12**) catalyzed addition of alkynes to norbornadienes led us to test complex **10** in similar reactions (eq 1).[21] Similarly to the



Herrmann–Beller palladacycle, complex **10** was able to catalyze the addition of phenylacetylene to norbornadiene. Attempts to couple phenylacetylene with other alkenes such as styrene, butyl acrylate, and norbornene resulted in dimerization of phenylacetylene, however. Inspired by recent reports of the selective coupling of aryl acetylenes with propargyl alcohols or amines,[11,12] we examined the coupling of phenylacetylene with propargyl alcohol catalyzed by **10**.

Coupling of Acetylenes with Propargyl Alcohols. The reaction of phenylacetylene with 2.5 equiv of propargyl alcohol

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in acetonitrile with 2 mol % of **10** led to a 60% yield of linear enyne product **7a** (eq 2) and a 63% yield of propargyl alcohol

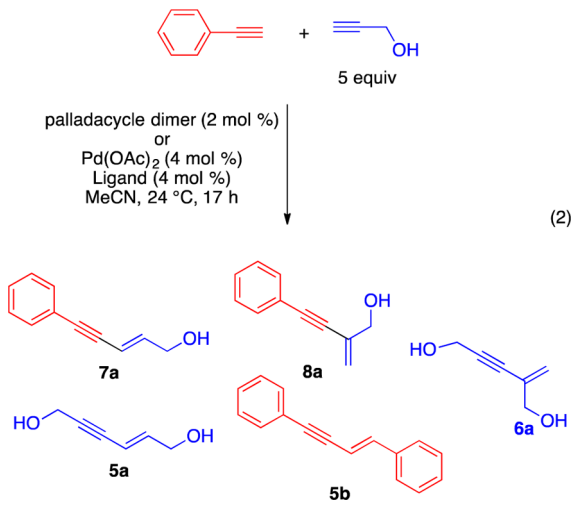


Table 1. Ligand Effect on Selectivity of Alkyne Dimerization[a]

		yield (%)[b]				
entry	Pd/L	7a	8a	5a	6a	5b
1[c]	**10**	56	2	63	5	8
2	**10**	74	2	150	9	4
3	**11**	0	0	0	0	0
4	**9**	36	10	76	20	8
5	**12**	10	18	16	49	0
6	DTBNpP[d]	44	18	118	18	4
7	TTBP[d]	35	11	78	18	8
8	P(*o*-tol)$_3$[d]	2	36	4	77	0
9	TNpP[d]	17	51	32	88	0
10	TDMPP[d]	0	2	0	10	0
11	no L[d]	0	0	0	0	0

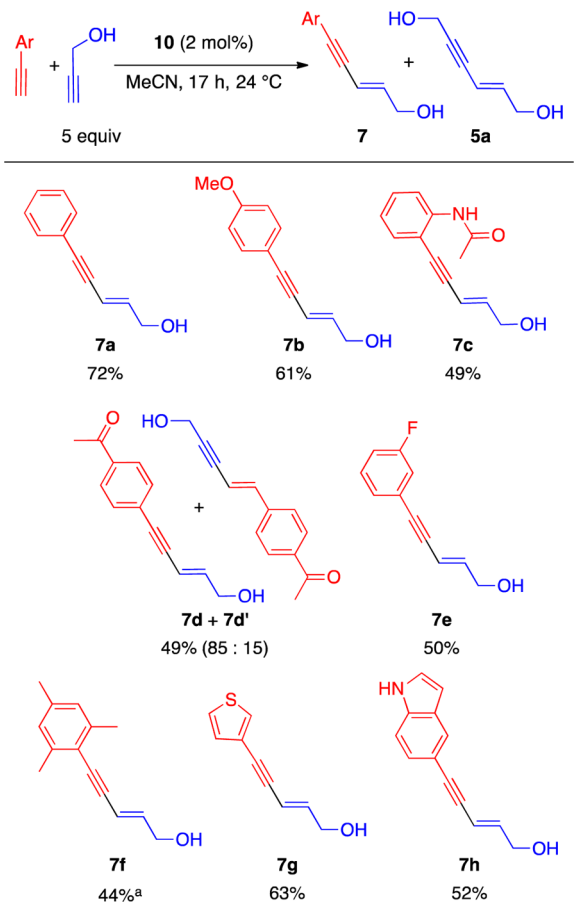
[a]Reaction run using conditions in eq 1 unless noted otherwise. [b]Product yields determined via ^{1}H NMR spectroscopy with an internal standard. All percentages are based on moles of phenylacetylene used. [c]2.5 equiv of propargyl alcohol used. [d]Ligand (4 mol %) used in combination with Pd(OAc)$_2$ (4 mol %).

dimer **5a** (Table 1, entry 1). Notably, the phenylacetylene homodimer **5b** and the branched enyne products **6a** and **8a** were produced in small amounts. An extensive solvent screen showed that nitrile solvents were most effective for this reaction, with acetonitrile providing the highest yield of enyne **7a** (Table S1 in the Supporting Information). Increasing the amount of propargyl alcohol to 5 equiv improved the yield of **7a** to 74% and resulted in minimal phenylacetylene homodimerization products (**5b**, entry 2). Using a larger excess of propargyl alcohol results in a larger amount of homodimer **5a** being produced (2:1 **5a**:**7a**), however.

