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NICKEL ACETYLACETONATE-INDUCED 1,4-ADDITIONS OF 1-ALKENYL(DISIAMYL)BORANES TO α,β-UNSATURATED KETONES, ESTERS AND NITRILES

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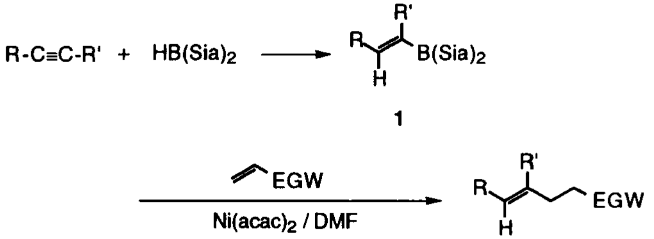
Abstract: The conjugate addition of 1-alkenyl(disiamyl)boranes to α,β-unsaturated ketones, esters, or nitriles was carried out in the presence of Ni(acac)$_2$ and triethylamine in DMF. The reactions provided γ,δ-unsaturated ketones, esters, and nitriles in high yields while retaining the original configuration of the 1-alkenylboranes. A similar addition reaction of 1-alkenyl(disiamyl)boranes to 1-acetyl-2-vinylcyclopropane produced the terminal and internal coupling products, 5,8-alkadien-2-on and 5-ethenyl-6-alken-2-on, in high yields in some cases with high regioselectivity favoring the terminal addition products.

The β-alkenylation of conjugated enones and related compounds has been shown to provide a highly useful and general procedure for appending unsaturated residues to cyclic and acyclic substrates. Although organocopper complexes[1] were widely used for the 1,4-addition of alkyl and 1-alkenyl groups to enones, several subsequent reports provided additional interesting applications and extensions of this methodology. Hooz[2] and Brown[3] reported the direct conjugate addition reactions of 1-alkynyl- and 1-alkenylalane or borane derivatives to enones. We achieved[3] the addition of 1-alkynyl- and 1-alkenyl(diisopropoxy)boranes to enones in the presence of BF$_3$ etherate. These reactions satisfactorily proceed with S-*cis* enones because the addition proceeds through a cyclic six-membered transition state involving a chelation between the metal center and the oxygen atom of the carbonyl. On the other hand, it was reported that some of transition-metal salts would catalyze the conjugate addition of organometallic compounds.[5] The addition of organozinc reagents[6] or (1-alkenyl)zirconium complexes[7] to both S-*trans* and S-*cis* enones has been carried out using a Ni(I)-catalyst. The efficiency of this unique catalytic method was amply demonstrated by the stereoselective synthesis of a side chain of prostaglandin.[8]

We now wish to report that the conjugate addition reaction of 1-alkenyl(disiamyl)boranes to α,β-unsaturated ketones, esters, and nitriles can readily proceed under similar conditions using $Ni(acac)_2$ (acac = 2,4-pentanedionato) (eq. 1).



(1)

The optimum conditions for carrying out the nickel-catalyzed addition of 1-octenylboranes were studied using methyl vinyl ketone as a substrate. The reaction that would achieve even greater synthetic utility is the reaction that can be affected only by catalytic amounts of $Ni(acac)_2$. The addition of (*E*)-1-octenyl(disiamyl)-borane to methyl vinyl ketone produced (*E*)-5-dodecene-2-one in 97%, 95%, 69% and 54% yields using 1 equivalent, 30 mol%, 20 mol% and 10 mol% of $Ni(acac)_2$, respectively, suggesting a potential ability for the catalytic use of $Ni(acac)_2$. However, most of the following reactions were carried out using a stoichiometric amount of $Ni(acac)_2$ since the catalytic use resulted in lower yields for other substrates or more sterically hindered alkenylborane reagents. The addition of one or two triphenylphophines to $Ni(acac)_2$ or the reduction of $Ni(acac)_2$ with diisobutylaluminum hydride (1 equiv)[7] was not effective for the present reaction. The conjugate addition produces the boron enolate intermediates which are highly susceptible to the Aldol condensation with carbonyl compounds. The presence of excess triethylamine (5 equivs) was effective to avoid the formation of such by-products. The 10-20% higher yields were commonly obtained in the presence of excess triethylamine.

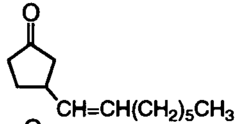
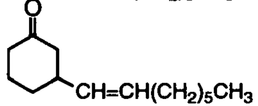
Various 1-alkenyl(dialkyl)boranes[9] underwent the addition of methyl vinyl ketone in DMF in the presence of 1 equiv of $Ni(acac)_2$ and 5 equivs of Et_3N.

