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Research paper

Palladium-catalyzed branch-selective hydroamidation of alkynes: bypassing basicity barrier via a ligand-enabled proton transfer strategy

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ABSTRACT

Branch-selective hydroamidation of alkynes offers an atom-economic route to α,β-unsaturated amides from CO and feedstock chemicals. However, applications of this catalysis strategy are limited by the need for excess additives and restricted substrate compatibility. Herein, we report a general and practical palladium-catalyzed protocol enabled by a picolinamide diphosphine ligand. This ligand acts as a proton shuttle to facilitate efficient hydroamidation of challenging amines and alkynes with excellent branched selectivity. The high catalytic activity is further supported by low acid loading, mild conditions, and decagram-scale applicability. Experimental observations and computational studies further elucidate the critical role of the picolinamide moiety in bypassing the basicity barrier within the catalytic cycle, offering new insights for ligand design in carbonylation chemistry.

1. Introduction

Catalytic carbonylation of alkynes leverages carbon monoxide (CO) as a C1 building block to access α,β-unsaturated carbonyl derivatives with excellent atom economy [1–5]. As an important extension, regioselective hydroamidation of alkynes incorporates amine nucleophiles to afford branched and linear α,β-unsaturated amides (Scheme 1A) [6–8]. In particular, tremendous efforts have been dedicated to the branch-selective hydroamidation, given the widespread applications of the branched amide products in pharmaceutical compounds and functional materials [9–12]. To this end, palladium-based catalysts for branch-selective hydroamidation have been advanced by the groups of Ali [13], Alper [14], and others [15–20], underscoring the academic significance and industrial potential of these transformations.

Despite considerable progress, hurdles remain in translating this catalytic transformation into a broadly applicable strategy (Scheme 1A). Reported catalyst systems are usually limited to aromatic amines, whereas reactions with aliphatic analogues display poor efficiency [16,17]. This limitation primarily stems from the fact that Pd-catalyzed hydroamidation generally proceeds through a hydride-cycle mechanism (Scheme 1B), which involves the generation of a palladium hydride species (**I**) to promote hydropalladation of the carbon-carbon triple bond [21,22]. As the basic conditions can deactivate palladium hydrides, aliphatic amines with higher basicity ($pK_{aH} > 9$) can inhibit this key hydropalladation step (**I** to **III**), thereby suppressing the formation of amide products (Scheme 1C, Path I) [23–26]. To address this challenge, Beller [25], Huang [20,26], and other groups achieved significant progress in hydroamidation with aliphatic amines. Nevertheless, existing methods often rely on stoichiometric acids, acid salts of amines, or masked amines to facilitate metal hydride formation [27–29].

Recently, we disclosed a class of pyridine-embedded amide diphosphines as practical ligands for catalytic carbonylation reactions [30–32]. Moreover, Drent [33,34], Beller [35–38], and others [39–41] introduced pyridine-containing ligands as proton shuttles in related hydroesterification reactions, demonstrating the accelerating effects of pyridine moieties. Taken together, we propose that the pyridine ring within our ligand scaffold would enable alkyne hydropalladation through a proton-transfer pathway (Scheme 1C, Path II), thus offering a

