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Catalytic stereoselective synthesis of all-carbon tetra-substituted alkenes *via Z*-selective alkyne difunctionalization†

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We report a Ni-catalyzed cascade reaction leading to the arylation of an alkyne-induced acyl migration and the formation of all-carbon tetra-substituted alkenes in good yields with exclusive *Z*-selectivity. This transformation involves the generation of a nucleophilic vinyl-Ni species through regioselective *syn*-aryl nickelation of the alkynes, followed by an intramolecular acyl migration. The steric and electronic properties of the phosphine ligands are crucial for achieving high regio- and stereocontrol in this migratory carbo-acylation process. The synthetic utility of the resulting *Z*-tetra-substituted alkenes is also demonstrated.

All-carbon tetrasubstituted olefins bearing four different carbon-based groups are ubiquitous motifs present in numerous natural products and have various applications from medicinal to materials chemistry (Fig. 1).[1–9] Due to their broad applications, significant research efforts are focused on developing general protocols for the challenging stereoselective synthesis, particularly for acyclic structures.[8,10–16] While strategies exist for synthesizing stereo defined *E*-alkenes, their thermodynamically less stable *Z*-isomers remain considerably more challenging. Achieving *Z*-alkenes with four distinct carbon-based substituents and an adjacent reactive functionality remains a formidable challenge.

Classical methods for forming carbon–carbon double bonds include carbonyl olefinations such as the Wittig reaction and its variants (*e.g.*, Julia, Peterson, McMurry, and Horner–Wadsworth–Emmons reactions), as well as metathesis reactions, elimination processes, and additions to triple bonds (Fig. 2a).[17–20] These methods are effective for producing di- or trisubstituted alkenes; however, they typically yield mixtures of stereoisomers when applied to tetrasubstituted alkenes.[11]

Additionally, their efficiency diminishes when faced with the high steric demands of tetra-substituted alkenes, making the selective synthesis of these structures a key area of research, particularly over the past years. An alternative approach involves the stereoselective insertion of two carbon-based groups across a C–C triple bond, either in a stepwise manner or through multicomponent strategies, offering a promising route for the synthesis of complex alkenyl products.[21–28] However, a major limitation in these transformations is the challenge of achieving regioselectivity, especially with alkynes that have substituents of similar steric or electronic properties. Therefore, developing a general method that enables the synthesis of highly substituted alkene with precise regio- and stereocontrol is crucial for expanding their synthetic utility. A commonly employed method for synthesizing tetrasubstituted alkenes, particularly those with four distinct functional groups, involves the carbometalation of internal alkynes to generate trisubstituted alkenyl metal

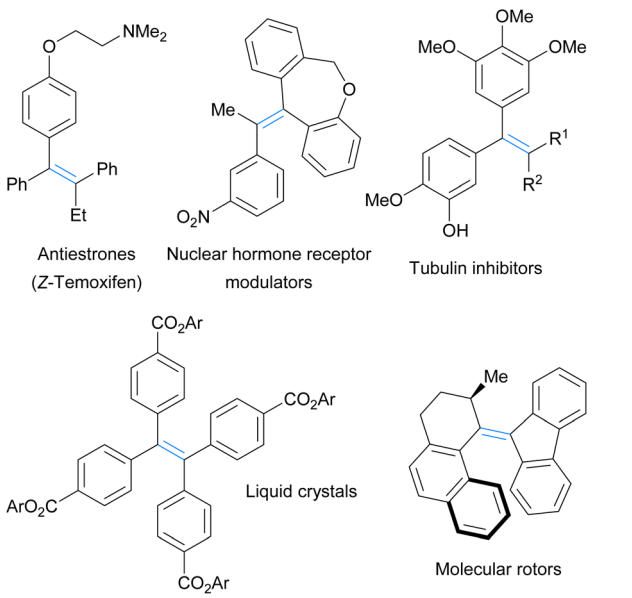

Fig. 1 Current applications for all-carbon tetra-substituted alkenes.

