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Dehydrative Cross-Coupling of Allylic Alcohols with Alkynes

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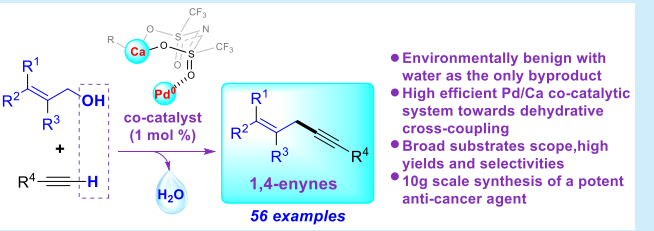
ABSTRACT: A highly efficient Pd/Ca catalytic system for the directly dehydrative cross-coupling of allylic alcohols with terminal alkynes was developed. This calcium salt cocatalyst facilitates the oxidative addition of the palladium catalyst (1 mol %) to the C−OH bond. Then, the in situ-generated hydroxide ion deprotonates the terminal alkynes to promote the formation of the allylalkynylpalladium intermediate, liberating water as the only byproduct. This proposed mechanism is also supported by density functional theory calculations. An anticancer agent was prepared from inexpensive starting materials on a 10 g scale.



The 1,4-enyne skeletons are identified as privileged motifs in organic synthesis[1] and biologically and pharmaceutically active molecules[2] (such as hypoxoside and rooperol[2a,c,g]). In particular, 1,5-aryl-disubstituted 1,4-enynes were found to have highly potent anticancer activity against human esophageal carcinoma cell growth in recent pharmacological investigations.[2a,e] This moiety is generally prepared from highly functionalized activated allylic compounds or preactivated alkynes with the assistance of large quantities of neutralizing agents/oxidants and thus generates a stoichiometric amount of metallic salt.[1f,3] Undoubtedly, the direct dehydrative cross-coupling between allylic alcohols and alkynes to access 1,4-enynes would be the most ideal approach.[4,5] However, the irreconcilable contradiction between acidity activator for C−OH bond activation and basic environmental condition required for maintaining the nucleophilic activity of terminal alkynes[1f] challenged the development of catalysts. To address this problem, the groups of Trost,[6] Jiang,[7] Kimura,[8] and Li[9] have paid an extensive amount of attention to this area since the 1990s. Unfortunately, 1,4-dienes, rather than 1,4-enynes, were delivered as the major products[6−8] (Figure 1a). In one report, 1,4-enynes were obtained by Li and Liu, who found a strong dependence on high catalyst (10 mol % Pa) and additive (25 mol % Ti) loadings.[9] On the contrary, Cu[10a] or Ga[10b] was also reported in a few cases to catalyze this reaction toward some special alcohols in a limited substrate scope via a carbocation mechanism; a rejuvenation of the dehydrative cross-coupling can still be anticipated via the creation of a new strategy capable of overcoming issues such as catalytic efficiency and a strong dependence on well-defined ligands and highly concentrated additives.[9]

In our continuing green chemistry efforts,[5a,11] we focused on the development of a greener and more efficient method for addressing the dehydrative cross-coupling of allylic alcohols with terminal alkynes. We envision the directly oxidative addition of palladium to the C−OH bond might occur, giving

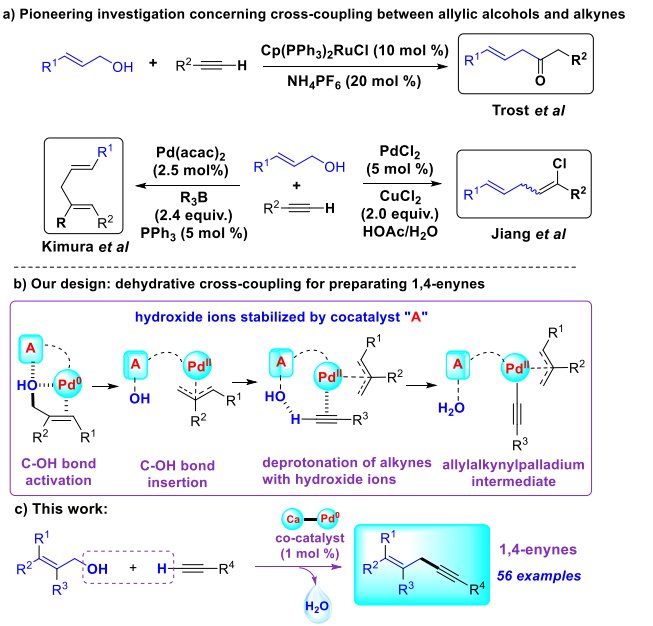


Figure 1. Development of dehydrative cross-coupling of allylic alcohols with alkynes.

