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Article

Atom-Economical Cross-Coupling of Internal and Terminal Alkynes to Access 1,3-Enynes

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Cite This: J. Am. Chem. Soc. 2021, 143, 3881−3888
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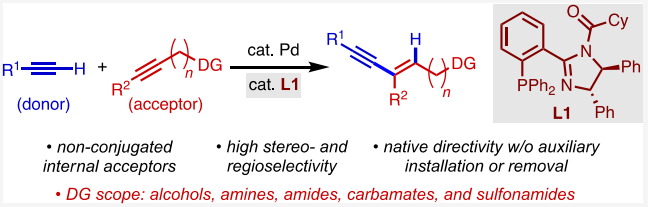
ABSTRACT: Selective carbon−carbon (C−C) bond formation in chemical synthesis generally requires prefunctionalized building blocks. However, the requisite prefunctionalization steps undermine the overall efficiency of synthetic sequences that rely on such reactions, which is particularly problematic in large-scale applications, such as in the commercial production of pharmaceuticals. Herein, we describe a selective and catalytic method for synthesizing 1,3-enynes without prefunctionalized building blocks. In this transformation several classes of unactivated internal acceptor alkynes can be coupled with terminal donor alkynes to deliver 1,3-enynes in a highly regio- and stereoselective manner. The scope of compatible acceptor alkynes includes propargyl alcohols, (homo)propargyl amine derivatives, and (homo)propargyl carboxamides. This method is facilitated by a tailored P,N-ligand that enables regioselective addition and suppresses secondary *E*/*Z*-isomerization of the product. The reaction is scalable and can operate effectively with as low as 0.5 mol % catalyst loading. The products are versatile intermediates that can participate in various downstream transformations. We also present preliminary mechanistic experiments that are consistent with a redox-neutral Pd(II) catalytic cycle.



INTRODUCTION

Catalytic methods that couple two distinct carbogenic fragments in a selective fashion constitute a core technology in organic synthesis with important applications in the pharmaceutical industry.[1] Classical palladium- and nickel-catalyzed C−C cross-coupling reactions between organohalides and organometallic reagents (Scheme 1A) are widely used but require prefunctionalized coupling partners that must be prepared in advance via multiple nonstrategic steps, detracting from the overall efficiency of the process.

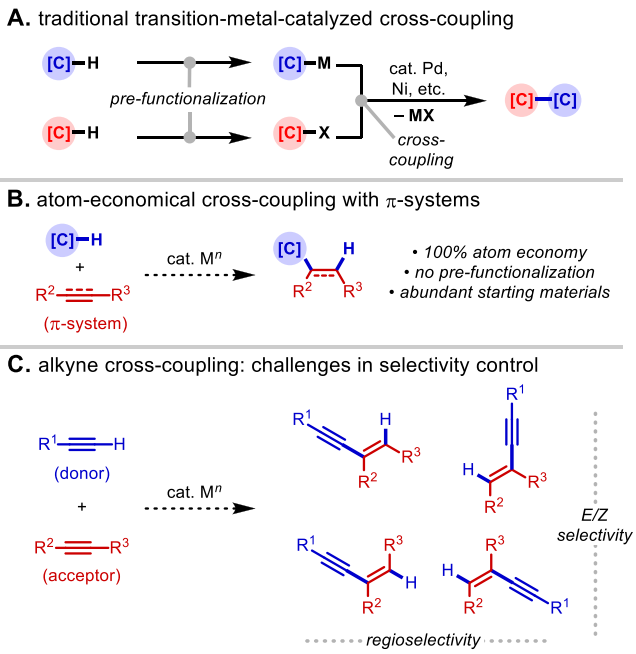
Thus, the development of C−C cross-coupling alternatives that directly employ unfunctionalized substrates and enable access to high-value products is of vital importance.[2] To this end, integrating π-systems (e.g., alkenes and alkynes) as cross-coupling components (Scheme 1B) is an attractive approach given the ability of π-systems to provide potential energy to the reaction, the ambiphilic reactivity profiles of these coupling partners, and their widespread availability as feedstock chemicals. Specifically, the cross-coupling of two different alkynes—a terminal donor alkyne capable of forming a metal−acetylide *in situ* and an internal acceptor alkyne capable of undergoing hydrofunctionalization—represents a promising strategy for C(sp)−C(sp^2) bond formation. If fully developed, this transformation would provide direct access to a range of 1,3-enynes without relying on prefunctionalization events that are typically required in the state-of-art methods, such as Sonogashira coupling.[4,9,10] The ability of 1,3-enynes to participate in diverse downstream transformations makes them extremely valuable building blocks in organic synthesis.[3,4] In addition, the 1,3-enyne moiety is found in bioactive natural products,[5,6] clinical therapeutics,[7] and supramolecular assemblies.[8] Herein, we describe a ligand-promoted, palladium-catalyzed method to couple donor alkynes with a variety of acceptor alkynes that takes advantage of coordination of a native Lewis basic functional group on the acceptor to enhance reactivity and control selectivity.

