Nickel-Catalyzed Difunctionalization of Unactivated Alkenes Initiated by Unstabilized Enolates

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Supporting Information Placeholder

ABSTRACT: This report demonstrates the possibility of a nickel-catalyzed difunctionalization of unactivated alkenes initiated by an unstabilized enolate nucleophile. The process tolerates a diverse range of electrophiles, including aryl, heteroaryl, alkenyl, and amino electrophiles. An electron-deficient phosphine ligand and a tetrabutylammonium salt additive were crucial for promoting efficient vicinal difunctionalization.

The use of first row transition metals to facilitate challenging C–C bond formations is an ongoing endeavor. In particular, nickel-catalyzed C–C bond formation has received tremendous attention over the past decade owing to nickel's Earth abundance and distinct reactivity relative to palladium. These features have motivated the development of innovative transformations that add value to readily available starting materials.[1] In this regard, the 1,2-difunctionalization of unactivated alkenes is a powerful synthetic strategy that enables the rapid and modular construction of molecular complexity through the simultaneous installation of two new C–C bonds, and provides access to libraries of chemically diverse compounds.[2]

Despite the advances in nickel-catalyzed C–C bond formation, alkene difunctionalization reactions that tolerate a broad range of heterocycles remains a significant challenge.[3a] This challenge originates due to the stronger bonds that nickel forms to basic heterocycles relative to palladium, resulting in substrate and product inhibition, which lead to catalyst deactivation.[3b] The continued development of general processes for alkene vicinal difunctionalization reactions that tolerate a diverse range of heterocycles is an important goal for broadening access to pharmaceutically relevant chemical space.

Alkene difunctionalization initiated by electrophiles is well-established and has led to many elegant synthetic methodologies that demonstrate the breadth of reaction partners that can be used.[2] More recently, reductive strategies for alkene difunctionalization employing two electrophiles have also emerged.[4]

In contrast, first row transition metal catalyzed alkene difunctionalization initiated by nucleophiles is much less explored, and is orthogonal to approaches employing halide starting materials (Figure 1A).[5] Fu reported an aryl-9-BBN-initiated enantioselective cyclization/alkylation reaction using a nickel/1,2-diamine catalyst system.[6] Brown demonstrated that aryl boronic ester nucleophiles can initiate a copper-catalyzed

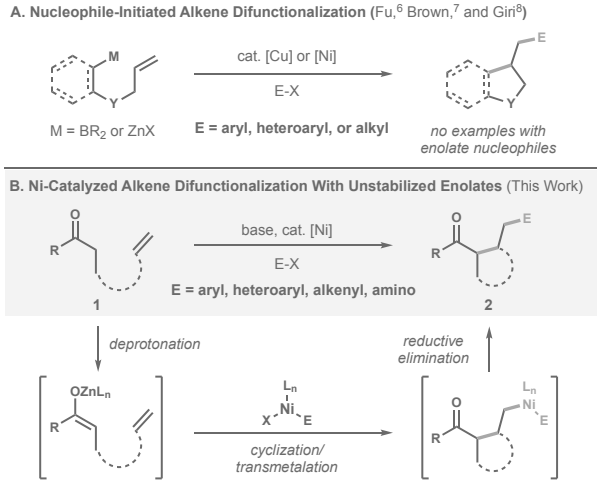


Figure 1. First Row Transition Metal-Catalyzed Alkene Difunctionalization

cyclization/arylation process with a tethered alkene.[7] Giri showed that aryl or alkylzinc halides bearing a tethered olefin can engage in a radical cyclization/arylation reaction under copper catalysis.[8] Alkene difunctionalizations employing enolates as nucleophiles, however, are limited to doubly activated enolates, and have only been achieved using Pd-catalysis.[9]

