Non-Stabilized Vinyl Anion Equivalents from Styrenes by N-Heterocyclic Carbene Catalysis and Its Use in Catalytic Nucleophilic Aromatic Substitution

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Supporting Information Placeholder

ABSTRACT: A protocol for the catalytic nucleophilic activation of unactivated styrenes is reported, which enables the generation of a non-stabilized alkenyl anion equivalent as a transient intermediate. In the reaction, N-heterocyclic carbenes add across styrenes to generate ylide intermediates, which can then be used in intramolecular nucleophilic aromatic substitution reactions of aryl fluorides, chlorides and methyl ethers. The method allows for the straightforward access to complex polyaromatic compounds.

Originating from thiamine-catalyzed Benzoin condensation reactions, N-heterocyclic carbene (NHC) catalysis has become a powerful tool in organic synthesis, enabling the generation of transient nucleophiles that are otherwise difficult to access.[1] The most common mode of activation by NHCs involves the formation of a Breslow intermediate from an aldehyde, which allows the electrophilic carbonyl carbon to serve as a nucleophile (*i.e.*, the equivalent of an acyl anion) (Figure 1a, top).[2] The activation of α,β-unsaturated carbonyl compounds is also possible, since a deoxy-Breslow intermediate is generated, which can serve as a vinyl anion equivalent stabilized by a β-carbonyl group (Figure 1a, bottom).[3] As represented by these examples, NHCs can activate a series of carbonyl-based electrophiles that are susceptible to nucleophilic addition by NHCs. If this type of nucleophilic activation by NHCs could be applied to non-carbonyl, less polarized unsaturated bonds, *i.e.*, those of styrenes, it would allow for the *catalytic* generation of a non-stabilized vinyl anion equivalent **A** (Figure 1b). In fact, Glorius and Matsuoka independently reported that the dimerization of electron-deficient styrenes can be catalyzed by a triazole-based NHC, likely through the formation of an ylide intermediate similar to **A** (Figure 1c).[4] However, this dimerization is the only reported example of the activation of styrene derivatives by an NHC, and the synthetic potential of intermediate **A** remains virtually unexplored to date. Herein, we report on the nucleophilic activation of unactivated styrenes by an NHC and its use in catalytic S_NAr reactions (Figure 1d).

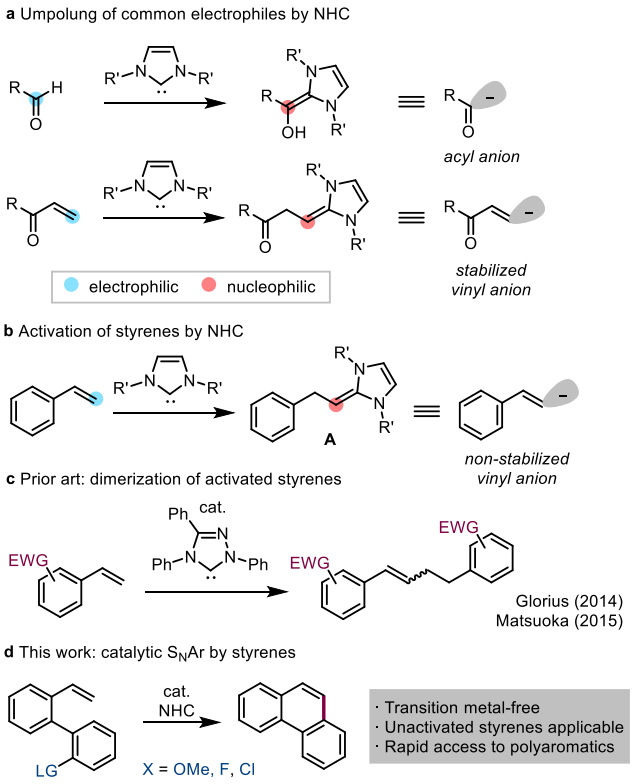

Figure 1. Nucleophilic Activation of Organic Electrophiles by NHC Catalysis

In the triazole-based NHC-catalyzed dimerization of *activated* styrenes, it was reported that a styrene dimerization product was not formed, even though a styrene-NHC adduct was obtained in modest yield (45%) when stoichiometric amounts of these components were reacted at 160 °C.[4a] These observations indicate that, enhancing the nucleophilicity of, not only the NHC itself, but also the ylide intermediate generated by the reaction of NHCs with styrenes is critical for the successful catalytic processes via nucleophilic activation of unactivated styrenes. Based on these considerations, we initially evaluated the nucleophilic indices[5] of the ylide intermediates that would be expected to be formed by the reaction of a series

