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Isolation and Structural Characterization of a Titanacyclopropane as Key Intermediate in the Double Aryl Grignard Addition to 2-(Arylethynyl)pyridine Derivatives

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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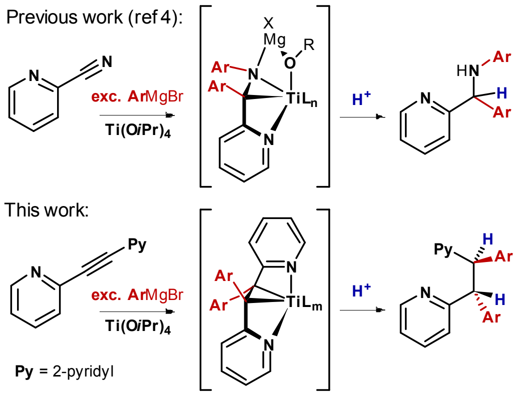
A titanacyclopropane species, which is a key reaction intermediate in the Ti(O*i*Pr)$_4$-mediated double aryl Grignard addition to 1,2-di(pyridin-2-yl)ethyne and related alkynes, was isolated and fully characterized. Based on this observation a one-pot synthesis of diarylated 1,2-di(pyridin-2-yl)ethanes and 2-(1,2,2-triarylvinyl)-pyridines was developed, including the tetraarylation of V-shaped 2,6-bis(arylethynyl)pyridines.

In situ generated bis(alkoxy)titanacyclopropanes generated by reaction of Ti(IV) alkoxides and aliphatic Grignard reagents have given rise to a large variety of titanium mediated organometallic reactions. It has been the pioneering work by Kulinkovich and Sato which has established the synthetic potential of minimally ligated titanacyclopropane species. Reaction patterns range from the 1,2-insertion of esters, amides and nitriles into the titanacyclopropane ring[1] to the synthesis of allylic/allenylic titanium reagents,[2] intramolecular nucleophilic acyl substitution (INAS) reactions,[3] diverse couplings of alkynes and alkenes[4] as well as related transformations.[1-5] Since Ti(O*i*Pr)$_4$ and many Grignard reagents are available in bulk at low price, the multicomponent reactions based on this approach provide an attractive route to highly functionalized synthetic targets.

In the case of Sato's reagent the in situ generated titanacyclopropane acts as a Ti^{II} synthon in reactions with functionalized alkynes, activating them towards attack by electrophiles. Conversely, nucleophilic attack of C≡X/C≡C triple bonded substrates, which are appropriately "anchored" to a Ti^{IV} centre should be enhanced. We recently developed Ti(O*i*Pr)$_4$-mediated carbo- and azaphilic double aryl Grignard addition to 2-pyridinecarbonitriles CN-bonds[6] in which the pre-coordination of the pyridyl unit preceded the double intramolecular nucleophilic attack by the transfer of the aryl groups from the Grignard reagents to both the carbon and nitrogen atom of the C≡N group (Scheme 1, top). For this transformation an azatitanacyclopropane intermediate, generated in a multistep reaction sequence, has been postulated based on isolated and characterized intermediates and systematic DFT modeling of the reactivity of the in situ generated species.



Scheme 1 Ti(O*i*Pr)$_4$-mediated double arylation of 2-cyanopyridine (top) and 1,2-di(pyridin-2-yl)ethane (bottom) *via* formation of azatitana- and titanacyclopropane species, respectively.

The observed carbo- and azaphilic Grignard addition to the nitrile group inspired us to extend the double arylation to related C≡C triple bonded substrates. This not only provided the opportunity to obtain additional insight into the multistep reaction mechanisms of such transformations but might also lead to stuctural evidence for the key reactive intermediates involved. In this work we show that double addition to 2-alkynylpyridine triple bonds gives rise to the corresponding titanacyclopropane species for which one derivative could be isolated and completely structurally characterized. Protonolysis of the titanacyclopropane diastereoselectively yielded tetraarylated alkanes (Scheme 1, bottom; Scheme 2).