1-Octenyl(disiamyl)borane, 9-(1-octenyl)-9-borabicyclo[3.3.1]nonane and 1-(1-octenyl)-3,6-dimethylborepane yielded 97%, 67% and 60% of unsaturated ketone, respectively. However, disiamylborane can be the best reagent of choice because of its hydroboration of terminal alkynes is highly regioselective avoiding the contamination of the dihydroboration byproduct. On the other hand, vinylic boronates, such as 2-(1-octenyl)-1,3,2-benzodioxaborole, did not provide the addition product at all.

In Table 1, the results of the reaction of representative 1-alkenyl(disiamyl)-boranes and α,β-unsaturated carbonyl compounds in the presence of 1 equivalent of $Ni(acac)_2$ and an excess of triethylamine are summarized. Both S-*cis* and S-*trans* α,β-unsaturated ketones afforded 1,4-addition products in good yield (entries 1-5). The reaction evidently proceeded with complete retention of the stereochemistry of the 1-alkenylboranes. Thus, the GC examinations of the adducts revealed only a single peak and the ^1H NMR spectra was also consistent with the presence of a single stereoisomer. The coupling constant between two vinylic protons using Eu(dpm) as a shift reagent displayed 16 Hz indicating the presence of a *trans* double bond. House[10] has suggested that the reduction potentials can be used to determine the suitability of substrate towards a 1,4-addition of organocuprates, and perhaps toward the additions of other organometallic reagents. The nickel-induced conjugate addition of 1-alkenylboranes exhibited a similar order of reactivity highly sensitive to the substituents. The addition to acrylonitrile gave a better result than methyl acrylate (entries 6 and 7), but their methyl substituted derivatives such as crotononitrile (39%) and methacrylonitrile (entry 8, 45%) resulted in relatively lower yields.

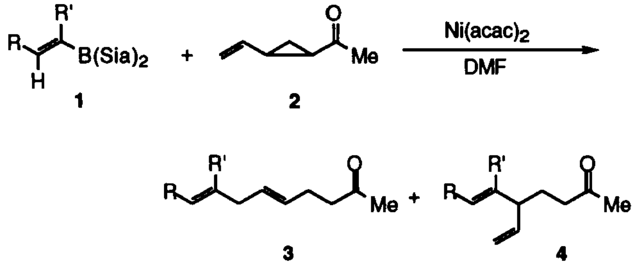
The 1,6-conjugate addition of 1-alkenyl(disiamyl)boranes to 2-acetyl-1-vinylcyclopropane **2** was readily accomplished under similar conditions (Eq. 2). 2-Butenyl(disiamyl)borane selectively provided the terminal addition product **3**, presumably due to the steric hindrance of alkenyl group, but terminal 1-alkenylboranes afforded a mixture of terminal and internal addition products, **3** and **4**, similar to the addition of organocopper reagents to **2**.[11] The 1,6-addition of 1-octenyl(disiamyl)borane to 1-benzoyl-2-vinylcyclopropane or 1-cyano-1-ethoxycarbonyl-2-vinylcyclopropane also produced a mixture of two adducts favoring terminal addition products. The stereochemistry derived from 1-alkenylboranes was completely retained during the addition, but the C(5-6) bond in **3** gave a mixture of *cis* and *trans* isomers in a ratio of 1:9.

Table 1. Ni(acac)$_2$-Catalyzed Conjugated Addition of 1-Alkenyl(disiamyl)boranes[a]

Entry	Alkyne	α,β-Unsaturated compound	Conditions	Product[b]	Yield (%)[c]
1	$CH_3(CH_2)_5{-}C{\equiv}CH$	$CH_2{=}CHCOCH_3$	80 °C / 3 h	$CH_3(CH_2)_5CH{=}CHCH_2CH_2COCH_3$	97
2	$EtO_2C(CH_2)_2{-}C{\equiv}CH$	$CH_2{=}CHCOCH_3$	80 °C / 3 h	$EtO_2C(CH_2)_2CH{=}CHCH_2CH_2COCH_3$	71
3	$THPOCH_2{-}C{\equiv}CH$	$CH_2{=}CHCOCH_3$	80 °C / 3 h	$THPOCH_2CH{=}CHCH_2CH_2COCH_3$	56
4	$CH_3(CH_2)_5{-}C{\equiv}CH$	2-cyclopentenone	40 °C / 3 h		65
5	$CH_3(CH_2)_5{-}C{\equiv}CH$	2-cyclohexenone	25 °C / 16 h		69
6	$CH_3(CH_2)_5{-}C{\equiv}CH$	$CH_2{=}CHCO_2Me$	80 °C / 3 h	$CH_3(CH_2)_5CH{=}CHCH_2CH_2CO_2Me$	66
7	$CH_3(CH_2)_5{-}C{\equiv}CH$	$CH_2{=}CHCN$	25 °C / 24 h	$CH_3(CH_2)_5CH{=}CHCH_2CH_2CN$	96
8	$CH_3(CH_2)_5{-}C{\equiv}CH$	$CH_2{=}C(Me)CN$	25 °C / 24 h	$CH_3(CH_2)_5CH{=}C(Me)CH_2CH_2CN$	45

[a] The 1-alkenyl(disiamyl)boranes obtained by hydroboration of alkynes (1.1 equiv) with disiamylborane (1.1 equiv) were directly used for the next addition reaction to α,β-unsaturated compounds (1 equiv) in the presence of Et_3N (5 equiv) and Ni(acac)$_2$ (1 equiv).