of NHCs with styrene (Figure 2a). The findings indicated that ylides **A2**–**A4**, which are generated from imidazole-based NHCs, are more strongly nucleophilic than the triazole-based NHC (i.e., **A1**), with the ylide **A4** exhibiting the highest nucleophilic index value. We therefore examined the reaction of the unactivated styrene derivative **1a** with a 1.0 equiv of *N*-cyclohexyl-substituted NHC (*i.e.*, ICy). The postulated ylide intermediate **A4'** could be isolated in its protonated form **B** in 72% yield (Figure 2b). The successful formation of an ylide intermediate from an unactivated styrene prompted us to examine this species in catalytic intramolecular S_NAr reactions.[6] After several experiments (see SI for the details of reaction development), we established that the reaction of a styrene bearing an *ortho* fluorophenyl group (i.e., **1b**) can be quantitatively converted into phenanthrene **2b** by heating at 160 °C with a catalytic amount of ICy and K_2CO_3 (Figure 1c). This reaction represents the first catalytic S_NAr reaction in which styrenes are used as a latent nucleophile. Despite the relatively high reaction temperature, the reaction was clean with no byproducts being produced and no dimerization of **1b** was observed.

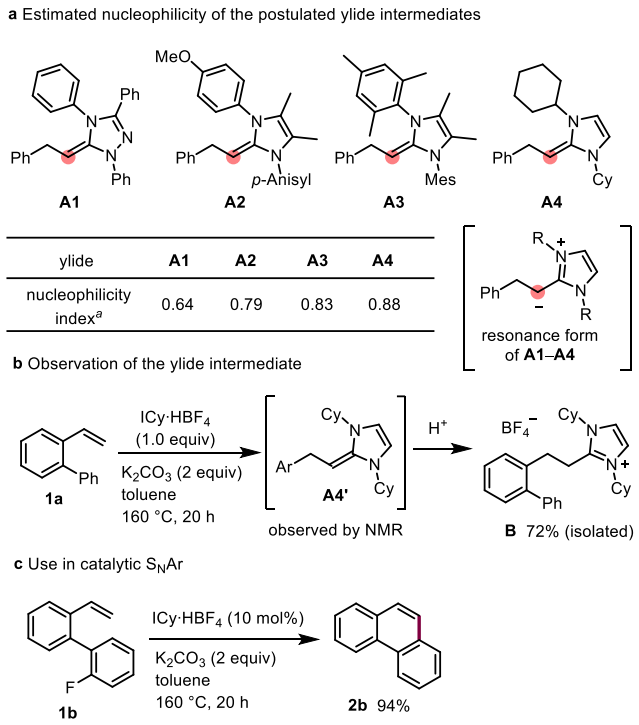

Figure 2. Theoretical and Experimental Investigations of the Ylide Formed from Styrene and NHC

[a]See ref 5 for details.