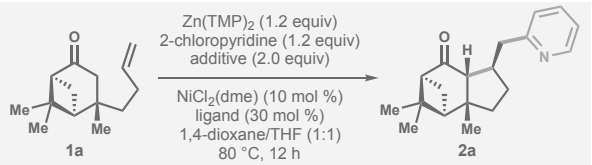
Notwithstanding these recent advances in nucleophile-initiated alkene difunctionalization, there have been no reports employing unstabilized metal enolates as nucleophilic partners, despite their ease of preparation via deprotonation of the corresponding carbonyls. *Herein we report a nickel-catalyzed vicinal difunctionalization of an alkene with an unstabilized enolate and a range of aryl, vinyl, and amino electrophiles (Figure 1B).* This synthetic strategy expands the capabilities of alkene difunctionalization reactions by enabling the use of abundantly available ketones as nucleophiles without the need for pre-activation in a separate step.[10]

Monofunctionalization of unactivated alkenes with unstabilized enolates can be achieved via the Conia-Ene reaction,[11] but requires high temperatures and has poor functional group compatibility. Advances in transition metal catalysis have enabled α-alkylation of unstabilized enolates with unactivated olefins under much milder conditions using precious metal catalysts such as Pd,[12] Au,[13] Rh,[14] or Ir,[15] but have not led to alkene difunctionalization reactions.

We previously reported an oxidative cycloalkenylation of ketones using allyl-nickel catalysis to promote β-hydride elimination of a primary alkyl nickel species.[16] The current study investigates the scope of electrophiles that can be employed for an enolate-initiated alkene difunctionalization using an appropriate ligand and additive to promote reductive elimination of a related primary alkyl nickel species. In particular, we were interested in the scope of heteroarenes that could be incorporated due to their importance in pharmaceutical motifs, as well as the general challenges encountered in effecting nickel-catalyzed transformations with these substrates.[17]

Using **1a** as our model substrate, $Zn(TMP)_2$ as base for enolate formation, 2-chloropyridine as the model electrophile, and 10 mol % of $NiCl_2$(dme) as precatalyst, we found that alkene difunctionalization was indeed feasible, and **2a** could be obtained in 33% yield in the absence of ligand and additive (Table 1, entry 1). While the related cycloalkenylation product was observed in 9% yield, the fully saturated, 5-exo cyclization product between the enolate and alkene was observed as the major byproduct (52%). Consistent with our previous ketone functionalization reactions employing $Zn(TMP)_2$ as base, kinetic enolate formation was necessary for optimal efficiency.[16]

Table 1. Optimization of Alkene Difunctionalization



Entry	Ligand	Additive	Yield (%)[a]
1	none	none	33 (100)
2	bpy, box, terpy, pybox, pyrox	none	5-32 (47-87)[b]
3	PCy_3	none	35 (100)
4	PPh_3	none	38 (100)
5	P(*p*-OMe-C_6H_4)$_3$	none	55 (100)
6	P(*p*-CF_3-C_6H_4)$_3$	none	60 (100)
7	P(*p*-CF_3-C_6H_4)$_3$	$ZnBr_2$	60 (100)
8	P(*p*-CF_3-C_6H_4)$_3$	$MgBr_2$	63 (100)
9	P(*p*-CF_3-C_6H_4)$_3$	LiBr	45 (75)
10	P(*p*-CF_3-C_6H_4)$_3$	TBABr	75 (92)
11	P(*p*-CF_3-C_6H_4)$_3$	TBAI	80 (95)[c]
12	none	TBAI	60 (100)

[a]^{1}H-NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. Conversion is indicated in parentheses. [b]See Supporting Information for details. [c]Isolated yield.

We next introduced ligands and additives to promote reductive elimination. Bidentate and tridentate nitrogen-based ligands (entry 2), which are commonly employed for Ni-catalyzed alkene functionalizations,[2,6] provided lower yields for our desired transformation. Monodentate trialkyl (entry 3) and triaryl (entry 4) phosphine ligands provided small but measureable ligand effects, which led us to explore the role of electronic effects using other commercially available triaryl phosphine ligands. Ultimately, we found that the electron-deficient triaryl phosphine ligand P(*p*-CF_3-C_6H_4)$_3$ (entry 6) provided a substantial increase in yield of the difunctionalization product (60%).

