Nickel-Catalyzed Deaminative Sonogashira Coupling of Alkylpyridinium Salts Enabled by a New NN_2 Pincer Ligand

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Abstract

Alkynes are amongst the most valuable functional groups in organic chemistry and widely used in chemical biology, pharmacy, and materials science. However, the preparation of alkyl-substituted alkynes still remains elusive. Herein, a novel transformation is disclosed that enables the coupling of terminal alkynes with alkylpyridinium salts under Ni-catalysis. Key to the success of this coupling was the development of a new and readily accessible amide-type pincer ligand. This ligand allows naturally abundant alkyl amines as alkylating agents in Sonogashira reactions for the first time, and leads to diverse alkynes in excellent yields under mild conditions. Salient merits of this chemistry include broad substrates scope and functional group tolerance, gram-scale synthesis, one-pot transformation, versatile late-stage derivatizations as well as the use of inexpensive pre-catalyst and readily available substrates. The high efficiency and strong practicability bode well for the widespread applications of this strategy in constructing functional molecules, materials, and fine chemicals.

Introduction

Alkynes are one of the most valuable functional groups in organic chemistry because they are not only served as versatile synthetic building blocks for diversified chemical transformations, but also common structural motifs in a wide range of natural products, bioactive molecules and organic materials[1–3]. For example, introduction of an alkyne into a drug molecule could provide remarkable benefits in its biological activity, such as enhanced lipophilicity, bioavailability and metabolic stability (Fig. 1a). In addition to the widely used as functional tags in biochemistry for bioconjugation based on “alkyne-azide click chemistry”[4], recent researches also indicated that alkynes have a privileged application in Raman imaging due to their unique and strong Raman scattering peaks in a cellular silent region that is free of interference from most endogenous molecules (Fig. 1b)[5–9]. Therefore, lots of efforts have been made to develop efficient methods for the construction of alkynes. Among these available transformations, the transition-metal-catalyzed Sonogashira coupling of aryl/vinyl electrophiles with terminal alkynes has proven to be one of the most powerful approaches for C(sp^2)-C(sp) bond formation[10,11]. However, the incorporation of nonactivated, β-H-containing alkyl electrophiles in Sonogashira reaction to construct C(sp^3)-C(sp) bond still remains a formidable challenge, presumably due to the following issues (Fig. 1c): (1) the reluctance of alkyl electrophiles to undergo oxidative addition with a metal catalyst, (2) the propensity of the resulting alkylmetal intermediates to undergo intramolecular β-hydride elimination, (3) the poor nucleophilicity of the sp-hybridized carbon in alkynes, and (4) the low concentration of the transmetalating species generated in situ in reaction medium. Moreover, the facile cyclotrimerization and/or oligomerization of terminal alkynes under the catalysis of low-valent metal is another obstacle that renders such coupling a more intractable objective[12,13]. In a pioneering study, Fu and co-workers realized Pd/Cu-cocatalyzed Sonogashira coupling of nonactivated primary alkyl iodides and bromides by the use of a N-heterocyclic carbene (NHC) ligand[14]. Later on, a few elegant strategies for this transformation were developed based on the discovery of new catalytic systems including Pd/bisoxazoline-derived NHC ligand[15], Ni/NN_2 pincer ligand[16,17], Ni/pyridine bisoxazoline system[18], and

NHC pincer nickel(II) complex[19] (Fig. 1d). Despite these significant advances, the scope for alkyl-Sonogashira-type reactions is still relatively limited. Particularly, the electrophilic partners in such reactions are largely limited to alkyl halides[20], and the need of copper(I) salt as cocatalyst might also cause some detrimental effects to the reaction, such as the undesired Glaser coupling of terminal alkynes and the complicated procedure in workup[21]. Thus, developing new approaches to access such coupling with more alternatives especially in copper-free conditions is highly important and appealing.

Alkyl amines are naturally abundant and readily available feedstock chemicals, and the prevalence of amino group in numerous bioactive molecules, pharmaceuticals and natural products provides expedient opportunities for late-stage functionalization and bioconjugation[22,23]. In this context, using alkyl amines as alkylating agents in organic synthesis would have many privileged advantages when compared to the traditional platforms using alkyl halides. However, such a promising transformation is still underexploited owing to the high bond dissociation energy of C(sp^3)-N bond[24–26]. In a seminal work, Watson et al. demonstrated that pyridinium salts, also known as “Katritzky salts” which are easily formed from primary amines and pyrylium salt, could be used as alkyl radical precursors in cross-coupling with arylboronic acids[27]. Since then, many elegant approaches based on the utilization of these redox active amines for deaminative functionalization such as arylation[28–30], borylation[31,32], alkenylation[33], allylation[34], alkyl-Heck-type reaction[35,36], carbonylation[37], alkylation[38–41], difluoromethylation[42] and C-heteroatom bond-forming reactions[43–45] have been established. However, the deaminative alkynylation of alkyl amines to form C(sp^3)-C(sp) bond still remains elusive. Although Gryko[46] and Han[47] have independently realized such transformation via photoredox or nickel-catalyzed reductive cross-coupling strategy recently, the need for tedious preparation of the corresponding alkynylating agents (e.g. alkynyl sulfones or bromides) limited their practical applicability and accessibility. In addition, the limited substrates scope and the use of largely excess reductants in both protocols further disfavored their utilizations in synthesis. Therefore, the direct coupling of terminal alkynes with alkylpyridinium salts in redox-neutral fashion for the synthesis of important alkynes would be highly desirable in terms of both atom-economy and practical application. To the best of our knowledge, however, such a straightforward and practical protocol has not been achieved.

Following our keen interest in nickel-catalyzed cross-coupling reactions[48,49], herein, we report the first general and efficient nickel-catalyzed Sonogashira coupling of alkylpyridinium salts via C-N bond activation under Cu-free conditions (Fig. 1e). The newly designed and readily accessible amide-type NN_2 pincer ligand (6-methyl-*N*-(quinolin-8-yl)picolinamide **L4**) was found to be crucial for this transformation, allowing the coupling to occur under mild reaction conditions with excellent yields and high functional group tolerance.

Results

Optimization study. Initially, the coupling of phenethylpyridinium salt **1a** and phenylacetylene **2a** was selected as the model reaction for optimization (Table 1). To realize such transformation, we envisaged

that a pincer ligand might be feasible due to its strong and tridentate bonding mode to the metal center, thereby possibly stabilizing the alkylnickel intermediate[50] and suppressing the undesired Glaser coupling[51,52]. Thus, the ligands were firstly screened by using 10 mol% $NiCl_2$(glyme) as catalyst, K_3PO_4 as base in tetrahydrofuran (THF) at 80 °C. When pyridine bisoxazoline (pybox), the most efficient ligand in Liu's work[18], was applied to this reaction, the desired product **3a** was obtained in 4% yield and the main product was 1,4-diphenylbutadiyne derived from the homocoupling of **2a** (entry 1). While the use of a more electron-rich and bulky 4,4',4"-tritert-butyl terpyridine (ttbtpy) in this process, the yield of **3a** was improved to 53% (entry 2). Much to our delight, the yields of **3a** could be further improved to 87% and 83% respectively, when amide-type pincer ligand (e.g. *N*-(pyridin-2-ylmethyl)picolinamide (**L1**) or *N*-(quinolin-8-yl)picolinamide (**L2**)) was used (entries 3–4), though they were seldom used as ligands in transition metal-catalyzed cross-coupling reactions[53–56]. This discovery encouraged us to synthesize two new sterically more hindered methylated derivatives **L3** and **L4** as ligands. Gratifyingly, the yield was significantly improved to 96% by employing **L4** (entry 6). The reasons for the high efficiency of **L4** are still unclear at present, but probably related to its steric hindrance and rigidity. Screening of nickel catalysts revealed that $Ni(acac)_2$ was ineffective (entry 7), whereas the inexpensive, air- and moisture-stable $NiCl_2{\cdot}6H_2O$ gave the best result (entry 8). Subsequently, the effect of base was examined. K_2CO_3 resulted in a slightly diminished yield (entry 9). However, the reaction completely shut down by using Et_3N, a frequently-used base in palladium-catalyzed Sonogashira coupling of aryl halides (entry 10)[11]. Lowering the amount of catalyst or reaction temperature led to a reduced yield in different extent (entries 11–12). Control experiments indicated that $NiCl_2{\cdot}6H_2O$, **L4** and K_3PO_4 were all essential for achieving the transformation (entries 13–15) (For a detailed optimization study, see Supplementary Information).