Palladacycle dimer **11** with bridging bromides failed to catalyze the reaction, which shows the key role of the basic acetate ligands (Table 1, entry 3). The TTBP-derived palladacycle dimer **9** gave **7a** as the major product, but with lower selectivity and yield (entry 4). The Herrmann–Beller palladacycle **12** gave the branched enyne **8a** as the major product, but in low yield and selectivity (entry 5). The palladacycle precatalyst played a key role in determining the regioselectivity of the coupling reaction. DTBNpP in combination with Pd(OAc)$_2$ also gave linear enyne product **7a** as the major product, but with lower selectivity and yield than for palladacycle **10** (entry 6). In the case of TTBP, the yield and product distribution of the in situ catalyst (entry 7) were nearly identical with those of complex **9**. This result may reflect the lower stability of palladacycle **9**, resulting in the κ^1-DTBNpP complex being the active species when **9** is used.. Tri-*o*-tolylphosphine (P(*o*-tol)$_3$) in combination with Pd(OAc)$_2$ gave **8a** as the major product, as for the Herrmann–Beller palladacycle (**12**), but with higher selectivity and yield (entry 8). Trineopentylphosphine (TNpP) also gave **8a** as the major product (entry 9). Tris(2,6-dimethoxyphenyl)phosphine (TDMPP), which Trost and co-workers[12b,22] used in many of their pioneering alkyne dimerization studies, gave only trace amounts of product under the conditions optimized for palladacycle **10** (entry 10) but exclusively formed branched isomer **8a**. Palladium(II) acetate without added ligand failed to give any coupled products (entry 11).

Under the optimized conditions, enyne **7a** was isolated in a 72% yield (Table 2). The linear propargyl alcohol dimer side product **12** can be easily separated via column chromatography due to its higher polarity. It can also be removed via aqueous extraction prior to column chromatography. Therefore, formation of **5a** does not impede isolation of product **7a**. Enyne **7a** is an intermediate in Novo Nordisk's GMP-kilo-

Table 2. Dimerization of Arylacetylenes with Propargyl Alcohol



[a]Reaction performed at 80 °C.

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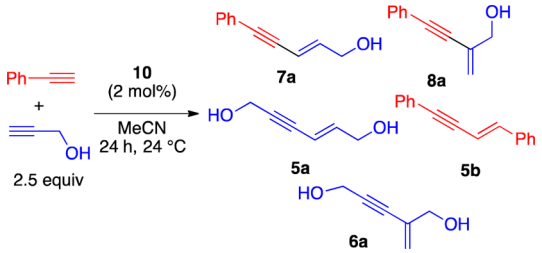
Table 3. Optimization of Alkyne Dimerization with 2.5 Equiv of Propargyl Alcohol



entry	additive (equiv)	atm	yield (%)[a] 7a	8a	5a	5b	6a
1		N_2	56	2	63	8	5
2		air	55	0	55	8	0
3[b]	AcOH (1)	N_2	0	0	0	0	0
4[b]	K_2CO_3 (1)	N_2	35	0	54	20	0
5[b]	CuI (0.04)	N_2	2	0	1	0	0
6	H_2O (1)	N_2	55	0	54	6	1
7	H_2O (1)	air	56	0	58	6	0
8	EtOH (1)	N_2	57	10	61	3	10
9	EtOH (1)	air	60	0	61	5	0
10	1,3-propanediol (1)	N_2	55	1	58	8	7
11	1,3-propanediol (1)	air	54	0	52	6	0
12	trimethylolethane (1)	N_2	58	1	37	4	6
13	trimethylolethane (1)	air	75 (72)	1	64	0	0
14	trimethylolethane (1)	O_2	67	1	47	0	0

[a]Yields of products determined via ^{1}H NMR analysis with an internal standard. Yields in parentheses are of isolated product. [b]Reaction conducted with 5 equiv of propargyl alcohol.

laboratory synthesis of the PPAR-agonist NNC 61-4655 (**4**).[3] Novo Nordisk produced enyne **7a** in four steps with an overall yield of 19%. The synthesis involved conversion of phenylacetylene to 3-phenylpropiolaldehyde followed by Wittig–Horner olefination and reduction of the resulting enynoate ester. The direct coupling of phenylacetylene and propargyl alcohol produces the same product in one step and in much higher yield. The reaction uses inexpensive starting materials and occurs with high atom economy.