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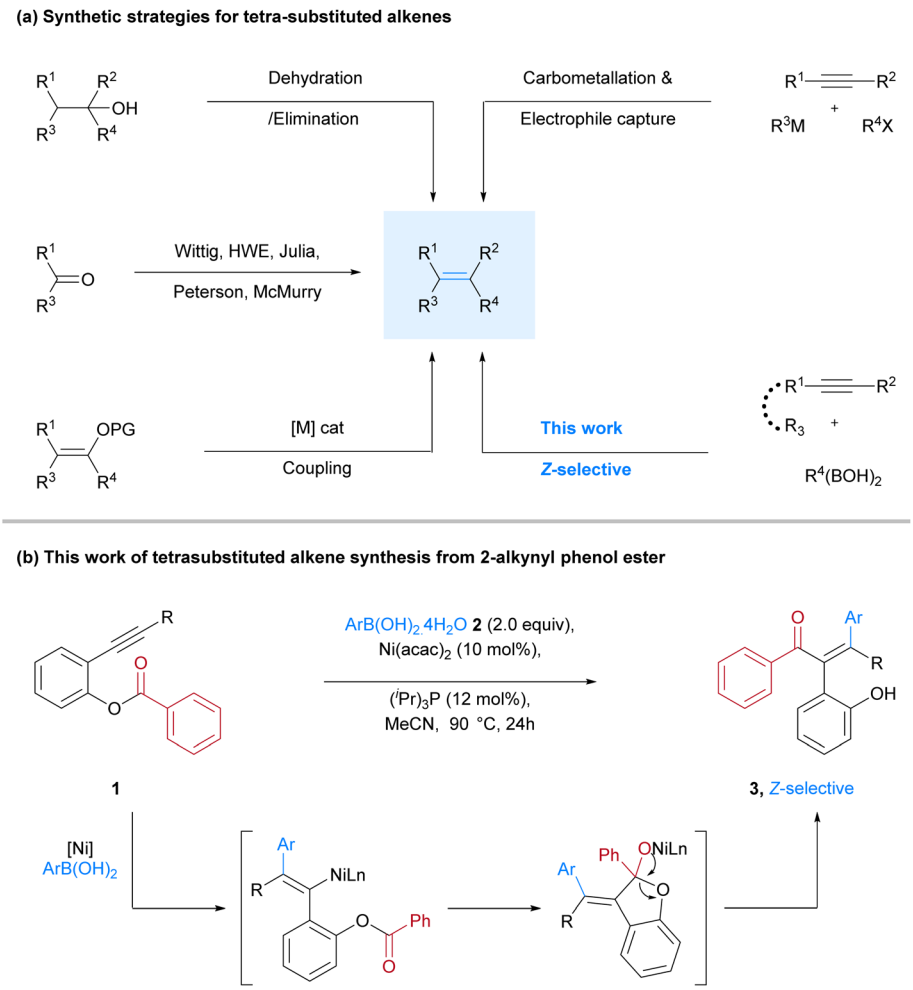
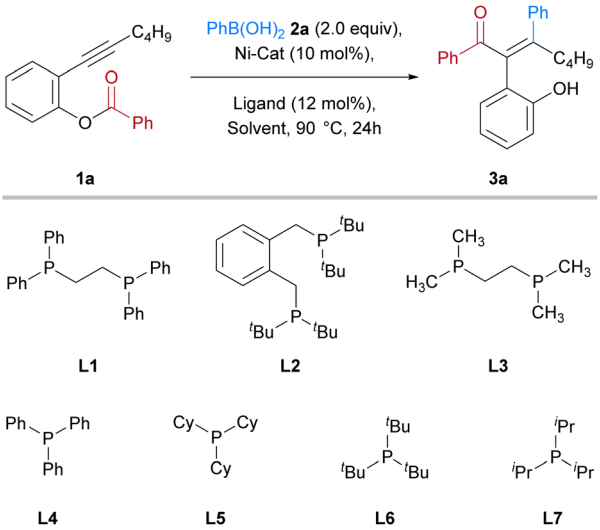