Substrate scope. With the optimized coupling conditions in hand, the scope of alkynes was first evaluated using **1a** as the coupling partner. For some cases that the products were unseparated from the excess terminal alkynes, *p*-methoxylphenethylpyridinium salt **1b** was used instead of **1a**. As shown in Fig. 2, the arynes bearing both electron-donating and electron-withdrawing groups could participate in this transformation delivering the products (**3b-3 k**) in excellent yields. Various synthetically important functional groups including methoxyl, arylhalide, ester, acetyl, trifluoromethyl, formyl and free amino were all perfectly accommodated. Particularly noteworthy was that aryl chlorides and bromides, popular electrophilic partners in Sonogashira reactions[10], remained inert under our optimized reaction conditions, highlighting the exquisite chemoselectivity of this transformation. Additionally, the presence of an ortho formyl did not hamper the reaction. Strikingly, terminal alkyne (**2 l**) containing a boronate ester group was also successfully engaged in this transformation with its C-B bond intact, thus allowing for further diversification. Heteroaromatic rings such as pyridine and thiophene that might deactivate a metal catalyst by coordination, and 1-ethynylcyclohexene could also smoothly undergo the transformation giving the corresponding products (**3 m-3o**) in excellent yields. More importantly, aliphatic alkynes (**2p-2t**) could also be coupled in high efficiency. The functional groups such as Cl, NHBoc, and OH were well tolerated, affording the products (**3r-3t**) in high to excellent yields with excellent selectivity. Finally,

triisopropylsilyl- and trimethylsilyl-capped alkynes were also suitable substrates to obtain the products (**3u-3v**) in high yields.

Next, the generality of alkyl amines was evaluated as shown in Fig. 3. Various primary alkyl (**1b-1 l**) and benzylpyridinium salts (**1 m-1o**) were all suitable substrates for this transformation, and the desired products (**4b-4o**) could be obtained in high to excellent yields. However, the secondary alkylpyridinium salts (e.g. **1t**) exhibited a dramatic drop in reaction efficiency (**4t**, 74%) under the optimized conditions. Then reoptimization of secondary alkylpyridinium salts was conducted by exploring various reaction parameters. Gratifyingly, 98% yield of **4t** could be obtained by changing the solvent to DMF. Under the slightly modified conditions, diverse secondary alkylpyridinium salts underwent this coupling smoothly to give the desired products (**4p-4w**) in high to excellent yields. Similarly, good functional group tolerance was observed, as exemplified by the well compatible with methoxyl, trifluoromethoxyl, bromide, indole NH, alkenyl, *tert*-amine, acetal, hydroxyl and chloride. More importantly, heterocyclic units such as thiophene (**1f**), pyridine (**1 g**), indole (**1 h**), tetrahydropyran (**1 s**) and piperidine (**1t**) which are prevalent in medicinally relevant molecules were competent substrates. In addition, benzylpyridinium salts especially electron-rich benzylic salts which are not suitable in Gryko's work[46] could be coupled with high efficiency (**4 m-4n**), emphasizing the robustness of our strategy in synthetic applications. It is worth noting that both cyclic (**1p-1u**) and acyclic secondary amines (**1v-1w**) could be readily applied to this protocol with high to excellent yields.

It is worth highlighting that this protocol was amenable to a one-pot transformation in which pyrylium salt, alkyl amine and the cross-coupling reagents were added simultaneously in a single step, and 78% yield of the product **3a** could be obtained without further reoptimizing the reaction conditions (Fig. 4a). Additionally, a gram-scale reaction was successfully performed using **1a** and **2c** under the optimized conditions producing **3c** in 87% yield, exemplifying the practicability and scalability of this process (Fig. 4b).

Late-stage derivatizations. To further demonstrate the broad applicability of this method, late-stage functionalization of natural products and medicinally relevant molecules were conducted (Fig. 5). A series of pyridinium salts and alkynes derived from drugs and bioactive compounds underwent this transformation with good to excellent yields (**5–20**). This general protocol could be successfully applied for rapid construction of alkyne-labelled derivatives of biomolecules (**5–9**). The readily attached alkynyl group is expected to serve as a labeling tool to facilitate further chemical biology studies and as a handle for rapid entry to complex derivatives. Likewise, this versatile method can be also applied in the further functionalization of alkynyl-containing bioactive molecules or intermediates (**10–14**). Notably, the virtues of the current method were further illustrated by the successful coupling of two drug molecules for assembling their drug-like hybrids **15–20**, highlighting the potential applications of this chemistry in the discovery of pharmaceutical candidates.

Mechanistic studies. To understand the reaction mechanism, a series of experiments were performed. When the radical trapping reagent TEMPO was added to the reaction mixture, only trace of **3a** was

obtained with the concurrent formation of TEMPO-adduct **21** in 16% yield (Fig. 6a). In addition, a radical-clock experiment was also conducted by employing cyclopropylmethyl pyridinium salt **1x**. Instead of normal cross-coupling product **4x**, a ring-opened product **22** was achieved in high yield (Fig. 6b). These results suggest that an alkyl radical may be involved in this transformation. To further elucidate the role of the nickel catalyst in this reaction, a Ni(II) complex **Int-1** was synthesized by simple exposure of $NiCl_2{\cdot}6H_2O$ and **L4** in tetrahydrofuran at room temperature and characterized by X-ray crystallography. Gratifyingly, a high yield of **3a** was obtained when **Int-1** was applied to this catalytic transformation (Fig. 6c). However, when $Ni(cod)_2$ was used as the catalyst, a remarkable decrease in efficiency was observed and only a moderate yield of **3a** was achieved (Fig. 6d). These results indicate that Ni(II) complex **Int-1** is likely involved as a competent catalytic species in this chemistry rather than a Ni(0) species.

Although a detailed mechanism awaits further studies, a plausible mechanism is depicted in Fig. 6e based on the reactions of Katritzky salts[27–47] and Ni/pincer-ligand catalyzed cross-coupling of other alkyl electrophiles[54,57–59]. Initially, coordination of **L4** to the Ni center followed by ligand exchange to form a Ni(II) complex **Int-1**. It may undergo transmetalation with alkyne promoted by base to give intermediate **A**. Single-electron transfer (SET) from **A** to pyridinium **1** generates a Ni(III) complex **B** and an alkyl radical, which recombines with another molecule of **A** to give a Ni(III) species **C**. Reductive elimination from **C** furnishes the desired product and an unstable Ni(I) intermediate **D**, which quickly undergoes comproportionation with **B** to regenerate **A** and **Int-1** for the next catalytic cycle.

Discussion

In summary, we have achieved a highly efficient and general Sonogashira coupling of alkylpyridinium salts by the development of a new Ni/NN_2 pincer ligand catalytic system. Notably, this is the first time to realize the coupling of terminal alkynes with naturally abundant alkyl amines, extremely expanding the substrate scopes used in Sonogashira reactions. The virtues of this reaction are illustrated by the broad substrates scope, well functional group tolerance in both coupling partners as well as the efficient diversification of natural products and medicinally relevant molecules. Further mechanism investigation and application of this catalytic system for the cross-coupling with other electrophiles are currently ongoing in our laboratories.

Methods

General procedure for Sonogashira coupling of primary alkylpyridinium salts. In a nitrogen-filled glovebox, $NiCl_2{\cdot}6H_2O$ (0.03 mmol, 7.1 mg), **L4** (0.03 mmol, 7.9 mg), anhydrous K_3PO_4 (0.39 mmol, 82.8 mg), primary alkylpyridinium salt (0.3 mmol) and tetrahydrofuran (1.5 mL) were successively added to an oven-dried sealable Schlenk tube (10.0 mL) followed by addition of terminal alkyne (0.45 mmol) via microliter syringe *(If terminal alkyne is a solid, it was added before the solvent)*. Then the tube was securely sealed and taken outside the glovebox. And it was immersed into an oil bath preheated at 80 or

50 ^{o}C. After stirring for 24 h, the reaction mixture was cooled to room temperature and filtered through a short pad of silica gel. Then the filter cake was washed with dichloromethane or ethyl acetate. The resulting solution was concentrated under vacuum and the residue was purified by column chromatography on silica gel to afford the corresponding product.