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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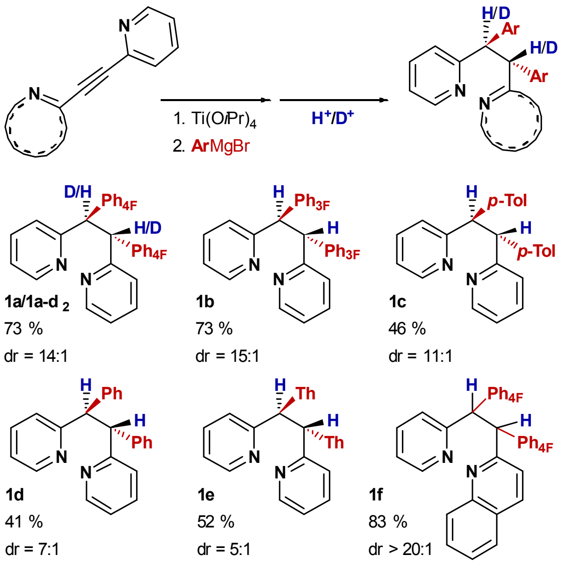


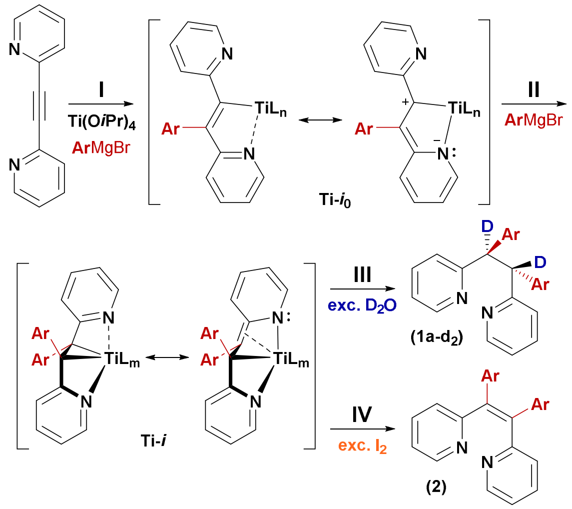
Scheme 2 Diastereoselective Ti(O*i*Pr)$_4$-mediated double aryl Grignard additions to 1,2-di(pyridin-2-yl)ethyne and derivatives. Ph$_{4F}$ = 4-F-C$_6$H$_4$-, Ph$_{3F}$ = 3-F-C$_6$H$_4$-, Th = 2-thienyl. Ti(O*i*Pr)$_4$: 1.0 equiv, RT, 5 min. ArMgBr: 3.5 equiv, −78°C during the addition then 40°C, 2 days. Protonolysis with H_2O (**1a, 1f**), D_2O (**1a-d$_2$**) or CF_3COOH (**1b-e**).

The initial proof of concept was provided by the straightforward one-pot diarylation of 1,2-di(pyridin-2-yl)ethyne by consecutive addition of a stoichiometric amount of Ti(O*i*Pr)$_4$ and 3.5 equivalents of an arylmagnesium bromide reagent (Scheme 2). The reaction conditions were optimized for the addition of 4-fluorophenylmagnesium bromide which gave the corresponding tetraarylalkane **1a** in good yield upon aqueous work-up. The racemate of the *anti* diastereoisomer was obtained as the main product in a diastereomeric ratio (dr) of 14 : 1 with respect to the alternative *meso* product (Scheme 2).

Similarly, in all other cases (**1b-f**) the homochiral diastereomer was found to be the main product with dr values ranging between >20:1 and 5:1 (Scheme 2). The identification of the major diastereomer and the determination of the dr values was achieved by NMR spectroscopy using Eu(hfc)$_3$ as chiral shift reagent.

Deuterolytic work-up lead to full deuteration of the two sp^3 carbon atoms (**1a-d$_2$**). Furthermore the addition of an excess of elemental iodine before the hydrolytic step gave *cis*-1,2-diaryl-1,2-di(pyridin-2-yl)ethene (**2**) in 60% yield. Given these experimental results, as well as the results of our previous study on the diarylation of the corresponding 2-cyanopyridines (vide supra), a titanacyclopropane-based reaction pathway is proposed, the key elements of which are represented in Scheme 3. An alkyne arylation/coordination step (**I**) gives rise to a titanacyclic intermediate (**Ti-*i*$_0$**). Such a monoarylated adduct is expected to exhibit pronounced polarization at the C=C bond due to the ortho-branched pyridin-2-ylene system. This would favour either a direct or - as in the case of the nitrile analogue, metal mediated second aryl addition (**II, Ti-*i***). Deuterolysis of the titanacyclopropane complex **Ti-*i***, finally gives the expected tetraarylalkane (**III, 1a-d$_2$**), while reaction with iodine would oxidatively release a tetraarylalkene (**IV, 2**).