Fig. 2 (a) Synthetic strategies for multi-substituted alkenes; (b) nickel-catalyzed stereoselective synthesis of all-carbon tetra-substituted alkenes *via* *Z*-selective alkyne difunctionalization

nucleophiles. These intermediates then react with different electrophiles, often through transition metal-catalyzed cross-coupling processes.[21,25–42] Intramolecular capture, particularly in the form of arylative cyclization, occurs readily, facilitating the formation of cyclic scaffolds with good efficiency.[43–47] Prompted by these reports and by our continuing research interests in nickel-catalyzed transformations,[48–52] we envisioned that by using alkyne-tethered phenolic ester substrate, regioselective *syn*-aryl nickelation of an alkyne would generate nucleophilic vinyl Ni [II] species that may undergo nucleophilic addition to the carbonyl carbon of tethered ester group (Fig. 2b).[47,53,54] We anticipated that the careful choice of bulkier ligands[55–66] could assist in the C–O bond cleavage of the intermediate which would result in subsequent intramolecular acyl group migration[67] and formation of tetrasubstituted alkene products in a stereoselective manner (Fig. 2b). Herein, we describe the successful development of a nickel-catalyzed tandem alkyne hydroarylation acylation strategy, which proceeds with complete *Z*-selectivity and high regioselectivity to produce a variety of tetra-substituted alkene products in good-to-excellent yields. The key to the success of this method is the use of Ni-catalysts with bulky monodentate phosphine ligands.

We began our study by reacting 2-hexynyl phenol ester **1a**, synthesized in two steps from 2-iodophenol, with phenyl boronic acid **2a** using various nickel catalysts in acetonitrile at 90 °C (Table 1). Notably, when using $Ni(acac)_2 \cdot 4H_2O$ in combination with the bidentate phosphine ligand 1,2-bis(diphenylphosphino)ethane (**L1**), the desired alkene product **3a** was obtained with high stereoselectivity, achieving a 57% yield (Table 1, entry 1). Analysis of the purified reaction mixture by ^1H NMR spectroscopy confirmed the formation of the expected tetrasubstituted alkene **3a** with excellent *Z*-selectivity. The choice of the ligand had a significant effect on the reactivity and selectivity of the transformation.[68–71] Systematic studies of various bidentate and monodentate ligands revealed that the use of bulkier monodentate ligands afforded better yield and selectivity (Table 1, entries 1–7). Among the ligands tested, triisopropylphosphine ligand (**L7**) demonstrated the highest

Table 1 Optimization of nickel-catalyzed aryl-acylation of alkynes[a]



Entry	Ni-catalyst	Solvent	L	Yield[b,c] (%)	$Z:E$
1	$Ni(acac)_2 \cdot 4H_2O$	MeCN	**L1**	57	99 : 1
2	$Ni(acac)_2 \cdot 4H_2O$	MeCN	**L2**	52	99 : 1
3	$Ni(acac)_2 \cdot 4H_2O$	MeCN	**L3**	39	95 : 5
4	$Ni(acac)_2 \cdot 4H_2O$	MeCN	**L4**	52	96 : 4
5	$Ni(acac)_2 \cdot 4H_2O$	MeCN	**L5**	80	99 : 1
6	$Ni(acac)_2 \cdot 4H_2O$	MeCN	**L6**	87	99 : 1
7	**$Ni(acac)_2 \cdot 4H_2O$**	**MeCN**	**L7**	**90[c]**	**99 : 1**
8	$Ni(OAc)_2 \cdot 4H_2O$	MeCN	**L7**	84	99 : 1
9	$Ni(ClO_4)_2 \cdot 6H_2O$	MeCN	**L7**	57	98 : 2
10	$NiBr_2 \cdot 3H_2O$	MeCN	**L7**	62	98 : 2
11	$Ni(COD)_2$	MeCN	**L7**	86	98 : 2
12	$Ni(acac)_2 \cdot 4H_2O$	Dioxane	**L7**	66	99 : 1
13	$Ni(acac)_2 \cdot 4H_2O$	THF	**L7**	62	99 : 1
14	$Ni(acac)_2 \cdot 4H_2O$	MeCN : 2-Me THF	**L7**	78	99 : 1
15	$Ni(acac)_2 \cdot 4H_2O$, K_2CO_3, $CsCO_3$	MeCN	**L7**	0	NA