The NHC-catalyzed S_NAr can be applied to a range of styrene derivatives (Figure 3). With respect to the scope of the leaving group, chlorides (**1c**) and even a MeO group (**1d**) successfully participated in this catalytic cyclization reaction, highlighting the strong nucleophilicity of the ylide intermediate. Functional groups, including chlorides (**1f**, **1s**), fluorides (**1m**, **1r**), ketones (**1g**) and esters (**1l**), were also found to be compatible in this reaction. The high nucleophilicity of the ICy-derived ylide intermediate allows even an electron-rich fluoride such as **1e** to efficiently participate in this S_NAr reaction under identical conditions. When electron-deficient aryl fluorides **1g** and **1h** were used as substrates, the use of ICy failed to afford the cyclized products, possibly because ICy directly attacked the aryl fluoride moiety, with the formation of a 2-arylated imidazolium salt.[7] This pitfall can be avoided by using a bulkier and less nucleophilic NHC catalyst (i.e., $IMxy^{Me}$),[8] which delivered the corresponding phenanthrene derivatives in good yields. Regarding the electronic nature of the styrene moiety, both electron-deficient (**1i**) and electron-rich (**1j**) substrates successfully participated in this NHC-catalyzed S_NAr reaction. This method was also found to be applicable to the cyclization of π-extended (**1p**) and heteroaromatic (**1q**) substrates. An *ortho* MeO group is selectively substituted in preference to halide groups at the other position (i.e., **1r**, **1s**), indicating that an entropic factor overrides the innate reactivity of the leaving group. Although styrene derivatives bearing two or more substituents on the alkene moiety failed to participate in this reaction, the 1,1-diarylethene derivative **1t** could be cyclized successfully, presumably because the presence of an additional aryl group stabilizes the anionic charge that is developed by the initial addition of NHC. Moreover, the 1,3-diene derivative **1u** can also be activated by NHC and cyclized to form naphthalene **2u**, a reaction that likely proceeds via the ylide intermediate **C**, which can serve as a 1,3-dienyl anion equivalent. Superficially, one might conclude that the NHC-catalyzed S_NAr of styrene derivatives is similar to a Pd-catalyzed intramolecular Mizoroki-Heck reaction. However, 6-endo products are not formed in the Pd-catalyzed reactions of these styrene derivatives, but, rather, 5-exo products (*i.e.*, fluorene derivatives) are produced and, therefore, the Mizoroki-Heck reaction is complementary to our NHC-catalyzed S_NAr (see SI for details).

The mechanism responsible for the reaction was investigated theoretically using DFT calculations (Figure 4). The nucleophilic addition of ICy to styrene **1b** occurs via **TS1** with an activation barrier of 32.9 kcal/mol, which is in agreement with the experimental observation that the reaction needs to be heated at 160 °C for the reaction to reach completion. The resulting **IM1** isomerizes to the more stable ylide **IM3** by 1,2-proton migration via a stepwise deprotonation/protonation sequence, rather than a direct concerted 1,2-migration mechanism.[2a,9] The subsequent nucleophilic aromatic substitution was found to proceed in a concerted manner via **TS4** without generating any discrete intermediate.[6,10] The β-elimination of ICy from **IM4** occurs through a E1cB-type mechanism via **IM6**. The initial 1,2-addition of ICy to styrene **1b** requires the highest energetic barrier, and therefore is most likely the rate-determining step of this reaction. The computed energy profiles also support the absence of a primary kinetic isotope effect for hydrogens at the vinylic positions (k_H/k_D = 1.02, see SI for details).

This catalytic S_NAr protocol serves as a reliable method for the construction of polycyclic frameworks via multiple cyclization processes. For example, the Suzuki-Miyaura coupling of the dibromide **3** with (2-vinylphenyl)boronic acid (**4**) affords the double cyclization precursor **5**, which can readily be converted into benzo[k]tetraphene (**6**) by treatment with ICy (Figure 5a). Similarly, the dibromide **7** can be arylated to form another double cyclization precursor **8**, which undergoes a selective catalytic S_NAr reaction, to provide dibenzo[a,l]tetracene (**9**, Figure 5b). It should be noted that the NHC-catalyzed S_NAr reaction described here permits the use of poor leaving groups, such as F or OMe, which are unreactive under standard cross-coupling conditions. As a result, the synthesis of biaryl units bearing these groups is straightforward, as shown in Figure 5a and b. Multiple cyclizations that proceed via a cascade process are also possible. When an aryl fluoride bearing two alkene moieties, i.e., **10**, was reacted under ICy-catalyzed conditions, a dihydrobenzo[g]chrysene skeleton could be constructed in a one pot reaction (Figure 5c). This example demonstrates that the styrene-derived ylide intermediate is sufficiently nucleophilic to add across an internal alkene, when it is tethered to the substrate. Moreover, this catalytic S_NAr reactions is scalable, as evidenced in the synthesis of **13** in a 1.8 gram quantity (Figure 5c). The remaining methoxy group in **13** can serve both as a handle for the

introduction of an additional cyclization unit at the *ortho* position and as a leaving group in the second cyclization, thus allowing for the synthesis of picene (**14**). The examples shown in Figure 5 demonstrate the powerful nature of this styrene activation strategy in the selective construction of polyaromatic skeletons.