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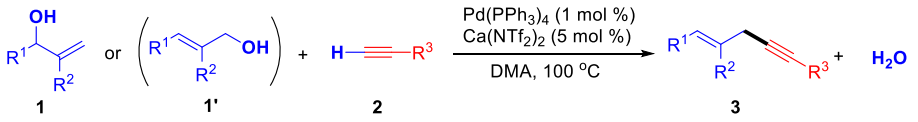
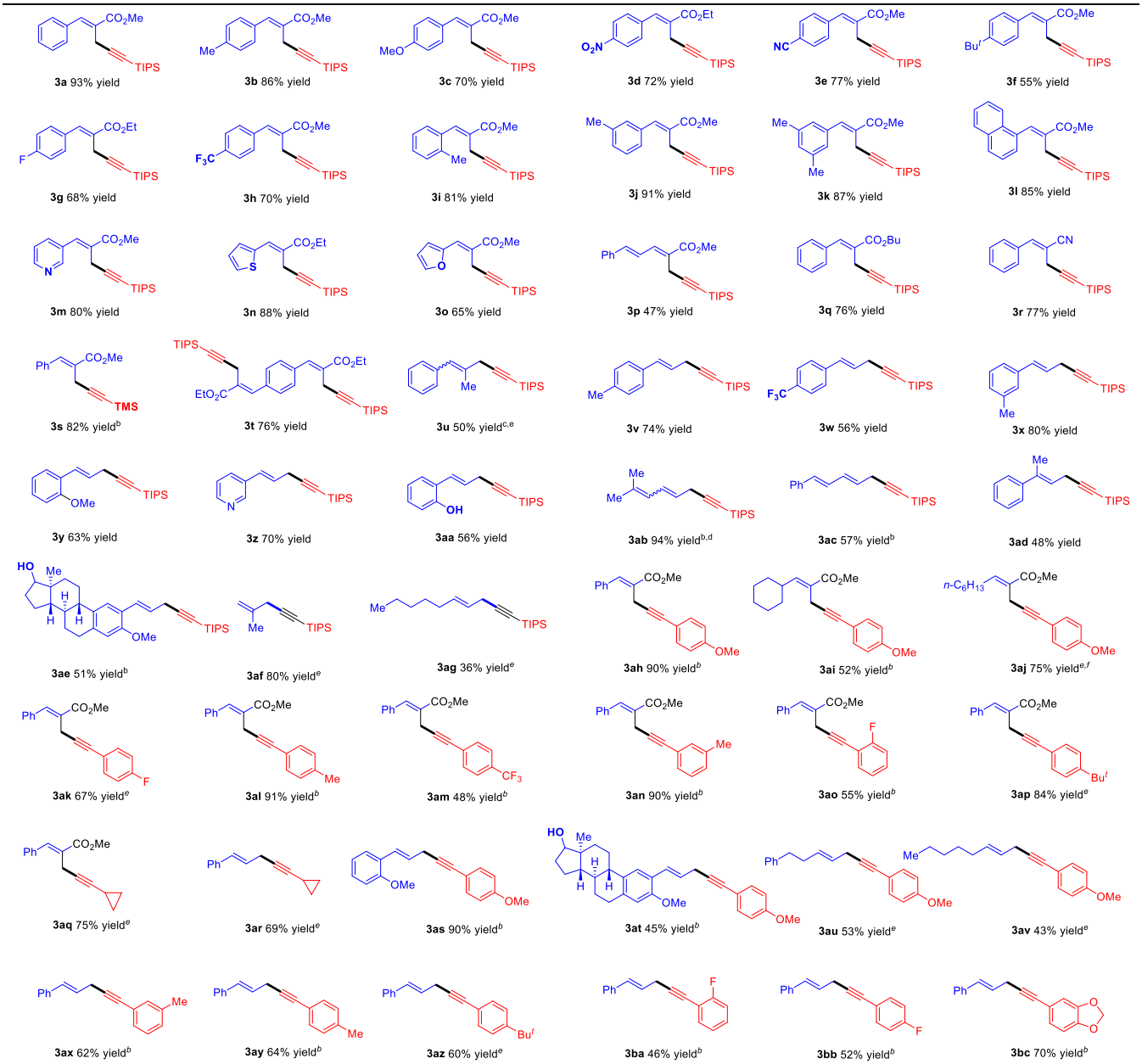
Scheme 1. Dehydrative Cross-Coupling of Allylic Alcohols with Alkynes[a]





[a]MBH alcohol (1.0 equiv, 0.2 mmol), ethynyltriisopropylsilane (2.5 equiv), $Pd(PPh_3)_4$ (1.0 mol %), $Ca(NTf_2)_2$ (5.0 mol %), NH_4PF_6 (5.0 mol %), H_2O (30 mol %), DMA (2.0 mL), Ar, 100 °C (oil bath), isolated yields. TIPS = triisopropylsilyl. [b]$Pd(PPh_3)_4$ (1.0 mol %), $Ca(NTf_2)_2$ (5.0 mol %), *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethylphosphoramide (HMPA) (1.2 mol %), triethylamine (1.0 mol %). [c]**3u**, a *Z*/*E* ratio of 2/1. [d]**3ab**, a *Z*/*E* ratio of 5/1. [e]$Pd(PPh_3)_4$ (3.0 mol %), $Ca(NTf_2)_2$ (10.0 mol %), HMPA (3.6 mol %), triethylamine (3.0 mol %). [f]α/γ = 2/3. For **3s**, ethynyltrimethylsilane (10 equiv) was used. **3a**−**3av** were prepared from **1**, and **3ax**−**3bc** were prepared from **1**′.