[a] All reaction were carried out on a 0.2 mmol scale. [b] Yield determined by GC using dodecane as an internal standard. [c] Isolated yield.

reactivity and was selected for further investigation due to its cleaner reaction profile and excellent *Z*-selectivity (99 : 1) (Table 1, entry 7). We also evaluated various commercially available Ni-salts in combination with ligand **L7**, which yielded comparable reactivity (entries 8–11). However, using Ni(0) in place of Ni(II) led to slightly reduced reactivity and selectivity (entry 11). Acetonitrile (MeCN) emerged as the optimal solvent among those tested (entries 12–14). Control experiments confirmed that both the Ni complex and ligand were crucial for the reaction's success. Reducing the catalyst loading to 5 mol% had a detrimental effect on the reaction, resulting in lower yields and longer reaction times. The use of bases, typically used for coupling reactions, resulted in no product formation as the substrate is prone to ester hydrolysis (entry 15). Changing the substrate to the corresponding acetylated phenol resulted in the formation of the corresponding benzofurane product (*vide infra*).

With the optimized conditions established, we next explored the scope of the aryl acylation reaction of alkynes. We began by examining the suitability of various aryl boronic acids (**2**) as coupling partners (Fig. 3). Generally, the steric and electronic properties of the phenyl ring in *para*- and *meta*-substituted aryl boronic acids did not significantly influence the reaction yield. Both electron-rich and electron-deficient aryl boronic acids, featuring substituents such as methyl, *t*-butyl, halogen, trifluoromethyl, *o*-phenoxy, and cyano-groups, successfully reacted with *o*-hexynyl phenol ester **1a**, producing the corresponding rearranged products **3** in good yields (**3a–3l**). In most cases, boronic acids bearing electron-donating groups (*e.g.*, **3j**) resulted in slightly higher yields compared to those

