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Nickel-catalyzed multicomponent coupling reaction using ynones*

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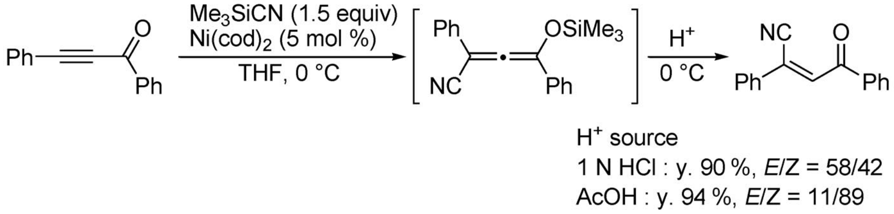
Abstract: Conjugate addition of Me_3SiCN to ynones is smoothly catalyzed by $Ni(cod)_2$ to give β-cyano-silyloxyallenes quantitatively. Subsequent treatment of the silyloxyallenes with *N*-bromo succinimide (NBS) provides the tetrasubstituted α-bromo-β-cyanoenones in high yields (up to 95 %) with excellent *Z*-selectivity (*E*/*Z* = up to >1/99). X-ray crystallographic analysis shows a bent structure of the α-bromo-β-cyanoenone due to deconjugation of the π-bond and the carbonyl group. Furthermore, three-component coupling reactions of ynones, dialkylzinc, and aldehydes are catalyzed by $Ni(cod)_2$ to provide tetrasubstituted olefins.

Keywords: catalyst; multicomponent coupling; nickel; olefins; ynones.

Because tetrasubstituted olefins are of interest for the development of light- and/or electron-responsive materials such as liquid crystals and molecular devices including sensors, switches, and motors [1], the efficient regio- and stereoselective synthesis of tetrasubstituted olefins having four different functional groups becomes an important task for synthetic organic chemists [2]. We report herein a Ni(0)-catalyzed multicomponent coupling reaction using ynones to provide highly functionalized tetrasubstituted olefins.

Conjugate addition of cyanide ion has been studied extensively for supplying functionalized molecules [3,4]. In 2006, Shibasaki et al. reported an elegant example of a Ni(0)-catalyzed conjugate addition of Me_3SiCN with cyclohexenones, which has been applied to the synthesis of Tamiflu [5]. Recently, a cooperative catalysis system using Ni(0) and $Gd(OTf)_3$ has also been developed for the conjugate addition of cyanide to various enones including acyclic substrates [6].

During the course of our program to develop a Ni(0)-catalyzed multicomponent coupling reaction [7], we found that the conjugate addition of cyanide ion to ynones was smoothly catalyzed by $Ni(cod)_2$, and the corresponding trisubstituted β-cyanoenone was obtained in high yield (Scheme 1) [8,9].



Scheme 1 $Ni(cod)_2$-catalyzed conjugate addition of Me_3SiCN to ynones.

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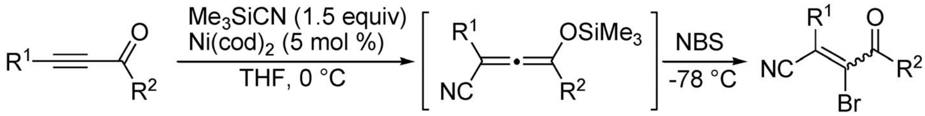
Though the *E*/*Z* selectivities of the obtained β-cyanoenones were low when the reactions were quenched by 1 N HCl, quenching with AcOH improved the *Z*-selectivity to a 11:89 *E/Z* ratio. In the Ni(0)-catalyzed reaction of ynones and Me_3SiCN, the predominant formation of the silyloxyallene was confirmed by ^{1}H-NMR analysis of the reaction mixture. Moreover, the Ni(0)-catalyzed reaction of diphenylynone and *t*-$BuMe_2SiCN$ gave the corresponding silyloxyallene in 64 % isolated yield (rt, 3 h). The mild reaction conditions are an alternate way of synthesizing silyloxyallenes without use of the 1,2-Brook rearrangement [10].

