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Cross-coupling reaction of thermally stable titanium(II)-alkyne complexes with aryl halides catalysed by a nickel complex

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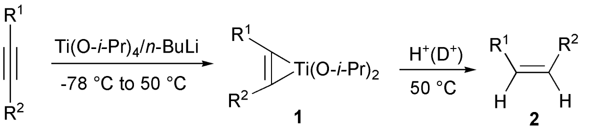
The first cross-coupling reaction of thermally stable titanium(II)–alkyne complexes with aryl iodides in the presence of a catalytic amount of Ni(cod)$_2$ is presented.

Alkyne–metal complexes prepared from low-valent early transition metal compounds such as Ti(II), Zr(II), Nb(III), and Ta(III) are very useful synthetic reagents since they are known to function as 1,2-dicarbanionic olefins.[1–4] Nonmetallocene (η^2-alkyne)Ti(O-i-Pr)$_2$ is an especially versatile synthetic reagent and a wide variety of reactions have been explored by Sato and coworkers.[1,5] However, the Ti(II)–alkyne complexes thus obtained are thermally unstable and can only be used below −30 °C.

On the other hand, much less attention has been paid to Ti compounds as substrates in transition metal catalysed reactions.[6] It is well-known that the transition metal catalysed cross-coupling reaction of organic halides with Mg, B, Sn, and Si compounds is one of the most straightforward methods for C–C bond formation.[7] However, there is only one example of the cross-coupling reaction using a Ti compounds, in which thermally stable Ti(IV) compounds such as MeTi(O-i-Pr)$_3$ and PhTi(O-i-Pr)$_3$ were employed as substrates.[8]

Quite recently, Eisch and coworkers reported that Ti(II)–alkyne complexes prepared from alkynes and Bu$_2$Ti(O-i-Pr)$_2$ generated from Ti(O-i-Pr)$_4$ and BuLi at −78 °C were thermally stable at 25 °C.[9] Their work prompted us to report our independent finding that thermally stable Ti(II)–alkyne complexes can be utilized as substrates in transition metal catalysed reactions. In this communication, we report an unprecedented transition metal catalysed cross-coupling reaction of Ti(II)–alkyne complexes with aryl halides. The Ti(II) complexes were stable even at 50 °C and Ni catalysed reaction afforded coupling products in good yields.

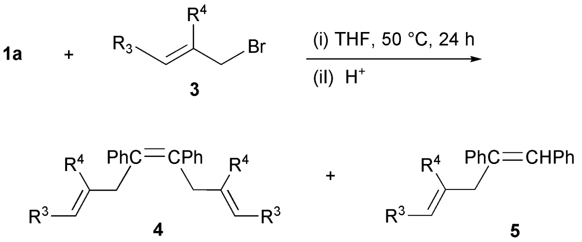
Thermally-stable Ti(II)–alkyne complexes (**1**) were successfully generated by slow addition of 2 equiv. of n-BuLi as a reducing reagent (for the Ti(IV) to Ti(II) process) to a mixture of Ti(O-i-Pr)$_4$ and alkyne in THF at −78 °C followed by raising the temperature to 50 °C (eqn. 1).



(1)

Then, the THF solution of **1** was stirred for an additional hour at 50 °C prior to further reaction. The formation of diphenylacetylene complex (**1a**) was verified by hydrolysis or deuteriolysis of the reaction mixture affording *cis*-stilbene or *cis*-stilbene-d_2 (> 98% D) in almost quantitative yield (entry 1, Table 1). As for the reducing reagent, n-BuLi is appropriate to stabilize the Ti(II)–alkyne complex at 50 °C. The use of s-BuLi also works similarly as judged by the formation of *cis*-stilbene in high yield (95%) after the hydrolysis. However, other reducing reagents affect the thermal stability of **1** considerably: **1a** prepared with i-PrMgBr or n-BuMgBr *in lieu* of n-BuLi was not stable and afforded *cis*-stilbene in quite low yield (~ 20%) after hydrolysis at 50 °C. As for a titanium compound, when TiCl$_2$(O-i-Pr)$_2$ or Ti(O-t-Bu)$_4$ was employed instead of Ti(O-i-Pr)$_4$ in entry 1 (Table 1), **1** was not so stable and the yield of *cis*-stilbene was less than 50%. Thus, the Ti(O-i-Pr)$_4$–n-BuLi–alkyne system is suitable for generation of the thermally stable **1**. Various thermally stable Ti(II)–alkyne complexes (**1b–f**) were successfully generated as evidenced by the excellent yields of **2** after hydrolysis at 50 °C (entries 2–6, Table 1).

For further evaluation of the thermal stability of **1**, the allylation reaction of **1** with allylic bromides (**3**) at 50 °C was carried out (eqn. 2, Table 2).