Previous research has demonstrated the viability of the envisioned coupling, while also illustrating challenges to be anticipated in pursuing a general terminal donor/internal acceptor cross-coupling (Scheme 2A). Trost reported pioneering work on redox-neutral, palladium-catalyzed terminal alkyne homocoupling in 1987,[12] with improved scope and selectivity subsequently being realized by Trost, Pfaltz, Gevorgyan, and others over the ensuing decades.[3,11−29] Cross-coupling between a terminal alkyne and an electronically activated (i.e., conjugated) alkyne has also been described.[11−29] Relevant to the approach described herein, Trost has also described

Received: December 2, 2020
Published: March 8, 2021

https://dx.doi.org/10.1021/jacs.0c12565
J. Am. Chem. Soc. 2021, 143, 3881−3888

Scheme 1. Comparison of Different Approaches to C−C Cross-Coupling



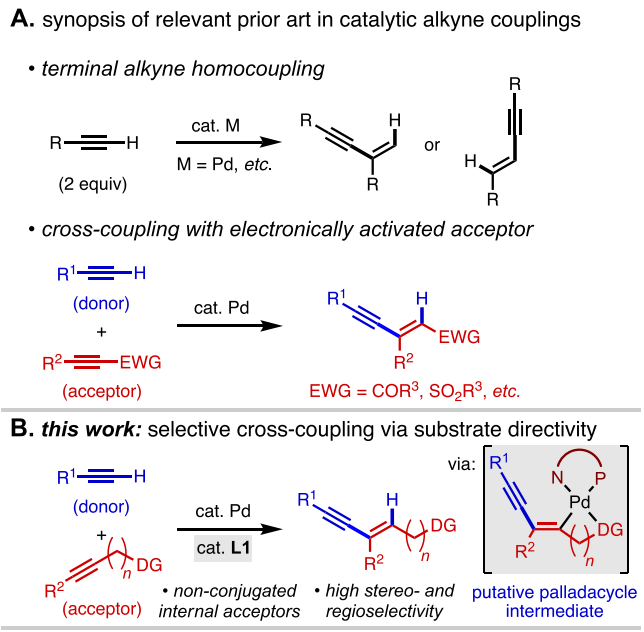
examples in which silyl-substituted and terminal propargyl alcohols are coupled with terminal alkynes, leading to C(sp)−C(sp^2) bond formation proximal to the alcohol.[14] While useful in their own right, existing methods are limited in scope, regioselectivity, stereoselectivity/specificity, and efficiency. Therefore, widespread adoption in preparative syntheses has been hampered.

We envisioned that the challenges outlined above could be surmounted by adopting a substrate directivity approach, in which a Lewis basic site on the acceptor alkyne—ideally a native functional group, like a free alcohol, would coordinate to the metal catalyst to facilitate downstream elementary steps. In particular, the bidentate coordination between the catalyst and acceptor alkyne would serve to activate the π-system through induced π-Lewis acid activation. An alkynylpalladium(II) species would be formed from the donor alkyne followed by directed 1,2-migratory insertion of the alkynylpalladium(II) species to the acceptor alkyne. This process would lead to the regioselective formation of the alkenyl-palladacycle intermediate through stabilization of one of regioisomeric transition states (Scheme 2B). The chelation-stabilized intermediate structure would then undergo protodepalladation to close the catalytic cycle. This hypothesis builds on our previous work using bidentate directing groups for alkyne hydrofunctionalizations[30,31] but would obviate auxiliary attachment and removal steps.[32]