In summary, we report on the development of a strategy for the nucleophilic activation of styrenes using NHCs and the successful application to intramolecular S_NAr reactions. The transient ylide intermediate is sufficiently nucleophilic to substitute for tethered aryl fluorides, chlorides and methoxides. This protocol was shown to be useful for the synthesis of a series of polyaromatic compounds. Further applications of this catalytic nucleophilic activation of styrenes and other alkenes is currently underway in our laboratory.

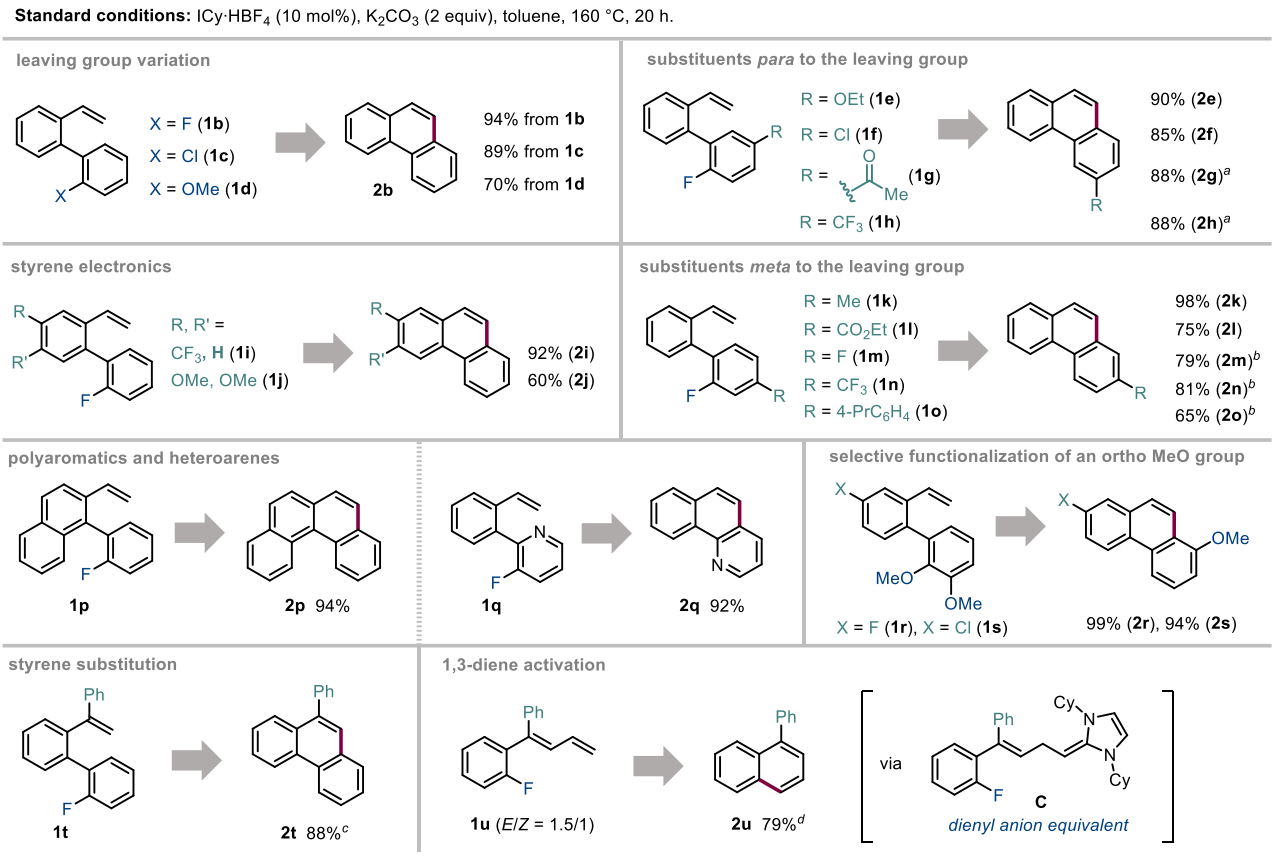

Figure 3. Scope of the NHC-Catalyzed S_NAr Using Styrene Derivatives

[a]Using IMxy^{Me}·HCl (30 mol%), instead of ICy·HBF$_4$, and CsF, instead of K_2CO_3. [b]Using ICy·HBF$_4$ (20 mol%). [c]Using ICy·HBF$_4$ (30 mol%) for 48 h. [d]Using ICy·HBF$_4$ (30 mol%).