The cross-dimerization of aryl acetylenes and propargyl alcohol tolerates a variety of aryl acetylene coupling partners (Table 2). Enyne **7b** derived from electron-rich (4-methoxyphenyl)acetylene was isolated in 61% yield. 2-Ethynylacetanilide gave a lower yield of enyne **7c**, presumably due to the steric demand of the substrate. Enynes **7d**,**e** derived from electron-poor aryl acetylenes were produced in lower yields primarily due to lower selectivity for the aryl acetylene to act as the donor acetylene, which resulted in formation of the homodimer of the aryl acetylene. Enyne **7d** was isolated as a mixture along with the isomer **7d′**, in which propargyl alcohol acts as the donor acetylene. The more sterically hindered 2-ethynyl-1,3,5-trimethylbenzene gave only 45% conversion after 24 h at 60 °C. 2-Ethynyl-1,3,5-trimethylbenzene does not self-dimerize under the reaction conditions, which has been previously observed with aryl acetylenes containing two ortho substituents.[23] Increasing the temperature to 80 °C resulted in full consumption of the aryl acetylene, and enyne **7f** was isolated in 44% yield. The heterocyclic aryl acetylenes 3-ethynylthiophene and 5-ethynyl-1*H*-indole gave good yields of the linear enyne products **7g**,**h**. However, 2-ethynylpyridine failed to react under the optimized reaction conditions.

Further optimization was desired in order to decrease the amounts of noncommercially available or more expensive propargyl alcohols (Table 3). Since we hypothesized that deprotonation of phenylacetylene by acetate plays a key role in the reaction, the pH of the reaction was modified by addition of acetic acid or potassium carbonate. Both additives greatly hindered the reaction, resulting in low yields (entries 3 and 4). Copper(I) salts often play key roles in the reaction of alkynes, but surprisingly a catalytic amount of copper(I) iodide shut down the reaction (entry 5). The addition of water, ethanol, 1,3-propandiol, or trimethylolethane had very little effect on the reaction (entries 6, 8, 10, and 12) on running under inert conditions. Interestingly, reactions performed in air (entries 2, 7, 9, 11, and 13) showed improved regioselectivity for linear products **7a** and **8a**, with no branched products being observed (**6a**, **8a**). With trimethylolethane as an additive in the presence of air, the yield of **7a** increased to 75% with only 2.5 equiv of the propargyl alcohol (entry 13) with no other byproducts other than **5a**. Running the reaction under 1 atm of oxygen increased the yield relative to a nitrogen atmosphere but resulted in a lower yield in comparison to that in the presence of air (entry 14).

Under the newly optimized conditions, enyne **7a** could be isolated in a 72% yield (Table 3). Propargyl alcohols with an sp^2-hybridized substituent on C1 gave good yields of enyne products (Table 4). Reacting phenylacetylene with 1-(4-methoxyphenyl)-2-propyn-1-ol afforded **7i** in 73% yield. NMR analysis of the crude product showed 22% of the homodimer of the propargyl alcohol and no other enyne byproducts. The improved selectivity for cross-coupling over dimerization of the propargyl alcohol may be due to the increased steric hindrance of the propargyl aryl group. Other 1-aryl-substituted propargyl alcohols gave the resulting enyne products **7j–l** in good yields (61–73%). The presence of electron-donating or -accepting substituents on the propargyl

