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Reductive hydrobenzylation of terminal alkynes *via* photoredox and nickel dual catalysis†

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A photoredox/nickel dual catalyzed reductive hydrobenzylation of alkynes and benzyl chlorides by employing alkyl amines as a stoichiometric reductant is described. This synergistic protocol proceeds *via* Markovnikov-selective migratory insertion of an alkyne into nickel hydride, followed by cross-coupling with benzyl chloride, providing facile access to important 1,1-disubstituted olefins. This reaction enables the generation of nickel hydride by utilizing readily available alkyl amines as the hydrogen source. The mild conditions are compatible with a wide range of aryl and alkyl alkynes as well as chlorides.

Alkenes are ubiquitous in chemical synthesis, not only as important structural motifs in pharmaceuticals, agrochemicals, and natural products,[1] but also as versatile building blocks for numerous valuable transformations.[2] Therefore, the development of efficient methodologies for their synthesis has been extensively pursued. Among various synthetic strategies,[3] transition-metal-catalyzed hydrofunctionalization of simple and readily accessible alkynes represents one of the most efficient methods to synthesize substituted alkenes.[4] Impressive progress has been achieved in hydroarylation of alkynes;[5] nonetheless, catalytic hydroalkylation of alkynes remains underexplored and is highly sought after.

Migratory insertion of alkynes into metal hydride bonds followed by alkyl couplings represents an efficient approach for the catalytic hydroalkylation of terminal alkynes.[6,7] Notably, the Lalic group has developed a series of Cu–H enabled hydroalkylations of terminal alkynes with various alkyl electrophiles, allowing for the regio- and stereo-selective preparation of diverse alkenes.[6a,b,f,g] Despite impressive progress, these precedents are known to furnish 1,2-disubstituted alkenes with *anti*-Markovnikov selectivity, and rare examples of Markovnikov hydroalkylation of alkynes to forge 1,1-disubstituted alkenes, which are prevalent in biologically active compounds,[8] have been disclosed (Fig. 1).

In 2016, Fu and co-workers reported the first example of nickel-catalysed[9] hydroalkylation of terminal alkynes with alkyl iodides in the presence of silanes, affording 1,1-dialkyl alkenes with excellent Markovnikov selectivity.[7a] Migratory insertion of Ni–H into alkynes deters the regioselectivity, while the use of highly reactive iodides is required to facilitate the subsequent alkyl coupling. Additionally, silanes are typically employed as the stoichiometric reductants in these metal hydride-enabled hydroalkylation reactions.[7,8] It would be interesting to explore simple and abundant agents as the hydrogen source of metal hydride.[7c,10] Following our continuous interest in the area of photoredox/nickel dual catalysis,[11,12] we herein report a photoredox/Ni-catalyzed reductive hydroalkylation of

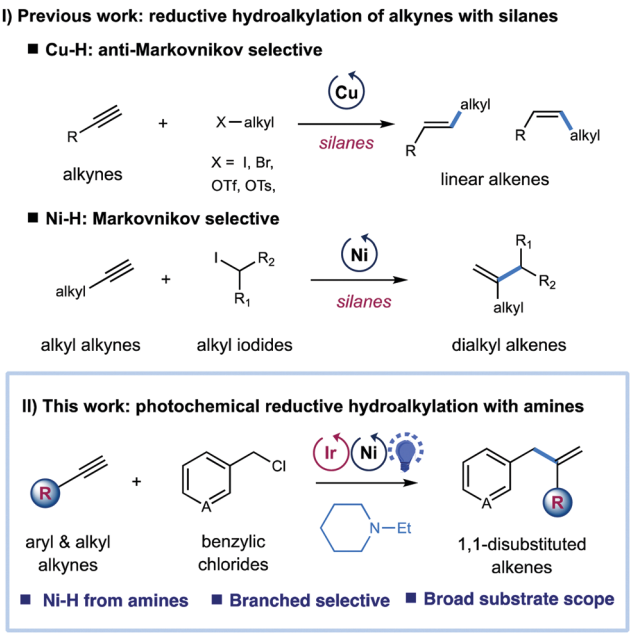

Fig. 1 Metal hydride-enabled reductive hydroalkylation of alkynes.