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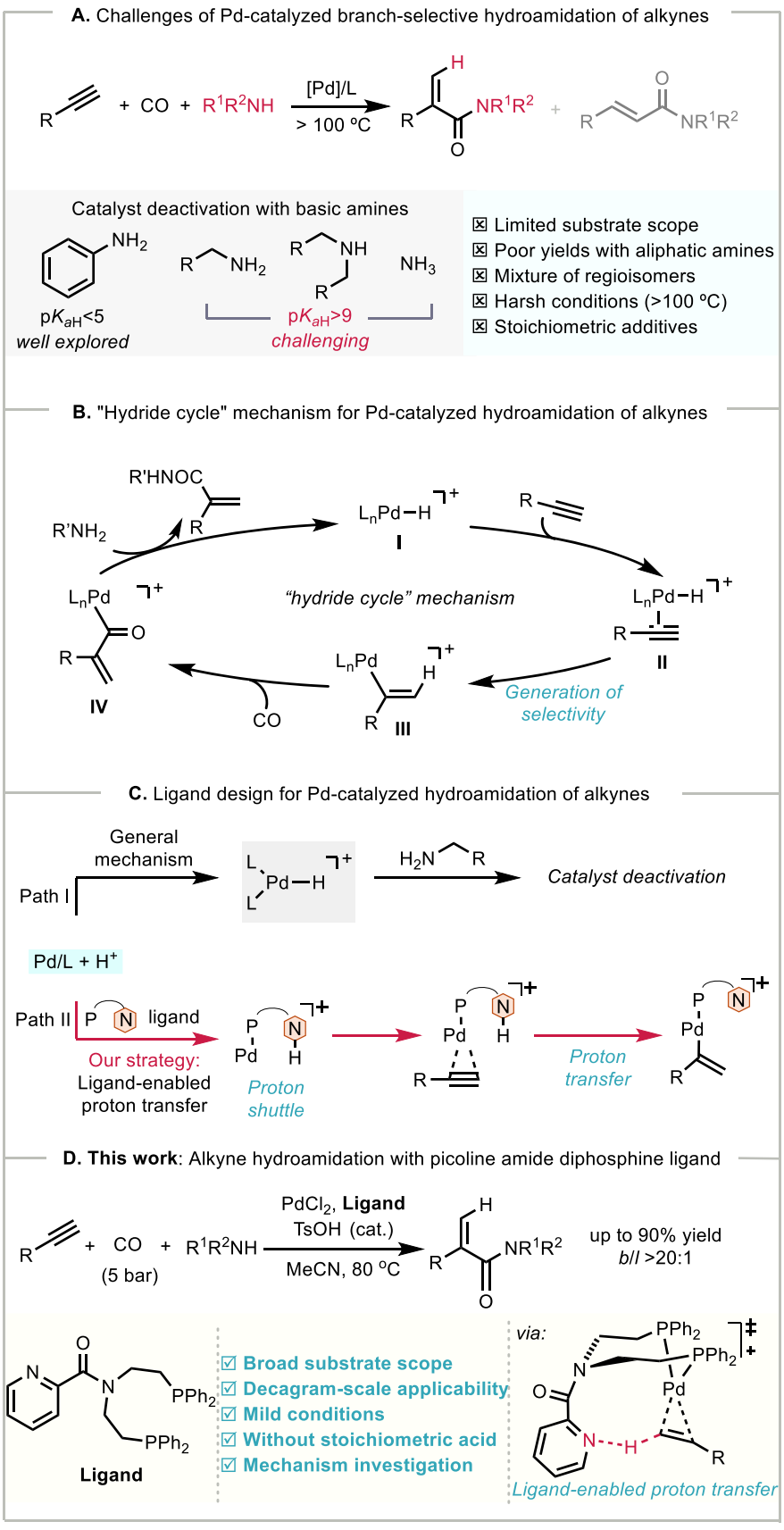


Scheme 1. Overview of Pd-catalyzed branch-selective hydroamidation of alkynes.

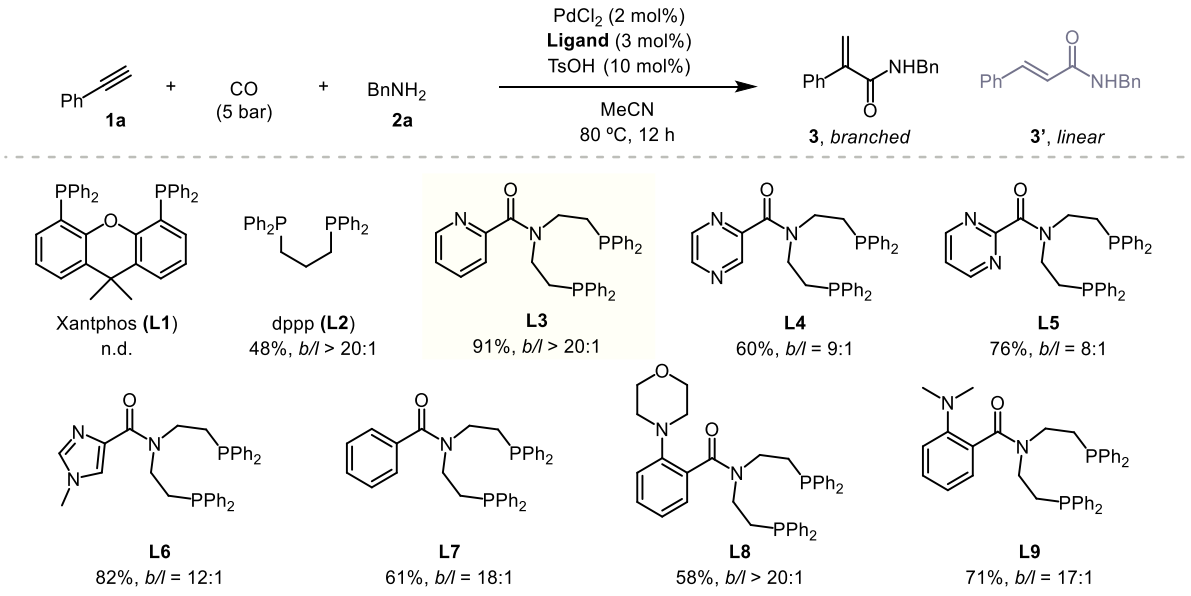
complementary and efficient hydroamidation protocol [30,42–44]. Herein, we report a Pd-catalyzed hydroamidation of alkynes with high branched selectivity enabled by the picolinamide diphosphine ligand, which tolerates basic amines and challenging alkynes without requiring excess additives (Scheme 1D).