RESULTS AND DISCUSSION

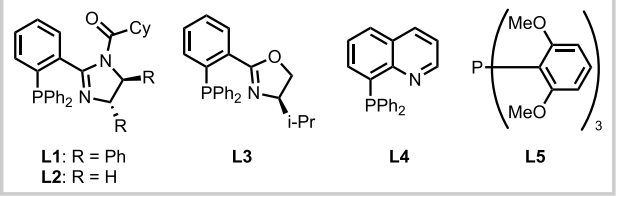
1. Reaction Optimization. To reduce this idea to practice, we selected 2-propyn-1-ol, an internal propargyl alcohol, as a model acceptor alkyne and TIPS-acetylene as the donor alkyne (Scheme 2C). Pilot experiments with various ligand/precatalyst combinations (data not shown) indicated that the initial cross-coupling is fast and quickly followed by *E*/*Z*-isomerization. Hence, we deliberately used an extended reaction time of 16 h in order to identify conditions and ancillary ligands that would allow selective coupling while

Scheme 2. Approaches to Redox-Neutral Alkyne Coupling and Optimization of Conditions



entry	variation from standard conditions	yield[a]	*syn*:*anti*[b]	r.r.[b]
1	(none)	77%[c]	>20:1[c]	>20:1[c]
2	**L2** as ligand	70%	1:1.5	>20:1
3	**L3** as ligand	95%	4.6:1	>20:1
4	**L4** as ligand	99%	2.3:1	>20:1
5	**L5** as ligand	66%	>20:1	1:1.4
6	w/o NH_4OAc	68%	>20:1	>20:1
7	HOAc in place of NH_4OAc	n.r.	—	—
8	NaOAc in place of NH_4OAc	74%	>20:1	>20:1
9	Cs_2CO_3 in place of NH_4OAc	n.r.	—	—
10	CsCl in place of NH_4OAc	60%	>20:1	>20:1
11	$(PhCN)_2PdCl_2$ as precatalyst	n.r.	—	—
12	$Pd(OAc)_2$ as precatalyst	39%	3.3:1	>20:1
13	MeCN as solvent	80%	>20:1	>20:1
14	toluene as solvent	80%	>20:1	>20:1