With an optimal ligand in hand, we turned our attention to salt additives to promote the desired alkene difunctionalization reaction as we[16] and others[18] have often observed dramatic changes in reactivity and selectivity when salt additives are employed in transformations involving organozinc species. Unfortunately, the addition of salts such as $ZnBr_2$ (entry 7) and $MgBr_2$ (entry 8) did not provide a marked improvement in the yield of **2a**. Furthermore, the addition of LiBr (entry 9) led to a depreciation in conversion, which is likely due to a detrimental effect of lithium salts for the initial alkene carbometalation event. This result demonstrates the importance of using lithium salt-free $Zn(TMP)_2$ for this transformation. Despite the versatility and utility of salt-free $Zn(TMP)_2$ for effecting challenging transformations with enolates, its limited commercial availability and inefficient synthesis in the literature[19] led us to develop a convenient and scalable procedure for accessing this reagent in high yield and purity (see Supporting Information for details).

We then turned our attention to tetrabutylammonium salts (entries 10 and 11) as they have previously been demonstrated to promote nickel-catalyzed cross couplings of alkylzinc halides.[20] Indeed, TBAI (entry 11) was found to be optimal, and provided **2a** in 80% yield, favoring the *cis*-fused bicycle product with the arene disposed on the convex face. Interestingly, if TBAI was used without a ligand (entry 12), we observed a comparable result to entry 6, wherein only ligand was employed.

When aryl electrophiles were employed rather than heteroaryl electrophiles, tetrabutylammonium triflate (TBAOTf) was found to be a more effective additive, especially for the formation of 6-membered rings (see Supporting Information for details). Notably, the use of other triflate salts led to no reaction, thereby highlighting the importance of the tetrabutylammonium cation. We speculate that a tetrabutylammonium salt with a weakly-coordinating triflate anion provided improved results due to a salt metathesis that could take place at the nickel center to generate a more cationic nickel species to facilitate both migratory insertion and reductive elimination.[21] Unfortunately, this phenomenon was not general with heteroaryl electrophiles, potentially due to the coordinating ability of these basic groups. Consequently, both TBAI and TBAOTf were explored as additives during our investigation of the heteroarene electrophile scope.