π-allylpalladium intermediates and hydroxide ions with the assistance of a suitable cocatalyst. Subsequently, the in situ-generated hydroxide ions can serve as the base to deprotonate the terminal alkynes, delivering water as the only byproduct. Then, the reaction process could heavily favor the desired π-allylalkynylpalladium intermediate rather than the competitive allylvinylpalladium or dialkynylpalladium pathways (Figure 1b). Herein, we report a highly efficient Pd/Ca catalytic system for the direct dehydrative cross-coupling between allylic alcohols and alkynes (Figure 1c). The assumed mechanism was also demonstrated by DFT calculations. (*E*)-1-Methoxy-4-(5-phenylpent-4-en-1-yn-1-yl)benzene (an inhibitor of human esophageal carcinoma cell growth; IC_{50} = 10 μg/mL; 2.5 times more active than rooperol)[2a] can be conveniently prepared on a 10 g scale from commercially available and ubiquitous

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feedstocks, namely, (*E*)-3-phenylprop-2-en-1-ol and 1-ethynyl-4-methoxybenzene.

The reaction of methyl 2-[hydroxy(phenyl)methyl]acrylate (**1a**) with ethynyltriisopropylsilane (**2a**) was selected as a model. Without other cocatalysts, palladium itself could not promote the reaction [Supporting Information (SI), Table 1, entries 1−3]. In searching for a powerful cocatalyst (SI, Table 1, entries 4−7), we paid special attention to alkaline earth metals,[12] which are abundant and exhibited amazing catalytic activities in many transformations.[13] In particular, calcium salts are powerful catalysts for Friedel−Crafts and related cationic cycloadditions[14−16] developed by the groups of Niggemann,[14] Gandon,[15] and others[16] owing to their high activities toward alcohols and epoxides. Inspired by these studies and investigations related to the Trost−Tsuji reaction,[17] we envision the combination of an alkaline earth metal with palladium might be a solution for this challenging dehydrative cross-coupling. To our delight, with the assistance of $Ca(NTf_2)_2$ (20 mol %) and $Pd(PPh_3)_4$ (10 mol %), the reaction proceeded smoothly with dioxane as the solvent to afford the desired product in 69% yield (SI, Table 1, entry 6). In all the tested case, the solvent DMA (*N*,*N*-dimethylacetamide) give the best yield (SI, Table 2). The temperature and reaction time had substantial influences on the outcome of this reaction (SI, Table 3, entries 1−5). NH_4PF_6 was identified as a powerful additive for accelerating the transformation (SI, Table 3, entries 6−10). In sharp contrast with the previous study,[9] in which a high palladium loading (10 mol %) combined with a well-defined ligand was vital to the success of the cross-coupling reaction, $Pd(PPh_3)_4$ (1 mol %) in cooperation with $Ca(NTf_2)_2$ (5 mol %) exhibited excellent catalytic activity in our developed method (SI, Table 3, entries 11−18). Even $Pd(PPh_3)_4$ (0.5 mol %) combined with $Ca(NTf_2)_2$ (10 mol %) can promote this transformation, albeit with a lower yield (SI, Table 3, entries 19 and 20). Further investigations revealed that water (SI, Table 3, entries 21−25) and the counterions also play an important role in this reaction. $Ca(NTf_2)_2$ and $Ca(OTf)_2$ worked well, whereas $CaCl_2$ was ineffective in this transformation (SI, Table 3, entries 26 and 27).

Under the optimized reaction conditions, we examined the reactions between Morita−Baylis−Hillman (MBH) alcohols **1** and ethynyltriisopropylsilane (**2a**). As shown in Scheme 1, a variety of MBH alcohols were amenable to this protocol. The electronic properties (**3a**−**h**) and position (**3b**, **3i**, and **3j**) of the phenyl substituents on the MBH alcohols have little effect on the yield. Even allylic alcohols bearing highly active groups such as nitryl (**3d**), cyano (**3e**), and trifluoromethyl (**3h**) could furnish the desired products in good yields. Monosubstituted and polysubstituted (**3k**) as well as fused-aromatic (**3l**) MBH alcohols smoothly reacted with ethynyltriisopropylsilane (**2a**) under the identified conditions. MBH alcohols bearing heteroaryl substituents, such as pyridien-2-yl (**3m**), thiophen-2-yl (**3n**), and furan-2-yl (**3o**), were also well tolerated. Moreover, a cinnamoyl group was tolerated, delivering a synthetically useful 2,4-dienoate skeleton with an alkyne moiety (**3p**). Sterically demanding allylic alcohols can also proceed smoothly (**3f** and **3q**), but in some cases, the yields were lower. A comparable result was obtained even when the ester group was replaced with a cyano group (**3r**). Ethynyltrimethylsilane was also compatible with the reaction conditions (**3s**), and the convenient deprotonation of the TMS (trimethylsilyl) group will facilitate further elaboration. A double dehydrative allylalkynyl cross-coupling was also demonstrated with the generation of **3t** in good yield.