Complex **Ti-*if*** was isolated prior to the hydrolytic work-up of the product mixture by solvent removal and extraction of the solid residue with toluene/pentane 10:1 followed by direct crystallization at −40°C. In this way single crystals of **Ti-*if*** suitable for X-ray diffraction were obtained and the spectroscopic characterization of the complex by ^{1}H, ^{13}C{^{1}H} and ^{19}F{^{1}H} NMR spectroscopy was achieved. Hydrolysis quantitatively gave the reaction product **1f**.



Scheme 3 Proposed reaction pathway for the synthesis of diarylated 1,2-di(pyridin-2-yl)ethanes/ethenes. Ar = 4-F-C$_6$H$_4$-.

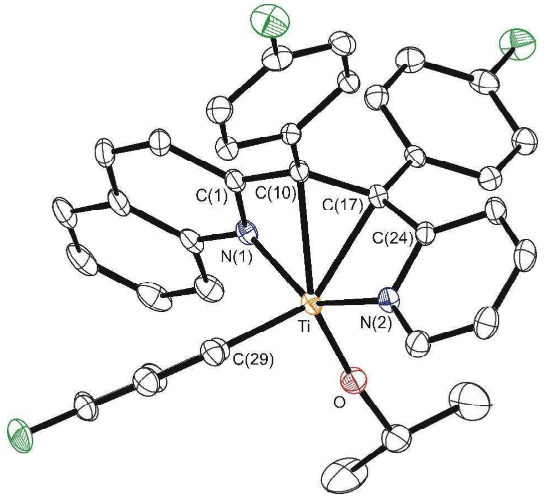


Figure 1 Molecular structure of complex **Ti-*if*** isolated from the product mixture. Thermal ellipsoids set at the 50% probability level. H-atoms have been omitted for clarity. Selected bond lengths ([Å]) and angles ([°]): Ti-C(10) 2.3915(12), Ti-C(17) 2.1757(12), Ti-C(1) 2.4685(12), Ti-C(24) 2.6476(12), Ti-N(1) 1.9951(11), Ti-N(2) 2.1894(11), C(1)-C(10) 1.4084(17), C(10)-C(17) 1.4970(16), C(17)-C(24) 1.4754(17), O-Ti-C(29) 109.47(5), Ti-O-C(35) 172.86(10), C(17)-Ti-C(10) 37.89(4).

The key features of the molecular structure of complex **Ti-*if*** depicted in Figure 1 are the titanacyclopropane motif as well as the additional 4-fluorophenyl group which is directly coordinated to the metal. Notably, the two heteroaryl groups coordinate to the metal center with very different Ti-N bond lengths [Ti-N(1) 1.9951(11), Ti-N(2) 2.1894(11)]. This breach of

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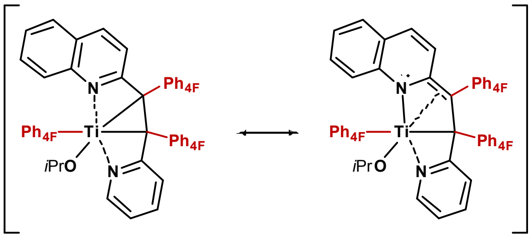
symmetry also translates to the two titanacyclopropane carbon atoms with bond lengths of 2.3915(12) and 2.1757(12) for Ti-C(10) and Ti-C(17), respectively. These observed values lie within the expected length range for functionalized titanacyclopropanes.[7] The C(1)-C(10) bond is considerably shorter than the C(17)-C(24) bond [1.4084(17) vs. 1.4754(17) Å, respectively], which is consistent with some double bond character of the former.