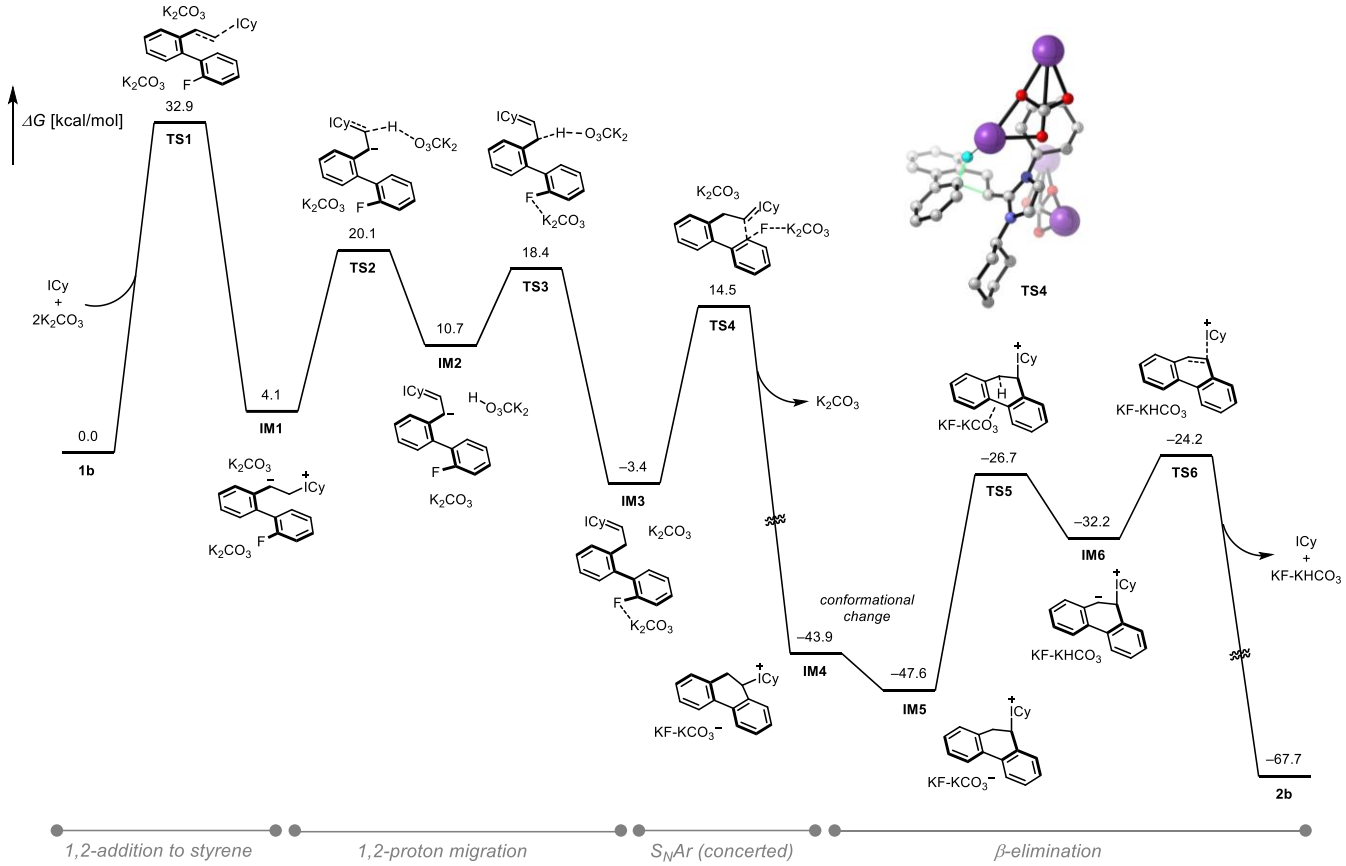

Figure 4. Computed Energy Profiles of the ICy-Catalyzed S_NAr of **1b**[a]

[a]DFT calculations at the M06-2X/6-311+G**, PCM (toluene)//M06-2X/6-31G*, PCM (toluene) level of theory.

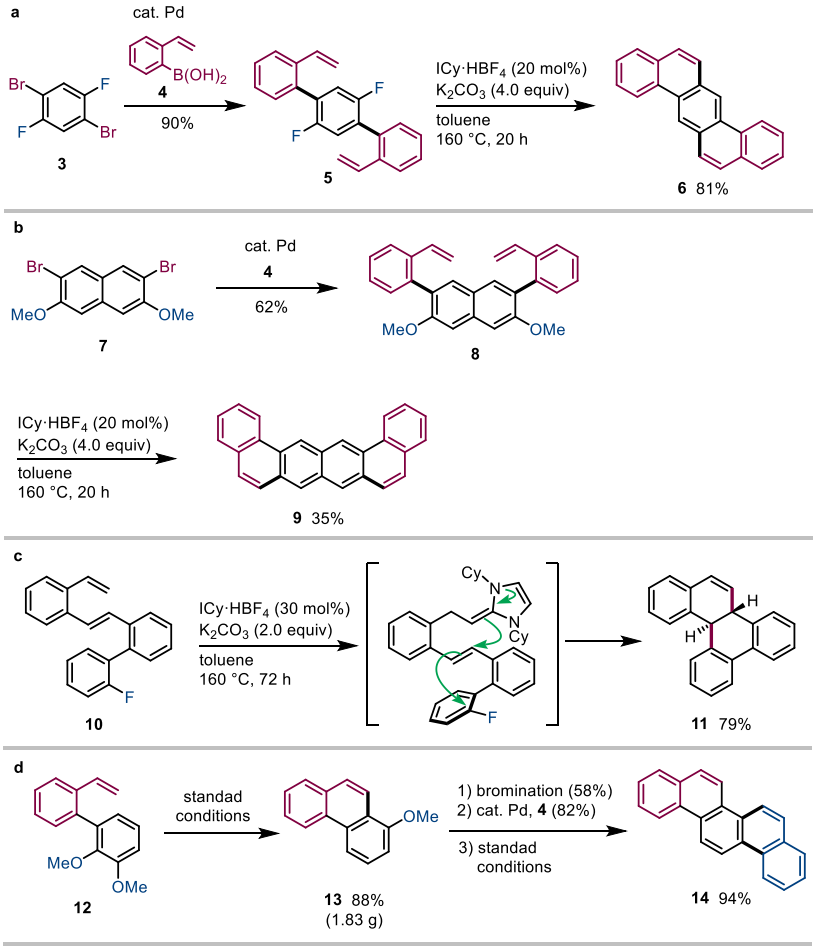

Figure 5. Rapid Access to Polyaromatics

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Detailed experimental procedures, characterization of new compounds and computational details (PDF)

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was supported by Scientific Research on Innovative Area “Hybrid Catalysis” (JP20H04818) from MEXT, Japan. We also thank the Instrumental Analysis Center, Graduate School of Engineering, Osaka University, for their assistance with HRMS.

Supporting Information is available on http://dx.doi.org/########.

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