2. Results and discussions

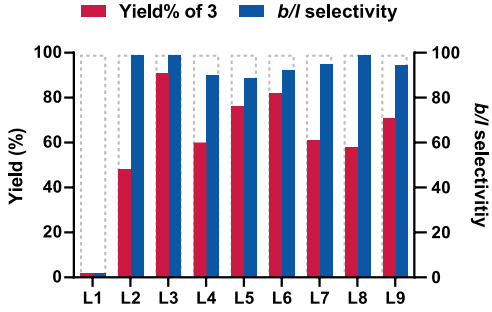
To escape the limitation of aromatic amines as less basic (and thus privileged) partners in Pd-catalyzed hydroamidation of alkynes, we initiated our study with phenylacetylene (**1a**) and benzylamine (**2a**) as the substrates. In the presence of $PdCl_2$ (2 mol%) and catalytic TsOH in MeCN, ligands that are widely used for carbonylative transformations exhibited low catalytic activity under the reaction conditions. For instance, using Xantphos (Table 1, **L1**) showed no catalytic activity, and using dppp (**L2**) as the ligand gave the desired branched product **3** in a moderate 48% yield.

On the basis of prior efforts [45,46], we synthesized a series of amide diphosphines (**L3-L9**) and examined their reactivity. When picolinamide diphosphine **L3** was employed as the ligand (Table 1), the desired α,β-unsaturated amide **3** was obtained in 91% yield, together with exclusive branched selectivity (b/l > 20:1). To elaborate on the influence of the ligand structures on catalyst activity, we evaluated other amide diphosphines by replacing the pyridine moiety with other heterocycles. Pyrazines (pKa_H = 0.6) and pyrimidines (pKa_H = 1.3) are considered less basic than pyridines (pKa_H = 5.3). Ligands derived from pyrazine (**L4**) and pyrimidine (**L5**) delivered **3** only in moderate yields (60% and 76% yields). Basic and nucleophilic imidazole was also introduced to the ligand structure (**L6**), which afforded the hydroamidation product in 82% yield but with a compromised b/l ratio (12:1). The limited reactivity of **L4** and **L5** can be attributed to the challenging generation of protonated *N*-heterocycles in the presence of amine substrates. On the other hand, we propose that the imidazolium species generated from the more basic imidazole in **L6** disfavors proton transfer to the alkyne substrate, leading to decreased reactivity. As such, the basicity of picolinamide in **L3** falls within the ideal range to facilitate proton transfer in the desired alkyne hydroamidation. Replacing the pyridine ring with a neutral benzene ring also showed decreased catalytic activity (**L7**, 61%, b/l = 18:1). Attaching disubstituted amines to the *ortho*-position of the benzene ring in **L7** afforded ligands **L8** and **L9**.

Table 1
Reaction optimization.[a].



