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Synthesis of Tetrasubstituted Alkenes by Tandem Metallacycle Formation/Cross-Electrophile Coupling

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Supporting Information Placeholder

ABSTRACT: Nickel-catalyzed cross-electrophile couplings have recently emerged as highly effective and practical methods for the formation of C-C bonds. By merging this process with well-established π - π coupling chemistry, a new method for the synthesis of tetrasubstituted alkenes has been developed. The procedure relies on the use of chlorosilanes as a means of generating reactive vinylnickel intermediates, which are capable of undergoing a reductive cross-electrophile coupling with alkyl halides. The method not only generates highly substituted allylic alcohol derivatives, but also obviates the need for stoichiometric organometallic nucleophiles and provides greatly improved scope and functional group tolerance compared with previously developed methods.

The reductive coupling of two different electrophilic components, often referred to as "cross-electrophile couplings," is a highly useful and practical strategy for C-C bond construction.¹ This approach has been applied in a variety of contexts, most often to create C_{sp}^{2} - C_{sp}^{3} bonds allowing efficient access to a variety of functionalized aryl, alkenyl, and acyl derivatives (Scheme 1a).² Under this reaction manifold, two components that are electrophilic in nature, such as an aryl halide and alkyl halide, are coupled with the use of an electron-rich nickel catalyst and a stoichiometric reductant.³ The chemoselectivity is typically derived from the propensity of the two electrophilic partners to react with nickel catalysts in differing oxidation states and the ability of Ni(II) intermediates to effectively capture carbon-centered radicals.⁴ This capability has also led to the merger of nickel catalysis with photoredox catalysis, a powerful approach that takes advantage of the ability of photoredox catalysts to generate free radicals from a variety of precursors including boranes, silicates, carboxylic acids, and C-H bonds, among others.⁵ A common feature of all of the above methods is that a carbon-centered radical adds to a nickel-based catalytic intermediate derived from a *single* reactive component (1, Scheme 1).

The oxidative cyclization of Ni(0) complexes of two different π -components to form Ni(II) metallacyclic intermediates forms the basis of many types of catalytic processes.⁶ Whereas the resulting metallacyclic intermediates are typically further functionalized by σ -bond metathesis, transmetallation, or migratory insertion pathways, we speculated that metallacycles generated via oxidative cyclization of an alkyne and an aldehyde (2, Scheme 1b) could participate in a cross-electrophile coupling via alkyl halide addition mediated by singleelectron processes. The successful realization of this concept would allow the formation of two new C-C bonds: one via the initial oxidative cyclization event and one via the subsequent cross-electrophile coupling. Herein, we report our initial illustrations of this strategy in the context of the alkylative cyclization of ynals (Scheme 1b).

Scheme 1. Proposed Merger of Cross-Electrophile Coupling and Alkyne-Aldehyde Oxidative Cyclization



(b) Alkyne-aldehyde oxidative cyclization/cross-electrophile coupling:



The above hypothesis was examined with aldehydealkyne couplings, which produce substituted allylic alcohols that are ubiquitous in synthesis and natural products.⁷ Early studies on aldehyde-alkyne couplings and ynal cyclizations utilized alkylmetal reagents such as dialkylzinc,⁸ trialkylaluminum,⁹ and trialkylboranes¹⁰ as reductants. The alkylmetal reagent can either serve as a reductant, or it can directly append an alkyl group to the distal site of the alkyne component.⁸ Several highly effective procedures have been developed for H-atom installation using silanes or boranes as the terminal reductant,^{6a,11} but strategies enabling the incorporation of functionalized alkyl fragments through this approach are rare, much more limited in scope, and require highly reactive organometallic reagents.^{8,12}

