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Catalytic Coupling Reactions

α-Olefins as Alkenylmetal Equivalents in Catalytic Conjugate Addition Reactions**

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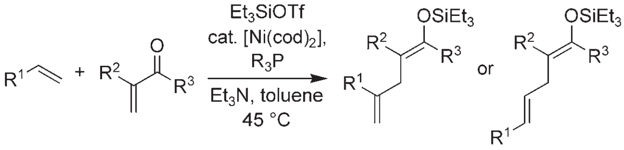
First documented over a century ago, conjugate additions are among the most utilized organic reactions. In carbon–carbon bond-forming variants, the nucleophile is typically organometallic. Earlier technology employed enolate, organolithium, Grignard, or organocopper reagents; more recently, organozinc and organoboron compounds have enhanced this transformation significantly.[1,2] Despite increased functional group tolerance, an organometallic or an organometalloid compound is nonetheless required in these powerful methods. Herein we describe a novel conjugate addition reaction in which a simple, unactivated alkene (ethylene, an α-olefin, or styrene) takes the place of the organometal reagent [Eq. (1)]. Thus, although an alkene is not an alkenylmetal reagent per se, it functions as one in this carbon–carbon bond-forming process.

Catalyzed polymerization of alkenes is one of the most important industrial processes,[3] and Ni-catalyzed two-alkene coupling reactions have also received significant attention, including hydrovinylation.[4] Montgomery and co-workers found that nickel complexes catalyze a wide variety of conjugate addition reactions,[5] but the closest precedent to the transformation reported herein (catalytic 1,4-addition of a simple alkene to unsaturated carbonyl groups) appears to be Lewis acid promoted conjugate addition of electron-rich alkenes.[6,7] In these cases migration of the double bond of the alkene nucleophile occurs, which is in contrast to the Ni-catalyzed reactions described below.



(1)

1 R^1 = H, alkyl, aryl; R^2 = alkyl, aryl; R^3 = H, aryl

2 for R^1 = alkyl

3 for R^1 = aryl

Ogoshi et al. reported that stoichiometric amounts of [Ni(cod)$_2$] (cod = 1,5-cyclooctadiene) and trimethylsilyl trifluoromethanesulfonate (Me$_3$SiOTf) effected intramolecular coupling of an alkene and an aldehyde, and shortly thereafter, we reported that α-olefins are excellent nucleophiles in intermolecular carbonyl addition reactions catalyzed by a complex derived from [Ni(cod)$_2$] and a phosphine or an N-heterocyclic carbene.[8] Depending on the nature of the ligand, addition occurs at either the terminus or the 2-position of the alkene. The latter provides direct access to allylic alcohol derivatives and the former yields products of a carbonyl–ene-like reaction. With the aim of broadening the scope of alkenes as nucleophiles in carbon-carbon bond-forming reactions, we turned our attention to electrophiles containing unsaturated carbonyl functional groups.

To focus on issues of alkene reactivity in initial studies, we selected ethylene as the coupling partner and decided to address issues of regioselectivity in subsequent experiments. Triethylsilyl trifluoromethansesulfonate (Et$_3$SiOTf) and catalytic amounts of [Ni(cod)$_2$] and Bu$_3$P afford good to excellent yields of the conjugate addition product, isolated as the enolsilane (Table 1, entries 1–4). Moreover, the stereoselectivity with respect to formation of the enolsilane is at least 92:8. Unsaturated ketones are also effective electrophiles (Table 1, entries 5–11), but proceed with lower selectivity in some cases.

As demonstrated in Table 1, entry 9, electron-rich enones are superior electrophiles, and certain heterocycles are also tolerated (Table 1, entries 10,11). Despite reduced selectivity, reactions with furan- and thiophene-containing enones proceed in high chemical yield. Overall, most of the above cases are highly selective, and thus the transformation represents a direct and stereoselective assembly of tetrasubstituted siloxyalkenes.[9,10]

Several observations regarding the optimum reaction conditions are noteworthy. Increasing either the ethylene pressure from 1 atm to 2 atm, or the scale of the reaction by fourfold resulted in only a marginal reduction in yield (Table 1, entries 2 and 6). Out of 25 additives investigated (see the Supporting Information), Bu$_3$P (Bu$_3$P = tributylphosphine) was by far the most effective ligand for coupling reactions of ethylene. Toluene is the superior solvent; for example, ethereal solvents such as Et$_2$O, THF, and 1,4-dioxane completely suppress the coupling reaction.