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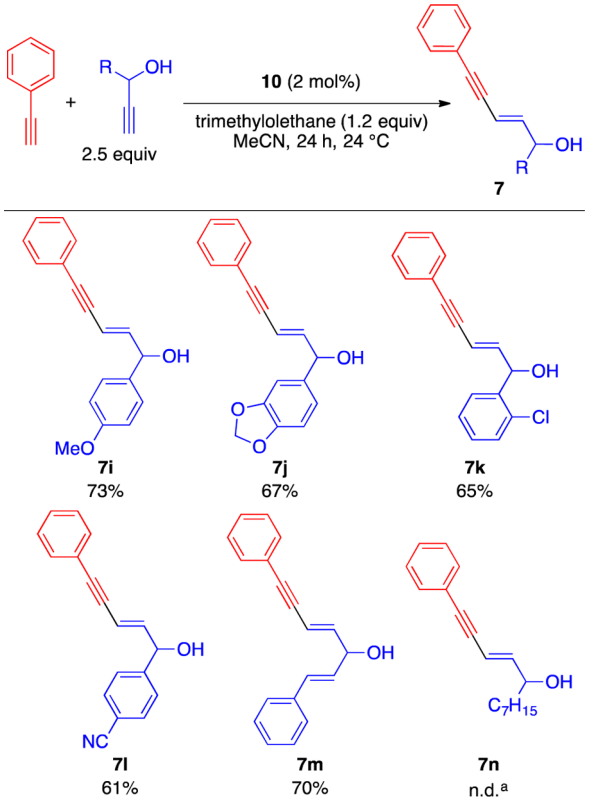
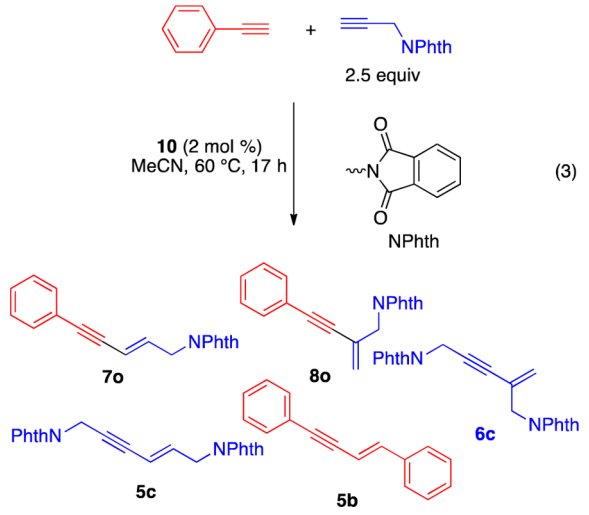
Table 4. Dimerization of Arylacetylenes with Substituted Propargyl Alcohols



[a]n.d. = not determined.

alcohol had little effect on the isolated yield. 1-Phenyl-1,4-heptadien-6-yn-3-ol gave dienyne **7m** in 70% yield. An aliphatic substituent on the propargyl carbon resulted in low conversion to **7n** with multiple isomeric products observed by ^{1}H NMR analysis.

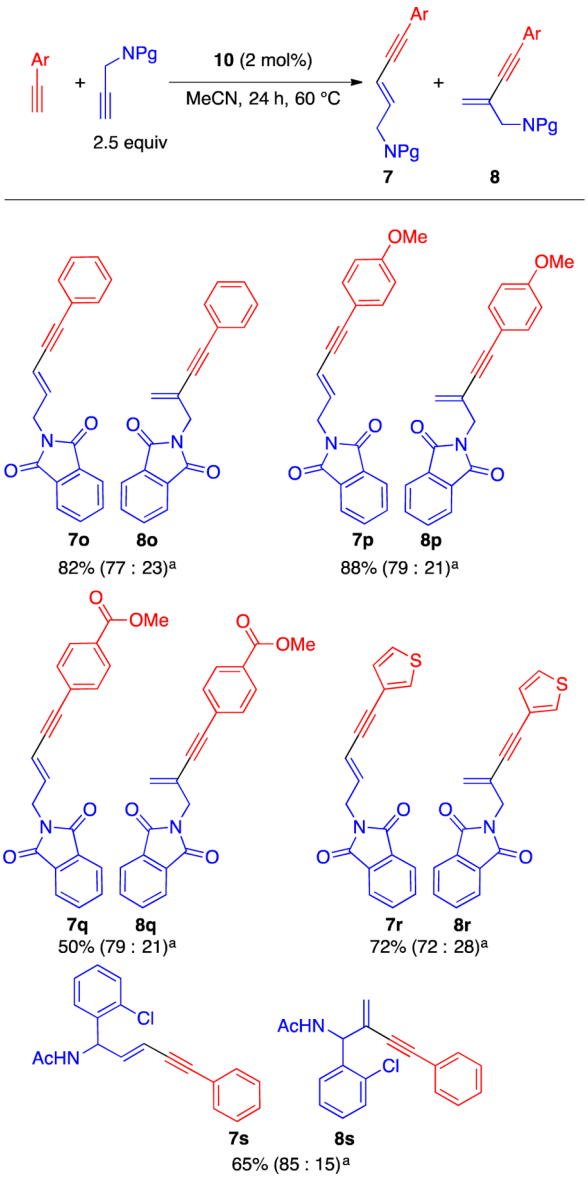
Coupling of Alkynes with Propargyl Amides. Next, propargylamines were examined as coupling partners with arylacetylenes. Coupling of *N*-propargylphthalimide with phenylacetylene produces a mixture of linear enyne **7o** (70%) and branched enyne **8o** (18%) as the cross-coupling products at 60 °C (eq 3). Little to no phenylacetylene dimerization



products (<1%) were observed using only 2.5 equiv of *N*-propargyl phthalimide. *N*-Propargylphthalimide dimers **5c** (120%, relative to phenylacetylene) and **6c** (60%) were produced in significant amounts with a similarly low regioselectivity observed for the cross-coupling reaction. Again, the more polar homocoupling products could be easily separated by column chromatography. The reason for the decreased regioselectivity for the *N*-propargyl amide in comparison to that for propargyl alcohol is unclear.