Next, secondary and tertiary allylic alcohols other than MBH derivatives were tested as the allylic coupling partner. As expected, the desired products (**3u**) can also be obtained when the ester group is replaced with a methyl. This result indicated that the reaction was not limited to electron-deficient allylic alcohols. A variety of aryl-substituted allylic alcohols were found to be fully compatible with this method (**3v**−**3aa**, **3ad**, and **3ae**), regardless of the electron-withdrawing or electron-donating groups on the phenyl ring. It should be noted that 1-(pyridin-3-yl)prop-2-en-1-ol could also deliver the desired product (**3z**) in high yield. Even a phenolic hydroxyl group was found to be well tolerated in this reaction; however, the corresponding 1,3-enyne (**3aa**) was obtained in a slightly lower yield. Remarkably, this method also allowed access to 4,6-dien-1-yne skeletons (**3ab**) from vinyl-substituted allylic alcohols. This will increase the opportunities for structural modification of the products and enhance their synthetic utility. Notably, tertiary allylic alcohols could undergo intramolecular elimination processes if they had an adjacent α-C−H bond, resulting in the desired product in moderate yield (**3ad**). A steroid moiety with an active hydroxyl group was also well tolerated (**3ae**), which further highlights the utility of this method in pharmaceutical studies. Moreover, nonconjugated allylic alcohols were also compatible (**3af** and **3ag**). **3af** can be isolated in high yield, while the sterically demanding **3ag** was obtained in lower yields only due to the competitive dimerization of **2a** (for detail, see the SI).

Having established the scope of the reaction with respect to allylic alcohols, we investigated the suitability of various terminal alkynes for this reaction. We varied the aryl acetylene in an attempt to prepare 1,5-diaryl-substituted 1,4-enyne skeletons, which are common in biologically and pharmaceutically active molecules in addition to being a privileged motif in organic synthesis.

To improve the overall performance, *N*,*N*,*N*′,*N*′,*N*″,*N*″-hexamethylphosphoramide (HMPA) (1.2 mol %) and triethylamine (TEA) (1.0 mol %) were introduced to replace NH_4PF_6. We found that the reaction was very sensitive to the acidity of the C(alkynyl)−H bond (**3ah** and **3ak**−**3ap**). Electron-deficient aryl acetylenes, to some extent, disfavored the transformation (**3ak**, **3am**, and **3ao**). The position of the substituents (*para*, *ortho*, and *meta*) on the phenyl ring has a limited effect on the transformation (**3ak**, **3an**, and **3ao**). Notably, a *tert*-butyl substituent at the phenyl ring could effectively participate in this transformation (**3ap**). Moreover, allylic alcohols with adjacent C−H bonds, which favored the self-dehydration process with the generation of conjugated 1,3-dienes, can also react with aryl acetylene to give the corresponding products (**3ai** and **3aj**) in moderate to high yields. In our preliminary investigation, alkyl acetylenes such as ethynylcyclopropane were found to be suitable substrates for this reaction (**3aq** and **3ar**). Allylic alcohols without ester substituents were also suitable substrates when reacted with aryl acetylene (**3ar**−**3av**). In the tested case, the reaction of nonconjugated allylic alcohols with aryl-substituted terminal alkynes was sluggish and thus gave the desired product in moderate yield (for details, see the SI). Finally, the reactions between ubiquitous feedstock cinnamyl alcohol and commercially available aryl acetylenes were investigated. The extensively investigated biologically active 1,5-diaryl-substituted 1,4-enynes (derivatives of natural products such as

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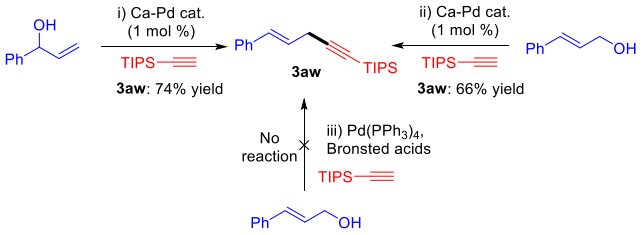
hypoxoside and rooperol, which exhibit good anticancer bioactivities) were obtained in moderate to high yields under our developed catalytic system (**3ax**–**3bc**).

Using our developed method, the same product, (*E*)-1-methoxy-4-(5-phenylpent-4-en-1-yn-1-yl)benzene (**3aw**), was obtained from both 1-phenylprop-2-en-1-ol and cinnamyl alcohol upon reaction with ethynyltriisopropylsilane (Scheme 2). These results indicate that the same π-allylpalladium intermediate was generated from the two isomeric allylic alcohols. Moreover, no reaction occurred in the absence of $Ca(NTf_2)_2$ or even when Bronsted acids, such as 4-methylbenzenesulfonic acid or benzoic acid, were used under the identified conditions (for details, see the SI).