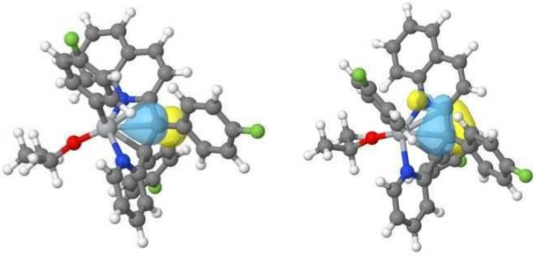
Three singlets of same intensity in the $^{19}F\{^1H\}$ NMR spectrum of **Ti-*if*** correspond to the three chemically distinct 4-fluorophenyl groups in the complex. In the ^{13}C NMR spectrum the titanacyclopropane carbon atoms resonate at 89.1 and 110.3 ppm, thus confirming a pronounced asymmetry in the system. Complex **Ti-*ia***, obtained as described for **Ti-*if*** except for starting from the coupling protocol described for **1a** (see SI), showed fully congruent spectroscopic features, hence excluding any role of the quinolyl group in the observed asymmetry of the titanacyclopropane unit.



Str1 **Str2**

Scheme 4 The key titanacyclopropane (**Str1**) and eneamidotitanium (**Str2**) resonance structures of **Ti-*if***.

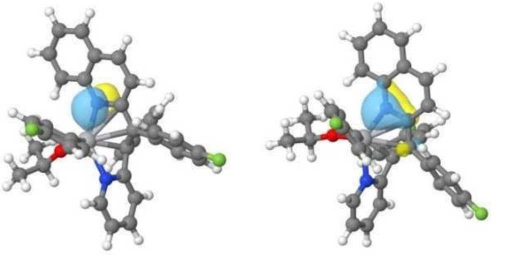
The bonding situation in **Ti-*if*** may be described with reference to two limiting structures: a classical titanacyclopropane with a coordinated quinoline (**Str1**, Scheme 4, left), or an ene-amido type description (**Str2**, Scheme 4, right). B3LYP/6-311G geometry optimization of **Ti-*if*** was carried out and the calculated geometry was found to be in good agreement with the experimental data. A Natural Bonding Orbital (NBO) analysis specifically for the resonance **Str1** indicates that the Ti-C(10) NBO is rather weakly populated for a σ-bond (1.348 e), when compared to the Ti-C(17) NBO (1.689 e). Moreover, the second-order perturbation energy analysis showed a strong delocalization component of the electron density of σ[Ti-C(10)] into π^*[N(1)-C(1)] (ΔE_2 = 171 kcal mol^{-1}) (Figure 2).



Ti-C(10) NBO **Ti-C(10) NLMO**

Figure 2 Comparison between the strictly localized NBO associated to the Ti-C(10) bond and the delocalized situation in the corresponding NLMO for the Lewis structure **Str1**.

As a result, the NLMO corresponding to the Ti-C(10) σ-bond only contains 64% of the parent NBO character. The remaining electron density within this NLMO is spread over the π-system and delocalized onto Ti, N(1), C(1), and C(10) (Figure 2). In the NBO analysis of **Str2**, the Ti-N(1) NBO essentially involves a p atomic orbital (AO) on N(1) with a population of 1.625 e (Figure 3). The main delocalization pattern involves the Ti-N(1) π-bond that interacts with the vicinal π^* component between C(1) and C(10) (ΔE_2 = 50.8 kcal mol^{-1}). The resulting NLMO for Ti-N(1) retains 80% of the parent NBO character, the remaining of the 2e electron density being located in the π-system of the quinoline ring and of the C(1)-C(10) π-bond as illustrated in Figure 3. The NBO analysis of **Str1** and **Str2** points clearly to a description of the electronic structure of **Ti-*if*** as an ene-amido with a significant resonance between the nitrogen-centered p AO and the C(1)-C(10) π-bond.



Ti-N(1) NBO **Ti-N(1) NLMO**

Figure 3 Comparison between the strictly localized NBO associated to the Ti-N(1) bond and the delocalized situation in the corresponding NLMO for the Lewis structure **Str2**.

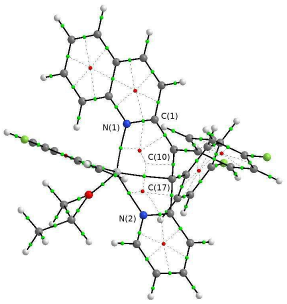


Figure 4 Bond (green) and ring (red) critical points resulting from an AIM analysis of the electronic structure of **Ti-*if***.

