$NbCl_3$-catalyzed [2+2+2] intermolecular cycloaddition of alkynes and alkenes to 1,3-cyclohexadiene derivatives†

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$NbCl_3$(DME)-catalyzed [2+2+2] intermolecular cycloaddition of alkynes and alkenes was successfully achieved to give 1,4,5-trisubstituted-1,3-cyclohexadiene derivatives in good yields.

Transition metal-catalyzed cyclotrimerization of alkynes has been extensively studied and provides a useful method for the synthesis of aromatic compounds.[1] In contrast, there have been limited work on the intermolecular cycloaddition of alkynes and alkenes because of the difficulty in controlling the chemo- and regioselectivity.[2,3]

In 1993, Rothwell and coworkers reported the intermolecular cycloaddition reaction of alkynes and alkenes to afford 1,3-cyclohexadienes by using a titanacyclopentadiene catalyst,[3] although this approach is remains problematic with regard to the yields and selectivity of the formation of 1,3-cyclohexadiene adducts. In addition, this method typically includes an isomerization step, which results in isomerized 1,3-cyclohexadiene adducts.[3]

As an alternative, low-valent niobium compounds are thermally stable and have been utilized as reagents as well as catalysts in several organic transformations.[4–7] We have recently reported several Nb(III)-mediated reactions with electrophiles.[4] Low-valent niobium and tantalum are also known to function as catalysts for the cyclotrimerization of alkynes.[8]

In this study, we found that a commercially available and thermally stable low-valent Nb(III) compound, $NbCl_3$(DME),[5a] serves as an efficient catalyst for the [2+2+2] intermolecular cycloaddition of terminal alkynes with alkenes, afford 1,4,5-trisubstituted-1,3-cyclohexadiene derivatives as the major products in good yield and selectivity. This reaction involves the unprecedented use of low-valent niobium(III) as the catalyst in an organic transformation, as well as providing an efficient and selective route to synthetically useful 1,3-cyclohexadiene derivatives.[9]

tert-Butylacetylene (**1a**) and 1-hexene (**2a**) were chosen as model substrates, and the reaction was carried out under various conditions (Table 1). For instance, a mixture of **1a** (2 mmol) and **2a** (2 mmol) in dichloroethane (1 mL) was allowed to react under the influence of a catalytic amount of $NbCl_3$(DME) (10 mol%) at 40 °C for 4 h, giving a mixture of 1,4-di-*tert*-butyl-5-butyl-1,3-cyclohexadiene (**3aa** as 1,4,5-adduct) and 1,3-di-*tert*-butyl-5-butyl-1,3-cyclohexadiene (**4aa** as 1,3,5-adduct) along with a small amount of tri-*tert*-butylbenzenes (**5a**)[10] in 72% total yield (entry 1).‡ It is noteworthy that the 2:1 cross-cyclotrimerization of **1a** and **2a** by the Nb complex was selectively catalyzed in preference to the cyclotrimerization of **2a**, which takes place very easily, to give 1,3-cyclohexadienes (**3aa** + **4aa**) in 83% selectivity. The reaction also proceeded with high regioselectivity to afford the 1,4,5-adduct (**3aa**) as a major product (**3aa** : **4aa** = 88 : 12). The regiostructures of the cycloaddition products (**3aa** and **4aa**) were characterized by ^1H and ^{13}C NMR, the resonances being assigned by means of 2D HMQC, HMBC, and NOESY spectroscopy (see ESI†).

Improvement of the yield and the selectivity of the **3aa** was attained by controlling the reaction conditions. Thus, the best yield and selectivity of **3aa** was achieved when the reaction of **1a** and **2a** was carried out with a 1:1 ratio (entry 1). However, when **1a** and **2a** were allowed to react in a stoichiometric ratio (namely 2 : 1), the yield and selectivity of the intermolecular cycloaddition products (**3aa** and **4aa**) were still high to moderate (entry 2).

The reaction was greatly affected by the solvent employed, and halogenated solvents such as 1,2-dichloroethane or dichloromethane resulted in a high selectivity for **3aa** (entries 1–3). The use of other solvents such as THF, dioxane, toluene and DME resulted in lower yields of **3aa** (entries 4–7).