Scheme 2. Control Experiments[a]

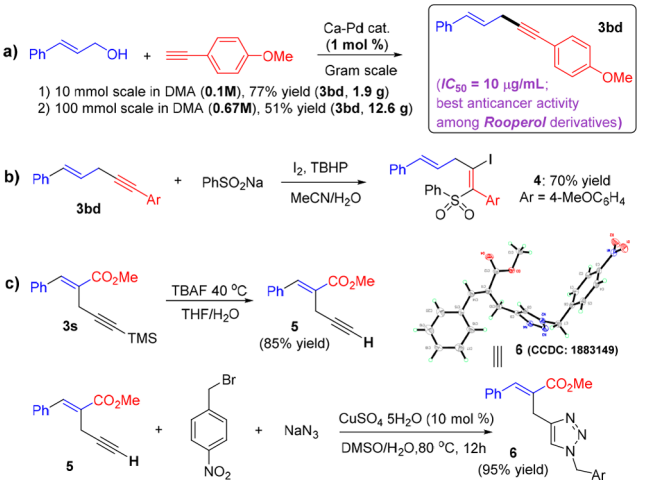


[a](i) $Pd(PPh_3)_4$ (1.0 mol %), $Ca(NTf_2)_2$ (5.0 mol %), NH_4PF_6 (5.0 mol %), 100 °C for 12 h; (ii) $Pd(PPh_3)_4$ (1.0 mol %), $Ca(NTf_2)_2$ (5.0 mol %), NH_4PF_6 (5.0 mol %), 100 °C for 20 h; (iii) $Pd(PPh_3)_4$ (1.0 mol %), Bronsted acids [*p*-TsOH (5 mol %) or $PhCO_2H$ (5 mol %)], 100 °C for 24 h.

Among the reported derivatives, (*E*)-1-methoxy-4-(5-phenylpent-4-en-1-yn-1-yl)benzene (**3bd**) was identified as having the highest bioactivity in the inhibition of human esophageal carcinoma cell growth (IC_{50} = 10 μg/mL; 2.5 times more active than rooperol).[2a] With our developed method, (*E*)-1-methoxy-4-(5-phenylpent-4-en-1-yn-1-yl)benzene (**3bd**) could be conveniently obtained on a gram scale (77% yield, 1.9 g) from 1-phenylprop-2-en-1-ol upon reaction with 1-ethynyl-4-methoxybenzene. Moreover, the high efficiency of the catalytic system was further supported by a 10 g scale reaction, which was conducted at a higher concentration (0.67 M). More than 10 g of desired anticancer agent **3bd** can be isolated, corresponding to a moderate yield (Scheme 3a). The 1,4-enynes obtained using our protocol are amenable to further synthetic transformations. Under mild conditions, the triple bond could be selectively bifunctionalized to afford **4** (Scheme 3b). The TMS moiety can be conveniently removed by treatment with TBAF in aqueous media (compound **5**), allowing further elaboration by click chemistry (compound **6**, CCDC 1883149) (Scheme 3c).

The detailed mechanism was still unclear; to elucidate the reaction mechanism, density functional theory (DFT) calculations were carried out using the Gaussian 09 computational program. The geometries were optimized in the gas phase at the B3LYP/DGDZVP level of theory, and then, single-point energies were determined at the B3LYP+D3-PCM/Def2TZVPP level of theory (for computational details, see the SI and SI references 4–10). 1-Phenylprop-2-en-1-ol and ethynyltriisopropylsilane were selected as the model reactants for the examination of the mechanism (Figure 2). Bicoordinate Pd(0) complex CAT-R was initially generated. Theoretically, the oxidative addition of Pd(0) to the C–OH bond could be performed directly by delivering the π-

Scheme 3. Synthesis of the Anticancer Bioactive Molecule 1,4-Dienyne Moiety and Related Modification



allylpalladium intermediate. However, the high free energy barrier (TS0 = 43.2 kcal/mol; for details, see the SI) of the corresponding transition state indicates that the process might not be readily accessible. With the assistance of $Ca(NTf_2)_2$, the transition from CAT-R to pre-COM occurred spontaneously with the release of 14.1 kcal/mol of free energy. Furthermore, the subsequent oxidative addition involving C–OH bond cleavage could be facilitated by $Ca(NTf_2)_2$ due to the formation of the Ca–OH bond. The traditional mechanism, loss of the leaving group from the face of the double bond opposite palladium (TS1′) to form the Pd(II)-complex INT-1, cannot completely be ruled out by control experiments (for details, see the SI). To account for the mechanism, a more reasonable pathway was proposed on the basis of the related investigation and our DFT calculations (TS-1 vs TS-1′). The existence of the interaction between OH and Pd[18] in addition to the coordination effect of electron-rich oxygen atoms (NTf_2) on palladium enabled the elimination of OH from the face of palladium in a neighborhood participation manner. The free energy barrier associated with TS-1 is only 12.3 kcal/mol, and the much more stable Pd(II) complex, INT-1, with an η^3-allyl ligand was delivered. Subsequently, the combination of INT-1 with alkyne **2** via a palladium–triple bond interaction affords INT-1-yne. The in situ-generated hydroxide ion then deprotonates the terminal alkyne through kinetically favored transition state TS-2 with a low free energy barrier (4.8 kcal/mol), promoting the formation of allylalkynylpalladium intermediates INT-2 and INT-2′. Finally, allyl–alkynyl bond formation via a reductive elimination (TS-3, with a free energy barrier of 24.2 kcal/mol for the elementary step) gives 1,4-enynes **3** (INT-3). The cocatalyst can be regenerated in the presence of an allylic alcohol. For the proposed multistep pathway, the rate-determining free energy barrier can be derived from the energetic span model,[19] which leads to a total barrier height of 29.6 kcal/mol, the free energy difference between INT-1 and TS-3, in line with the experimental temperature used.