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To address this limitation, we opted to explore the cyclization of ynal 3 utilizing a Ni(0) catalyst, a butyl halide as the second electrophilic reaction partner, and Mn as the terminal reductant to furnish tetrasubstituted alkene product 4. 2a,2d Initial attempts to generate product 4 under these conditions failed, and we reasoned that the metallacylic structure 2 possessing a cyclic framework and a Ni-O bond might behave very differently towards free radical additions compared with other Ni(II) halide species commonly invoked in cross electrophile couplings. Accordingly, triethylchlorosilane (Et₃SiCl) was explored as an additive, anticipating that its addition would convert metallacycle 2 into the open chain alkenyl Ni(II) halide more closely resembling the adduct derived from oxidative addition of a vinyl halide precursor to Ni(0).¹³

When commercially available NiBr₂·DME was used as the catalyst with 2,2'-bipyridyl (bipy) (5) as the ligand with triethylchlorosilane in DMPU, a modest 28% yield was observed (Table 1, entry 1). Optimization of the reaction conditions revealed that Mn was the best reductant, DMF the optimal solvent, and that other bipyridyl ligands were inferior to the parent 2,2'bipyridine, a welcome discovery given the low cost of this ligand.¹⁴ The reaction yield did not exceed $\sim 60\%$ when 1-iodobutane was used as the alkylating agent. We hypothesized that this was due to rapid reduction to form the alkyl radical, which dimerizes at a faster rate than the productive coupling reaction (dimerization of the alkyl halide is often observed as a side-product). By using more stable alkyl bromides in conjunction with an exogenous iodide salt, the yield was increased to 85% yield (Table 1, entry 3).¹⁵ Finally, the air- and moisturesingle component catalyst stable $(2.2)^{-}$ bipyridyl)nickel(II) iodide (7) was discovered to be a convenient and effective replacement for the in situ formed catalyst of NiBr₂ dme and 2,2'-bipyridine (Table 1, entry 5). Interestingly, we found that the product was observed as a mixture of E and Z isomers (vide infra), but increasing the concentration of the reaction mixture to 1.0 M led to very good selectivity for the formation of the *E* isomer (Table 1, entry 6).

Table 1. Optimization of Reaction Conditions for the Alkylative Cyclization Reaction

Ph.	0 H + nf	Et Ni(I lig	3 ^{SiCI} (1 I) cat. (jand (10 <u>An⁰ (2.0</u> solve	.5 equiv) 10 mol %) 0 mol %) 0 equiv) F nt, rt	obiet obiet
Entry	Catalyst	Ligand	Х	Solvent (conc.)	Yield, % $(E:Z \text{ ratio})^a$
1	NiBr ₂ ·dme	5	Ι	DMPU (0.2 M)	28 (86:14)
2	NiBr ₂ ·dme	5	Ι	DMF (0.2 M)	57 (82:18)
3 ^b	NiBr ₂ ·dme	5	Br	DMF (0.2 M)	85 (77:23)
4 ^c	NiBr ₂ ·dme	6	Br	DMF (1.0 M)	64 (89:11)
5 ^b	(bipy)NiI ₂ (7)	-	Br	DMF (0.2 M)	86 (73:27)
6 ^c	(bipy)NiI ₂ (7)	-	Br	DMF (1.0 M)	87 (89:11) ^d

Reactions run on 0.2 mmol scale using ynal **3** (1.0 equiv) and alkyl halide (2.0 equiv). ^aYield and *E:Z* ratio determined by ¹H NMR using trimethoxybenzene as an internal standard. ^b nBu_4NI (50 mol %) additive used. ^cNaI (50 mol %) additive used. ^dIsolated yield on 1.0 mmol scale using 5.0 mol % catalyst.