ligands

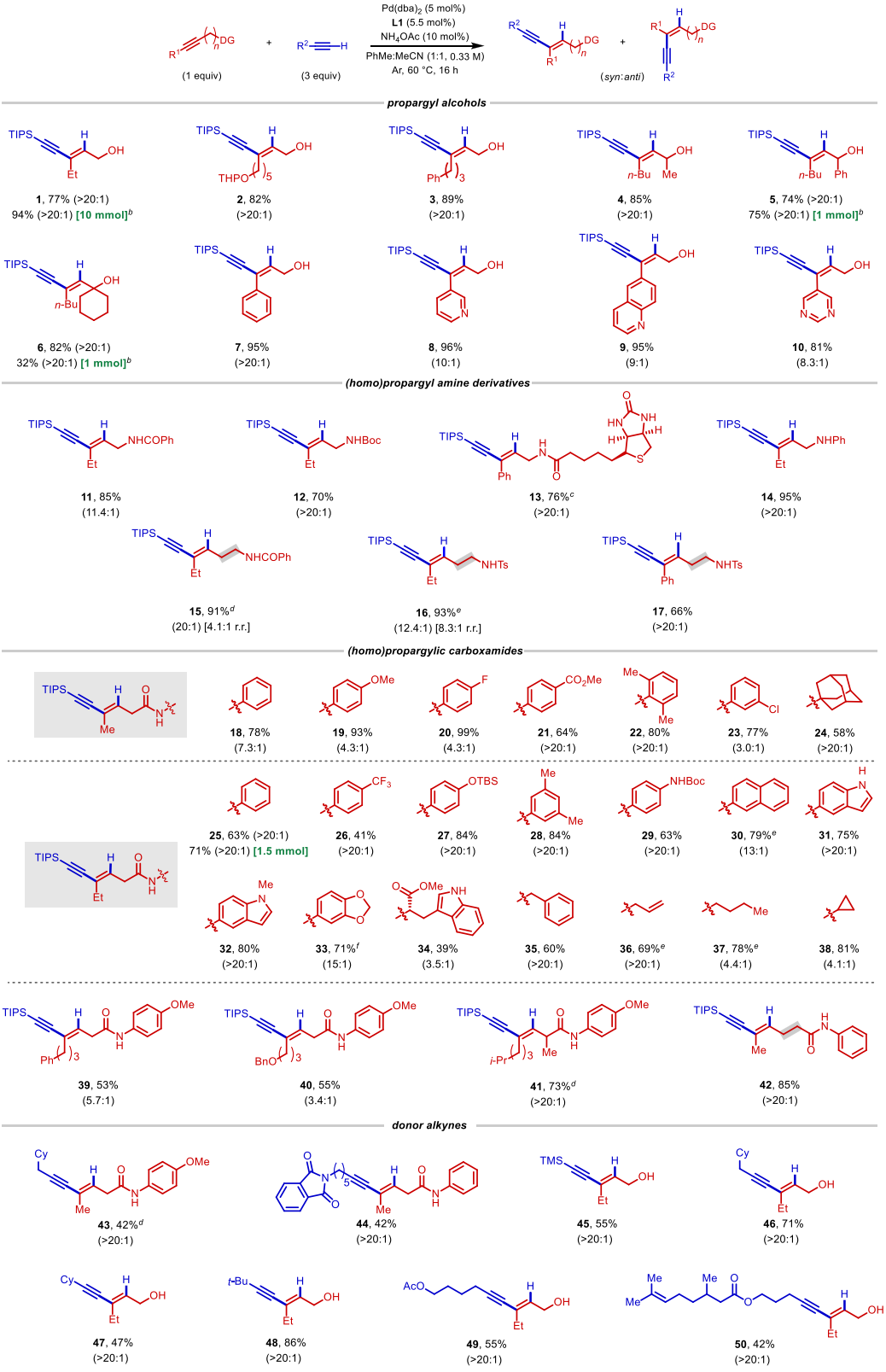


[a]^{1}H NMR yield with CH_2Br_2 as internal standard. n.r. = no reaction. [b]Determined by ^{1}H NMR analysis of crude reaction mixture. r.r. = regioisomeric ratio. [c]Isolated yield.

suppressing secondary isomerization. In summary, we found that phosphine ligands are essential for the reaction, as shown in previous studies.[3] In previous methodologies reported by Trost, **L5** was the optimal ligand,[12−14] but, in this case it barely provided any regiodifferentiation (entry 5). In contrast, the reaction was highly regioselective when P,N-bidentate ligands

https://dx.doi.org/10.1021/jacs.0c12565
J. Am. Chem. Soc. 2021, 143, 3881−3888

Table 1. Substrate Scope[a]



[a]Percentages represent isolated yields. In cases where two or more isomers were formed, percentages represent combined yields of isolated samples of each of the different isomers. Stereoisomeric ratios are shown in parentheses (*syn*:*anti*) and reflect the mass ratio of isolated samples unless otherwise specified; these ratios are consistent with those observed via ^{1}H NMR analysis of the crude reaction mixtures. See the Supporting Information (SI) for details. [b]0.5 mol % $Pd(OAc)_2$, 0.55 mol % **L2**, without NH_4OAc, 1.2 equiv donor alkyne, 20−48 h. [c]MeCN:*t*-AmylOH = 1:1. [d]$Pd(OAc)_2$ catalyst, without NH_4OAc. [e]10 mol % $Pd(dba)_2$, 11 mol % **L1**. [f]Stereoisomers were inseparable; ratio determined by ^{1}H NMR.

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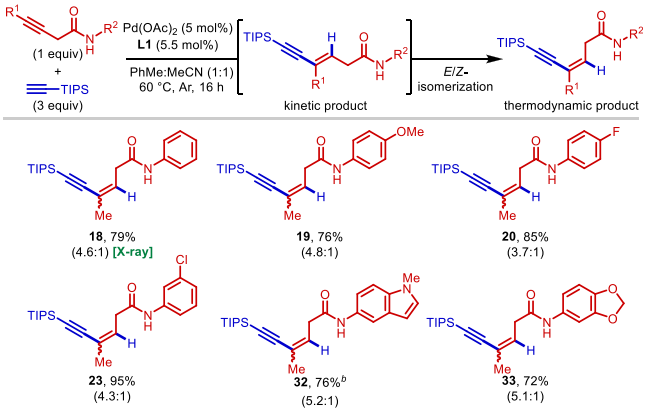


Figure 1. Representative examples of *anti*-selective cross-coupling. [a]Percentages represent combined yields of isolated samples of each of the different isomers. Stereoisomeric ratios are shown in parentheses (*anti*:*syn*) and reflect the mass ratio of isolated samples; these ratios are consistent with those observed via ^{1}H NMR analysis of the crude reaction mixtures. [b]10 mol % $Pd(OAc)_2$, 11 mol % **L1**.