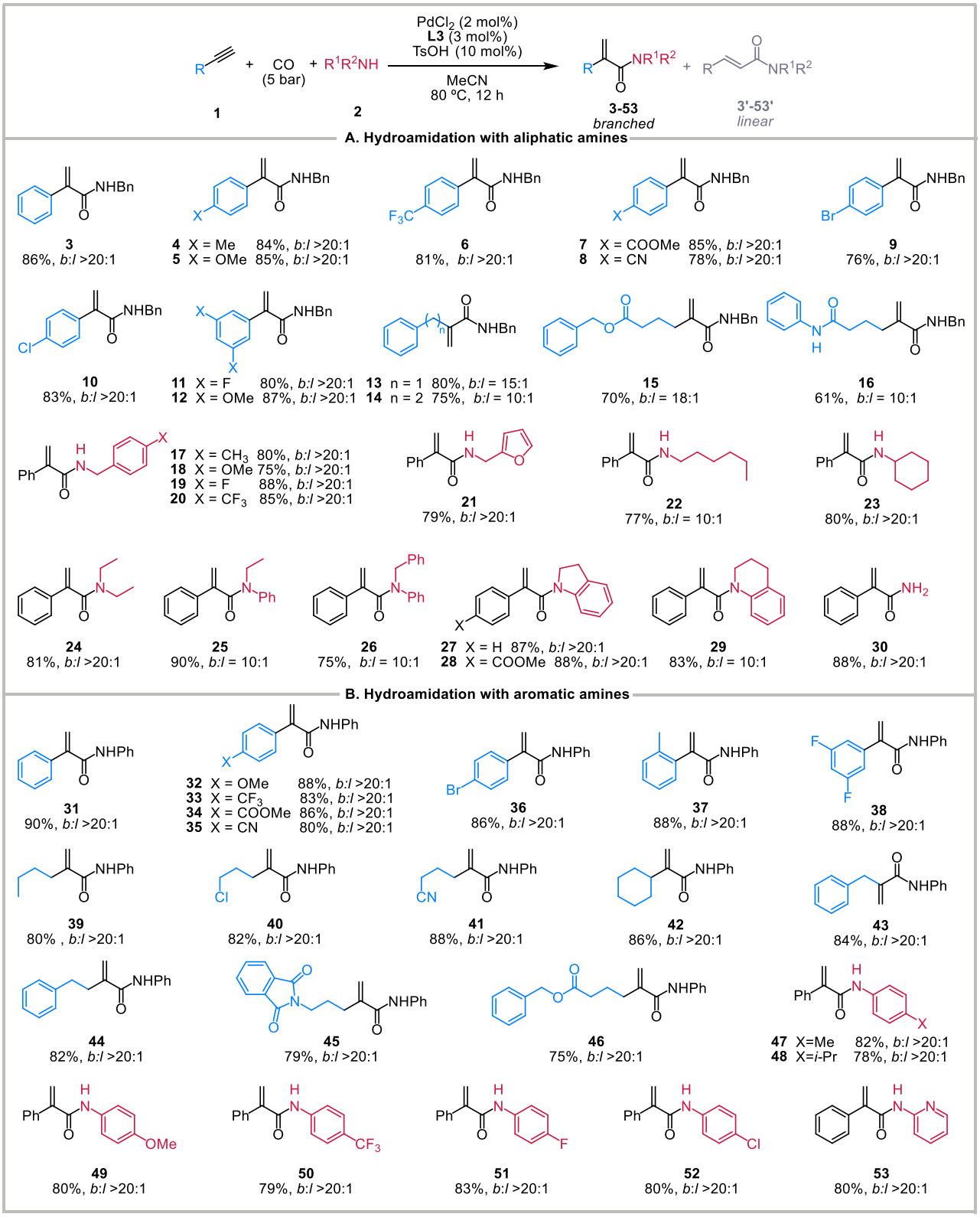
Entry	Variations from standard conditions	Conv. (%)	Yield (%)[b]	b/l ratio
1	none	>99	91 (86)[c]	>20:1
2	$Pd(OCOCF_3)_2$, instead of $PdCl_2$	87	76	>20:1
3	TFA, instead of TsOH	>99	83	>20:1
4	AcOH, instead of TsOH	65	58	>20:1
5	without TsOH	-	-	n.d.
6	1 bar of CO	>99	90[d]	88:12
7	60 °C	40	32	> 20:1
8	1 h	44	41	> 20:1



[a] Reactions were performed with **1a** (0.5 mmol), $PdCl_2$ (2 mol%), **L3** (3 mol%), **2a** (0.5 mmol), TsOH (10 mol%) in MeCN (1.0 mL), and all conversions and b/l ratios were determined by GC analysis using mesitylene as an internal standard.
[b] NMR yields were determined by using tetrachloroethane as an internal standard.
[c] Isolated yield.
[d] 48 h.

However, neither of these ligands outperformed **L3**. Thus, the pyridine moiety of **L3** is essential for optimal catalytic performance, allowing the catalyst to mediate the proton-transfer mechanism.