As for the catalyst precursor of this reaction, the low-valent Nb(III) complex, $NbCl_3$(DME), is highly efficient. When the Ta(III) analog, $TaCl_3$(DME), was used as a catalyst, preferential formations of the alkyne cyclotrimerization products (**5a**) (33% yield) as well as the dimerization product, 1,4-di-*tert*-butyl-1-buten-3-yne (9% yield), were observed, but the desired 1,3-cyclohexadiene adduct was not produced at all (entry 8). Other Nb(IV), Nb(V) and V(III) complexes such as $NbCl_5$, Cp_2NbCl_2 and $VCl_3(THF)_3$, were totally inactive as catalysts, and no cycloaddition products (**3aa**, **4aa**, or **5aa**) were formed at all (entries 9–11).

Under the optimized condition as shown in Table 1, entry 1, reactions of various 1-alkynes (**1a–d**) with 1-alkenes (**2b–2g**) were examined (Table 2). The selectivity of the adducts was greatly influenced by the bulkiness of substituents both on the alkynes and alkenes. The reaction of **1a** with **2b** or 1-decene (**2c**) led to the corresponding intermolecular cycloaddition products, 1,4-di-*tert*-butyl-5-hexyl-1,3-cyclohexadiene (**3ab**) or 1,4-di-*tert*-butyl-5-octyl-1,3-cyclohexadiene (**3ac**), respectively, with high chemo- (81–83%) and regioselectivities (91%) (entries 1–2). The best result for the formation of 1,3-cyclohexadiene was obtained in the reaction of **1a** with ethylene (**2d**), which afforded 1,4-di-*tert*-butyl-1,3-cyclohexadiene (**3ad**) in high yield (with 97% selectivity) (entry 3). The proximal substituents on the double bond of alkenes were found to decrease of the 1,3-cyclohexadienes (entries 4–7).

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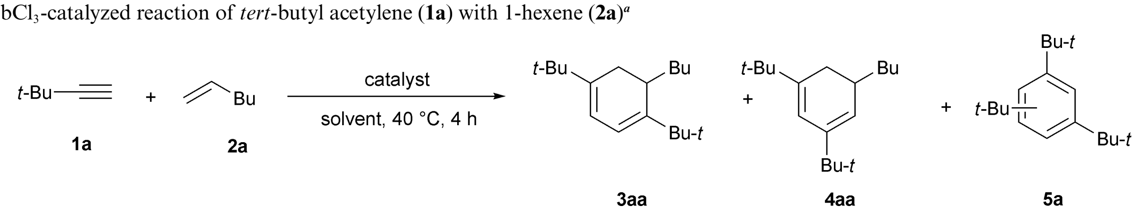
† Electronic supplementary information (ESI) available: Characterization data (^1H and ^{13}C NMR and MS) and other spectral data (^1H–^{13}C HMQC, HMBC and NOESY) of the products. See DOI: 10.1039/b820352k

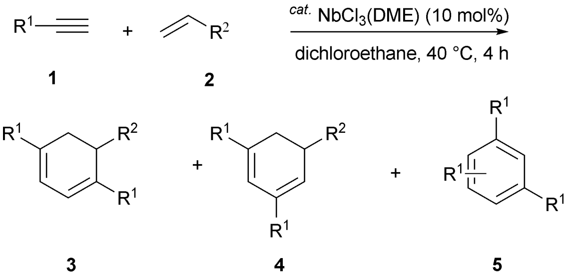
Table 1 $NbCl_3$-catalyzed reaction of *tert*-butyl acetylene (**1a**) with 1-hexene (**2a**)[a]



Entry	Catalyst	Solvent	Total yield (**3aa**–**5aa**)/%[b]	Selectivity for 1,3-cyclohexadienes (**3aa**+**4aa**)/%[c]
1	$NbCl_3$(DME)	$Cl(CH_2)_2Cl$	72 [67]	83 (88)
2[d]	$NbCl_3$(DME)	$Cl(CH_2)_2Cl$	66	70 (86)
3	$NbCl_3$(DME)	CH_2Cl_2	71	79 (90)
4	$NbCl_3$(DME)	THF	45	22 (8)
5	$NbCl_3$(DME)	Dioxane	64	36 (23)
6	$NbCl_3$(DME)	Toluene	3	47 (72)
7	$NbCl_3$(DME)	DME	0	—
8[e]	$TaCl_3$(DME)	$Cl(CH_2)_2Cl$	33	0
9[f]	$NbCl_5$	$Cl(CH_2)_2Cl$	0	—
10	Cp_2NbCl_2	$Cl(CH_2)_2Cl$	0	—
11	$VCl_3(THF)_3$	$Cl(CH_2)_2Cl$	0	—