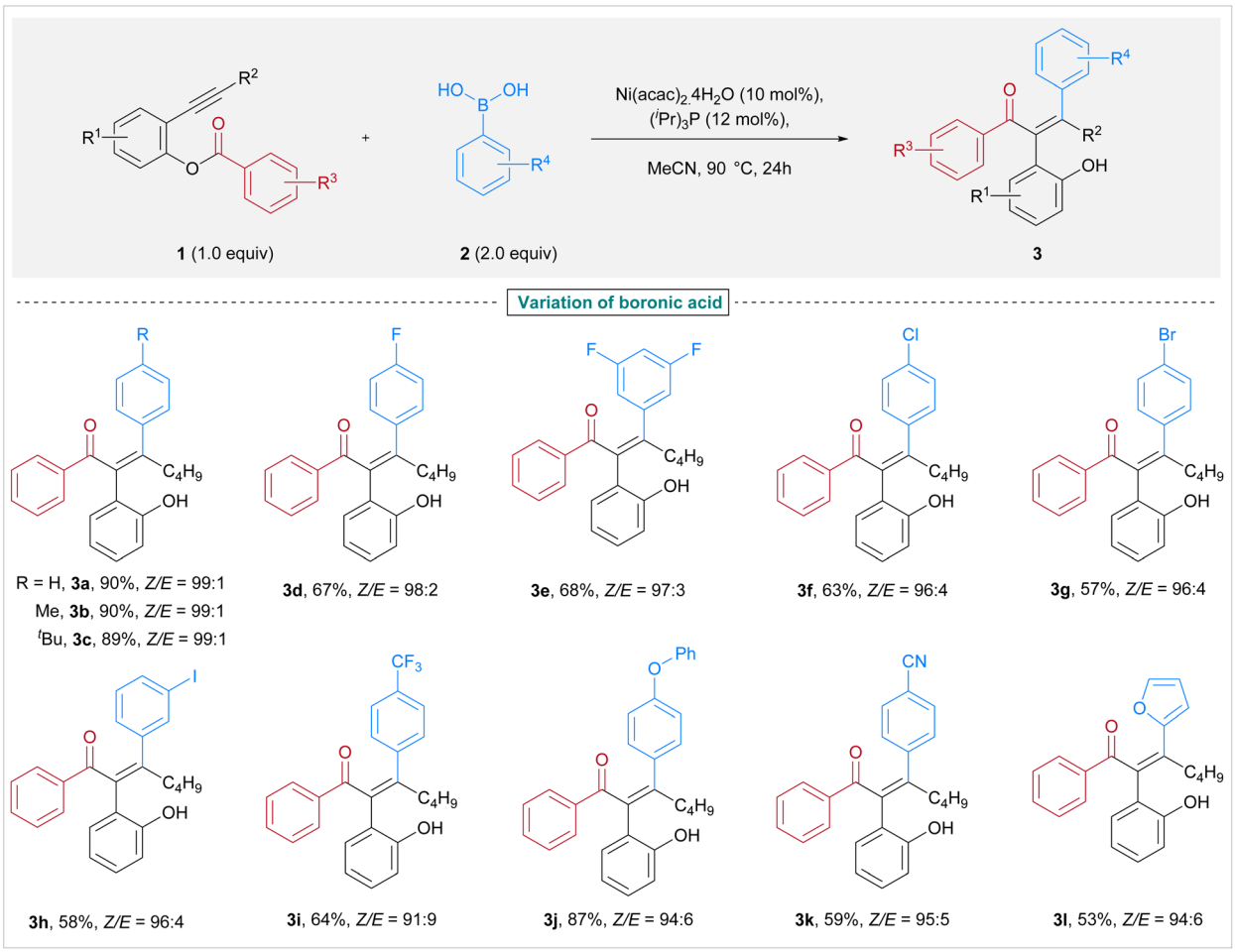


Fig. 3 Scope of Ni-catalyzed aryl-acylation of alkynes using boronic acids.

with electron-withdrawing groups (*e.g.*, **3k**). Additionally, hetero-aromatic boronic acids proved compatible with this reaction, delivering a lower yield of the desired product (**3l**). We then explored the generality of this Ni-catalyzed aryl acylation reaction with 2-alkynyl phenol esters **1**, featuring various ester groups in (Fig. 4). Variations in the ester group on the phenol did not significantly impact the reaction efficiency. The reaction conditions were well-tolerated with a range of ester groups, including strained cyclopropyl (**3n**), 4-methyl (**3m**), naphthyl (**3o**), *p*-chloro (**3p**), *o*-bromo (**3q**), pentafluoro (**3r**), electron-donating groups such as methoxy (**3s**) and *N*,*N*-dimethylamine (**3t**), as well as electron-withdrawing groups like nitro (**3v**). Additionally, heteroatomic thiophene-containing esters (**3w**) were also compatible. Notably, the reaction was not restricted to simple esters; phosphoryl esters also yielded the desired product, albeit as a *Z*/*E* mixture (77 : 23) (**3x**). Next, we investigated the reaction scope with variations in the alkyne side chain (R^2). When 2-alkynyl phenol ester **1** containing a shorter alkyl chain substituent on the alkynyl moiety was employed, the reaction afforded a single isomer, yielding 76% of the corresponding tetrasubstituted alkene (**3y**) as a white solid. The structure of (**3y**) was unambiguously confirmed through X-ray crystallographic analysis (CCDC: 2110836).

Reactions of **1**, bearing longer alkyl chain, heteroatomic, and phenyl group substituents on the alkyne moiety, also resulted in the formation of the corresponding tetra-substituted alkenes (**3z–3ac**) in high yields. We also examined substrates with various substituents on the phenol ring, including phenyl, methyl ester, fluoro, and chloro groups. In all cases, the expected products were obtained in good to excellent yields (**3ad–3ag**).