General procedure for Sonogashira coupling of secondary alkylpyridinium salts. In a nitrogen-filled glovebox, $NiCl_2{\cdot}6H_2O$ (0.03 mmol, 7.1 mg), **L4** (0.03 mmol, 7.9 mg), anhydrous K_3PO_4 (0.39 mmol, 82.8 mg), secondary alkylpyridinium salt (0.3 mmol) and *N, N*-dimethylformamide (1.5 mL) were successively added to an oven-dried sealable Schlenk tube (10.0 mL) followed by addition of phenylacetylene (0.45 mmol, 46.0 mg) via microliter syringe. Then the tube was securely sealed and taken outside the glovebox. And it was immersed into an oil bath preheated at 80 ^{o}C. After stirring for 24 h, the reaction mixture was cooled to room temperature and quenched with water. Then it was extracted with ethyl acetate or diethyl ether, washed with water and brine, and dried over anhydrous Na_2SO_4. The resulting solution was concentrated under vacuum and the residue was purified by column chromatography on silica gel to afford the corresponding product.

Data availability

Detailed experimental procedures and characterization of all new compounds can be found in the Supplementary Information. The authors declare that all the data supporting the findings of this study are available within the article and Supplementary Information files, and are also available from the corresponding authors upon reasonable request. CCDC 2035475 (**Int-1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Declarations

Competing interests

The authors declare no competing interests.

Author contributions

X.Z., and G.Z. conceived the idea and guided the project. X.Z., D.Q., C.J., and X.L. performed the experiments and analyzed the results. X.Z., X.L, and G.Z. wrote the manuscript.

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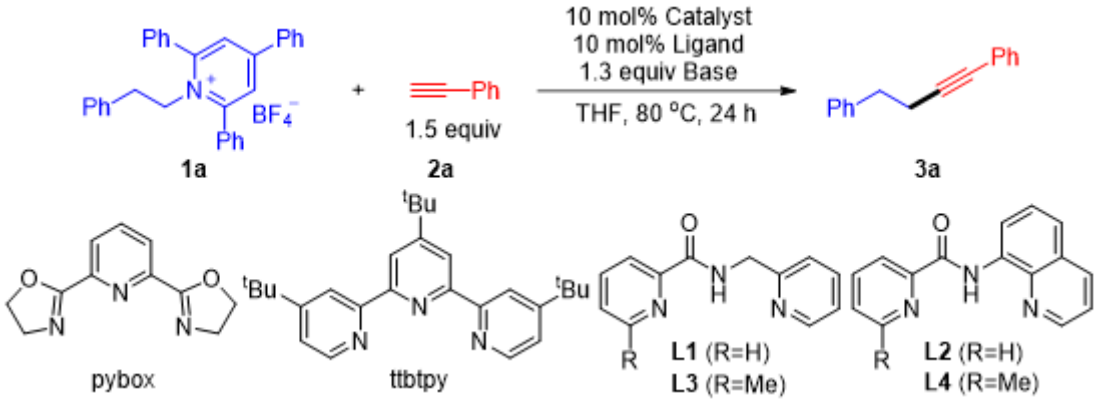
Tables

Table 1 Optimization of the Reaction Conditions[a].



Entry	Catalyst	Ligand	Base	Yield (%)[b]
1	$NiCl_2$(glyme)	pybox	K_3PO_4	4
2	$NiCl_2$(glyme)	ttbtpy	K_3PO_4	53
3	$NiCl_2$(glyme)	**L1**	K_3PO_4	87
4	$NiCl_2$(glyme)	**L2**	K_3PO_4	83
5	$NiCl_2$(glyme)	**L3**	K_3PO_4	40
6	$NiCl_2$(glyme)	**L4**	K_3PO_4	96
7	$Ni(acac)_2$	**L4**	K_3PO_4	7
8	**$NiCl_2·6H_2O$**	**L4**	**K_3PO_4**	**99 (97)[c]**
9	$NiCl_2·6H_2O$	**L4**	K_2CO_3	95
10	$NiCl_2·6H_2O$	**L4**	Et_3N	0
11[d]	$NiCl_2·6H_2O$	**L4**	K_3PO_4	91
12[e]	$NiCl_2·6H_2O$	**L4**	K_3PO_4	68
13	-	**L4**	K_3PO_4	0
14	$NiCl_2·6H_2O$	-	K_3PO_4	0
15	$NiCl_2·6H_2O$	**L4**	-	0

[a]Conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), Catalyst (10 mol%), Ligand (10 mol%), Base (1.3 equiv), THF (1.5 mL), 80 °C. [b]Determined by ^1H NMR using 1,3,5-trimethoxybenzene

as an internal standard. [c]Isolated yield. [d]5 mol% $NiCl_2 \cdot 6H_2O$ and **L4** were used. [e]Reaction was conducted at 60 °C.

Figures

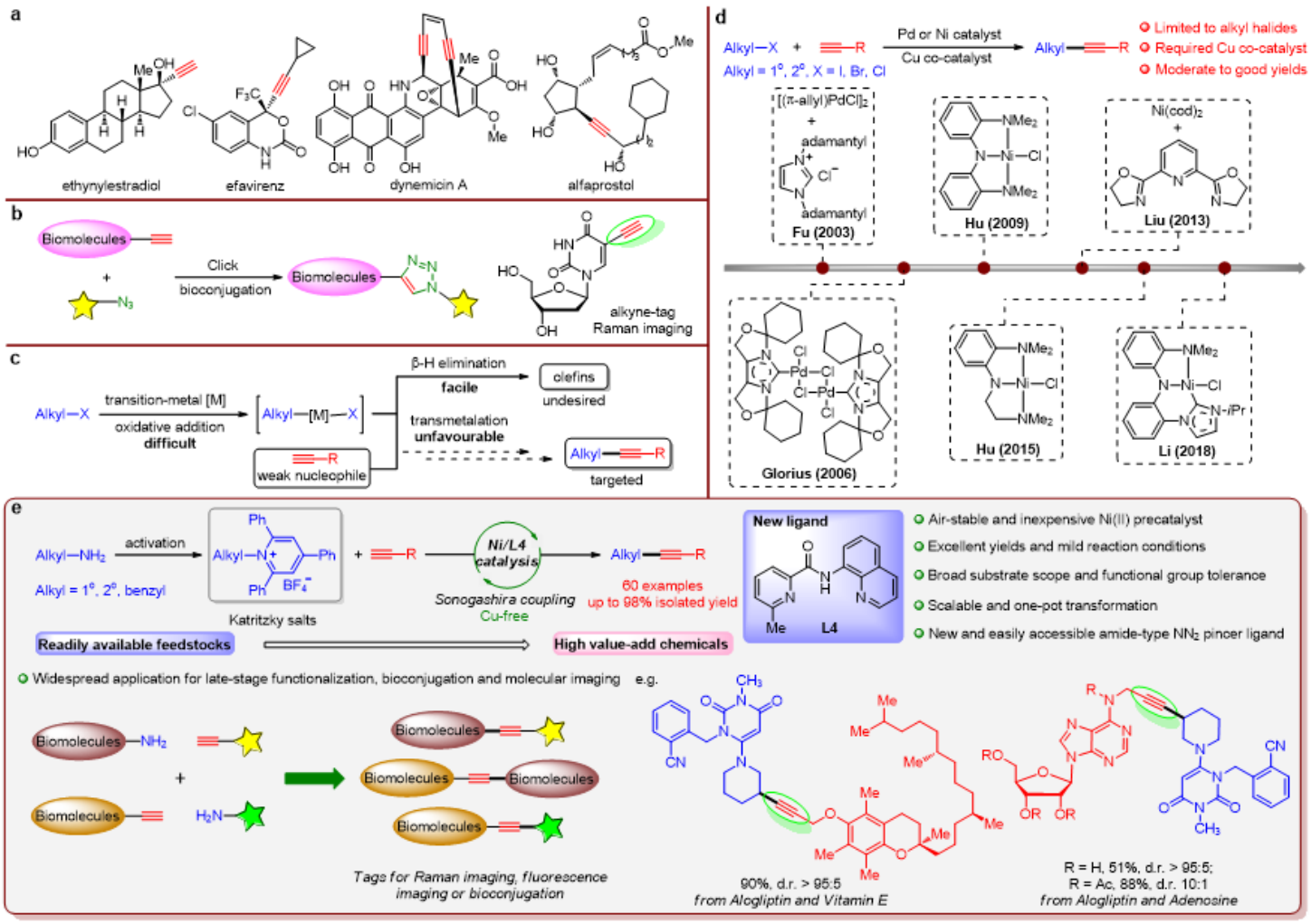


Figure 1

Significances and strategies for Sonogashira coupling of nonactivated alkyl electrophiles. a Representative alkynyl-containing drugs (ethynylestradiol, hormone drug for estrogen medication; efavirenz, antiretroviral drug for HIV/AIDS; dynemicin A, antitumor drug for cancer treatments; alfaprostol, veterinary drug for breeding control). b Important applications of alkynes in bioconjugation and molecular imaging. c Challenges in Sonogashira coupling of nonactivated alkyl electrophiles. d State-of-the-art catalytic systems for Sonogashira coupling of nonactivated alkyl electrophiles. e This work:

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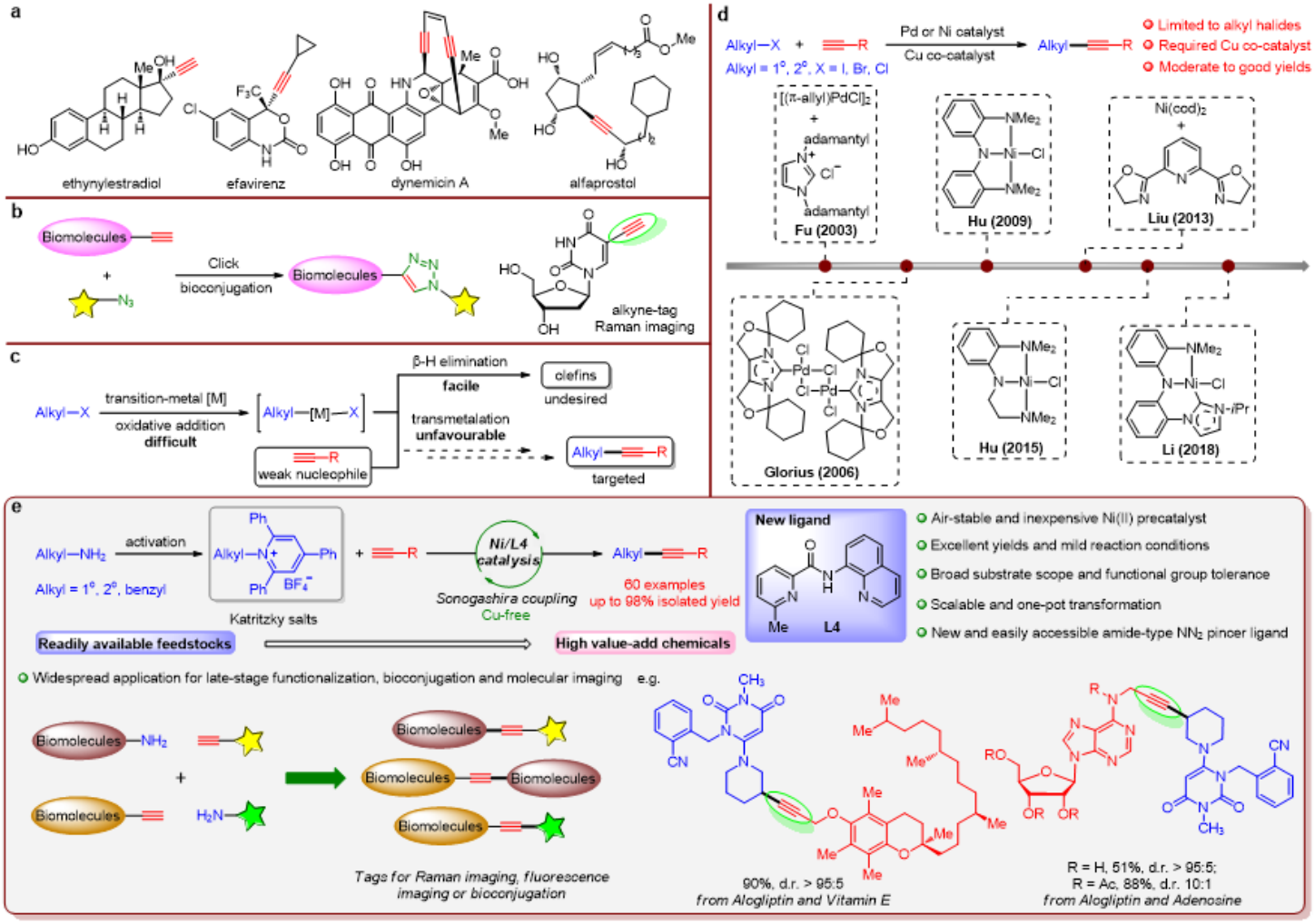