In conclusion, a highly efficient Pd/Ca cocatalytic system was developed to achieve the direct dehydrative Tsuji–Trost reaction from ubiquitous allylic alcohol feedstocks with commercially available terminal alkynes. The DFT calculations indicated that this cocatalyst enabled the oxidative addition of the palladium catalyst (1 mol %) to the C–OH bond without

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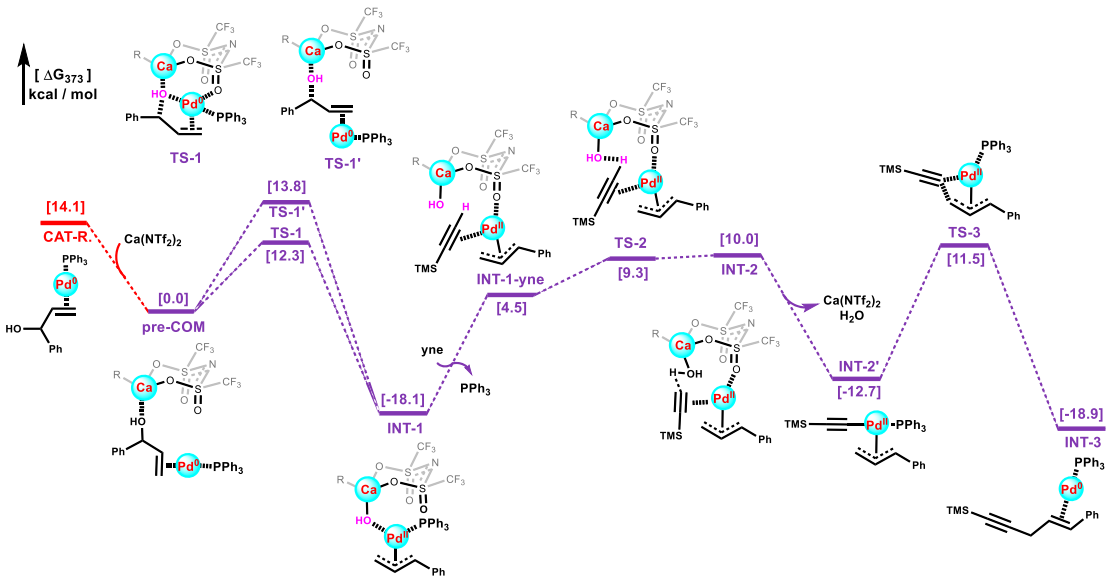

Figure 2. Free energy profile for the dehydrative cross-coupling reaction, at the B3LYP+D3-PCM/Def2TZVPP//B3LYP/DGDZVP level of theory.

the assistance of an external ligand or Bronsted acid. Subsequently, the hydroxide ion rather than water (in the traditional model, with the assistance of a Bronsted acid) was generated as the base, which can deprotonate the terminal alkyne to promote the formation of the allylalkynylpalladium intermediate and then liberate water as the only byproduct. A variety of 1,4-enynes could be conveniently isolated in high yields with broad functional group tolerance. Remarkably, the utility of the methodology has been highlighted by the direct preparation of anticancer agents (IC_{50} = 10 μg/mL) on a 10 g scale from commercially available feedstocks, (*E*)-3-phenyl-prop-2-en-1-ol and 1-ethynyl-4-methoxybenzene.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00108.

Experimental procedures, screening reaction conditions, NMR spectra of products, and DFT calculation methods and results (PDF)

Accession Codes

CCDC 1883149 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Wu, L. J.; Song, R. J.; Luo, S.; Li, J. H. *Angew. Chem., Int. Ed.* **2018**, *57*, 13308. (b) Pradhan, T. R.; Kim, H. W.; Park, J. K. *Angew. Chem., Int. Ed.* **2018**, *57*, 9930. (c) Almasalma, A. A.; Mejia, E. *Chem. - Eur. J.* **2018**, *24*, 12269. (d) Cui, X. Y.; Ge, Y.; Tan, S. M.; Jiang, H.; Tan, D.; Lu, Y.; Lee, R.; Tan, C. H. *J. Am. Chem. Soc.* **2018**, *140*, 8448. (e) Yang, S.; Rui, K. H.; Tang, X. Y.; Xu, Q.; Shi, M. *J. Am. Chem. Soc.* **2017**, *139*, 5957. (f) Harada, A.; Makida, Y.; Sato, T.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2014**, *136*, 13932. (g) Dabrowski, J. A.; Haeffner, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7694. (h) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7532. (i) Dabrowski, J. A.; Gao, F.; Hoveyda, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 4778.