With optimal reaction conditions in hand, we explored the scope of the alkyl components introduced via the cross-electrophile coupling approach (Scheme 2). It was quickly established that a variety of alkyl bromides bearing reactive functional groups such as esters (9), acetals (11), acetate-protected alcohols (12), and amides (13) were well tolerated, providing highly functionalized tetrasubstituted olefins. Trimethylchlorosilane could be used in place of triethylchlorosilane, giving good yield of product 8 with a slightly decreased E:Z ratio. Most reactions proceeded with excellent E:Z selectivity. β -Branched alkyl halides were introduced in good yield (14), although this led to a significant decrease in the E:Z selectivity. Substrate 15 bearing an alkyne substituent demonstrates the chemoselectivity of the ynal cyclization reaction.



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Scheme 2. Substrate Scope of Alkyl Bromides



Standard conditions: ynal (1.0 mmol), alkyl bromide (2.0 equiv), chlorosilane (1.5 equiv), Mn^0 (2.0 equiv), NaI (0.5 equiv), (bipy)NiI₂ (5.0 mol %) in DMF (1.0 M). Isolated yields after isolation by silica gel chromatography. *E:Z* ratios were determined by crude ¹H NMR.

After establishing the substrate scope of the alkyl halide component, we next turned our attention to variations of the ynal (Scheme 3). Ynals substituted with both electron rich (17) and electron-deficient (16, 18, 19, 20) arenes were well tolerated. Interestingly, the electron rich substrate 17 (p-OMe) reacted more efficiently with a lower catalyst loading (1 mol %), although the basis for this observation is currently unclear. Several functional groups known to be reactive in other nickelcatalyzed transformations such as an aryl boronic ester¹⁶ (21) and an aryl chloride 17 (25) underwent the alkylative coupling smoothly without competing reactivity. Electrophilic functional groups such as ketones (18), esters (19), and nitriles (20) were also well tolerated. These functional groups are often problematic in processes involving silanes or organozincs due to competing hydrosilylation and nucleophilic addition processes. Heterocycles such as thiophenes (22), protected indoles (23), and uracils (26) were all tolerated in the reaction, although the yield is diminished in the case of the uracil substrate 26.

The reaction is not limited to aryl-substituted ynals. An alkyl-substituted ynal participated smoothly (27), as did an ynal bearing a propargyl ether (28). For these alkyl-substituted ynals, tetrabutylammonium iodide was found to be superior to sodium iodide as an additive. An enynal also participated smoothly, providing a highly substituted 1,3-diene product (32). Finally, ynals bearing different backbone substitution were also tolerated. An oxygen-substituted ynal gave the exocyclic alkenyl tetrahydrofuran 29, while a malonate-derived ynal gave the exocyclic cyclopentene **30**. Pyrrolidines could be synthesized using a nitrogen-bearing ynal (**33**, **34**). Substrate **34** also shows that an alkyl halide bearing an acidic N-H group could be coupled effectively. Extending the ynal length produced exocyclic cyclohexene **31**. However, examination of the NOE correlations confirmed that the Z isomer is the major isomer formed in this reaction.

Scheme 3. Substrate Scope



Standard conditions: ynal (1.0 mmol), alkyl bromide (2.0 equiv), chlorosilane (1.5 equiv), Mn^0 (2.0 equiv), NaI (0.5 equiv), (bipy)NiI₂ (5.0 mol %) in DMF (1.0 M). Isolated yields after isolation by silica gel chromatography. *E:Z* ratios were determined by crude ¹H NMR. ^a1 mol % (bipy)NiI₂ used. ^b*n*Bu₄NI used in place of NaI. ^c2 mol % (bipy)NiI₂ used