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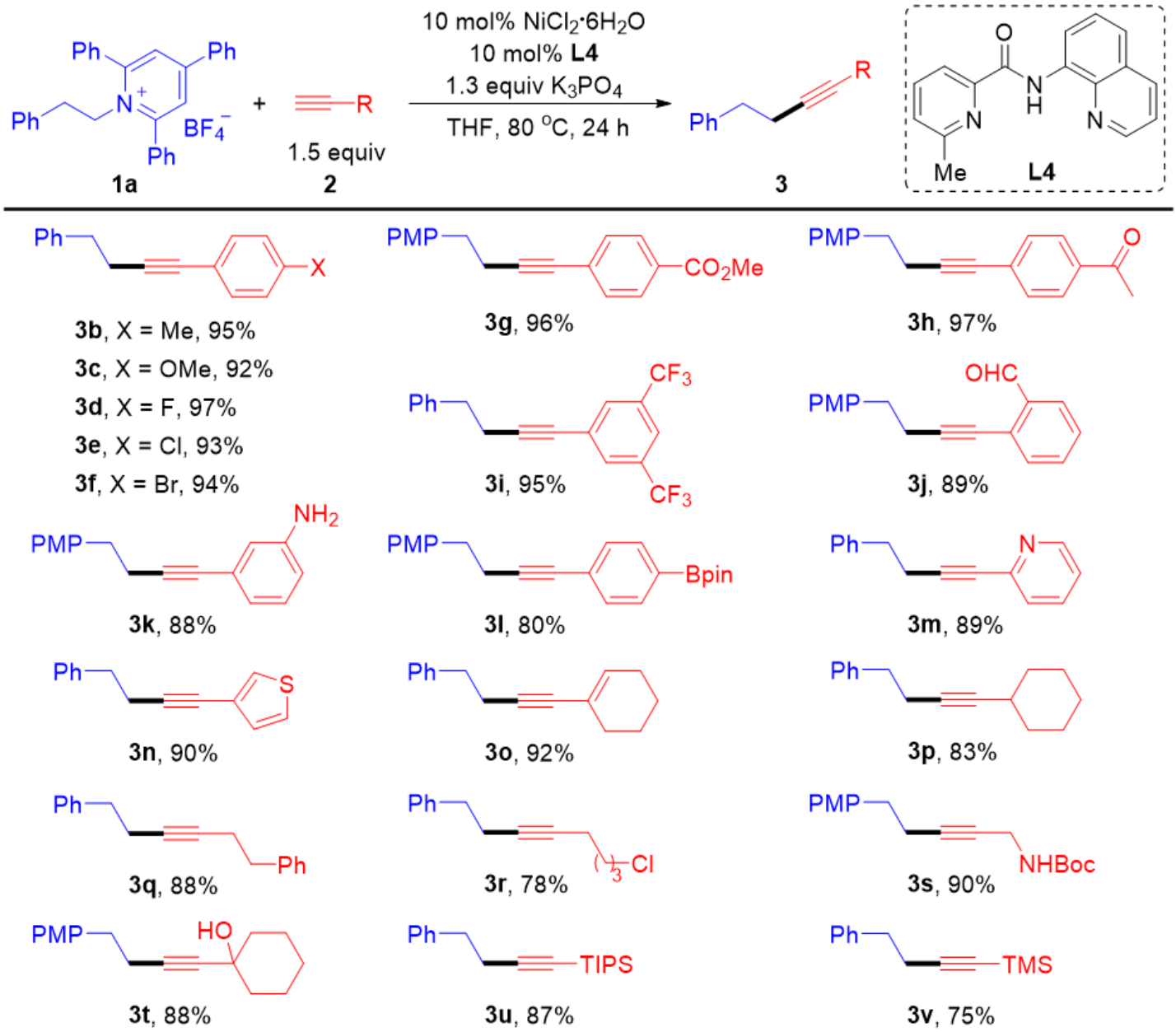
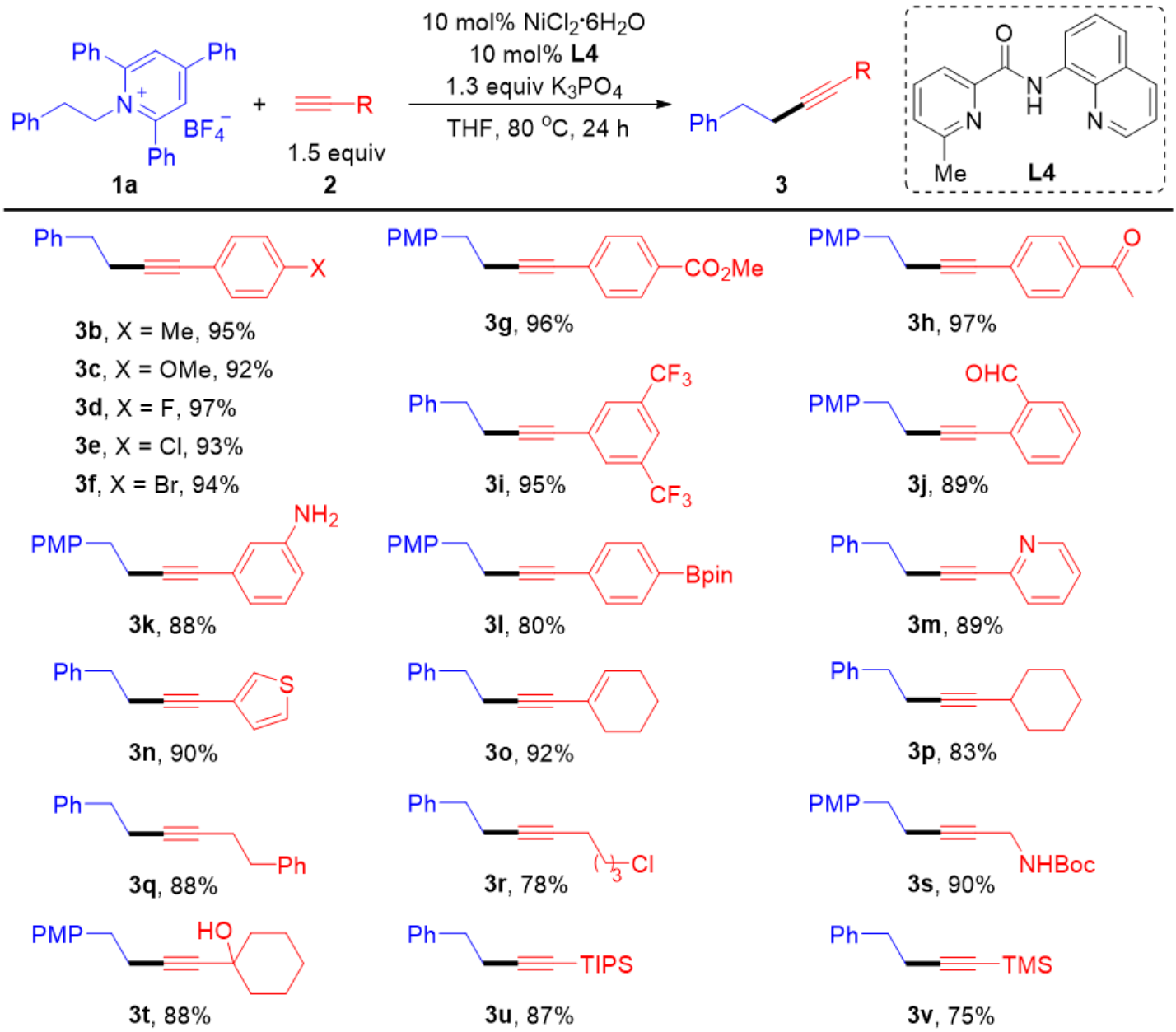


Figure 2

Scope of terminal alkynes. Reaction conditions: 1a (0.3 mmol), 2 (0.45 mmol), NiCl2·6H2O (10 mol%), L4 (10 mol%), K3PO4 (1.3 equiv), THF (1.5 mL), 80 oC. Isolated yields. For 3g, 3h, 3j, 3k, 3l, 3s and 3t, reactions were conducted using p-methoxyphenethylpyridinium salt 1b instead of 1a. PMP = p-methoxyphenyl.