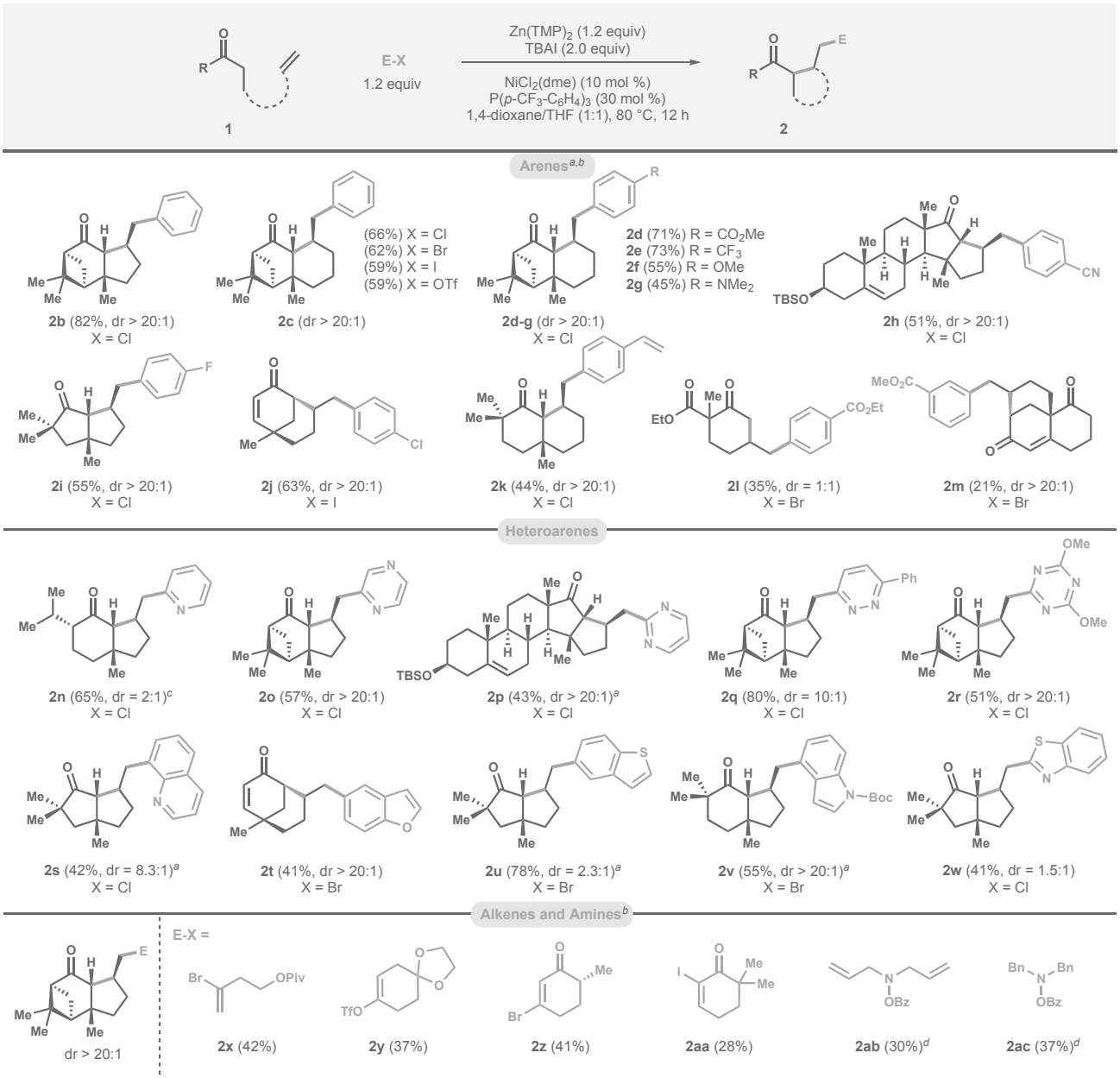
At this stage, we began to explore the scope of the alkene difunctionalization reaction with an emphasis on the scope of electrophiles that can be employed (Table 2). We first interrogated the effect of the leaving group on the aryl electrophiles: using halogenated benzene derivatives, we found that aryl chlorides, bromides, iodides, and triflates could all be employed to provide difunctionalized product **2c** with similar efficiency. These results demonstrate that practitioners can advantageously employ less reactive but more abundantly available aryl chlorides as electrophiles, without a decrease in reaction efficiency.[22]

We then explored electronic effects on the benzene ring using various 4-substituted chlorobenzenes. Electron-withdrawing groups such as $-CO_2Me$ (**2d**) and $-CF_3$ (**2e**) at the *para*-position provided excellent yields for the difunctionalization reaction. Gratifyingly, chlorobenzenes bearing electron-donating groups such as –OMe (**2f**) and $-NMe_2$ (**2g**) were also viable electrophiles, providing only slightly depreciated yields relative to the unsubstituted analog.

Next, a panel of ketones with pendant alkenes were subjected to the reaction conditions using a diverse set of aryl halides to demonstrate the generality of this transformation. Both 5- and 6-membered cyclic ketones could be employed, and both 5- and 6-membered rings could be constructed, giving access to bicyclo[4.4.0]decane, bicyclo[4.3.0]nonane, bicyclo[3.3.0]octane, and bicyclo[3.3.1]nonane ring systems.

Acyclic methyl ketones can be used to access functionalized cyclohexanones (**2l**). Aryl halides containing potentially reactive 4-CN (**2h**) and 4-F (**2i**) functionality were well tolerated. Using

Table 2. Substrate Scope of Alkene Difunctionalization



[a]TBAOTf was used instead of TBAI. [b]1,4-Dioxane was used as solvent. [c]2.0 equiv of $Zn(TMP)_2$ was used. [d]No TBAI was used.