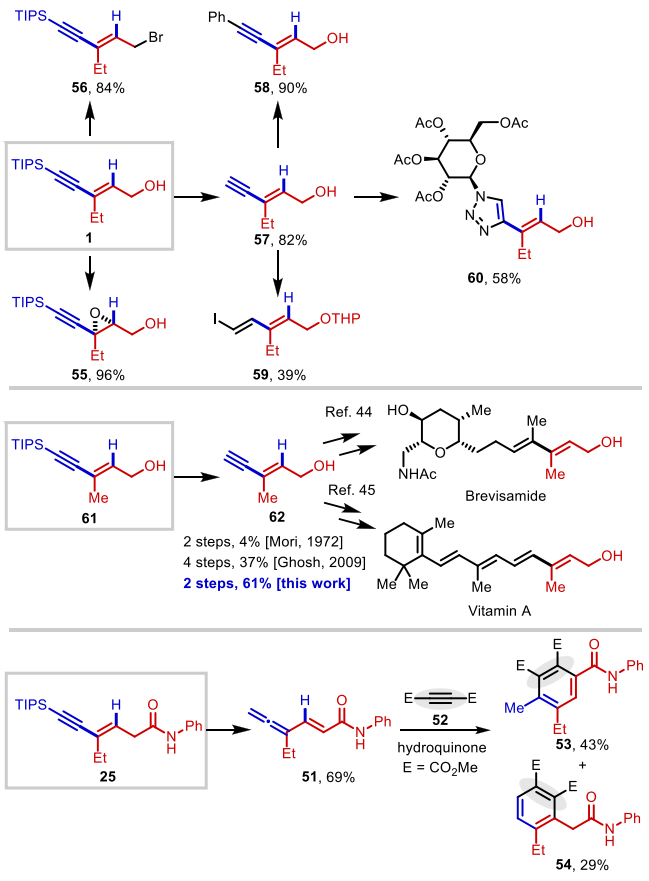


Figure 2. Product transformations and formal syntheses of natural products.

were used (entry 2–4). After examining **L2**–**L4**, we found that a bulky and rigid N-coordinating arm is beneficial for favoring the *syn*-product by suppressing secondary isomerization. In particular, the phosphinoimidazoline ligand **L1**, which is derived from diphenylethlenediamine and was previously developed at Boehringer Ingelheim,[33−37] was identified as the best ligand in terms of regio- and stereoselectivity. Further screening showed that the palladium source and the additive are important for reactivity (entry 6–12). The combination of $Pd(dba)_2$ and ammonium acetate provides the best yield. These general trends also held with a representative propargyl carboxyamide substrate that is more prone to secondary *E*/*Z* isomerization (see the Supporting Information (SI)).

2. Substrate scope. The substrate scope was tested with the optimized conditions (Table 1). Excellent reactivity and selectivity was maintained for propargyl alcohols with different substitution patterns (**1**–**7**). Notably, the reaction proceeds with the opposite sense of regioselectivity compared to the previously reported system by Trost,[14] consistent with the hypothesis that the hydroxyl group is serving as a directing group in this case. Heterocycles are well tolerated in this reaction, with only slightly diminished *E*/*Z* selectivity (**8**–**10**).

Furthermore, we examined the reactivities of other native directing groups—including amides, sulfonamides, and amines—none of which had been previously explored in alkyne cross-coupling. Propargyl benzamide (**11**), *N*-Boc-protected propargyl amine (**12**), and *N*-Ph propargyl amine (**14**) were all converted to the corresponding 1,3-enyne products, with the same selectivity as propargyl alcohols. Homopropargyl benzamide (**15**) and *N*-tosyl-protected homopropargyl amine (**16**) were also compatible, albeit with lower regioselectivity than propargyl amine derivatives. We also conducted a systematic study on the reactivities of (homo)propargyl carboxamides (**18**–**42**), which are highly challenging acceptors because their activated α-position can cause side reactions and secondary *E*/*Z* isomerization. We demonstrated that amides derived from various anilines and aliphatic amines worked well in the reaction, providing the products in good to excellent yield and with high selectivity. However, amides with small substituent groups (**37** and **38**) were more prone to isomerization, resulting in eroded stereoselectivity (*vide infra*). We further observed good yield and excellent selectivity with the different alkyl-substituted alkynes (**39**–**42**). Introducing alkyl branching at the α-position (**41**) or introducing an additional methyl spacer between the alkyne and the directing group (**42**) led to comparable reactivity compared to the substrates discussed above.