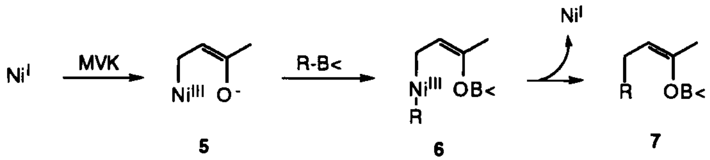
[b] All compounds are trans-isomers. [c] GC yields based on α,β-unsaturated compounds.



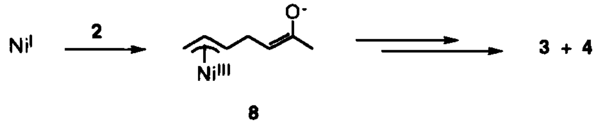
(2)

R = CH_2OCH_2Ph, R' = H	97%	70 : 30
R, R' = Et	65%	100: 0

Although the exact course of the addition process remains to be clarified, the preliminary study indicated that the reaction does not involve the formation of 1-alkenylnickel(II) species and its addition to the enones. Thus, the reaction can be explained by the similar mechanism[12] of the Ni(I)-catalyzed addition of (1-alkenyl)zirconium to enones, involving the oxidative addition of enone to the nickel(I) species to providing **5**, the transmetallation with 1-alkenylboranes (**5** → **6**), and finally the reductive elimination of boron enolate **7** (Eq. 3). The formation of terminal and internal addition products on the reaction with **2** (Eq. 2) suggests the formation of π-allylnickel intermediate **8**, which also accommodates the mechanism involving the oxidative addition of enones to the reduced nickel species (Eq. 4).[11]



(3)



(4)

In conclusion, we reported the synthesis of stereodefined γ,δ-unsaturated ketones, esters, and nitriles *via* the nickel-catalyzed conjugated addition of 1-alkenylboranes to α,β-unsaturated carbonyl compounds. Further synthetic application is anticipated due to the simplicity of our experimental procedure that does not require the isolation of the boron intermediates and enables the synthesis of a wide range of derivatives.

EXPERIMENTAL

Material: DMF was dried by distillation from CaH_2. Anhydrous nickel(II) acetylacetonate purchased from Nakarai Chemical Co., Japan was used directly.[13] 1-Acetyl-1-vinylcyclopropane[11] was prepared from acetone and 1,4-dibromo-2-butene in the presence of NaOH. The synthesis of a solution of 1-alkenyl(disiamyl)boranes in THF was previously reported.[14]

General procedure.

The following procedure for the preparation of 3-[(*E*)-1-octenyl]cyclopentanone is representative. A 100 ml-flask was charged with $Ni(acac)_2$ (10 mmol) and was flushed with nitrogen. DMF (50 ml), Et_3N (50 mmol), and a solution of (*E*)-1-octenyl(disiamyl)borane (1 M, 11 mmol) were then added at 0 °C. After being stirred for 30 min, 2-cyclopentenone (10 mmol) was added at 0 °C. The reaction mixture was gradually warmed to 40 °C over 1 h and was stirred for 3 h at that temperature. The reaction was then quenched with a saturated NH_4Cl solution. The product was extracted with hexane, washed with water four times, and finally dried over $MgSO_4$. GC analysis indicated the formation of the desired ketone in 65%.[6a] An analytically pure sample was obtained by chromatography over silica gel. *Nickel salts cause the explosion when contacted with hydrogen peroxide, thus the oxidation of borane residue with alkaline hydrogen peroxide should be avoided*; IR (neat) 1740 and 965 cm^{-1}; ^1H NMR δ 0.91 (t, 3 H), 1.35 (s, 8 H), 1.5-2.5 (m, 9 H), 5.1-5.6 (m, 2 H). The stereochemistry of the double bond was assigned to the trans by IR (-970 cm^{-1}) and ^1H NMR (J_{trans} = 16 Hz) by using Eu(dpm) as a shift reagent.

All other reactions were carried out by the above general procedure at the temperatures and the times indicated in Table 1.

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