Propargyl amides reacted effectively with a range of aryl acetylenes to afford generally high yields of mixtures of linear and branched products (Table 5). Products **7o** and **8o** derived from phenylacetylene were isolated in 82% yield as a 77:23 mixture favoring **7o.** *N*-Propargylphthalimide produced good yields of the linear enyne products with electron-rich (**7p**) and electron-poor (**7q**) aryl acetylenes as well as 3-ethynylth-

Table 5. Dimerization of Arylacetylenes with Propargyl Amines



[a]Value in parentheses is the ratio of regioisomers **7** and **8** determined by ^{1}H NMR spectroscopy.

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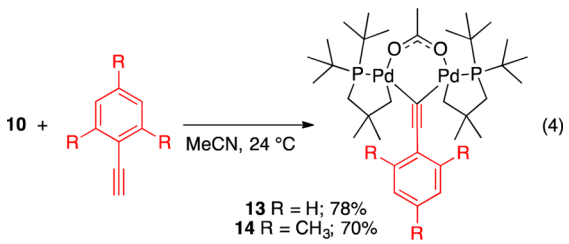
iophene (**7r**). Regioselectivities for these products ranged from 3:1 to 4:1 of **7**:**8**. Enyne **7s** containing a propargylacetamide was produced with slightly higher regioselectivity in comparison to the propargyl phthalimide substrates. The use of tosyl- and benzyl-protected amines was also explored but resulted in unsatisfactory selectivities or yields.

Mechanistic Studies. Monitoring the reaction of phenylacetylene with propargyl alcohol via ^{31}P NMR spectroscopy shows two major peaks after 3 h, a broad peak at 94.8 ppm (63%) and a sharper peak at 82.1 ppm (13%) ppm, along with minor peaks, including a broad feature around 81 ppm (18%) and small sharp peaks at 87.1 ppm (4%) and 44.2 ppm (2%). The broad peak at 94.8 ppm corresponds to **10**, and the other peaks above 80 ppm are likely palladacyclic species. The peak at 44 ppm corresponds to $Pd^0(DTBNpP)_2$. We hypothesized that one of the peaks in the 80 ppm region might be an acetylide complex derived from **10**. This complex was independently synthesized by mixing **10** with 2 equiv of phenylacetylene in acetonitrile for 5 min (eq 4). Cooling the reaction mixture to 0



°C and filtering the resulting yellow solid allowed for isolation and characterization of acetylide complex **13**. 2-Ethynyl-1,3,5-trimethylbenzene also reacts with **10** to form the mixed dimer **14**. Characterization of complexes **13** and **14** showed the presence of acetylide, acetate, and κ^2-*P,C*-DTBNpP ligands in a 1:1:2 ratio, suggesting a dipalladacyclic complex.

Complex **14** afforded X-ray-quality crystals that allowed the substitution pattern around the palladium center to be definitively determined. Complex **14** (Figure 1) crystallized in the monoclinic space group $P2_1/c$ with two molecular units in the asymmetric unit. The two molecules in the asymmetric unit have similar structural parameters. Data for one of the molecular structures are discussed here. A comparison of the two molecular structures can be found in Table S3 in the Supporting Information.

The solid-state structure of **14** (Figure 1) shows a μ-κ^2-C^1,C^1 binding mode for the acetylide anion. Bridging acetylide ligands can adopt a variety of bonding modes, with κ^1,η^2 being the typical structure.[24] The μ-κ^2 bonding mode is less common but has been reported for a variety of metals, including Pt,[25] Cu,[26] Ru,[27] and Mn.[28] There are no examples of palladium dimers with a μ-κ^2-C^1,C^1-bound acetylide ligand in the literature, however. As in other reported examples, the acetylide is unsymmetrically coordinated to the two palladium centers in the solid-state structure. The Pd1−C29 bond (2.071(2) Å) is shorter than the Pd2−C29 bond (2.159(2) Å), and the Pd1−C29−C30 angle (155.3(2)°) is larger than the Pd2−C29−C30 angle (117.5(2)°). The lack of symmetry does not appear to indicate an η^2 binding mode with Pd2, however. C30 of the acetylide is much farther (2.923(2) Å) from the Pd2 center than C29 (2.159(2) Å). In addition, the C29−C30 bond (1.211(3) Å) is typical for a carbon−carbon triple bond and remains essentially linear (C29−C30−C31 = 178.4(2)°).