(2) (a) Drewes, S.; Liebenberg, R. W. U.S. Patent 4652636, 1987. (b) Liebenberg, R. W.; Kruger, P. B.; Kruger, P. J. D.; De Vos Albrecht, C. F. Method of treating viral infections. U.S. Patent 5609874, 1997. (c) Daniewski, W. M.; Danikiewicz, W.; Gołębiewski, W. M.; Gucma, M.; Łysik, A.; Grodner, J.; Przybysz, E. *Nat. Prod. Commun.* **2012**, *7*, 917. (d) Cohen, F.; Konradi, A.; Choi, T. A. J.; Machajewski, T. D.; Kane, T. R.; Hildebrandt, D. J. WO Patent 223349, 2017. (e) Albrecht, C. F.; Theron, E. J.; Kruger, P. B. S. *Afr. Med. J.* **1995**, *85*, 853. (f) Keyes, R. F.; Carter, J. J.; Englund, E. E.; Daly, M. M.; Stone, G. G.; Nilius, A. M.; Ma, Z. *J. Med. Chem.* **2003**, *46*, 1795. (g) Li, J.; Kaoud, T. S.; LeVieux, J.; Gilbreath, B.; Moharana, S.; Dalby, K. N.; Kerwin, S. M. *ChemBioChem* **2013**, *14*, 66.

(3) (a) Rayabarapu, K. D.; Tunge, L. A. *J. Am. Chem. Soc.* **2005**, *127*, 13510. (b) Choe, J.; Yang, J.; Park, K.; Palani, T.; Lee, S. *Tetrahedron Lett.* **2012**, *53*, 6908. (c) Tummanapalli, S.; Muthuraman, P.; Vangapandu, D. N.; Shanmugavel, G.; Kambampati, S.; Lee, K. W. *RSC Adv.* **2015**, *5*, 49392. (d) Chen, H.; Deng, Z. M. *J. Organomet. Chem.* **2000**, *603*, 189. (e) Leadbeater, N. E. *J. Org. Chem.* **2001**, *66*, 7539. (f) Bieber, L. W.; da Silva, M. F. *Tetrahedron Lett.* **2007**, *48*, 7088. (g) Narayana Kumar, G. G. K. S.; Laali, K. K. *Org. Biomol. Chem.* **2012**, *10*, 7347. (h) Ma, S.; Zhang, A. *J. Org. Chem.* **2002**, *67*, 2287. (i) Nishikawa, T.; Isobe, M. *Biosci., Biotechnol., Biochem.* **1999**, *63*, 238. (j) Kiyotsuka, Y.; Kobayashi, Y. *J. Org. Chem.* **2009**, *74*, 7489.

(4) (a) Trost, B. M.; Schultz, J. E. *Synthesis* **2019**, *51*, 1. (b) You, S. L.; Dai, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 5246. (c) Braun, M.; Meier, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6952. (d) Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 4435. (e) Kumar, R.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2013**, *42*, 1121. (f) Sundararaju, B.; Achard, M.; Bruneau, C. *Chem. Soc. Rev.* **2012**, *41*, 4467. (g) Butt, N. A.; Zhang, W. *Chem. Soc. Rev.* **2015**, *44*, 7929.

(5) (a) Xie, P.; Wang, J.; Liu, Y.; Fan, J.; Wo, X.; Fu, W.; Sun, Z.; Loh, T. P. *Nat. Commun.* **2018**, *9*, 1321. (b) Jin, J.; MacMillan, D. W. C. *Nature* **2015**, *525*, 87. (c) Lee, D.-H.; Kwon, K.-H.; Yi, C. S. *Science* **2011**, *333*, 1613.

(6) (a) Trost, B. M.; Dyker, G.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 7809. (b) Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 5579.

(7) Huang, J.; Zhou, L.; Jiang, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 1945.

(8) Fukushima, M.; Takushima, D.; Satomura, H.; Onodera, G.; Kimura, M. *Chem. - Eur. J.* **2012**, *18*, 8019.

(9) Li, Y. X.; Xuan, Q. Q.; Liu, L.; Wang, D.; Chen, Y. J.; Li, C. J. *J. Am. Chem. Soc.* **2013**, *135*, 12536.

(10) (a) Ren, K.; Li, P.-H.; Wang, L.; Zhang, X. L. *Tetrahedron* **2011**, *67*, 2753. (b) Wu, C.; Zeng, H.; Liu, Z.; Liu, L.; Wang, D.; Chen, Y.-J. *Chin. J. Chem.* **2011**, *29*, 2732.