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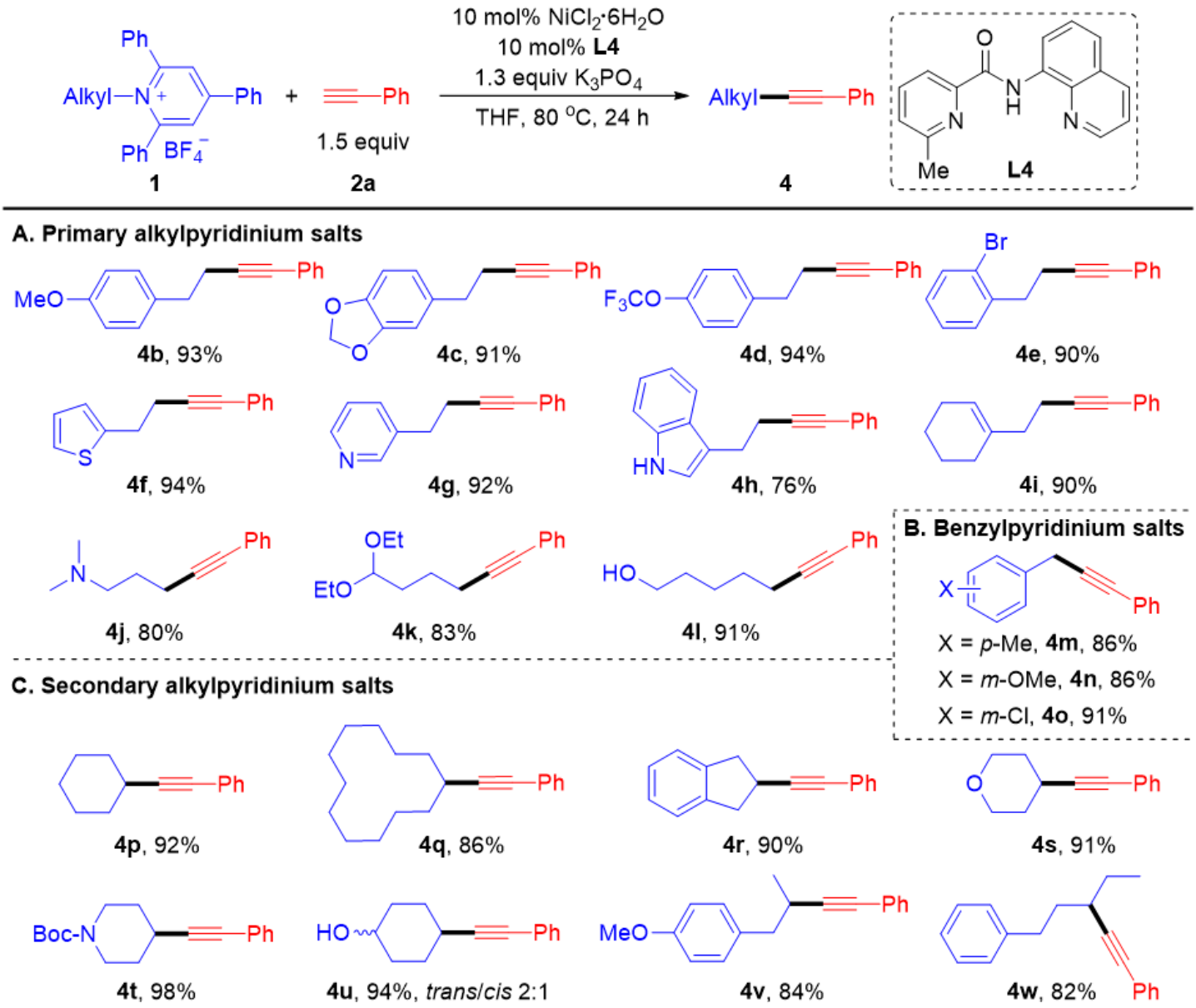
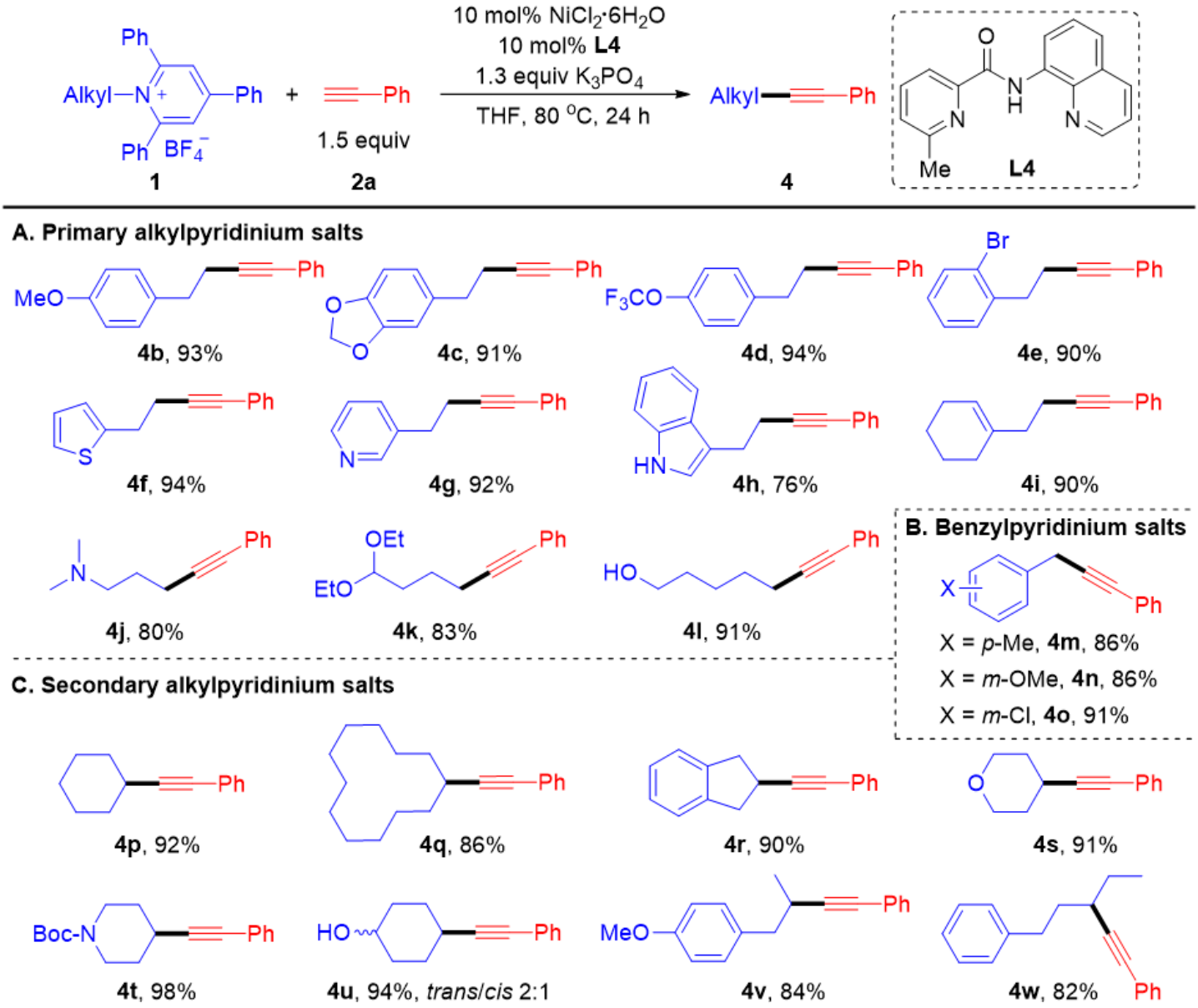


Figure 3

Scope of alkyl amines. Reaction conditions: 1 (0.3 mmol), 2a (0.45 mmol), NiCl2·6H2O (10 mol%), L4 (10 mol%), K3PO4 (1.3 equiv), THF (1.5 mL), 80 oC. Isolated yields. For 4g, 4h, 4p, 4q, 4r, 4s, 4t, 4u, 4v and 4w, reactions were conducted in DMF (1.5 mL). For 4m, 4n and 4o, reactions were conducted at 50 oC.



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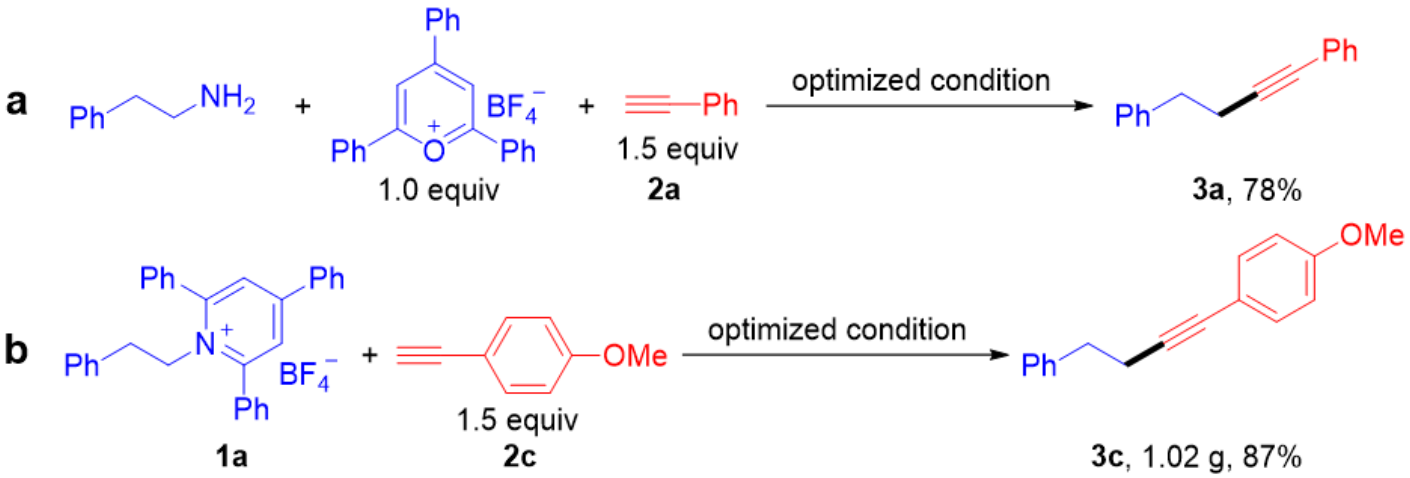
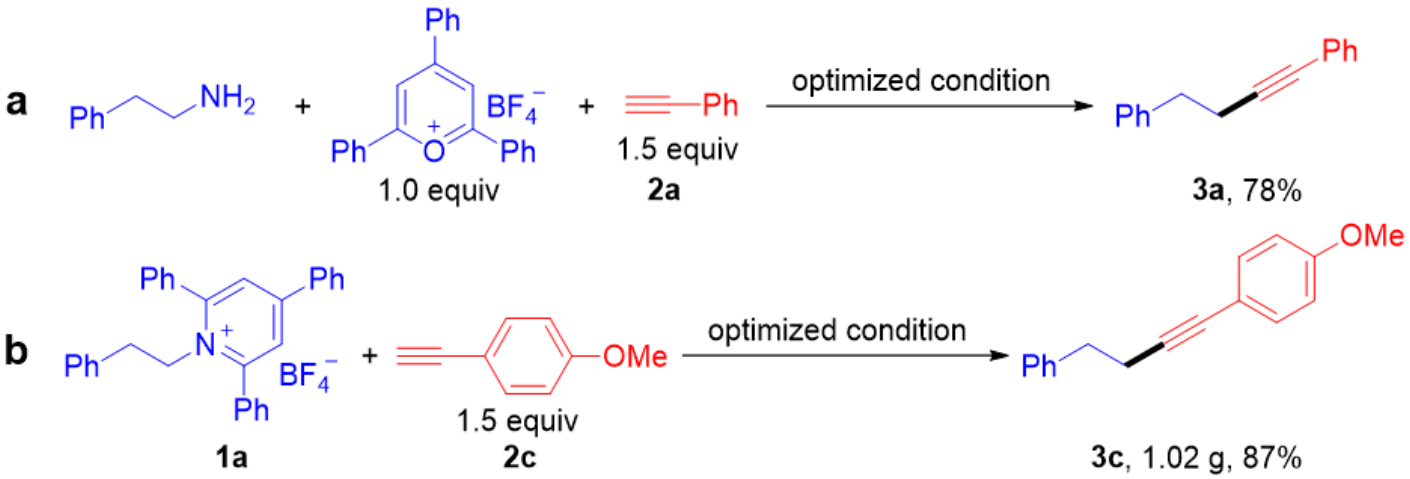


Figure 4

a One-pot transformation. b Gram-scale study.