Notably, expanding the scope of the *syn*-arylative rearrangement to include an amide moiety in place of the ester also proved successful under standard conditions, yielding the corresponding alkene derivative (**3ah**) in 52%. Furthermore, the scalability of our protocol was exemplified by the aryl-acylation of 2-hexynyl phenol ester **1a** on a 1.2-gram scale affording 84% of *Z*-alkene **3b**. We next showcased the synthetic utility of the products through a series of post-functionalization reactions (Fig. 5). PTSA-catalyzed dehydrative cyclization of (**3b**) yielded the corresponding 2,3-difunctionalized benzofuran[47,72,73] **4** in good yield. Treatment of **3b** with $LiAlH_4$ led to the selective reduction of the ketone moiety, providing the reduced product

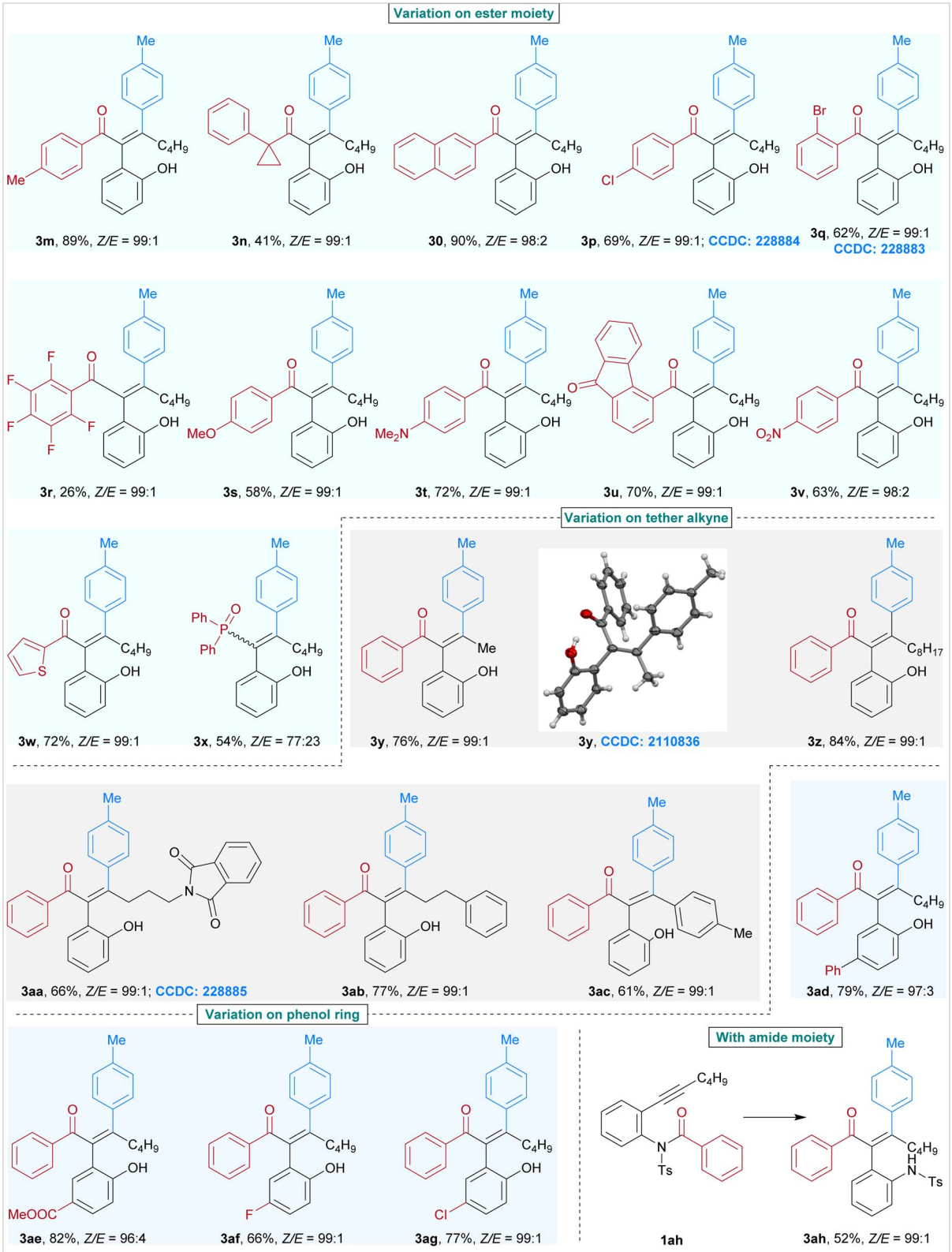


Fig. 4 Scope of variation in esters, tethered alkynes, and phenolic groups.