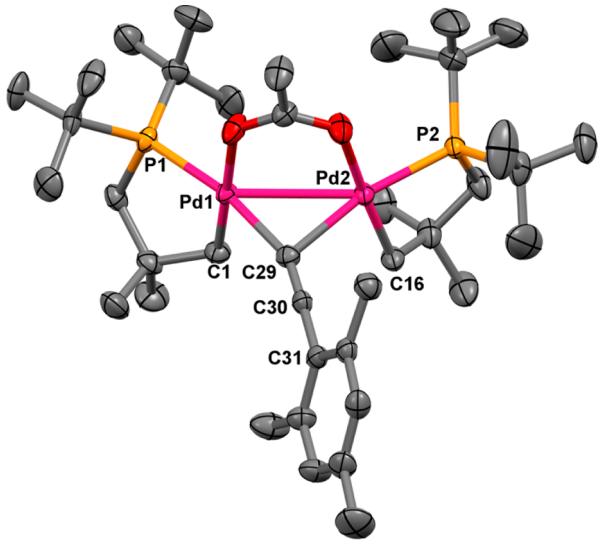
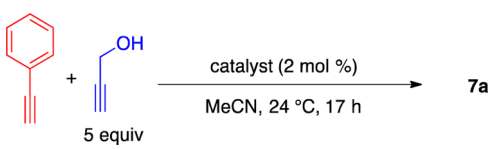


Figure 1. ORTEP diagram of one molecular unit of complex **14** (ellipsoids at 50% probability). Hydrogen atoms have been omitted for clarity. Selected bond distances (Å) and angles (deg): Pd1−P1, 2.2818(8); Pd1−C1, 2.039(2); Pd1−Pd2, 2.9093(9); Pd2−P2, 2.2358(9); Pd2−C16, 2.039(2); Pd1−C29, 2.071(2); Pd2−C29, 2.159(2); C29−C30, 1.211(3); P1−Pd1−C1, 82.12(6); P2−Pd2−C16, 82.00(6); Pd1−C29−C30, 155.3(2); Pd2−C29−C30, 117.5(2); C29−C30−C31, 178.4(2). Distances for the other molecule in the asymmetric unit can be found in the Supporting Information.

In solution, complex **14** appears symmetrical on the basis of ^{31}P, ^{1}H, and ^{13}C NMR data. A single set of κ^2-*P,C*-DTBNpP ligand resonances is observed in the ^{31}P, ^{1}H, and ^{13}C NMR spectra. In the ^{13}C NMR spectrum, the carbons of the acetylide moiety both appear as triplets due to coupling with the symmetrical phosphorus centers ($^3J_{C-P}$ = 77.6 Hz, $^4J_{C-P}$ = 13.8 Hz). Similar coupling patterns are seen for complex **13**. The solution data would suggest that the acetylide either is symmetrically coordinated or is rapidly isomerizing between two unsymmetric structures analogous to the solid-state structure.

Palladacycle **13** is a competent catalyst for the reaction of phenylacetylene with propargyl alcohol, but the yield of **7a** is about 10% lower in comparison to that using **10** as the catalyst (Table 6, entries 1 and 2). Hypothesizing that the decrease in yield was due to the lower amount of acetate anion present, 2 mol % of potassium acetate was added along with **13**. Doing so resulted in a yield of **7a** similar to that when **10** was used as the precatalyst (entry 3). The addition of 2 mol % of acetic acid

Table 6. Evaluation of Complex 13 as a Precatalyst



entry	catalyst	additive[a]	yield of **7a** (%)[b]
1	**10**		74
2	**13**		65
3	**13**	KOAc	73
4	**13**	AcOH	51

[a]2 mol % of additive. [b]Yields were determined via ^{1}H NMR spectroscopy with an internal standard.

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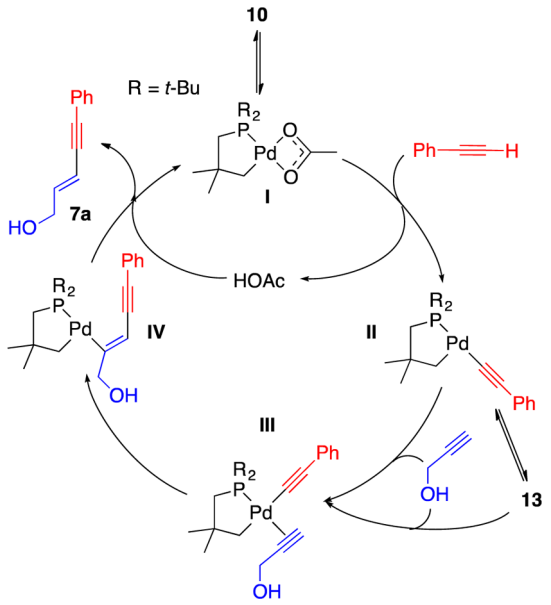
further decreased the yield of **7a** to only 51%. The catalytic competence of complex **13** suggests that it is involved in the catalytic cycle for this reaction.