(2)

In contrast to previous monoallylation reactions of **1** with **3** at low temperature (−50 °C, then warmed up to rt),[10] the reaction of **1a** with allyl bromide (**3a**) at 50 °C afforded diallylation product (**4a**) as a major product in high yield (99% yield and 90% selectivity, entry 1, Table 2). The allylation reactions with crotyl bromide (**3b**) and methallyl bromide (**3c**) similarly gave diallylation products as major product (entries 2 and 3, Table 2). The higher reaction temperature (50 °C) would favor the diallylation reaction.

Since the Ti(II)–alkyne complexes (**1**) are thermally stable at 50 °C, **1** may be utilized as substrates even in a transition metal

Table 1 Hydrolysis of thermally stable Ti(II)–alkyne complexes (**1**)[a]

Entry	R^1	R^2		Yield of **2**^{b} (%)
1	Ph	Ph	**1a**	99
2	p-CH$_3$C$_6$H$_4$	p-CH$_3$C$_6$H$_4$	**1b**	97
3	Ph	(CH$_3$)Si	**1c**	92
4	Ph	Me	**1d**	90
5	n-Pr	n-Pr	**1e**	95
6	(CH$_3$)$_3$Si	(CH$_3$)$_3$Si	**1f**	95

[a] Conditions: alkyne (0.50 mmol), Ti(O-i-Pr)$_4$ (0.50 mmol), n-BuLi (1.0 mmol as 1.6 M hexane solution) and THF (3.0 mL) at −78 °C, then warmed up to 50 °C. [b] GLC yields determined by the internal standard method.

Table 2 Allylation of Ti(II)–alkyne complex (**1a**) with allylic bromides (**3**)[a]

Entry	R^3	R^4		Yield (%) (**4** : **5**)^b
1	H	H	**3a**	99 (90^c : 10^c)
2	Me	H	**3b**	87 (77^d : 23^e)
3	H	Me	**3c**	77 (65^c : 35^e)

[a] Conditions: **1a** (0.50 mmol), **3** (2.0 mmol) and THF (3.0 mL) at 50 °C for 24 h. [b] GLC yields determined by the internal standard method. [c] E : Z = 2 : 8. [d] E : Z = 1 : 9. [e] E : Z = 1 : 1.

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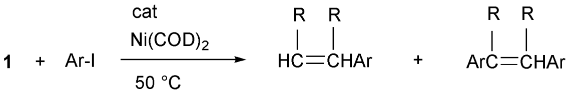
catalysed reaction carried out above room temperature. Among possible reactions, a cross-coupling reaction was chosen, and **1** was reacted with aryl iodide (**6**) in the presence of a nickel catalyst (eqn. 3).



$$\mathbf{1} + \text{Ar-I} \xrightarrow[50\ °\text{C}]{\text{cat Ni(COD)}_2} \overset{\text{R}\quad\text{R}}{\text{HC=CHAr}} + \overset{\text{R}\quad\text{R}}{\text{ArC=CHAr}} \qquad (3)$$

6 **7** **8**

$Ni(cod)_2$ showed the highest catalytic activity and cross-coupling products (**7a** and **8a**) were afforded in 81% total yield from **1a** and 4-iodobenzotrifluoride (**6a**) at 50 °C with 5 mol% of the nickel complex (entry 1, Table 3).† Other nickel or palladium catalyst precursors such as $Ni(acac)_2$, $Pd(OAc)_2$, and $Pd(PPh_3)_4$ only showed poor catalytic activity. The catalyst loading slightly affected the reaction: iodobenzene (**6b**) afforded the products in 60, 65, and 75% yields with 10, 40, and 100 mol% of $Ni(cod)_2$, (entries 2–4, Table 3). 3-Iodobenzotrifluoride (**6c**) and 1-fluoro-4-iodobenzene (**6d**) afforded the corresponding products in moderate yields (entries 5 and 6). As for aryl halides, iodides gave the best results, whereas the corresponding bromides, chlorides, and triflates afforded low yields (< 10%). Other Ti(II) complexes of di-*p*-tolylacetylene (**1b**), 4-octyne (**1e**), and 3-hexyne (**1g**) also provided the corresponding coupling products in moderate to high yields (entries 7–9, Table 3).