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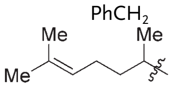
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Ni-catalyzed conjugate addition reactions of alkenes.[a]

Entry	R^1	R^2	R^3	Major product	Yield [%][b]	*E*/*Z* (**2**)[b]
1	H	Me	H	**2a**	52	95:5
2		*n*-hexyl		**2b**	76	95:5
					58[c]	95:5[c]
					64[d]	95:5 [d]
3		$PhCH_2$		**2c**	83	8:92
4[e,f]				**2d**	97	7:93
5		Me	Ph	**2e**	90	95:5
6		*n*Pr		**2f**	94	90:10
					86[d]	90:10[d]
7		*i*Pr		**2g**	78	13:87
8[g]		Ph		**2h**	70	n.d.
9[h]		Me	*p*-anisyl	**2i**	94	91:9
10		*n*Bu	2-furyl	**2j**	95	75:25
11		Et	2-thienyl	**2k**	95	75:25
12[f]	*n*-hexyl	*n*-hexyl	H	**2l**	67[i]	95:5
13[f]	Ph	*n*-hexyl	H	**3a**	70	81:19
14[f]		Me	*p*-anisyl	**3b**	55	91:9

[a] See the Supporting Information and Equation (1). Standard conditions (entries 1–11): Et_3N (1.5 mmol) and the enal or enone (0.25 mmol) were added to a solution of $[Ni(cod)_2]$ (0.075 mmol) and Bu_3P (0.15 mmol) in toluene (1.5 mL) at 23 °C under ethylene (1 atm). Triethylsilyl trifluoromethanesulfonate (0.44 mmol) was added dropwise at 0 °C. The mixture was stirred for 48 h at 45 °C and purified by chromatography (SiO_2). In some cases $CyPPh_2$ (Cy = cyclohexyl; entry 12) or tricyclopentylphosphine (entries 13,14) was used in place of Bu_3P. [b] Determined by ^1H NMR spectroscopy. [c] Ethylene pressure was 2 atm. [d] Fourfold larger scale (1 mmol enal used). [e] Compound **1d** added over 48 h. [f] Reaction time 72 h; a lower yield was obtained after a 24 h reaction time. [g] A dihydropyran from hetero-Diels–Alder reaction of 2 equiv of **1h** was isolated (13 %). [h] Reaction time 24 h. [i] Combined yield of **2l** and **2l′** (product ratio of **2l**:**2l** is 79:21; compound **2l′** is the result of the addition to the 1-position of 1-octene). See the text and the Supporting Information.

Significant effort was expended to reduce the rather high catalyst loading (30 mol %), however, small decreases in the amount of $[Ni(cod)_2]$ resulted in a significantly reduced yield. For example, **2b** was afforded in 49 % yield when 15 mol % $[Ni(cod)_2]$ was used (76 % yield under standard conditions). Similarly, a 63 % yield of **2f** was obtained at 20 mol % catalyst loading, down from 94 % yield at 30 mol % catalyst loading.

Other critical variables are the amounts of Et_3N and Et_3SiOTf employed. Decreasing or increasing the former lowered the yield or completely suppressed the reaction, and reducing the amount of Et_3SiOTf from 1.75 to 1.25 equivalents decreased the yield of **2b** from 76 % to 47 % under otherwise identical conditions. Additionally, Me_3SiOTf can be used in place of Et_3SiOTf, but this substitution tends to diminish the product yield.

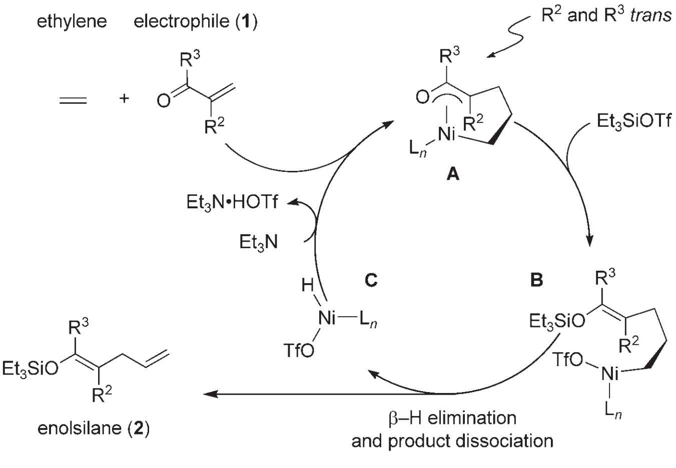
Unactivated monosubstituted olefins are also good coupling partners in this reaction. For example, 1-octene and 2-hexylacrolein are combined in 67 % yield, and with very high enolsilane *E*/*Z* selectivity (Table 1, entry 12). Coupling occurs in approximately 4:1 regioselectivity, favoring coupling at the 2-position of the alkene. Since there are comparatively a greater number of general methods for the preparation of 1-alkenyl organometallics (e.g., hydrometalation of terminal alkynes), the fact that 1-octene functions as a 2-alkenyl organometallic reagent highlights a particularly useful aspect of this reaction.

