

Deoxygenative C–C Bond-Forming Processes via a Net Four-Electron Reductive Coupling

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Supporting Information

ABSTRACT: The nickel-catalyzed coupling of enones or enals with alkynes in the presence of silane and titanium alkoxide reductants provides direct access to skipped diene products. The process involves a net four-electron reductive coupling and proceeds with deoxygenation of the starting enone or enal. A new class of well-defined nickel(0) precatalysts bearing an unhindered N-heterocyclic carbene ligand, which was developed in optimization of the process, is essential for the efficiency of the transformation. The strategy allows the high reactivity of α,β -unsaturated carbonyl substrates to be utilized in couplings with simultaneous extrusion of the oxygen atom, thus enabling a traceless strategy for alkene installation.

A vast array of catalytic methods have been developed for the union of two π components via carbon–carbon bond formation. The majority of such methods involve the redistribution of atoms without a net change in the oxidation state in the components. For example, the coupling of an alkene and an alkyne to produce a diene (product 1, Scheme 1),¹ the hydrovinylation of alkenes,² and the hydroacylation of

Scheme 1. Redox Description of Catalytic Coupling Processes



an alkyne or alkene with an aldehyde³ are representative examples of processes of this type. The participation of substrates lacking π bonds in processes of this type has more recently been made possible by sequential hydrogen transfer/ C-C coupling events, as illustrated by the coupling of an alcohol and an allene to produce a homoallylic alcohol.⁴ All of the above-mentioned processes share the characteristic of being completely atom-economical without a net formal change in oxidation state of the reactants.

A second group of processes that similarly enable the union of two π components involves catalytic methods conducted in

the presence of a reductant, wherein a net two-electron reduction of the starting components occurs during the coupling event. Examples of this type of process include the coupling of enones and alkynes to produce γ, δ -unsaturated ketones (product 2, Scheme 1),⁵ the coupling of aldehydes and alkynes to produce allylic alcohols,⁵ and the coupling of allylic alcohols with alkynes to produce skipped dienes.⁶ These processes share the characteristic of a net two-electron reduction accompanying the coupling event. In the course of exploring the development of catalytic reductive coupling methods, we observed an unexpected conversion of enones and alkynes to skipped diene products with complete deoxygenation of the enone substrate (product 3, Scheme 1). This process possesses the unique characteristic of a net fourelectron reduction accompanying the coupling event. The discovery, optimization, and mechanistic study of this process is described herein.

Prior reports from our laboratory described the efficient reductive coupling of enals and alkynes in the presence of silane reductants and $Ni(COD)_2$ (COD = 1,5-cyclooctadiene) with PCy₃ to produce (*Z*)-enol silanes 4 (Scheme 2). During efforts to extend this reactivity to enones rather than enals, exploration of a range of phosphine and N-heterocyclic carbene (NHC) ligands afforded low yields of the expected trisubstituted enol silanes, with alkyne hydrosilylation being the major side reaction. However, attempting the reaction with the unhindered NHC ligand ITol (5) while using $Ti(O-i-Pr)_4$ with Et_3SiH^8 led to the unexpected production of skipped diene 7 in 37% isolated yield.⁹ Omission of Ti(O-i-Pr)₄ or replacement of ITol with more common NHC ligands bearing ortho substituents on the N-aryl group such as IMes (N-mesityl) or IPr (N-[2,6-diisopropylphenyl]) failed to produce more than trace quantities of the skipped diene product 7. Replacement of $Ti(O-i-Pr)_4$ with isopropanol¹⁰ or the use of catalytic $Ti(O-i-Pr)_4$ $Pr)_4$ with excess isopropanol did result in production of 7, but in considerably lower isolated yield than when 1.1 equiv of $Ti(O-i-Pr)_4$ was used.

Among the many classes of NHC complexes of nickel that our group has explored in various contexts, ligands such as ITol that lack ortho substituents on the *N*-aryl group typically lead to low-yielding and inconsistent reactions compared with the substantially more robust analogous catalysts derived from IMes or IPr. Given this limitation and the unique behavior of ITol in promoting the formation of skipped diene 7, we examined the preparation of stable precatalysts of Ni(0)

Received: August 10, 2015

Scheme 2. Catalyst Optimization in Skipped Diene Formation



coordinated with ITol.¹¹ Among several classes of well-defined catalysts examined, Ni(0) complex **6** derived from methyl methacrylate, ITol·HBF₄, and Ni(COD)₂, had the desirable attributes of ease of preparation, moderate air stability, and high reactivity in the production of skipped dienes, as evidenced by the production of **7a** in 90% isolated yield (Scheme 2). On the basis of this outcome, the utility of catalyst **6** was employed in our further exploration of skipped dienes via the four-electron reductive coupling of enones and alkynes.

Utilizing the optimized procedure with catalyst 6, Et₃SiH, and $Ti(O-i-Pr)_4$, the production of skipped diene products from a range of alkynes (2.0 equiv) with enones and enals (1.0 equiv) was examined (Table 1). From a range of enone substrates, products 7a-i were obtained in good yields with >95:5 regioselectivity. Within these examples, the enone substrates included phenyl and methyl ketones with aromatic or aliphatic substituents at the enone β -position. The alkyne could be varied to include symmetrical or unsymmetrical alkynes, including aromatic alkynes, terminal alkynes, and alkynes bearing phthalimido or silyloxy functionality. Notably, cyclic enones such as cyclohexenone (not shown) were generally ineffective substrates in this transformation. The process was very effective with enal substrates to produce products 8a-e, including enals possessing aromatic or aliphatic β -substituents. Notably, an enal lacking β -substituents was an efficient substrate (giving product 8c), whereas enones lacking a β -substituent were ineffective in the transformation.