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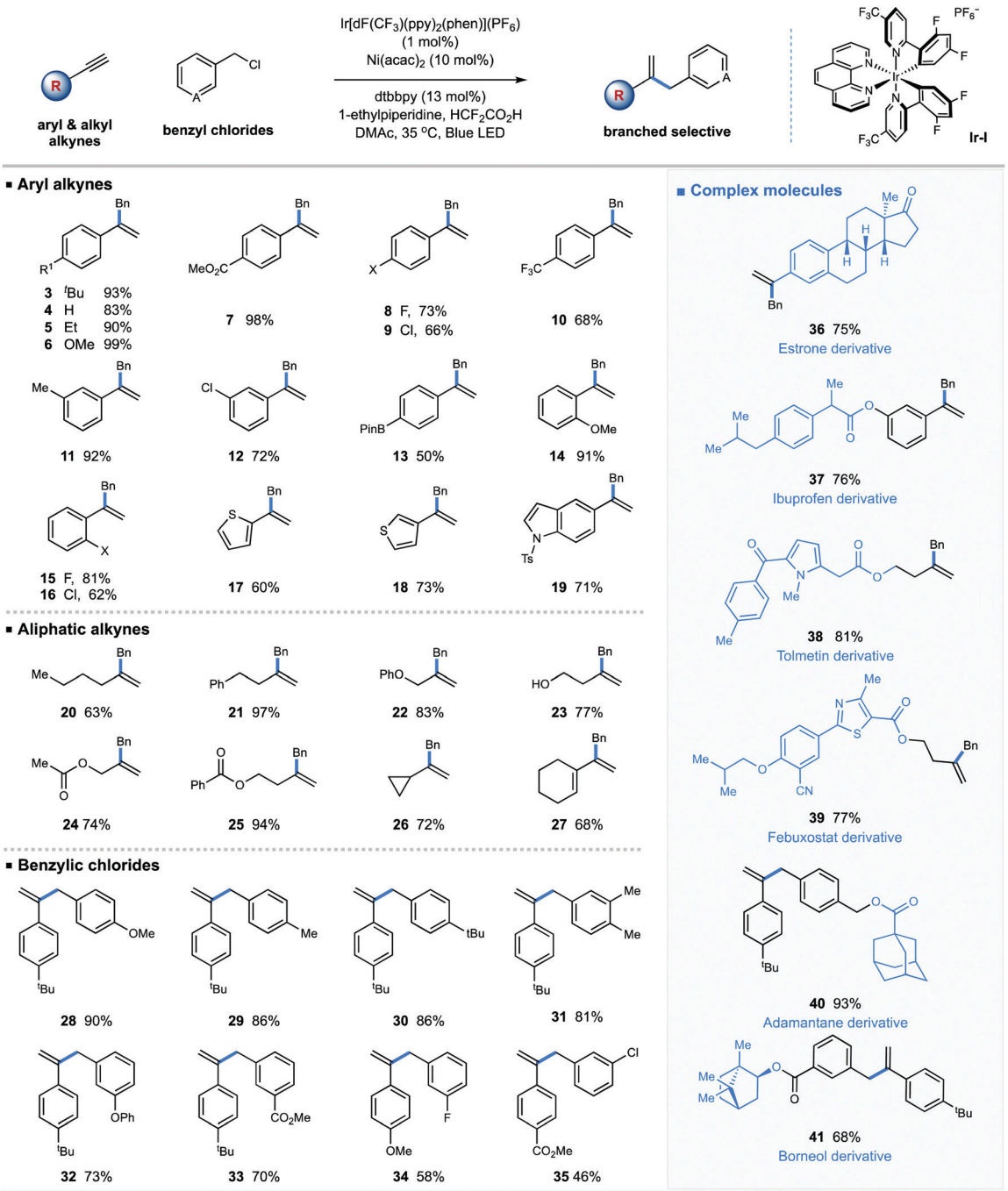
terminal alkynes and readily available benzylic chlorides with alkyl amine as the reductant, furnishing 1,1-disubstituted alkenes with Markovnikov selectivity. This photochemical reductive protocol enables the generation of nickel hydride from simple alkyl amines.[13] It should be noted that several examples of photoredox/nickel catalyzed hydroalkylations of alkynes with alkyl carboxylic acids or oximes have been previously disclosed, where migratory insertion of Ni–alkyl species is proposed.[7d,14]

We began our investigations by exploring the reductive hydroalkylation of aryl alkyne **1** with benzylic chloride **2** (see Tables S1–S6 in the ESI†). After careful optimizations, we found that a combination of Ir[dF(CF$_3$)(ppy)$_2$](Phen)PF$_6$, Ni(acac)$_2$, 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbbpy), 1-ethylpiperidine as the reductant, and difluoroacetic acid (HCF$_2$CO$_2$H) as the additive, with irradiation of the reaction mixture in DMAc with a 90 W Blue LED at 35 °C provided the optimal results, leading to the formation of the branched-selective product **3** in 93% isolated yield. Control