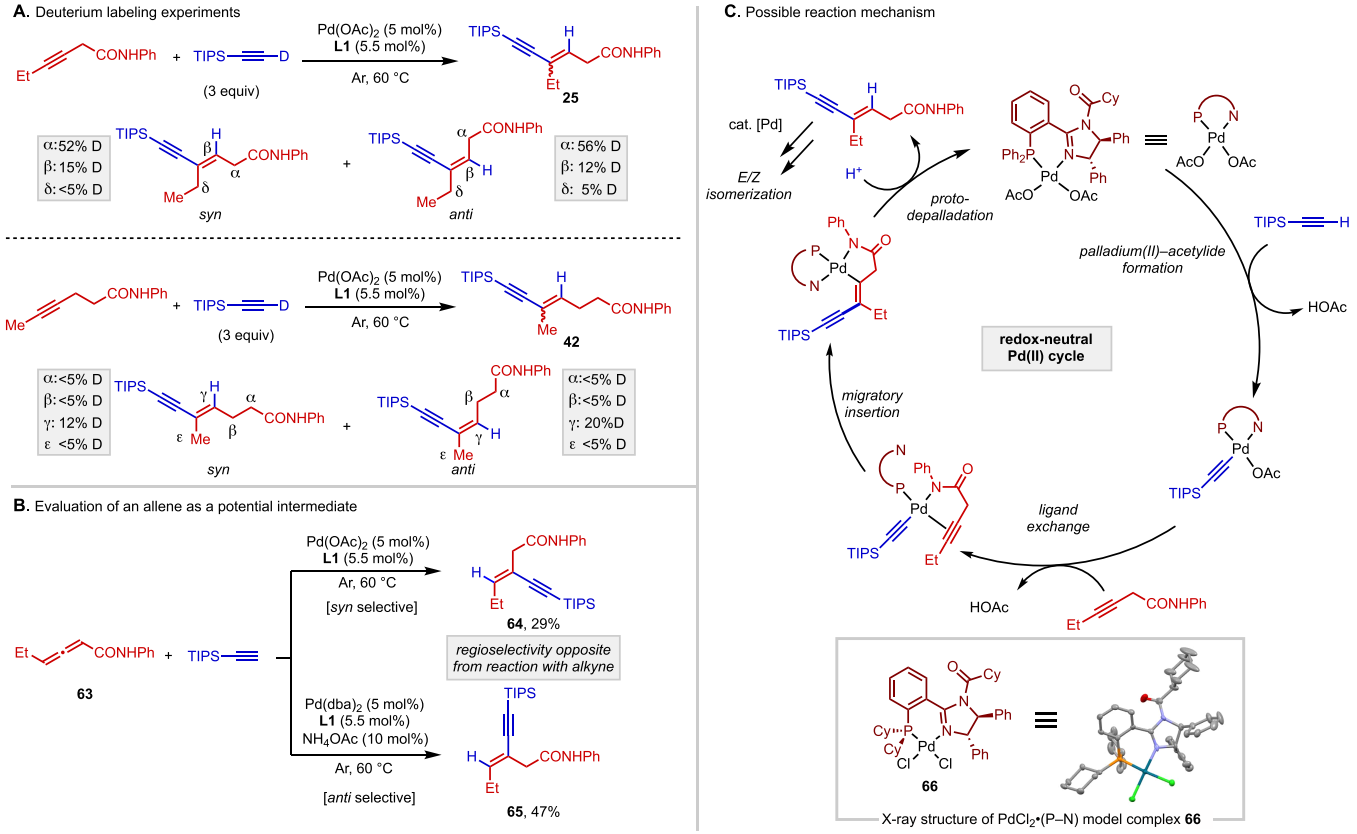
Different donor alkynes were also examined (**43**–**50**). We found that alkynes possessing different degrees of steric hindrance (**46**–**48**) or assorted functional groups (**44** and **49**) worked well as donor. Consequently, 1,3-enynes with a variety of substitution patterns can be accessed directly, without the need for TIPS deprotection and further functionalization.