4-chloro iodobenzene as electrophile (**2j**), the more reactive aryl iodide motif selectively participated in the cross-coupling reaction. 4-chlorostyrene (**2k**) was also successfully employed without functionalization of the activated alkene moiety. Alkene difunctionalization using a *meta*-substituted aryl electrophile (**2m**) was also successful, although low yields were observed as a result of the two enolizable positions of the Wieland-Miescher ketone scaffold.

Next, the scope of heteroaryl electrophiles were explored. A variety of electron-deficient heteroarenes could be employed, including pyridine (**2n**), pyrazine (**2o**), pyrimidine (**2p**), pyridazine (**2q**), and 1,3,5-triazine (**2r**). Although the basicity of these substrates could lead to coordination to nickel, these substrates are also highly electron deficient and reductive elimination should be facile. Furthermore, a variety of benzo-fused heterocyclic electrophiles were well-tolerated, including quinoline (**2s**), benzofuran (**2t**), benzothiophene (**2u**), Boc-protected indole (**2v**), and benzothiazole (**2w**). Notably, **2r**, **2t**, and **2u** represent additional examples of *meta*-substituted arenes whereas **2s** and **2v** represent *ortho*-substituted arenes.

In addition to arenes and heteroarenes, synthetically versatile alkenyl electrophiles could also be employed, including an –OPiv tethered 1,1-disubstituted alkenyl bromide (**2x**), an acetal containing alkenyl triflate (**2y**), a *β*-bromo enone (**2z**), and an α-

iodo enone (**2aa**). The modest yields are the result of arylation byproducts derived from ligand degradation (**SI-16**). To our delight, even electrophilic amines such as *N*,*N*-diallyl (**2ab**) and *N*,*N*-dibenzyl (**2ac**) *O*-benzoyl hydroxylamines could be employed to give tertiary amine products. Interestingly, the alkene carboamination reaction was more efficient without additives and enolate alkylation and alkenylation were observed to be the major byproducts. We expect further reaction development to provide improved yields for these more challenging electrophile classes.

Some notable trends in reactivity were observed during our substrate scope investigation. Under the optimized conditions, only unactivated terminal alkenes were tolerated. Polarized olefins bearing a $-CO_2Me$ moiety underwent efficient cyclization but did not participate in cross coupling. Subjecting a Ph-substituted internal alkene to the standard conditions led to no reaction, arguing against a Heck reaction/enolate cyclization mechanism.[9c] Consistent with these observations, no byproducts derived from a Heck reaction or α-arylation were ever observed. Additionally, for fused ring systems, if the ketone starting material does not possess a quaternary center at the *β*-position, trace product and low conversion was observed.

Preliminary mechanistic studies were conducted to better understand the role of alkylzinc intermediates in this transformation (Figure 2). When the Negishi reagent derived from **3** was prepared by direct insertion with Zn(0) in NMP[23] and subjected to our standard conditions for nickel-catalyzed cross-coupling with 2-chloropyridine, **2a** was not observed. An aqueous quench of this Negishi reagent revealed that ring-opened product **1a** and hydrodehalogenation product **4** were formed (Figure 2A).