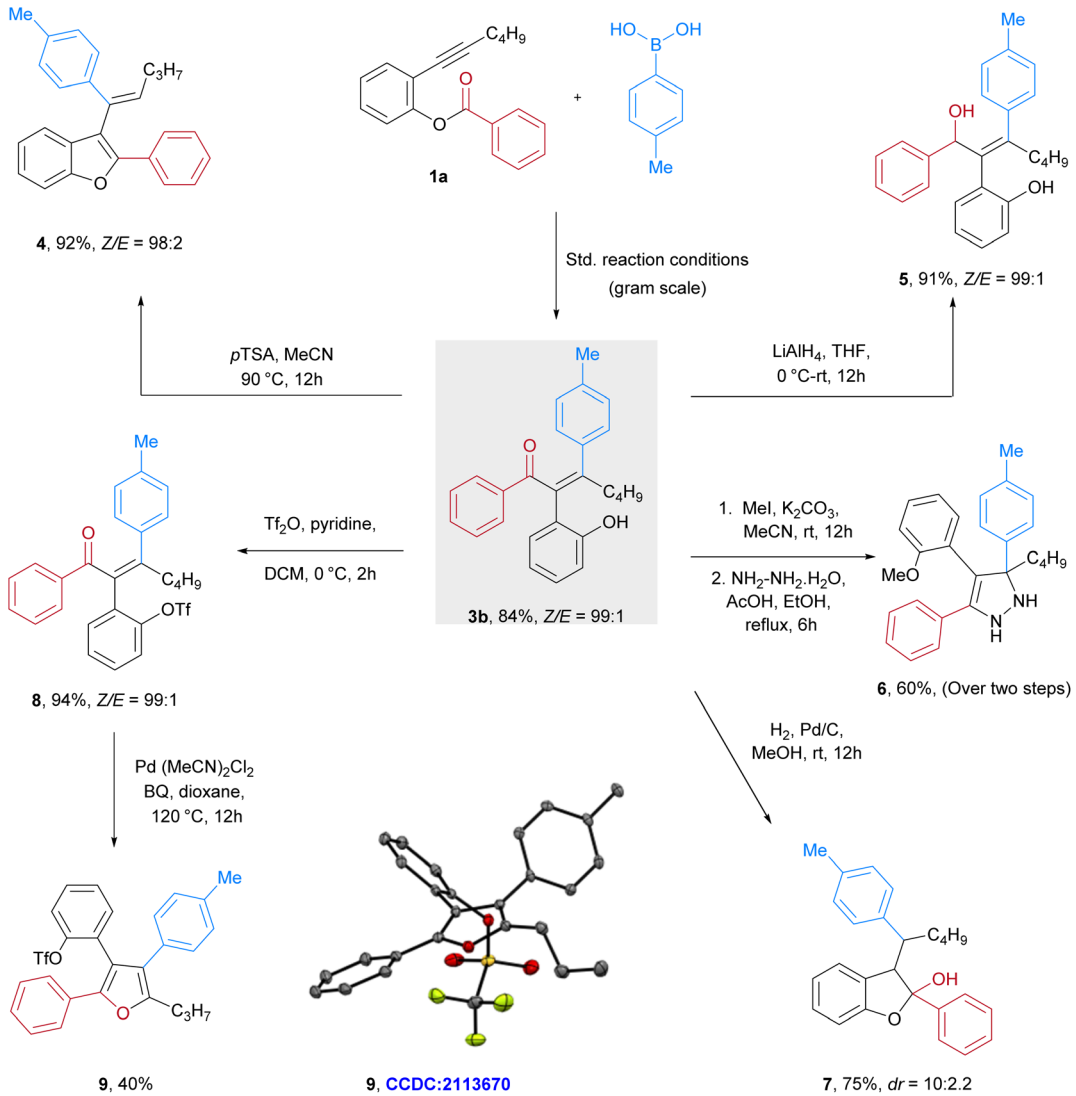


Fig. 5 Chemical transformations of **3b** to synthetically valuable building blocks.