A number of mechanisms have been proposed for the alkyne coupling reaction, including (1) base-assisted formation of a metal acetylide followed by carbometalation of the second alkyne, (2) oxidative addition of the alkyne C−H bond to a metal followed by hydrometalation and reductive elimination, and (3) generation of a metal vinylidene species followed by α migration of an acetylide.[8b] On the basis of the observations above, we propose a mechanism involving generation of a palladium acetylide followed by carbopalladation of the propargyl alkyne (Scheme 4). This mechanism is similar to

Scheme 4. Proposed Catalytic Cycle



that proposed by Tenaglia and co-workers for their Herrmann−Beller palladacycle catalyzed addition of alkynes to norbornadienes.[21] The palladacycle dimer **10** first dissociates to form monomer **I**. Phenylacetylene then undergoes acetate-assisted C−H activation with monomer **I** to form the Pd(II) acetylide intermediate **II** and release acetic acid. The stereochemistry of this species is unknown, but the more stable form would likely have the acetylide trans to the phosphorus. The critical role of acetate as a base can be seen by the lack of reactivity of bromide-bridged palladacycle **11**. Intermediate **II** is in equilibrium with the off-cycle mixed bridging acetylide dimer **13**. Intermediate **II** then coordinates propargyl alcohol to form **III**. Again, the stereochemistry of **III** is unknown, but we propose that **II** may isomerize to place the acetylide cis to the phosphorus, allowing the incoming alkyne to coordinate cis to the less sterically demanding carbon of the palladacycle. Complex **III** then undergoes migratory insertion to afford vinyl species **IV**. This insertion is the regioselectivity-determining step. Complex **13** could also potentially react directly with propargyl alcohol to give **III**. Intermediate **IV** then undergoes protonolysis with acetic acid generated in the initial step to form **7a** and regenerate monomer **I**. Alternatively **IV** could react directly with phenylacetylene to form **7a** and **II**.

We hypothesize that the palladacycle remains intact throughout the catalytic cycle and that no redox processes are involved. This hypothesis is supported by a number of observations. First, performing the reaction with a mixture of DTBNpP and $P(OAc)_2$ affords lower conversion and decreased regioselectivity. Although palladacycle **10** likely forms from DTBNpP and $Pd(OAc)_2$ during the catalytic reaction, the lower regioselectivity suggests that the κ^1-*P* Pd^{II}(DTBNpP) complex catalyzes the reaction less regioselectively than does palladacycle **10**. Second, ^{31}P NMR analysis of the reaction in progress shows that 98% of the phosphorus species present are palladacycles, primarily **10** and **13** (Figure S2 in the Supporting Information). Although $Pd(DTBNpP)_2$ accounts for 2% of the phosphine species, we do not think this plays a role in the selective product of **7** (vide infra). We cannot completely rule out the possibility of a small concentration of active species, however. Finally, the preparation of μ-acetylide **13** by reaction with **10** is consistent with a base-assisted mechanism to generate the acetylide intermediate, rather than oxidative addition of the C−H bond. Furthermore, complex **13** is catalytically competent in this reaction, showing that it is likely part of the catalytic system.

The chemoselectivity of this system is consistent with the systems reported by Trost,[12b] Oshovsky,[11] and Xu.[12a] The initial formation of the palladium acetylide **II** presumably occurs with modest selectivity, since both product **7** and the propargyl alcohol homodimer **5a** are formed in similar amounts in the reaction. Although propargyl alcohol is present in higher concentration, the higher of acidity of phenylacetylene allows it to compete effectively to form complex **II**. Complex **II**, or possibly **13**, then reacts selectively with propargyl alcohol over phenylacetylene to form complex **III**. This selectivity is shown by the lack of phenylacetylene homodimer **5b** formed in the reaction. The inductive effect of the propargyl oxygen or nitrogen is thought to lower the alkyne HOMO−LUMO gap, which makes it a better ligand.[11,12] In addition, the inductive withdrawing effect would make migratory insertion occur more readily.

At this time we can only speculate about the reasons for the unique nature of the regioselectivity of complex **10**. The results in Table 1 show that palladacycles derived from electron-rich and sterically demanding ligands (DTBNpP and TTBP) afford selectivity for the linear enyne product **7a**, with complex **10** providing the highest selectivity. In contrast, the Herrmann−Beller palladacycle derived from the less electron rich but sterically demanding tri-*o*-tolylphosphine preferentially affords the branched enyne isomer **8a** by a 2:1 ratio. Catalysts generated in situ from a phosphine and $Pd(OAc)_2$ appear to favor the branched enyne product **8**. In the case of DTBNpP, using a mixture of the ligand and $Pd(OAc)_2$ in place of **10** affords a lower level of regiocontrol, although linear product **7** is still favored. Tri-*o*-tolylphosphine affords branched enyne **8a** in higher selectivity (95:5) in comparison to the palladacycle (64:36 **8a**:**7a**).