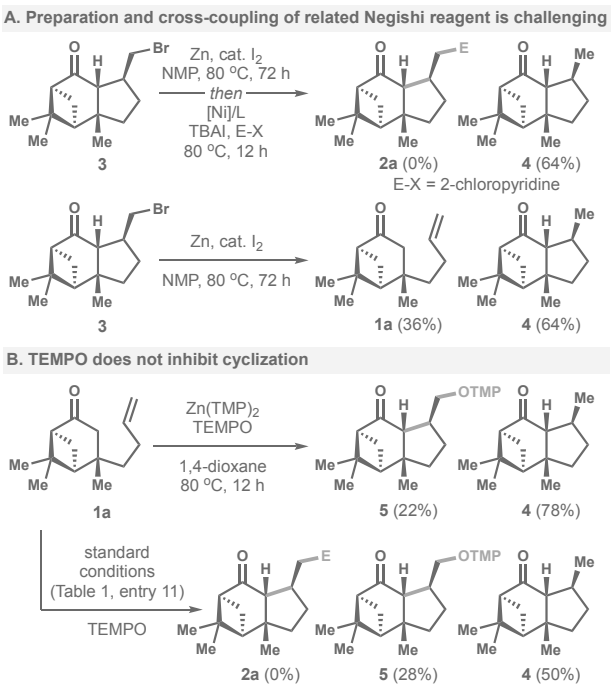


Figure 2. Investigations of the zinc-mediated cyclization.

The susceptibility of this Negishi reagent to ring opening, either by a radical[24] or anionic process[9] might point to the possibility of a reversible zinc cyclization. Attempts to prepare the Negishi reagent in ethereal solvents with other activators (LiCl, TMSCl, dibromoethane, etc.) led to poor conversions. Negishi reagent formation using the corresponding alkyl iodide led to higher conversions but provided similar ring opening and hydrodehalogenation products. These results highlight the difficulty of preparing and functionalizing Negishi reagents at this position, and demonstrates the utility of our methodology for overcoming this synthetic challenge.

In order to investigate the involvement of single electron pathways, model substrate **1a** was subjected to the standard conditions (Table 1, entry 11) in the presence of a stoichiometric amount of TEMPO (2,2,6,6-tetramethylpiperidinoxyl) (Figure 2B). While formation of cross-coupling product **2a** was inhibited, cyclization product **4** (50% yield) and TEMPO-adduct **5** (28% yield) were obtained as the major products. TEMPO-adduct **5** could be obtained in the absence of nickel-catalyst, suggesting that the alkylzinc species generated from the zinc-mediated cyclization (formally a metalloene reaction)[25] was likely responsible for the formation of TEMPO-adduct **5**. These results indicate that either a radical cyclization is not operative or the rate of the C–C bond forming cyclization proceeds faster than the rate of trapping with TEMPO (10^9 M^{-1} s^{-1}).[26] Furthermore, these results indicate that the alkylzinc species formed under our conditions can participate in single-electron pathways.[27,28]

Despite these studies on the zinc-mediated cyclization, cyclization via a nickel-mediated migratory insertion cannot be excluded. While the cyclization was selective for the *cis*-fused bicycle, the diastereoselectivity of the C–C bond forming cyclization was observed to be electrophile dependent, as exemplified by products **2s** (8.3:1 dr) and **2u** (2.3:1 dr), which were otherwise prepared under identical conditions. A compelling explanation for this variable selectivity is that the coordination sphere at nickel differs for the migratory insertion step. If olefin migratory insertion occurs with an aryl nickel enolate, it is expected that diastereoselectivity would be a function of the aryl group bound to nickel. Alternatively, if C–C bond forming cyclization were reversible and occurred at a rate competitive with C–C bond forming reductive elimination, variable diastereoselectivities could be the result of a compromise between kinetic and thermodynamic cyclization stereoselectivity. Deconvolution of the aryl halide steric and electronic influences on diastereoselectivity is further complicated by the possible reversibility of the cyclization step and the different innate stereoselectivities imparted by each ketone scaffold.

In conclusion, we developed the first nickel-catalyzed vicinal difunctionalization of unactivated alkenes initiated by unstabilized ketone enolates. This method enables efficient access to various bicyclic architectures with concomitant incorporation of a diverse range of synthetically useful and pharmaceutically relevant electrophiles. We expect this strategy for alkene difunctionalization to expedite multi-step synthesis campaigns and enable rapid access to libraries of complex materials.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and spectroscopic data for all new compounds including ^{1}H- and ^{13}C-NMR spectra (PDF).

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Notes

The authors declare no competing financial interests.

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