Aryl alkenes, in contrast, afford the opposite alkene regioselectivity (Table 1, entries 13,14). Coupling at the 2-position of styrene is not observed; carbon–carbon bond formation at the 1-position occurs exclusively, whether the electrophile is an enal or an enone.

The trends and observations noted above suggest a general mechanistic framework (Scheme 1). The proposed sequence of events is based largely on a crystal structure of a complex derived from $[Ni(cod)_2]$, Cy_3P (Cy_3P = tricyclohexylphosphine), a 1,3-diene, and benzaldehyde reported recently by Ogoshi et al.[11] We believe that the alkene (ethylene shown) and the electrophile (enal or enone **1**) afford an oxa-π-allyl nickel complex (**A**) during the formation of the carbon–carbon bond. The silyl triflate reacts with this species to give an enolsilane and a Ni^{II} complex (**B**) that undergoes rapid β-hydride elimination. Release of product **2** and Et_3N abstraction of TfOH from complex **C** affords a Ni^0 species (not shown) to complete the catalytic cycle.

The *E*/*Z* selectivity thus appears to be dictated by two factors that in most cases reinforce each other. The placement of R^2 and R^3 substituents away from each other and the chairlike chelation of Ni in complex **A** are consistent with the observed sense of alkene geometry. The superior performance of electron-rich enals and enones is consistent with the fact that reaction with silyl triflate is a critical step in the cycle. Mackenzie and co-workers reported Ni-catalyzed conjugate addition reactions between alkenyltributyltin reagents and α,β-unsaturated aldehydes that are assisted by chlorotrialkylsilanes and likely proceed via 1-((trialkylsilyl)oxy)allylnickel(II) intermediates.[7] In this vein, it is possible that the silyl triflate and enal (or enone) first combine and the resulting species then undergoes coupling with the alkene. Morken and co-workers proposed a similar sequence of events in Ni-catalyzed coupling reactions between allylboron reagents and enones.[12]

With the caveat that different ligands are used in coupling reactions of α-olefins ($CyPPh_2$) and styrene (PCy_3), our working hypothesis for the complementary regioselectivity in



Scheme 1. Proposed mechanistic framework.

these two cases is as follows: It is possible that the regioselectivity observed for styrene (coupling at the alkene 1-position) is due primarily to an electronic consideration, specifically, the formation of a benzylic Ni species. In conctrast, the sense of selectivity for α-olefins is that resulting from avoidance of steric repulsion between the Ni–ligand complex and the alkene substituent. We have proposed an explanation similar to the latter for the behavior of α-olefins in other Ni-catalyzed coupling reactions that we have developed.[8b–f]

Several aspects of this transformation are noteworthy. First, it is a rare example of selective conjugate addition of an alkenyl equivalent to an unsaturated aldehyde. Typically, in such reactions 1,2-addition is favored, or one observes complex mixtures.[1] The high *E*/*Z* selectivity in most cases also merits further comment. Enolsilanes are starting materials in a wide range of enantioselective transformations leading to carbonyl compounds with quaternary stereogenic centers in the α-position, in many cases with very high enantioselectivity.[13,14] The double bond configuration is generally critical for high facial selectivity, and thus the Ni-catalyzed conjugate addition reaction provides rapid access to important tri- and tetrasubstituted enolsilanes that would otherwise be difficult to prepare with high selectivity by enolization of an aldehyde or ketone[9] (Table 1, entry 2, compare allyl vs. *n*-hexyl). Finally, the products derived from ethylene possess a monosubstituted alkene that is an excellent substrate for catalytic olefin cross-metathesis reactions.[15] This combination therefore affords products that are regio-complementary to those of the Ni-catalyzed conjugate addition reaction with aliphatic, monosubstituted alkenes (e.g., 1-octene).

Our current efforts include expanding the scope and the utility of the conjugate addition of monosubstituted alkenes to unsaturated carbonyl compounds. More broadly, we continue to explore catalytic reactions that utilize simple, widely available chemical feedstocks, including α-olefins, and provide important synthetic intermediates in a single operation.

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