in excellent yield. We then aimed to transform **3b** into the highly functionalized pyrazole structure **6** through a selective five-membered ring cyclization using hydrazine hydrate. Additionally, Pd/C-catalyzed hydrogenation of **3b** produced substituted benzofuran-2-ol **7** in 75% yield. Additionally, we leveraged the phenol group on **3b** as a functional handle, converting it into the corresponding triflate **8** in 94% yield. This triflate was subsequently subjected to a Pd-catalyzed oxidative coupling reaction. Interestingly, an unexpected transformation occurred and yielded a tetrasubstituted furan **9**. The structure of the furan **9** was confirmed by X-ray crystallographic analysis (CCDC: 2113670). On the basis of the literature reports[47,53,54,57,74,75] and the experimental results we propose a catalytic cycle (Fig. 6). Initially, the nickel complex undergoes a transmetalation with boronic acids **2a** to form the aryl-Ni intermediate **A**, which regioselectively adds in *syn* fashion across the alkyne in **1a** to form the alkenyl-Ni species **B**. The organo-nickel intermediate **B** subsequently adds to the carbonyl carbon of the ester moiety that results in cyclic intermediate **C**. Finally, the C–O bond cleavage with ring opening leads to the formation of alkene product **3a** with acyl group migration along with the regeneration of the Ni complex.

In summary, we have developed an unconventional Ni-catalyzed approach for the synthesis of tetrasubstituted alkenes from alkynes and boronic acids. This method enables a one-step difunctionalization of internal alkynes through the simultaneous addition of both aryl and acyl groups across triple bonds, providing streamlined access to tetrasubstituted alkenes with high regio- and stereocontrol; challenging to achieve with conventional methods. The process exhibits excellent functional group compatibility and broad synthetic applicability, even in complex molecular settings. Its practicality is further demonstrated by gram-scale synthesis and diverse post-functionalization of complex molecules. This straightforward protocol opens new avenues in multi-substitution chemistry for acyclic, all-carbon tetrasubstituted *Z*-olefinic products.

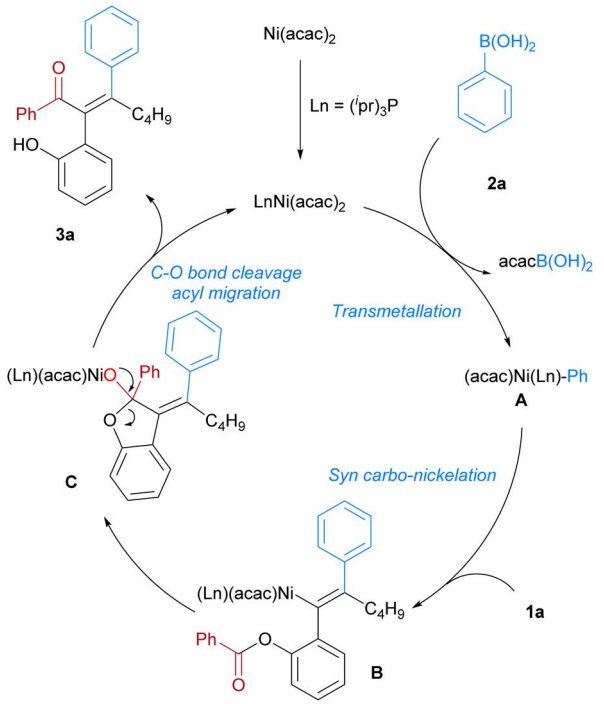


Fig. 6 Plausible mechanism of the Ni-catalyzed aryl-acylation of alkynes.

Data availability

Experiment procedures, characterization of the new compounds are available in the ESI.†

Author contributions

P. S. S., V. S. S., and M. R. conceived and designed the experiments. P. S. S., V. S. S. conducted the experiments, analyzed the data and wrote the manuscript, while M. R. supervised the project and the manuscript.

Conflicts of interest

The authors declare no competing financial interests.

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