A likely mechanism of the alkylative cyclization involves oxidative cyclization of the ynal by the Ni(0) catalyst to form nickelacycle 35, generating the first carbon-carbon bond (Scheme 4). Next, the nickel-oxygen bond is cleaved by the chlorosilane, generating the silvl ether and the vinylnickel(II) intermediate 36. Based on analogy to known cross-electrophile coupling mechanisms,^{4b} our original hypothesis suggested that free radical addition to 36 would lead to product via formation of Ni(III) intermediate 38 (path a). Alternatively, Mnmediated reduction of **36** to Ni(I) intermediate **37**,^{2g,13c,18} followed by oxidative addition of the alkyl halide, would also generate Ni(III) intermediate 38 (path b). Given that oxidative additions of alkyl halides to Ni(I) proceed through single electron transfer (SET) pathways,¹⁹ pathways a and b both ultimately involve a free radical addition to a Ni(II) species. Intermediate 38 is poised for rapid reductive elimination²⁰ to generate product along with Ni(I) intermediate 39 which is further reduced by Mn to complete the catalytic cycle. Experiments with stoichiometric Ni(0) catalysts indicate that product formation does not occur in the absence of reductant, which tentatively supports a mechanistic sequence involving formation of **37** (path b).²¹

Scheme 4. Mechanistic Proposal



The formation of mixtures of *E* and *Z* isomers is likely a result of the $Z \rightarrow E$ isomerization of the intermediate **36** or **37** generated after cleavage of the nickelacycle **35** by the chlorosilane (Scheme 4). It is currently unclear which intermediate undergoes isomerization, but E/Zisomerization of vinylnickel intermediates has been proposed in various transformations.^{2g,13a,22} We found that increasing the concentration of the reaction mixture to 1.0 M gave optimal *E*:*Z* ratios (Scheme 5a). Either oxidative addition of the alkyl halide to Ni(I) intermediate **37** (path b) or radical addition to Ni(II) intermediate **36** (path a) would be favored at high concentration compared with the rate of the isomerization process. Interestingly, the Z isomer predominates in the case of secondary alkyl bromides (Scheme 5b). The more extensive isomerization observed when secondary halides are used is likely driven by the more crowded steric environment slowing the rate of additions to **36** or **37** (depicted for **37**, Scheme 5c). By decreasing the concentration of the reaction mixture, the proportion of the Z isomer of product **40** derived from isomerization is increased. This concentration effect is also seen with primary alkyl bromides but to a lesser extent, wherein decreasing the concentration of the reaction mixture leads to an increased proportion of the minor Z isomer of the product (Scheme 5a). In the case of secondary alkyl halides, the E/Z selectivity of the reaction concentration.

Scheme 5. Effect of Reaction Concentration



Effect of reaction concentration on E/Z ratio using (a) primary alkyl bromide and (b) secondary alkyl bromide. (c) Proposed mechanistic pathway for isomerization ^aReaction performed with no NaI additive

The $Z \rightarrow E$ isomerization likely does not occur from a Ni(III) intermediate **38-Z** given the fast rate of reductive eliminations from Ni(III). Furthermore, the unimolecular nature of the conversion of **38** to product should not exhibit concentration-dependent E/Z selectivity. The strong dependence of product E:Z ratio on reaction concentration instead suggests that the rate of isomerization competes with a bimolecular reaction of **36** or **37**. Similar effects were demonstrated in nickel/photoredox catalyzed desymmetrization of *meso*-anhydrides, in which the ratio of diastereomeric keto-acid products could be adjusted by tailoring reaction conditions to favor or disfavor rapid capture of a putative Ni(II) intermediate.²³

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In conclusion, this work demonstrates the combination of nickel-catalyzed oxidative cyclization and reductive cross-electrophile coupling as a new approach for the catalytic union of aldehydes, alkynes, and alkyl halides. The use of chlorosilanes to generate a reactive vinylnickel(II) intermediate was essential in enabling the reductive cross-electrophile coupling. The reaction allows for the use of air-stable alkyl halides as alkylating reagents in place of preformed organometallic reagents previously employed, which significantly expands the scope and functional group tolerance of the procedure. Efforts to expand these findings towards other classes of cyclizations and multicomponent couplings are in progress.

ASSOCIATED CONTENT

Supporting Information

Experimental details, copies of spectra, and additional discussion of mechanism. This material is available free of charge via the Internet at http://pubs.acs.org.

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