[a] **1a** (2 mmol) was allowed to react with **2a** (2 mmol) in the presence of catalyst (0.2 mmol, 10 mol% based on **1a**) in solvent (1 mL) at 40 °C for 4 h. [b] Yields were determined based on **1a** used. The number in brackets is an isolated yield. [c] Determined by GC. The numbers in the parentheses show the selectivity (%) for **3aa**. [d] **1a** (2 mmol) and **2a** (1 mmol) were used. [e] 1,4-Di-*tert*-butyl-1-buten-3-yne was obtained as a by-product (9%). [f] A intractable mixture of unidentified oligomerization products was obtained.

Table 2 $NbCl_3$-catalyzed reaction of terminal alkynes (**1**) with 1-alkenes (**2**)[a]



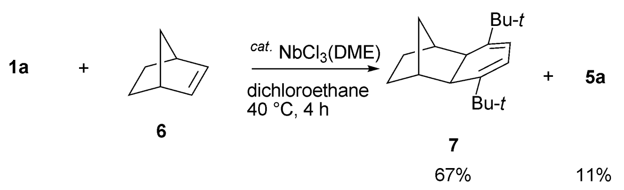
Entry	R^1 (alkyne)	R^2 (alkene)	Total yield (**3**–**5**)/%[b]	Selectivity for 1,3-cyclohexadienes **3**+**4**/%[c]
1	*t*-Bu (**1a**)	*n*-C_6H_{13} (**2b**)	70 [68]	83 (91)
2	*t*-Bu (**1a**)	*n*-C_8H_{17} (**2c**)	75 [72]	81 (91)
3	*t*-Bu (**1a**)	H (**2d**)[d]	78	97 (98)
4	*t*-Bu (**1a**)	$C_2H_5C(CH_3)_2CH_2$ (**2e**)	45	49 (84)
5	*t*-Bu (**1a**)	$PhCH_2$ (**2f**)	54	67 (86)
6	*t*-Bu (**1a**)	Ph (**2g**)	67 [67]	55 (83)
7	*t*-Bu (**1a**)	4-$CH_3C_6H_4$ (**2h**)	63	60 (83)
8	Ph (**1b**)	*n*-C_4H_9 (**2a**)	73	8 (100)
9	*c*-Hex (**1c**)	*n*-C_4H_9 (**2a**)	72	18 (100)
10	Hex (**1d**)	*n*-C_4H_9 (**2a**)	74	5 (100)
11	Ph (**1b**)	H (**2d**)[e]	56	45 (91)
12	Hex (**1d**)	H (**2d**)[e]	58	36 (100)

[a] **1** (2 mmol) was allowed to react with **2** (2 mmol) in the presence of $NbCl_3$(DME) (0.2 mmol, 10 mol% based on **1**) in dichloroethane (1 mL) at 40 °C for 4 h. [b] Yields were determined based on **1** used. The numbers in brackets are the isolated yields. [c] Selectivity (%) of 1,3-cyclohexadienes (**3**+**4**) was determined by GC. The numbers in the parentheses show the selectivity (%) of **3**. [d] **2d** (2 MPa) was used by using a 50 mL stainless steel autoclave.

The use of phenylacetylene (**1b**), cyclohexylacetylene (**1c**), and hexylacetylene (**1d**) as alkynes resulted in a lower selectivity for **3** and **4**. In these cases, formation of the alkyne cyclotrimerization products (**5**) was unavoidable (entries 8–10). However, the selectivity for the 1,3-cyclohexadienes (**3** and **4**) in the reaction of **1b** and **1d** was improved when ethylene (**2d**) was used (entries 11–12).