Next, we tried to trap the silyloxyallene with a halogen ion to obtain α-halo-β-cyanoenones [11]. After completion of the Ni(0)-catalyzed conjugate addition, 1.0 mol equiv of *N*-bromo succinimide (NBS) was added to the reaction mixture. Bromination at the α-position occurred smoothly at –78 °C to give α-bromo-β-cyanoenones with high isolated yields (Table 1).

Table 1 Ni(0)-catalyzed synthesis of α-bromo-β-cyano tetrasubstituted enones.



Entry	R^1	R^2	Yield (%)	*E*/*Z*
1	Ph	Ph	94	>1/99
2	Ph	4-$MeOC_6H_4$	89	>1/99
3	Ph	4-BrC_6H_4	84	>1/99
4	4-$MeOC_6H_4$	Ph	95	>1/99
5	Ph	Me	44	>1/99
6	2,4,5-triMeC_6H_2	Ph	99	72/28
7	*n*-Bu	Ph	90	60/40
8	*n*-Pr	Et	79	67/33
9[a]	*t*-Bu	Ph	90	>1/99

[a]Conjugate addition was carried out at rt.

In the current Ni(0)-catalyzed reaction, aromatic ynones were smoothly converted to α-bromo-β-cyano tetrasubstituted enones with high (*Z*)-selectivity (Table 1, entries 1–4). Both electron-enriched and -deficient aromatic rings are compatible in the substrate for keeping the highly (*Z*)-selective enone formations. The structure of (*Z*)-α-bromo-β-cyano tetrasubstituted enones were confirmed by nOe experiments after conversion to the allylic alcohols by reduction of the enones (Fig. 1).

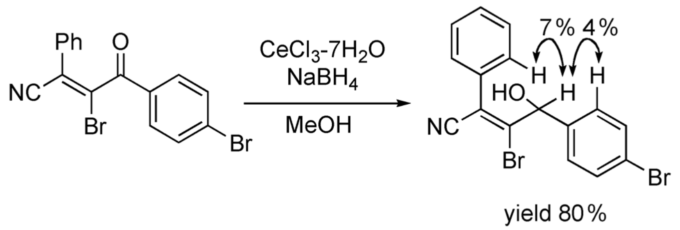


Fig. 1 Reduction of α-bromo-β-cyano tetrasubstituted enones and nOe experiments.

If the alkyl substituent was employed at R^2, the chemical yield was reduced, although the (*Z*)-enone was obtained (entry 5). The bulky aromatic ring or alkyl substituent at R^1 reduced stereoselectivity dramatically (entries 6–8). However, *t*-Bu substituent at R^1, surprisingly, gave the product with again high (*Z*)-selectivity. The structure of the compound obtained in entry 9 of Table 1 was identified by X-ray crystallographic analysis as shown in Fig. 2. The X-ray structure depicted in Fig. 2 suggests an extremely bent enone structure caused by deconjugation of the π-bond and the carbonyl group due to significant steric repulsion between the carbonyl group and the *t*-Bu substituent (θ O=C–C=C = 81.1°).

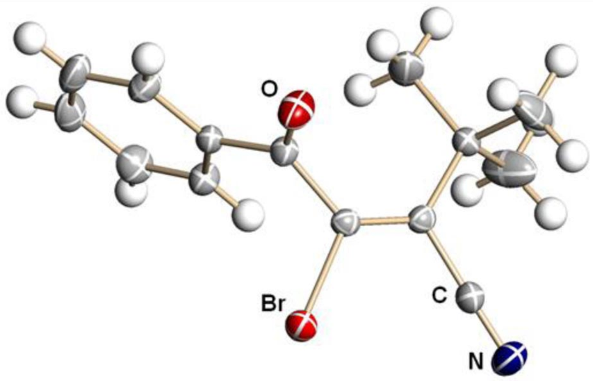
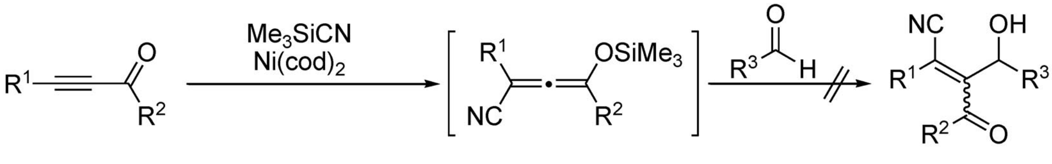


Fig. 2 ORTEP diagram of α-bromo-β-cyano-tetrasubstituted enones (Table 1, entry 9).