The regioselectivity in this reaction would be determined by the conformation of the alkyne that is favored for migratory insertion (Scheme 5). Steric bulk at the metal center would be expected to favor insertion to place the metal at the terminal carbon, leading to the branched enyne product **8**. A common feature of the results in Table 1 is that the palladacyclic complexes provide a higher proportion of the linear enyne **7** in comparison to the nonpalladacyclic catalyst systems. We do not know the stereochemistry of the proposed palladium acetylide acetylene intermediate. The structure with the acetylide trans to the Pd−C bond would be expected to be more stable. The isomer of complex **III** shown in Scheme 5 may be favored

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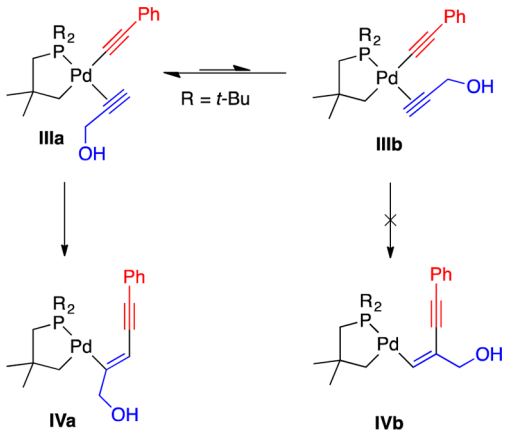
Scheme 5. Regioselectivity of Migratory Insertion



sterically, however, as it places the smaller acetylide ligand next to the larger phosphorus group. It is possible that palladacycles provide a relatively open coordination site cis to the Pd−C bond of the palladacycle. Coordination of the alkyne in this position may provide a higher concentration of rotomer **IIIa**, which leads to the linear enyne product. This steric effect cannot solely explain the regioselectivity effects seen; however, as the P(*o*-tol)$_3$-based palladacycle favors branched product **8a** in contrast to the palladacycles derived from bulky alkylphosphines. The electron-donating ability of DTBNpP and TTBP appears to further enhance the selectivity for the linear product. A more electron deficient metal center would be expected to have a stronger preference to insert with the metal at the less substituted carbon. The more electron rich metal center in **10** may weaken the electronic preference, allowing the steric preference to take over.

Additives also play a role in the selectivity of the alkyne coupling reaction, although we do not fully understand these effects at this time. One interesting observation was that the presence of air suppressed the formation of branched enynes **8a** and **6a** in the coupling of phenylacetylene and propargyl alcohol. It is not clear how the presence of oxygen affects the coupling reaction. One possible hypothesis is that air serves to reoxidize any Pd(0) species formed during the reaction. A small of amount of Pd^0(DTBNpP)$_2$ is observed during the catalytic reaction. It is possible that this species, or something related, promotes formation of the branched isomer. Further mechanistic studies are needed to test this hypothesis.

Lower regioselectivity is seen for propargyl amide substrates in comparison to propargyl alcohol. It is possible that the increased steric demand of the phthalimide substituent results in an increased preference for insertion to occur with the palladium at the terminal carbon of the propargyl amide to give branched product **8**. This steric preference may partially offset the inherent preference for complex **10** to afford the linear product **7**. The details of these selectivity effects will require further study to fully elucidate.

CONCLUSION

In conclusion, the first selective synthesis of linear (*E*)-enynols **7**, found in a number of biologically active compounds, from terminal aryl alkynes and propargyl alcohols has been reported. The reaction proceeds with low catalyst loadings, operates under mild conditions, and does not require the addition of stoichiometric acids or bases. This methodology affords (*E*)-4-phenyl-2-penten-4-yn-1-ol, a key intermediate in the synthesis of type 2 diabetes treatment candidate NNC 61-4655, in good yield in one step from inexpensive precursors. In comparison, the reported process-scale synthesis requires four steps in 19% overall yield.[3] Mechanistic insights were found by isolating and obtaining a crystal structure of the first example of a μ-κ^2-C^1,C^1-acetylide palladacycle complex (**14**). μ-Acetylide complex **13** is observed under the catalytic conditions and serves as a competent precatalyst for the alkyne cross-dimerization reaction. We propose that this species serves as an off-cycle resting state in the catalytic mechanism. Although we can not definitively account for the unique regioselectivity observed with complex **10**, it appears that the palladacycle provides the necessary steric and electronic properties to favor formation of linear enyne products over the more commonly observed branched enynes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b01541.

Full experimental procedures and characterization data, solvent screen results, VT-NMR of complex **10**, in situ ^{31}P NMR of the catalytic reaction, crystal structure data and refinement details for **14**, and ^{1}H, ^{13}C, and ^{31}P NMR spectra for the palladium complexes and compounds reported in Tables 2, 4, and 5 (PDF)

Crystallographic data for **14** (CIF)

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Notes

The authors declare no competing financial interest.

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