Next, we screened other reaction dimensions of the Pd/**L3**-catalyzed hydroamidation (Table 1, entries 1–7 and Table S1-S5). The protocol accommodates different palladium pre-catalysts, yielding **3** with generally high branched selectivity (Table 1, entry 2 and Table S2). For example, reactions employing $Pd(OCOCF_3)_2$ achieved hydroamidation



Scheme 2. Reaction scope. (A) Substrate scope for hydroamidation with aliphatic amines. (B) Substrate scope for the hydroamidation with aromatic amines. Standard conditions: alkynes (0.5 mmol), $PdCl_2$ (2 mol%), **L3** (3 mol%), amines (0.5 mmol), TsOH (10 mol%) in MeCN (1.0 mL), CO (5 bar), 80 °C. Reported yields are isolated yields. *b/l* ratios were determined by GC analysis using mesitylene as an internal standard.

of **2a** in 76% yield and >20:1 *b/l* ratio. A catalytic amount of acid is required to initiate the reaction, but acids weaker than TsOH, such as TFA ($pK_a = -0.25$) and AcOH ($pK_a = 4.76$), can be used with slight decreases in yields (Table 1, entries 3–5). Complete conversion was also achieved at atmospheric pressure of CO with extended reaction time (Table 1, entry 6), although lower CO pressure decreased the rate of migratory insertion and led to slightly lower selectivity (*b/l* = 88:12). While lowering the temperature to 60 °C resulted in only moderate conversion (Table 1, entry 8), the high selectivity was comparable to that achieved under the optimal conditions. The catalytic efficiency was further evaluated by reducing the reaction time to 1 hour, which delivered the branched product with 41% yield.

With optimized reaction conditions in hand, we next assessed the substrate scope of the process. The hydroamidation of benzylamine (**2a**) and various aromatic alkynes has been achieved in good to excellent yields (Scheme 2A, **3**–**12**). Substituents with distinct electronic properties were well tolerated. Notably, alkynes bearing electron-withdrawing substituents (**6**–**8**) can pose significant challenges in previously reported protocols [15], but good yields and branched selectivity were obtained with our ligand **L3**. Halogen atoms also remained intact under optimized conditions, providing handles for further derivatization (**9**–**11**). Carbonylation of aliphatic alkynes can lead to decreased yields and branched selectivity [47], resulting from the reduced stabilization of vinylpalladium intermediates without aromatic conjugation and competing β-hydride elimination. Nevertheless, using the established conditions, a representative series of aliphatic alkynes was transformed in satisfactory yields and selectivities (**13–16**). Pre-installed ester (**15**) and amide (**16**) groups were also tolerated.

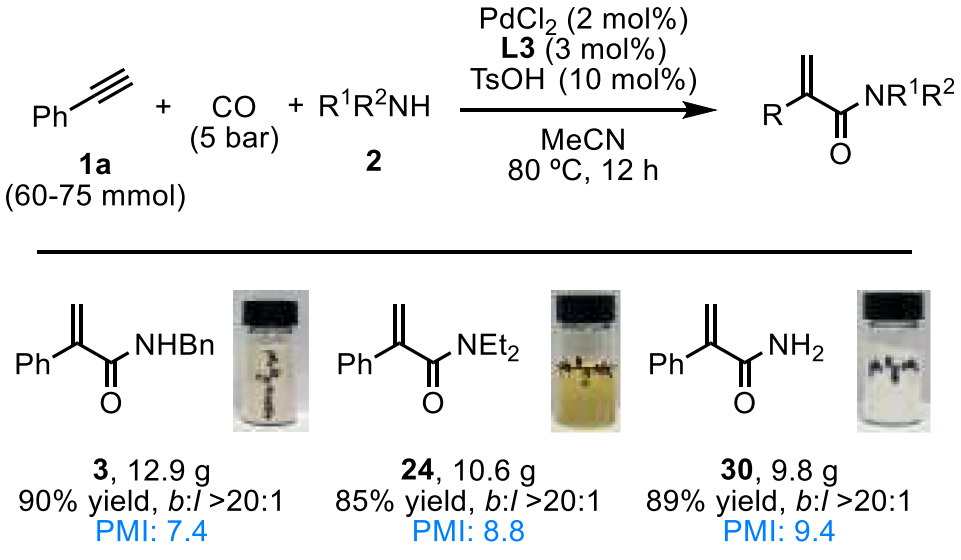
Furthermore, we investigated the scope of other aliphatic amines (**17–29**). Benzylamines with different aromatic substituents (**17–20**) proved viable substrates. Amine counterpart with a furan ring was successfully employed during the reaction, yielding the desired product **21** smoothly. Branched amide **23** was obtained in excellent selectivity using bulky cyclohexylamine, reinforcing the robustness of our catalyst system. To further examine amine compatibility, hydroamidation of disubstituted amines was performed under standard conditions, and tertiary amides were obtained without loss of catalytic performance (**24–29**). Pharmaceutically related indoline (**27** and **28**) and tetrahydroquinoline (**29**) also reacted well, affording the corresponding products in high yields and selectivity. Specifically, amide **28** was obtained in 88% yield, showing that this hydroamidation protocol is compatible with the reaction of disubstituted amines and electron-withdrawing alkynes. Previous reports of hydroamidation with ammonia relied on the use of excess ammonium salts. Notably, our protocol represents the first example of alkyne hydroamidation using ammonia, which provided amide **30** with satisfactory 88% yield and excellent atom economy.