To evaluate the viability of this method in more structurally intricate settings, we introduced bioactive molecules and natural products onto each of the alkyne coupling partners and tested whether reaction performance was impacted. Biotin (**13**), tryptophan (**34**), and citronellic ester (**50**) were all found to be compatible with this method. This suggests the potential of applying this method for late-stage modification of complex targets.

We performed several representative examples on larger scale. First, we found that by directly applying the standard conditions, product **25** could be prepared on 1.5 mmol scale in slightly improved yield compared to the small-scale experiment (71% versus 63%). Next, we evaluated more demanding conditions, with an eye toward further scale-up. We employed $Pd(OAc)_2$ instead of $Pd(dba)_2$, given that the former is more widely used in process chemistry. In addition, we decreased the catalyst, ligand, and donor alkyne loadings to 0.5 mol %, 0.55

https://dx.doi.org/10.1021/jacs.0c12565
J. Am. Chem. Soc. 2021, 143, 3881−3888

Scheme 3. Mechanistic Studies and Proposed Mechanism



mol %, and 1.2 equiv, respectively. We also used structurally simplified ligand **L2** *in lieu of* **L1**, noting that with this ligand it was necessary to monitor reaction progress more carefully to avoid secondary *E*/*Z* isomerization. Under these modified conditions, products **5** and **6** were prepared on 1 mmol scale. While the yield and selectivity for acceptor **5** was comparable to the small-scale reaction (75% versus 74%; > 20:1 in both cases), sterically hindered acceptor **6** was not fully consumed, even after elongated reaction time, resulting in diminished yield compared to the small-scale trial (32% versus 82%). The decrease in this case could be due to the slower rate of donor–acceptor cross-coupling, which allows the donor alkyne to be competitively consumed via homodimerization. Last, using these modified conditions, we prepared product **1** on 10 mmol scale (gram-scale) in 94% yield.

3. Stereodivergent Alkyne Cross-Coupling. As mentioned above, during the course of this study we found that the propargyl carboxamide products are especially prone to isomerization, presumably due to the presence of acidic α-protons.[38] By taking advantage of the fact that the *anti*-isomer is thermodynamically favored (see SI), we identified conditions that allowed *in situ* isomerization to deliver the *anti*-isomer as the major product with synthetically useful levels of *anti*/*syn* selectivity (Figure 1).[39] In this way, the transformation could be rendered stereodivergent by simply changing the palladium source and the additive.

4. Product Transformations. Various transformations of the 1,3-enyne products were examined to underscore the preparative utility of this method (Figure 2). Epoxidation (**55**) on the alkene moiety and conversion of the alcohol to a bromide (**56**) were successfully carried out. Removing the TIPS protecting group on the alkyne moiety enabled other alkyne-functionalizing reactions such as Sonogashira arylation (**58**),[40] hydrozirconation/iodination (**59**),[41] and 1,2,3-triazole formation via click chemistry (**60**).[42] Additional transformations were carried out on the 1,3-enyne derived from propargyl carboxamides. Upon TIPS deprotection of compound **24**, the resulting product underwent *in situ* isomerization to the conjugated allenyl alkene (**51**), likely due to the acidity of the α-protons. Compound **51** could then be transformed to highly substituted benzenes **53** and **54** through Diels–Alder cycloaddition.[43]

1,3-Enynes are important building blocks that are often involved in total syntheses of natural products.[4] For instance, **62** is a common intermediate in the syntheses of brevisamide[44] and vitamin A.[45] Ghosh and co-workers synthesized **62** in 37% yield over four steps. López and co-workers followed a procedure reported by Mori and prepared **62** in 4% yield over two steps.[46] In contrast, by using the alkyne cross-coupling method, we obtained **62** in 61% yield over two steps from commercially available materials. This improvement of efficiency is significant given that **62** is an early stage intermediate in both syntheses (Figure 2).