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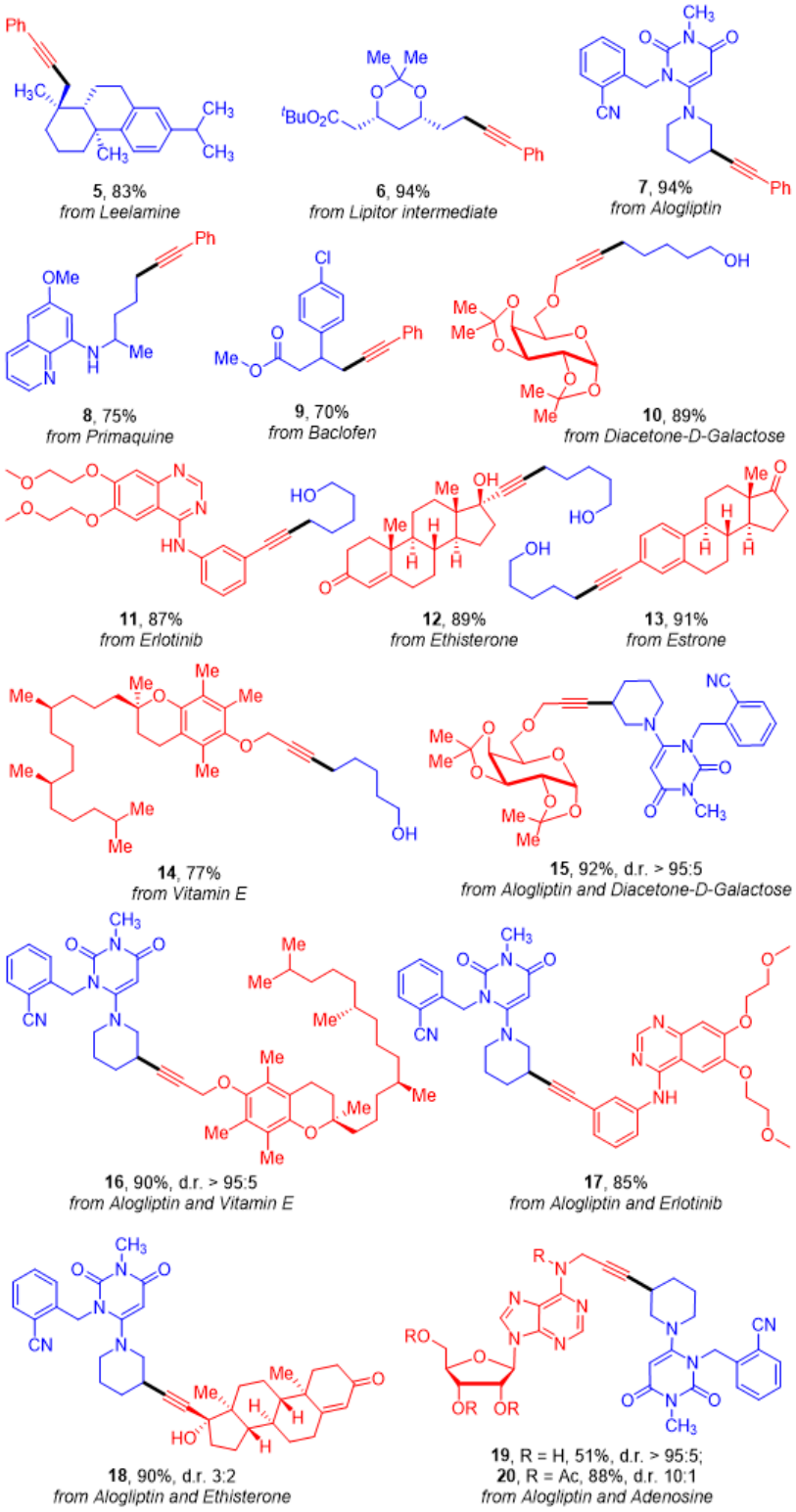
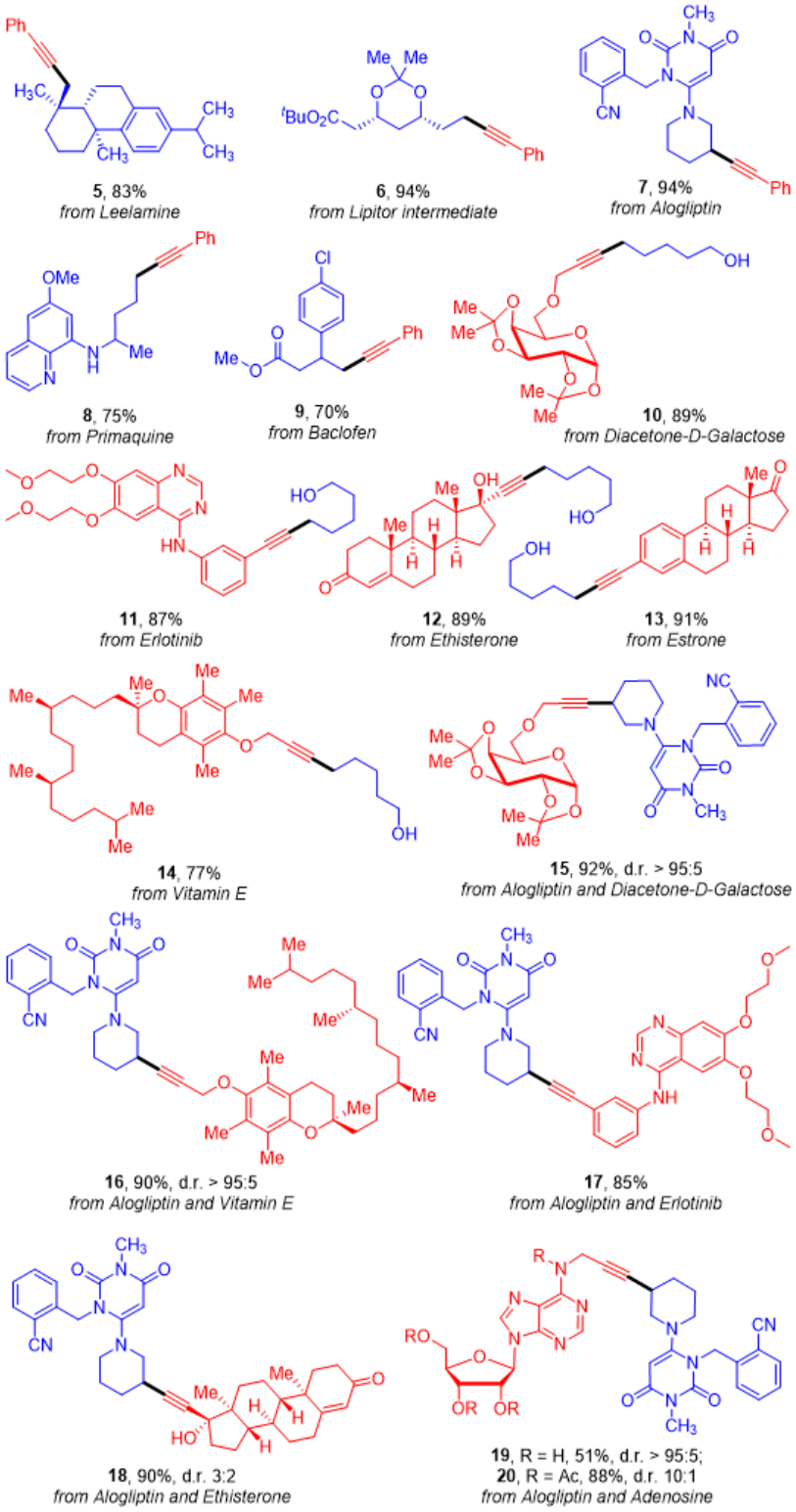


Figure 5

Late-stage modification of natural products and medicinally relevant molecules. Reaction conditions: pyridinium salt (0.3 mmol), alkyne (0.45 mmol), NiCl2·6H2O (10 mol%), L4 (10 mol%), K3PO4 (1.3 equiv), THF (1.5 mL), 80 oC. Isolated yields. For 7, 9, 15, 16, 17, 18, 19 and 20, reactions were conducted in DMF (1.5 mL).