Reactions of various alkynes with the aromatic amines were also investigated (Scheme 2B). Aromatic amines underwent hydroamidation with generally good yields (**31–53**). Substituted aromatic alkynes were also compatible with aromatic amines (**31–38**). Aliphatic alkynes were also transformed in good yields and selectivity (**39–46**). Notably, hydroamidation of substrates that could potentially react with amines (**45** and **46**) under harsh conditions proceeded without observation of side reactions. Different aniline derivatives reacted well, even though substitutions on the aromatic ring largely affect their electronic properties (**47–52**). To our delight, 2-aminopyridine, which can coordinate to metal catalysts, reacted smoothly to yield branched amide **53**.

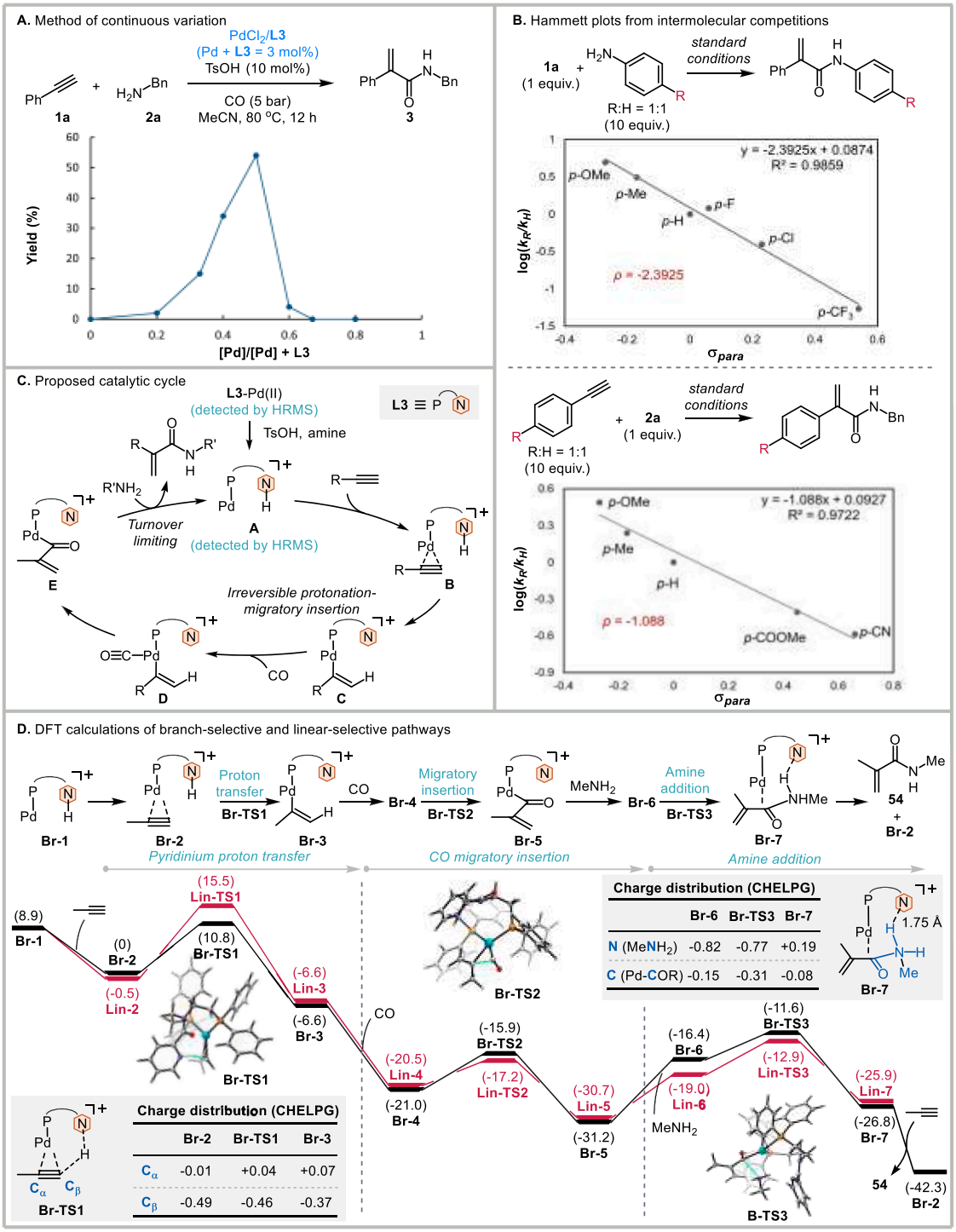
Having established the scope of this **L3**-enabled hydroamidation, we demonstrated the scalability using representative amines (benzylamine, diethylamine, and ammonia). Decagram-scale reactions were achieved without decline in yields or regioselectivity (Scheme 3A). The standard conditions allowed for a 100-fold scale-up of the model reaction, affording product **3** in 90% yield (12.9 g) and with a process mass efficiency (PMI) of 7.4. Diethylamine was also transformed to give **24** in satisfactory 85% yield (10.6 g) without further optimization. Preceding protocols for the hydroamidation of ammonia relied on ammonium salts, such as NH_4Cl and NH_4HCO_3, which compromised atom economy and increased waste generation (PMI = 31.3~36.2). Efficiency of our protocol was further validated by the scale-up hydroamidation using ammonia, which provided amide **30** in 89% yield (9.8 g, *b/l* > 20:1, PMI = 9.4).