5. Mechanistic Studies. We next probed the mechanism of the reaction by first investigating the oxidation state of the catalytically active palladium species. At the outset we considered three potential scenarios: (1) Pd(II)-assisted metal–acetylide formation followed by migratory insertion and protodepalladation; (2) oxidative addition of Pd(0) into the C(alkynyl)–H bond followed by acetylide insertion and C(alkenyl)–H reductive elimination; (3) oxidative addition of Pd(0) into the C(alkynyl)–H bond followed by hydride insertion and C(sp^2)–C(sp) reductive elimination. First, we monitored the reaction by in situ ^{1}H NMR and did not

https://dx.doi.org/10.1021/jacs.0c12565
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observe a signal consistent with metal−hydride, ruling out such a species as a possible catalyst resting state (Figure S14−S17). Reactions performed with $Pd(OAc)_2$ as precatalyst and $Pd(dba)_2$ as precatalyst led to formation of the same intermediate, as observed by *in situ* ^{31}P NMR (29.64 ppm), suggesting the oxidation state of the precatalyst does not dictate catalyst speciation to an appreciable extent. The chemical shift of the catalyst resting state is consistent with a Pd(II)−phosphine complex.[47] An isotope labeling experiment was then carried out with deuterated TIPS-acetylene, and less than 30% of deuterium was incorporated at the alkenyl position (Scheme 3A). The mixture of H/D incorporation is consistent with a protodepalladation pathway but not with a metal hydride pathway.

In the particular case of propargyl carboxamide substrates, a possible pathway is initial alkyne isomerization to an allene (**63**) followed by migratory insertion.[48] To test whether this pathway is operative, **63** was prepared and subjected to *syn*- and *anti*-selective conditions (Scheme 3B). In both cases, 1,3-enynes with opposite regioselectivity were obtained (**64** and **65**). Thus, the desired products are not generated from allene intermediates.

Consistent with earlier literature reports,[37] by combining $Pd(MeCN)_2Cl_2$ and P,N-ligands, we were able to cleanly prepare **L**•$PdCl_2$ complexes ligated with P,N-ligands, which could be characterized by NMR (see the SI). While $PdCl_2$•**L1** could not be characterized by crystallography, the X-ray crystal structure of model complex **66** where the phenyl groups on the phosphorus atom are replaced with cyclohexyl groups demonstrates that the ligand adopts a bidentate coordination mode in the solid state (Scheme 3C). In this arrangement one of the Ph groups of the diphenylethlenediamine moiety is brought into close proximity to a chloride ligand. A possible explanation for **L1**'s unique ability to suppress secondary isomerization is thus that its steric bulk effectively crowds out reassociation of the trisubstituted alkene moiety of the product.[49,50]

CONCLUSION

In conclusion, we have developed a selective method to deliver 1,3-enynes from two different alkynes by taking advantage various synthetically useful native directing groups. Gram-scale synthesis with 0.5 mol % catalyst loading was demonstrated. The 1,3-enyne products were successfully transformed by different diversification reactions. Furthermore, preliminary mechanistic studies shed light on a possible reaction mechanism (Scheme 3C), in which Pd(II) serves as the active catalyst with the reaction initiated by Brønsted-base-assisted palladium−acetylide formation from the donor alkyne. Next, the palladium−acetylide undergoes *syn*-1,2-migatory insertion into the acceptor alkyne. Finally, protodepalladation releases the 1,3-enyne product with concomitant regeneration of the active Pd(II) catalyst.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c12565.

Experimental details, NMR, X-ray, and other data (PDF)

(ZIP)

Accession Codes

CCDC 2036755 and 2036758−2036759 contain 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.

ACKNOWLEDGMENTS

This work was financially supported by Boehringer Ingelheim Pharmaceuticals and the National Institutes of Health (R35GM125052). We gratefully acknowledge the Nankai University College of Chemistry for an International Research Scholarship (T.T.), the National Science Foundation for an REU Fellowship (DBI-1759544, O.A.) and Graduate Research Fellowship (DGE-1842471, O.A.), and the Honjo International Scholarship Foundation for a Scholarship (R.M.). We thank Prof. Arnold L. Rheingold and Dr. Milan Gembicky (UCSD) for X-ray crystallographic analysis. We are grateful to

Dr. Jason S. Chen, Brittany Sanchez, and Emily Sturgell for assistance with prep-LC purification and HRMS analysis. We appreciate Andrew M. Romine and Dr. Yingyu Liu for proofreading this manuscript and providing kind support.

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