(11) (a) Zhao, K.; Shen, L.; Shen, Z. L.; Loh, T. P. *Chem. Soc. Rev.* **2017**, *46*, 586. (b) Liu, Y.; Xie, P.; Sun, Z.; Wo, X.; Gao, C.; Fu, W.; Loh, T.-P. *Org. Lett.* **2018**, *20*, 5353. (c) Xie, P.; Fan, J.; Liu, Y.; Wo, X.; Fu, W.; Loh, T.-P. *Org. Lett.* **2018**, *20*, 3341. (d) Wo, X.; Xie, P.; Fu, W.; Gao, C.; Liu, Y.; Sun, Z.; Loh, T.-P. *Chem. Commun.* **2018**, *54*, 11132. (e) Xie, P.; Wang, J.; Fan, J.; Liu, Y.; Wo, X.; Loh, T.-P. *Green Chem.* **2017**, *19*, 2135.

(12) (a) Xie, P.; Li, S.; Liu, Y.; Cai, X.; Wang, J.; Yang, X.; Loh, T.-P. *Org. Lett.* **2020**, *22*, 31−35. (b) Xie, P.; Wo, X.; Yang, X.; Cai, X.; Li, S.; Gao, C.; Fu, W.; Sun, Z.; Loh, T.-P. *Green Chem.* **2019**, *21*, 5207−5211. (c) Xie, P.; Fu, W.; Wu, Y.; Cai, X.; Sun, Z.; Li, S.; Gao, C.; Yang, X.; Loh, T.-P. *Org. Lett.* **2019**, *21*, 4168−4172.

(13) (a) Bauer, H.; Alonso, M.; Färber, C.; Elsen, H.; Pahl, J.; Causero, A.; Ballmann, G.; De Proft, F.; Harder, S. *Nat. Catal.* **2018**, *1*, 40. (b) Kobayashi, S.; Yamashita, Y. *Acc. Chem. Res.* **2011**, *44*, 58. (c) Harder, S. *Chem. Rev.* **2010**, *110*, 3852. (d) Crimmin, M. R.; Casely, I. J.; Hill, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2042. (e) Ward, B. J.; Hunt, P. A. *ACS Catal.* **2017**, *7*, 459. (f) Wu, X.; Zhao, L.; Jin, J.; Pan, S.; Li, W.; Jin, X.; Wang, G.; Zhou, M.; Frenking, G. *Science* **2018**, *361*, 912.

(14) (a) Stopka, T.; Niggemann, M. *Chem. Commun.* **2016**, *52*, 5761. (b) Rauser, M.; Schroeder, S.; Niggemann, M. *Chem. - Eur. J.* **2015**, *21*, 15929. (c) Fu, L.; Niggemann, M. *Chem. - Eur. J.* **2015**, *21*, 6367. (d) Gao, S.; Stopka, T.; Niggemann, M. *Org. Lett.* **2015**, *17*, 5080. (e) Stopka, T.; Niggemann, M. *Org. Lett.* **2015**, *17*, 1437. (f) Begouin, J. M.; Capitta, F.; Wu, X.; Niggemann, M. *Org. Lett.* **2013**, *15*, 1370. (g) Haven, T.; Kubik, G.; Haubenreisser, S.; Niggemann, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4016. (h) Meyer, V. J.; Niggemann, M. *Eur. J. Org. Chem.* **2011**, *2011*, 3671. (i) Niggemann, M.; Meel, M. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 3684.

(15) (a) Morcillo, S. P.; Leboeuf, D.; Bour, C.; Gandon, V. *Chem. - Eur. J.* **2016**, *22*, 16974. (b) Morcillo, S. P.; Presset, M.; Floquet, S.; Coeffard, V.; Greck, C.; Bour, C.; Gandon, V. *Eur. J. Org. Chem.* **2016**, *2016* (15), 2688. (c) Lebœuf, D.; Schulz, E.; Gandon, V. *Org. Lett.* **2014**, *16*, 6464.

(16) (a) Sandridge, M. J.; France, S. *Org. Lett.* **2016**, *18*, 4218. (b) Davies, J.; Leonori, D. *Chem. Commun.* **2014**, *50*, 15171.

(17) (a) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203. (b) Tenaglia, A.; Heumann, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2180. (c) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1. (d) Kazmaier, U. *Curr. Org. Chem.* **2003**, *7*, 317. (e) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813. (f) Jensen, T.; Fristrup, P. *Chem. - Eur. J.* **2009**, *15*, 9632. (g) Milhau, L.; Guiry, P. J. *Top. Organomet. Chem.* **2011**, *38*, 95.

(18) (a) de Oliveira Silva, J.; Angnes, R. A.; Menezes da Silva, V. H.; Servilha, B. M.; Adeel, M.; Braga, A. A. C.; Aponick, A.; Correia, C. R. D. *J. Org. Chem.* **2016**, *81*, 2010. (b) Angnes, R. A.; Oliveira, J. M.; Oliveira, C. C.; Martins, N. C.; Correia, C. R. D. *Chem. - Eur. J.* **2014**, *20*, 13117.

(19) Kozuch, S.; Shaik, S. *Acc. Chem. Res.* **2011**, *44*, 101.

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