3. Mechanistic studies

Next, we sought to elucidate the salient mechanistic features of this hydroamidation system based on mechanistic studies and preceding reports [19,27,28]. The method of continuous variation (Job plot) was applied to the catalytic system of $PdCl_2$ and **L3**. By varying the respective fractions of $PdCl_2$ and **L3** while fixing their total concentration (3 mol%), the formation of a 1:1 complex between $PdCl_2$ and **L3** was confirmed, consistent with our previous ^1H NMR studies (Scheme 4A) [30,48]. Hammett plots against standard σ values were constructed from intermolecular competitions. A reaction constant of $\rho = -2.39$ was observed for pairs of substituted anilines (Scheme 4B). The negative



Scheme 3. Scalability and PMI values of Pd/**L3**-catalyzed hydroamidation.



Scheme 4. Mechanistic studies of alkyne hydroamidation. (A) Method of continuous variation (Job plot). (B) Hammett analysis. (C) DFT calculations of Gibbs free energy profile (kcal mol^{-1}). DFT calculations were performed using PBE0-D4/def2-TZVP/SMD(MeCN)//PBE0-D3/def2-SVP. CHELPG, charges from electrostatic potentials using a grid-based method.

slope and the magnitude of the reaction constant are consistent with the proposed identity of the rate-determining step, in which the attack of amines on the acylpalladium species forges the amide functionality. On the other hand, a Hammett plot derived from aryl alkynes indicated a negative reaction constant of $\rho = -1.09$. We attribute this value to the irreversible formation of the viny- or acylpalladium intermediates (see DFT calculations, *vide infra*), in which the electron-rich alkynes facilitate rapid pyridinium proton transfer [49,50].

Based on these experimental observations and computational results (*vide infra*), we propose the catalytic cycle depicted in Scheme 4C. A catalytic amount of TsOH and amines promote the formation of the pyridinium Pd(0) species (**A**), consistent with the molecular compositoin detected by high-resolution mass spectrometry (HRMS). Coordination of alkyne substrates affords the Pd species **B** that readily accepts a proton from the pyridinium group of **L3**, and this proton transfer establishes the desired branched selectivity. The resulting vinylpalladium species **C** undergoes CO coordination and migratory insertion to form acylpalladium **E**, and the process from **A** to **E** is considered irreversible. The

addition of amine yields α,β-unsaturated amide products and regenerates pyridinium **A**.