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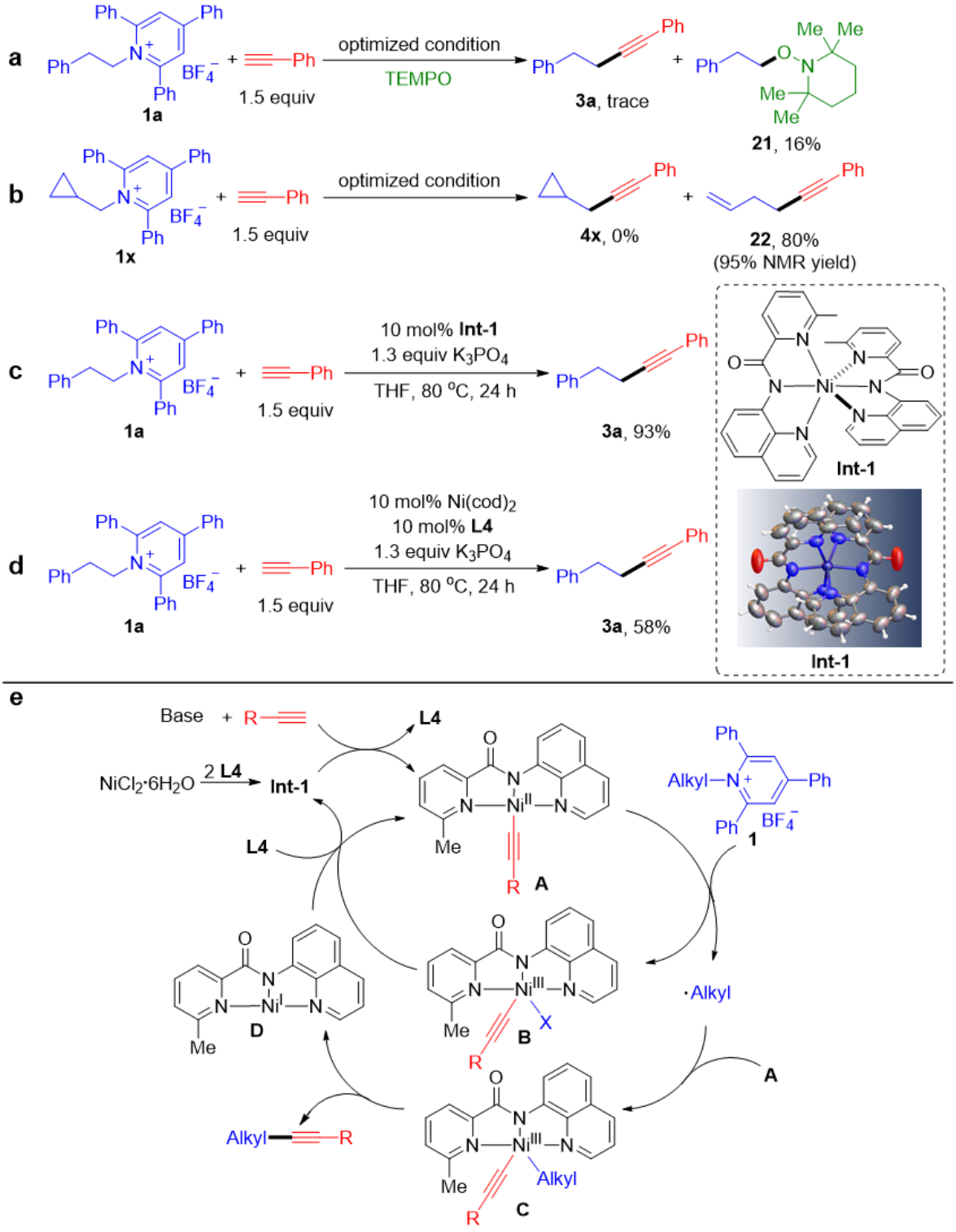
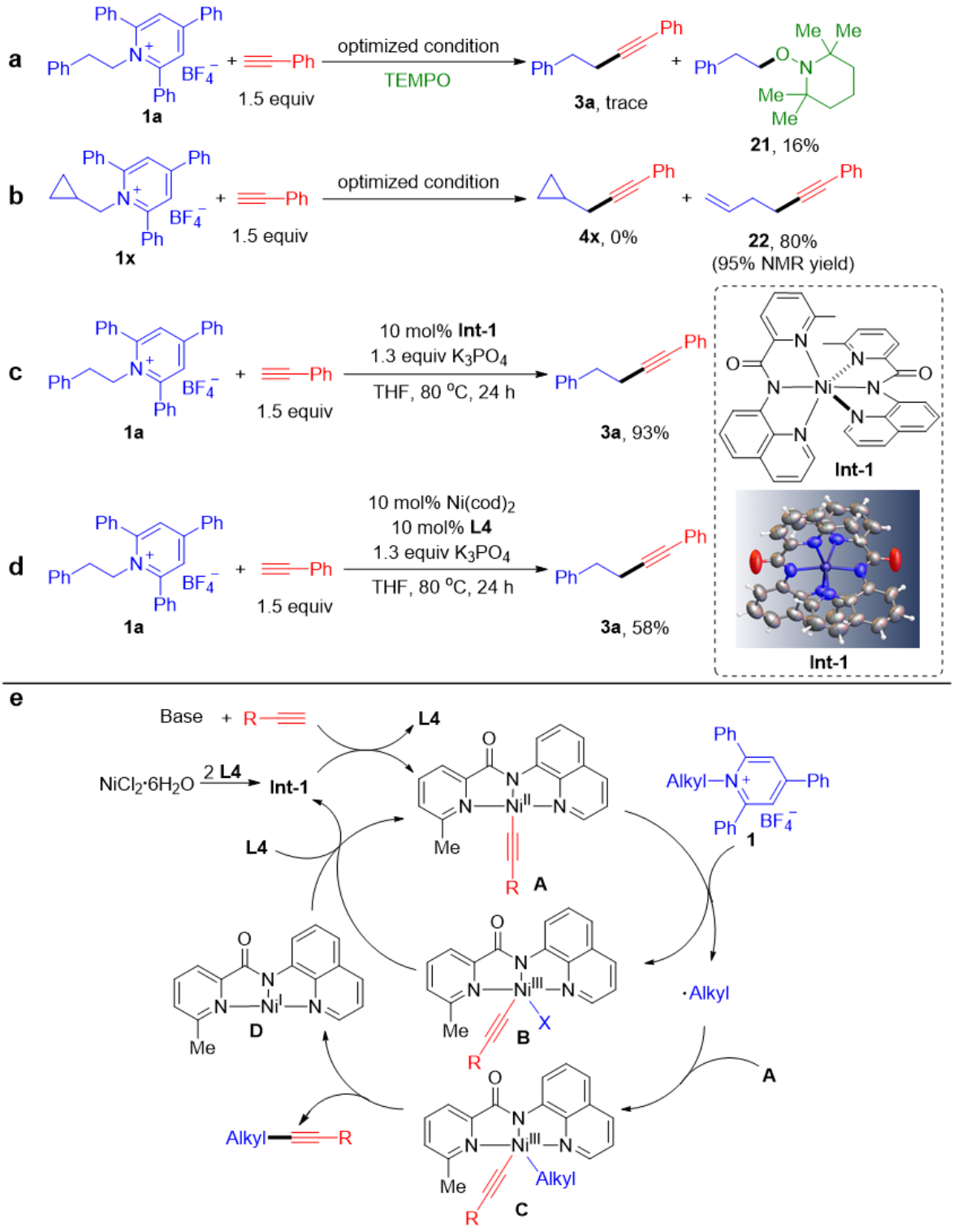


Figure 6

Preliminary mechanistic studies. a Radical trap experiment. b Radical clock experiment. c Catalytic transformation using Int-1 as catalyst. d Catalytic transformation using Ni(cod)2 as catalyst. e Proposed reaction mechanism.



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