Although all attempts to isolate or fully characterize **1** were unsuccessful, we measured the ^{13}C NMR spectrum of **1a** in THF-d_8 (0.3 M). In the aliphatic region of the spectrum, two peaks at 28.4 and 72.6 ppm were assignable to methyl and methine carbons of the *i*-Pr group, respectively. These two resonances were not consistent with the *i*-Pr carbons of *i*-PrOLi (30.6 and 64.4 ppm) and Ti(O-*i*-Pr)$_4$ (26.8 and 76.6 ppm) in the same solvent and at the same concentration. This result might suggest that **1** did not exist as a simple mixture of (η^2-alkyne)Ti(O-*i*-Pr)$_2$ and *i*-PrOLi, but was obtained as an ate-type complex[11] such as $[(\eta^2\text{-alkyne})\text{Ti(O-}i\text{-Pr)}_4]^{2-}\cdot 2\text{Li}^+$, which might cause the thermal stability of **1**. Further study on the structure and thermal stability of **1** is currently in progress.

Table 3 Nickel-complex catalysed cross-coupling reaction of Ti(II)–alkyne complexes (**1**) with aryl iodides (**6**)[a]

Entry	R (= R^1 = R^2)	Ar	Yield (%) (**7** : **8**)[b,c]
1	Ph (**1a**)	*p*-$CF_3C_6H_4$ (**6a**)	81 (74[d] : 26[e]) (**7a** : **8a**)
2[f]	**1a**	Ph (**6b**)	60 (65 : 35) (**7b** : **8b**)
3[g]	**1a**	**6b**	65 (55 : 45) (**7b** : **8b**)
4[h]	**1a**	**6b**	75 (40 : 60) (**7b** : **8b**)
5	**1a**	*m*-$CF_3C_6H_4$ (**6c**)	55 (89[i] : 11[e]) (**7c** : **8c**)
6	**1a**	*p*-FC_6H_4 (**6d**)	40 (90[e] : 10[e]) (**7d** : **8d**)
7	*p*-$CH_3C_6H_4$ (**1b**)	**6a**	72 (79[d] : 21[e]) (**7e** : **8e**)
8	*n*-Pr (**1e**)	**6a**	48 (84[i] : 16[e]) (**7f** : **8f**)
9	Et (**1g**)	**6d**	41 (93[d] : 7[e]) (**7g** : **8g**)

[a] Conditions: **1** (0.50 mmol), **6** (2.0 mmol), $Ni(cod)_2$ (0.025 mmol, 5 mol%), and THF (3.0 mL) at 50 °C for 24 h. [b] GLC yields determined by the internal standard method. [c] In addition to the coupling products, 3,6-dihydro-2,2,4-trimethyl-5,6-diphenyl-2*H*-pyran was obtained (5–20%) in entries 1–6: ^1H NMR ($CDCl_3$) δ 1.42 (s, 3H), 1.48 (s, 3H), 1.60 (s, 3H), 1.93 (d, J = 15 Hz, 1H), 2.56 (d, J = 16 Hz, 1H), 5.25 (s, 1H), 6.76 (d, J = 4 Hz, 2H), 7.08–7.18 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3), 23.6 (CH_3), 30.9 (CH_3), 42.4 (CH_2), 71.4 (C), 78.1 (CH), 126.1 (CH), 126.6 (CH), 127.2 (CH), 127.6 (CH), 127.8 (CH), 128.3 (CH), 129.4 (CH), 133.6 (C), 139.3 (C), 141.3 (C); HRMS (EI) calc. for $C_{20}H_{22}O$: *m*/*z* 278.1671. Found: *m*/*z* 278.1666. Anal. calc. for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 85.99, H, 7.88%. [d] $E : Z$ = 4 : 6. [e] $E : Z$ = 1 : 1. [f] $Ni(cod)_2$ (0.050 mmol, 10 mol%). [g] $Ni(cod)_2$ (0.20 mmol, 40 mol%). [h] $Ni(cod)_2$ (0.50 mmol, 100 mol%). [i] $E : Z$ = 3 : 7.

Notes and references

† A mixture of diphenylacetylene (89 mg, 0.50 mmol), Ti(O-*i*-Pr)$_4$ (115 mg, 0.50 mmol) and THF (3.0 mL) was placed with a magnetic stirring bar in a 20 mL round-bottomed flask under an argon flow. The mixture was cooled to −78 °C and *n*-BuLi (1.0 mmol, 1.6 M solution in hexane) was added dropwise over 5 min. Then, the reaction mixture was slowly warmed to 50 °C over 1 h and stirred at the same temperature for an additional hour. To this solution, **6a** (544 mg, 2.0 mmol) and $Ni(cod)_2$ (7 mg, 0.025 mmol) were added and the reaction mixture was stirred at 50 °C for 24 h. After the reaction, the whole mixture was passed through a short silica gel column to afford a clear yellow solution. GLC and GC-MS analyses of the reaction mixture showed the formation of the cross-coupling products (**7a** and **8a**)[12] in 81% yield. Isolation of the cross-coupling products for NMR analysis was carried out by column chromatography (silica gel with hexane/CH_2Cl_2, 95/5).

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