Although the reason why the products were obtained with (*Z*)-selective manner is not clear at present, the density functional theory (DFT) calculation suggests that the (*Z*)-isomers are more stable than the (*E*)-isomers [12]. The deconjugation of the π-bond and the carbonyl group of the products observed in Fig. 2 would effectively influence to give the most stable conformation of (*Z*)-isomer.

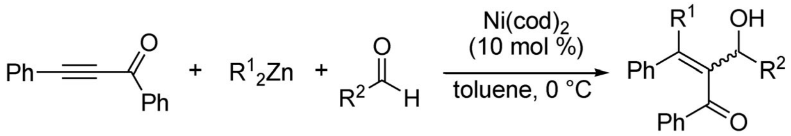
We next examined the reaction of the silyloxyallenes with aldehydes as an alternative method for producing the Morita–Baylis–Hillman (MBH)-type adduct having a tetrasubstituted olefin. Unfortunately, the reaction did not proceed, and only the protonated β-cyanoenone was obtained (Scheme 2). The use of various Lewis acids also resulted in failure. We assumed that the reactivity of the silyloxyallene was not sufficient to react with the aldehyde directly, and the presence of the cyano functionality was not compatible in the Lewis acid-activation for the Mukaiyama-type aldol reaction.



Scheme 2 Attempted synthesis of an MBH-type adduct having a tetrasubstituted olefin.

To avoid this problem, we examined the reaction using alkylzinc [13]. In the $Ni(cod)_2$-catalyzed reaction of ynone and diethylzinc, an intractable mixture of products was obtained. The $Ni(cod)_2$-catalyzed reaction of aldehyde and diethylzinc was also relatively slow. Nevertheless, interestingly, the reaction of diphenylynone, benzaldehyde, and diethylzinc was smoothly catalyzed by $Ni(cod)_2$ (10 mol %) at 0 °C to give the three-component coupling adduct in 81 % yield (Table 2, entry 1). Both electron-deficient and -enriched aromatic aldehydes could be utilized in the three-component coupling reaction. Aliphatic aldehydes could also be employed. The structure of the coupling products was confirmed by nOe experiments of the minor (*Z*)-isomers (Fig. 3). Surprisingly, when dimethylzinc was utilized in the reaction, inversed *E*/*Z* selectivity was observed in up to 1/6.6 ratio (Table 2, entry 5).

Table 2 Ni(0)-catalyzed coupling reaction of diphenylynone, dialkylzinc, and aldehydes.



Entry	R^1	R^2	Time (h)	Yield (%)	*E*/*Z*
1	Et	Ph	20	81	1.5/1
2	Et	4-$MeOC_6H_4$	21	67	1.6/1
3	Et	4-ClC_6H_4	13	58	2.2/1
4	Et	*i*-Pr	21	70	1.2/1[a]
5	Me	Ph	21	84	1/6.6

[a] The stereochemistry has not been identified.

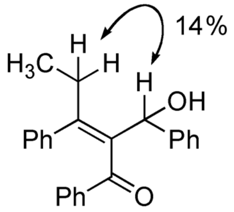
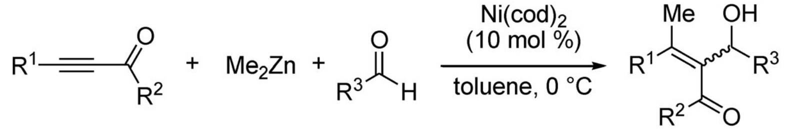


Fig. 3 nOe experiments of (*Z*)-isomer.

Although the *E*/*Z* selectivity obtained in the current study is not satisfactory, further substrate generality was examined using dimethylzinc and the results are shown in Table 3. As the substituents (R^1 and/or R^2) on the ynones, both aromatic and aliphatic substrates could be converted to the three-component coupling products with moderate stereoselectivity.

Table 3 Ni(0)-catalyzed coupling reaction of ynones, dimethylzinc, and aldehydes.