Scheme 1 Substrate scopes. Reaction conditions: Ir[dF(CF$_3$)(ppy)$_2$](Phen)(PF$_6$) (1 mol%), Ni(acac)$_2$ (10 mol%), dtbbpy (13 mol%), alkynes (0.2 mmol), benzyl chlorides (1.3 equiv.), HCF$_2$CO$_2$H (2.0 equiv.), 1-ethylpiperidine (3.0 equiv.), DMAc [0.025 M], 35 °C, 24 h. 90 W blue LEDs. Isolated yields.

reactions in the absence of photocatalyst, nickel catalyst, reductant, acid, or light disclosed that all these reaction parameters were required for this transformation to proceed, while a low yield of alkene **3** was still observed in the absence of ligand.

The use of 1-ethylpiperidine as the stoichiometric reductant proved to be optimal, since switching to other commonly employed alkyl amines (triethylamine, diisopropylethylamine, *etc.*) resulted in significant decreases in reaction efficiency. Similar to previous reports,[15] we also found that an acidic additive has an intriguing effect on this transformation, where difluoroacetic acid gave much higher yields than trifluoroacetic acid and formic acid.

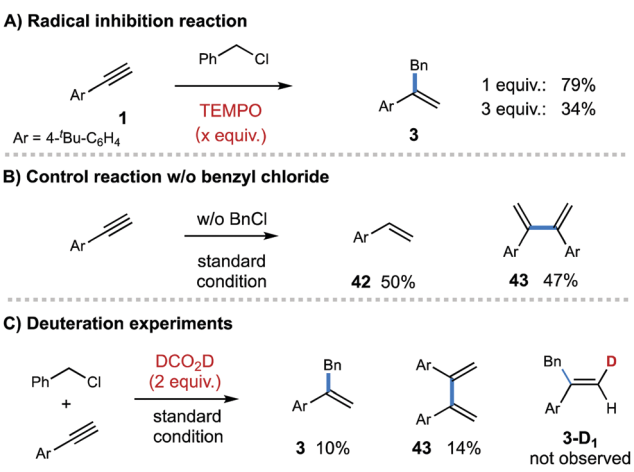
With the optimized reaction conditions in hand, we next turned our attention to exploring the generality of this photochemical hydroalkylation protocol. As depicted in Scheme 1, a wide range of terminal aryl alkynes bearing electron-donating, -withdrawing, and -neutral substituents could participate well in this synergistic protocol, generating the desired α-benzylic alkenes with exclusive Markovnikov selectivity (**3–16**, 50–99%). The mild condition is compatible with a series of functional groups, including esters, trifluoromethylates, boronate esters, and halides, offering useful handles for further synthetic manipulations (**7–10** and **12–13**, **15–16**, 50–98%). Steric hindrance of alkynes showed little impact on the reaction efficiency, and alkynes with *ortho*-substituents all reacted smoothly with high efficiency (**14–16**, 62–91%). Heteroaryl alkynes, such as thiophenyl and indolyl proved to be viable substrates, delivering the corresponding heteroaryl-substituted alkenes with moderate yields (**17–19**, 60–73%). Besides (hetero)aryl alkynes, terminal aliphatic alkynes also were competent substrates in this reductive hydroalkylation system (**20–26**, 63–97%). Aliphatic alkynes tethered with esters, ethers, and free alcohols were all well-tolerated, further demonstrating the robust compatibility of this protocol (**20–25**, 63–97%). The reaction of cyclopropyl acetylene afforded the cyclopropyl retained adduct **26** in 72% yield. Furthermore, we found that cyclohexylene-incorporated alkyne was a viable coupling partner, furnishing 1,3-diene product **27** with moderate efficiency. It should be noted that internal arylalkynes were applicable substrates, albeit with poor selectivity (see Scheme S2 in the ESI†), whilst (trimethylsilyl)acetylene was not a suitable substrate for this reaction.

Next, we examined the scope of benzylic chlorides under the optimal conditions (Scheme 1). A wide range of benzylic chlorides incorporated with *para-* and/or *meta*-substituents such as alkyl, ethers, esters, and halides, were suitable coupling partners, furnishing the α-benzyl alkenes with exclusive Markovnikov selectivity and moderate to high efficiency (**28–35**, 46–90%). Nonetheless, neither secondary benzyl chlorides nor nonactivated alkyl chlorides worked in this protocol (see Scheme S3 in the ESI†).