It was reported by Rothwell and coworkers that the Ti-catalyzed intermolecular cycloaddition of alkynes and alkenes gave isomerized 1,3-cyclohexadienes as major products,[3] which are formed through the 1,5-hydrogen shift[11] within the initially produced titananorbornene intermediate. This is in sharp contrast to our Nb(III)-catalyzed reaction, which did not involve such an isomerization pathway. For instance, the reactions of **1a** with **2d** gave 1,4-di-*tert*-butyl-1,3-cyclohexadiene[12] (**3ad**) as the major adduct in the present system (see entry 3, Table 2), but afforded 2,6-di-*tert*-butyl-1,3-cyclohexadiene as a major adduct by Rothwell's method. Similarly, the reaction of **1a** with **2g** gave a mixture of 1,4-di-*tert*-butyl-5-phenyl-1,3-cyclohexadiene (**3ag**) and 1,3-di-*tert*-butyl-5-phenyl-1,3-cyclohexadiene (**4ag**) in our system, but afforded 2,6-di-*tert*-butyl-4-phenyl-1,3-cyclohexadiene as the major adduct by Rothwell's method.

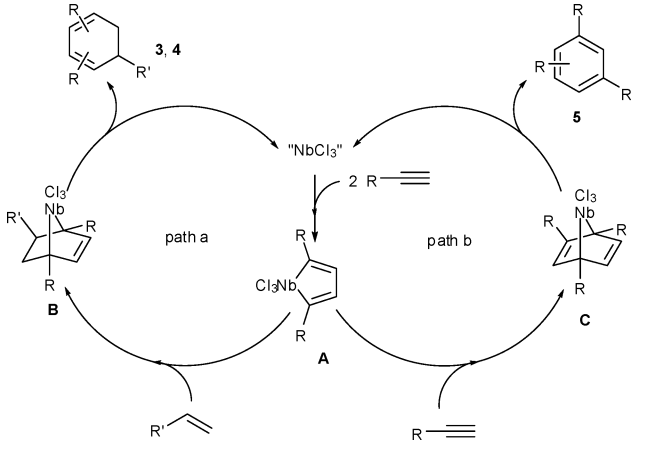
This reaction can be successfully extended to the reaction of **1a** and norbornylene **6** under the optimized reaction condition to give the cycloaddition product (**7**) in the *exo*,*exo* form[13] in 67% yield, along with the formation of **5a** (11%) (Scheme 1).



Scheme 1

Although it is not possible to confirm a detailed reaction mechanism at this stage, the cycloaddition of alkynes with alkenes is thought to proceed in a similar way to the previously reported Ta-[7,1b] and Ti- catalyzed cycloaddition[3] with alkynes *via* the formation of a metallacyclopentadiene as a key intermediate.

Thus, a plausible reaction pathway is shown in Scheme 2. This reaction would be considered to proceed through a niobacyclopentadiene intermediate **A** formed by the oxidative cyclization of two alkyne molecules on the low-valent niobium catalyst. When bulky substituents such as *tert*-Bu are present on the niobacyclopentadiene, the attack of (sterically less congested) olefins upon **A** might take place preferentially to afford a niobanorbornene intermediate **B**, resulting in 1,3-cyclohexadienes (**3** and **4**) as the major products (path a). On the other hand, less bulky alkynes lead to the formation of cyclotrimerization products through competing attack of a third alkyne upon **A** to form niobanorbornadiene **C** (path b).



Scheme 2 A plausible reaction pathway.

Unlike the Ti-catalyzed system,[3] the present Nb-catalyzed reaction did not involve an isomerization step, which is probably due to a relatively thermally stable niobanorbornene intermediate.[14]

In conclusion, we have developed a new highly active catalytic system for selective [2+2+2] cycloaddition of alkynes and alkenes. Further investigation with regard to the detailed reaction mechanism and the application of this reaction is currently in progress.

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Notes and references

‡ A typical reaction procedure is as follows (Table 1, entry 1): A mixture of **1a** (2 mmol, 164 mg), **2a** (2 mmol, 168 mg), $NbCl_3$(DME) (0.2 mmol, 58 mg), and 1,2-dichloroethane (1 mL) was stirred for 4 h at 40 °C under Ar. The yields of the products were estimated from the peak areas based on the internal standard technique using GC (53% (**3aa**), 7% (**4aa**) and 12% (**5a**)). The products were isolated as a mixture of **3aa**, **4aa** and **5a** (by silica gel column chromatography using *n*-hexane as eluent) due to the difficulty in completely separating them.

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