Because of the novelty of the four-electron reductive coupling and the unusual combination of reactive components, a series of experiments were conducted to better understand the mechanism of this process (Scheme 3). Given the precedent for two-electron reductive couplings to generate enol silane products (i.e., product 4, Scheme 2),⁷ we envisioned that enol silane production followed by reductive cleavage of

Table 1. Scope of Skipped Diene Formation

Communication



Scheme 3. Evaluation of Potential Intermediates



the C–OSiEt₃ bond was the likely operative mechanistic pathway.¹² However, attempts to reduce compound **4a** under the reaction conditions failed to produce skipped diene **8a**. A second alternative considered was that enal 1,2-hydrosilylation was followed by alkyne addition to the resulting silylated allylic alcohol.⁶ However, exposure of the silylated allylic alcohol derived from cinnamaldehyde to the reaction conditions also failed to produce skipped diene product **8a**.

Important insight was gained from deuterium-labeling studies in the production of *d*-4a and *d*-8a from cinnamaldehyde and 1phenylpropyne (Scheme 4). Using the previously published procedure with PCy₃ as the ligand and Et₃SiD as the reductant,^{7a} the deuterium label is exclusively introduced on the alkyne-derived terminus of the product *d*-4a, as expected. However, in the skipped diene production using catalyst 6 with Et₃SiD, deuteration of the enal-derived terminal methylene group exclusively cis to the central carbon was observed in

Scheme 4. Deuterium-Labeling Studies



product (5-d)-8a, and no label incorporation in the alkynederived terminus was observed. With Ti(O-*i*-C₃D₇)₄, 91% deuterium incoporation in the alkyne-derived terminus was observed in product (1-d)-8a, and no label incorporation at the enal-derived terminus was observed.

On the basis of these experiments, a mechanism that explains the surprising outcome of these labeling experiments can be formulated (Scheme 5). Oxidative cyclization of the enone and alkyne with Ni(0) provides seven-membered metallacycle 9 with an η^1 nickel *O*-enolate motif,^{13,14} and σ -bond metathesis of the silane with the Ni-O bond provides nickel hydride intermediate 10 bearing an enol silane functionality. This intermediate serves as a common intermediate leading to twoelectron or four-electron reductive coupling pathways. With PCy₃ as the ligand, reductive elimination of the C-H bond provides the observed enol silane product 4 in analogy to previous reports.⁷ However, the unique reactivity illustrated by the unhindered NHC ligand ITol likely suppresses the efficiency of reductive elimination while allowing coordination and insertion of the tethered enol silane functionality via species 11 to provide intermediate 12. Bond rotation in 12 to produce rotamer 13 is then followed by anti elimination of the silvloxy group, promoted by the Lewis acid $Ti(O-i-Pr)_{4}^{15}$ to provide intermediate 14 with isopropoxy transfer from Ti to Ni. Extrusion of acetone¹⁰ to generate **15** and reductive elimination of the C-H bond provide the observed product 7/8.

Several experimental observations support the abovepostulated mechanistic pathway. The η^1 nickel *O*-enolate form of metallacycle **9** (Scheme 5) is supported by the observed (*Z*)-enol silane stereochemistry of **4** and is consistent with prior crystallographic analysis of the analogous tmeda and bipyridine metallacycles.¹³ While stereoselective formation of the 1,2-*trans*-alkene generated by enone couplings (product 7, Table 1) could potentially be biased by the thermodynamic stability of the *trans*-alkene, the stereochemical outcome of aldehyde coupling [product (5-*d*)-8a, Scheme 4] using Et₃SiD removes this bias. Starting from the known stereochemistry of 9, syn addition to (*Z*)-enol silane 11 followed by anti silyloxy elimination in the conversion of 13 to 14 explains the net stereochemical outcome. The overall positional selectivity using Et₃SiD and Ti(O-*i*-C₃D₇)₄ [comparing products (5-*d*)-8a and (1-*d*)-8a, Scheme 4] is fully consistent with the proposed mechanistic pathway. In particular, the diverging mechanisms from intermediate 10 leading to changes in position of deuterium incorporation explain the labeling outcomes in the production of *d*-4a and *d*-8a.

In summary, a new synthetic entry to skipped dienes involving deoxygenative coupling of enones or enals with alkynes has been developed. The process is formally a fourelectron reductive coupling, which enables the high reactivity of unsaturated carbonyl substrates to be utilized while providing products that are free of the carbonyl functionality. Deuteriumlabeling studies documented an unusual outcome in which Et_3SiH and $Ti(O-i-Pr)_4$ both play key roles as reductants in the transformation. Future studies will explore the utility of this new mechanistic pathway in other classes of transformations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08448.

X-ray crystallographic data for catalyst 6 (CIF) Experimental details and copies of spectra (PDF)

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The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by NSF Grant CHE-1265491. The authors thank Jeff Kampf for the crystallographic analysis of



Scheme 5. Operative Mechanistic Pathways

DOI: 10.1021/jacs.5b08448 J. Am. Chem. Soc. XXXX, XXX, XXX–XXX catalyst **6** and Michael Robo and Jeannie Kochkodan for assistance in the synthesis and evaluation of catalyst **6**.

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