We performed density functional theory (DFT) calculations [51] to further explore the mechanistic details. Propyne and methylamine were used as model substrates of Pd/**L3**-catalyzed hydroamidation of alkynes (Scheme 4D). The catalytically active species was computed to be **Br-1** (Pd coordinated to the bidentate **L3**), consistent with the Job plot analysis (Scheme 4C). Coordination of propyne affords pyridinium **Br-2**, which is transformed into the branched vinylpalladium **Br-3** ($\Delta G = -6.6$ kcal/mol). The transition state (**Br-TS1**) for this exothermic transformation features a direct proton transfer from the pyridinium nitrogen to the terminal carbon atom of the alkyne (N_{pyr}-H = 1.34 Å, C_β-H = 1.40 Å), and its low activation energy barrier ($\Delta G^{\ddagger}$ =10.8 kcal/mol) supports the high activity of ligand **L3**. Coordination and migratory insertion of CO lead to the exothermic formation of acylpalladium **Br-5** from **Br-4** via **Br-TS2** ($\Delta G^{\ddagger}$ =5.1 kcal/mol). The intermediate **Br-5** is computed to be 31.2 kcal/mol more stable than the starting alkyne complex (**Br-2**), and its formation is therefore considered irreversible. The addition of methylamine converts **Br-5** to **Br-7** via **Br-TS3** with an energy barrier of 19.6 kcal/mol and is determined to be turnover-limiting [52]. Finally, ligand exchange with propyne releases the branched product **54** and regenerates the active species **Br-2**. For the corresponding linear-selective transformation, a similar reaction pathway was calculated. The proton transfer of **Lin-1** occurs with an activation energy of $\Delta G^{\ddagger}$ = 16.0 kcal/mol, generating the linear intermediate **Lin-3** via **Lin-TS1**. Exothermic migratory insertion of CO forges acylpalladium intermediate **Lin-5**, which is 30.7 kcal/mol more stable than the starting **L1**. Methylamine addition to the acylpalladium **Lin-5** ($\Delta G^{\ddagger}$ =17.8 kcal/mol for **Lin-TS3**) yields the linear amide product. Notably, for the proton-transfer step (**Br-2** to **Br-3** and **Lin-2** to **Lin-3**), the branch-selective pathway (**Br-TS1**) features a lower activation energy barrier than the corresponding linear analogue (**Lin-TS1**, $\Delta\Delta G^{\ddagger}$ = 4.7 kcal/mol), consistent with the excellent *b/l* ratios observed in the reactions. Given the highly exothermic natures of proton transfer and CO migratory insertion, the regioselectivity is established during these irreversible steps (**Br-2** to **Br-5**), regardless of the comparable energies of the transition states for methylamine addition in branched and linear pathways (**Br-TS3** and **Lin-TS3**).

Further analysis of the charge distributions [53] of the computed pathway agrees with our experimental results. For the amine addition step, an increase in positive charge at the amine nitrogen atom was observed across the series **Br-6** (−0.82), **Br-TS3** (−0.72), and **Br-7** (+0.19). This trend explains the accelerating effect of electron-donating substituents on the amine derivatives observed in the Hammett relationship analysis (Scheme 4B). The calculated scenario generates the protonated amide product (**Br-7**), in which the amide hydrogen is stabilized by the pyridine of the ligand through a hydrogen bond. For the pyridinium proton transfer step, both alkyne carbon atoms exhibit decreased negative charges from **Br-2** to **Br-3** (*e.g.,* C_β: −0.49 to −0.37). This result further supports the reaction constant ($\rho = -1.09$) observed in intermolecular competition experiments shown in Scheme 4B.

4. Conclusions

In summary, we have developed an efficient catalyst system for branch-selective hydroamidation with a picolinamide diphosphine ligand. The incorporation of this ligand enhances catalyst activity and regioselectivity through a proton-transfer mechanism. This protocol accommodates previously challenging amines and alkynes with diverse basicities and electronic properties without the need for stoichiometric additives. As a result, our method demonstrates robust practicability at a decagram scale under mild conditions. Experimental studies and DFT calculations reveal the crucial role of the pyridine moiety in the ligand scaffold as a proton shuttle, which overcomes the basicity barrier and promotes alkyne activation. Overall, these results provide mechanistic insights into hydroamidation reactions and may contribute to the catalyst design of related transformations.

CRediT authorship contribution statement

Ding Liu: Writing – original draft, Visualization, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jiaxin Cheng:** Investigation, Formal analysis. **Yuan Tao:** Investigation, Formal analysis. **Jianai Chen:** Investigation, Formal analysis. **Yajiao Zhang:** Project administration, Methodology, Investigation, Conceptualization. **Xiao Xiao:** Writing – review & editing, Project administration, Investigation, Formal analysis, Conceptualization. **Fen-Er Chen:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mcat.2026.116009.

Data availability

Data will be made available on request.

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