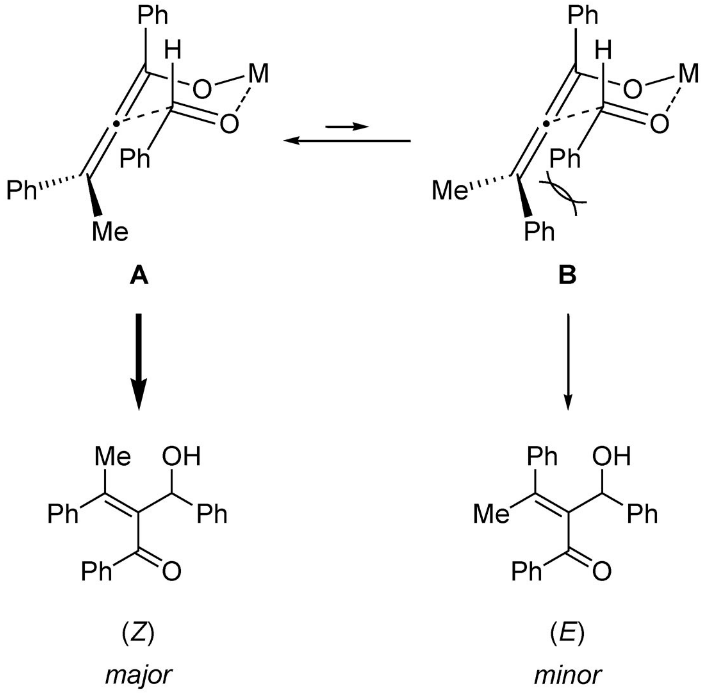


Entry	R^1	R^2	R^3	Time (h)	Yield (%)	*E*/*Z*
1	Ph	Ph	Ph	21	84	1/6.6
2	*n*-Pr	Ph	Ph	15	53	1/3.5
3	*n*-Pr	Ph	4-ClC_6H_4	15	64	1/3
4	*n*-Pr	Ph	*i*-Pr	18	73	1/2.7
5	Me_3Si	Ph	Ph	12	80	1/60
6	Ph	Et	Ph	16	56	1/4.9[a]

[a] The stereochemistry has not been identified.

In some cases, the use of PPh_3 and/or dppp as an achiral ligand was effective for improving the chemical yields of the three-component coupling product. For example, for the three-component coupling reaction examined in entry 2 of Table 3, the product was obtained in 70 % yield (*E*/*Z* = 1/3.2) by adding 20 mol % of PPh_3.

The working hypothesis why the products were obtained with (*Z*)-stereoselective manner in the reaction using Me_2Zn was illustrated in Scheme 3 [13b,14]. After the nucleophilic addition of Me_2Zn to ynone, the intermediary generated metalloxy allene will react with aldehyde. If the reaction proceeds in the six-membered transition state, two possible transition structures (**A** and **B**) can be considerable corresponding to the formation of (*Z*)- and (*E*)-isomers, respectively. In the reaction of Me_2Zn, diphenylynone, and benzaldehyde, the larger Ph substituent at β-position in the metalloxy allene would cause the steric repulsion with the phenyl group of aldehyde in **B**. Thus, the formation of major (*Z*)-isomer would be explained via a pathway though the more stable transition structure **A**. This role reasonably agrees with the inversion of major isomer from (*Z*)- to (*E*)-form in the reaction using Et_2Zn as shown in Table 2, because ethyl is larger substituent than phenyl group. Finally, based on the hypothesis, we succeeded to get the three-component coupling product with quite high (*Z*)-selectivity by utilizing a trimethylsilyl-substituted ynone in up to 1:60 *E*/*Z* selectivity (Table 3, entry 5).



Scheme 3 Working hypothesis for giving (*Z*)-isomer as a major product.

In conclusion, a facile conjugate addition of Me_3SiCN to ynones is presented using the simple $Ni(cod)_2$ catalyst. The reaction of silyloxyallenes with NBS provides tetrasubstituted α-bromo-β-cyanoenones in a (*Z*)-selective manner. Moreover, we developed a Ni-catalyzed multicomponent coupling reaction of ynones, aldehydes, and dimethylzinc to give the MBH-type adducts having a tetrasubstituted olefin. Further examination of Ni(0)-catalyzed multicomponent coupling reactions is in progress, including a mechanistic study on the Ni(0) catalysis.

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