To further demonstrate the synthetic utility of this photoredox/nickel reductive hydroalkylation protocol, we have examined several complex molecules derived from biologically active drugs and natural products. As illustrated in Scheme 1, alkyne derivatives of estrone, ibuprofen (anti-inflammatory drug), Febuxostat (xanthine oxidase inhibitor), and Tolmetin (anti-inflammatory drug) all underwent selective coupling with benzylic chlorides, furnishing the corresponding substituted alkenes with moderate to high efficiency (**36–39**, 75–81%). Furthermore, benzylic chlorides derived from Adamantane and Borneol also proved to be suitable coupling partners (**40–41**, 68–93%).

To probe the possible reaction pathway, several preliminary mechanistic studies have been performed (Scheme 2). The addition of radical inhibitor TEMPO to the template reaction didn't shut down the productive reactivity; 34% of product **3** was still obtained in the presence of 3 equivalents of TEMPO (Scheme 2A). These results, together with the formation of the cyclopropyl retained product **26** in the case of cyclopropyl acetylene (Scheme 1), suggested that this hydroalkylation reaction might not involve a radical intermediate. On the other hand, control reactions without benzyl chlorides led to the formation of styrene **42** and 1,3-diene **43** (Scheme 2B). We surmised that Ni–H species could be involved,[10a] and the formation of 1,3-diene **43** could proceed *via* migratory insertion of alkyne into the Ni–H bond followed by dimerization of vinyl nickel. To further unravel the hydrogen source of Ni–H species, deuteration experiments were performed. In the presence of deuterium-labeled DCO_2D, the reaction of alkyne 1 and benzylic chloride led to 10% of product **3** together with 14% of 1,3-diene **43**, without the observation of the deuterium-labeled product **3-D1** (Scheme 2C). These results indicated that alkyl amines other than acids might be the hydrogen source for Ni–H species in this photochemical reaction.

Although elucidation of a detailed mechanism requires further studies, we have proposed a plausible reaction pathway for this photoredox/nickel catalyzed hydroalkylation of alkynes based on these mechanistic studies. As shown in Scheme S1 in the ESI,† upon irradiation with visible light, the photoexcited catalyst $^*Ir^{III}$ ($E_{1/2}^{*III/II}$ = +1.39 V *vs.* SCE)[16] undergoes a single-electron transfer (SET) event with alkylamine($E_{P/2}$ = +1.1 V *vs.* SCE)[17] to form the reducing photocatalyst Ir^{II} as well as amino radical cation **A** (see Section 6 in the ESI† for fluorescence quenching studies, determination of the fluorescence quantum yield, and light-on/light-off experiments). The latter one **A** undergoes a deprotonation to give amino radical **B**, which then is trapped by Ni(0) **C** to afford alkyl–Ni^I species **D**. Subsequent rapid β-hydride elimination of alkyl–Ni^I **D** releases Ni–H species **E**. At this juncture, migratory insertion of Ni–H **E** into the



Scheme 2 Mechanism studies.

alkyne *via* Markovnikov selectivity gives branched vinyl–Ni^{I} species **F**, which undergoes oxidative addition with benzyl chloride to form (vinyl)(benzyl)Ni^{III} species **G**. Subsequent reductive elimination of **G** would produce the alkene product as well as Ni^{I} species **H**. Another SET event between the reducing Ir^{II} {$E_{1/2}{}^{III/II}$ = −1.25 V *vs.* SCE }[16] and Ni^{I} **H** {$E_{1/2}[Ni^{II}/Ni^{0}$ = −1.2 V *vs.* SCE]}[18] regenerates the ground state photocatalyst Ir^{III} and Ni(0) to close the two catalytic cycles. Nevertheless, another potential reaction pathway, which proceeds *via* selective insertion of benzyl–nickel species[19] into alkynes followed by protometallation, could not be ruled out. Compared with Jamison's protocol which utilizes the electron-rich phosphine ligand to facilitate the oxidative addition of benzylic chloride with Ni(0),[19] the generation of nickel hydride from alkyl amines seems to be favored over that of nickel–benzyl in our dual photoredox/nickel reaction.

In summary, we have reported a dual photoredox and nickel catalyzed Markovnikov selective hydrobenzylation of terminal alkynes with benzyl chlorides, furnishing a wide array of 1,1-disubstituted alkenes with high efficiency and excellent selectivity. Mechanistic studies suggest that the generation of nickel hydride with alkyl amine as the hydrogen source could be involved in this photochemical synergistic protocol.

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Conflicts of interest

There are no conflicts to declare.

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