The AIM analysis of the electron density of **Ti-*if*** confirms the NBO analysis (Figure 4). There is no bond critical point (BCP) between Ti and C(10), whereas there is one between Ti and C(17). In addition, the values of the ellipticity ε at various BCPs are in agreement with the description of Ti-*if* as an ene-amido complex. For the two BCPs between Ti and N, that associated with Ti-N(1) has ε = 0.142, whereas that for Ti-N(2) has ε = 0.022. This clearly indicates more developed π-character for the bond between Ti and N(1) while the values of ε for the N(1)-C(1), C(1)-C(10) and C(10)-C(17) (0.052, 0.224 and 0.122, respectively) also reflect a stronger π-component for the C(1)-C(10) bond and a significant σ-character for the N(1)-C(1) bond, again in agreement with the proposed ene-amido Lewis structure. When extended to 2-(arylethynyl)pyridine derivatives, in which the aryl unit is not pyridine-derived, the usual synthetic

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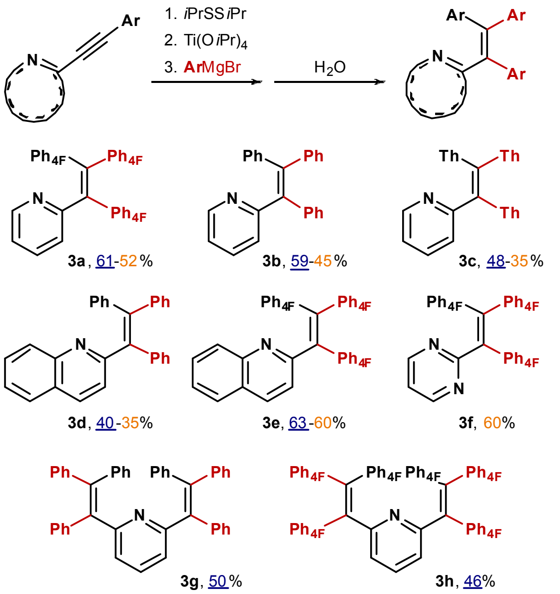
protocol gave the corresponding tetraarylalkenes instead of the expected tetraarylalkanes in low to moderate yields. A substantial increase in the isolated yield was achieved in presence of 1.5 equivalents of diisopropyl disulfide (Scheme 5).



Scheme 5 Ti(O*i*Pr)$_4$-mediated diarylation of 2-(arylethynyl)pyridine derivatives and tetraarylation of V-shaped 2,6-bis(arylethynyl)-pyridines. Ph$_{4F}$ = 4-F-C$_6$H$_4$-, Th = 2-thienyl. *i*PrSS*i*Pr: 1.5 equiv (**3a-f**) or 3.0 equiv (**3g, h**), 5 min, RT. Ti(O*i*Pr)$_4$: **1.0 equiv**/**0.1-0.2 equiv**, 5 min, RT. ArMgBr: 2.5 equiv (**3a-f**) or 5.0 equiv (**3g, h**), −78°C during the addition then 40°C, **1-3 days**/**7 days**.

The presence of 1.5 equivalents of the mild oxidizing agent isopropyl disulfide, replacing the I$_2$ employed in step **IV** in Scheme 3, allowed for the use of a catalytic amount of Ti(O*i*Pr)$_4$ (10-20 mol-%), with comparable isolated yields but a slower product generation. The titanacyclopropane intermediate **Ti-*if*** may be viewed as a "masked" Ti(II)-olefine π-complex, and the ability of alkyl disulfides to undergo oxidative addition at Ti(II) centers is known reactive pattern.[8] The resulting bis(isopropylsulfido) species then reacts with the Grignard reagent and the alkynylpyridine substrate to regenerate **Ti-*if***. This protocol was successfully extended to V-shaped 2,6-bis(arylethynyl)pyridines, giving the expected 2,6-bis(1,2,2-triarylvinyl)pyridines **3g** and **3h** as the respective tetraarylation products. The facile access to such target compounds is of particular interest due to their properties as fluorophors, as have been recently reported for **3g** and related meta-branched 2,6-bis(1,2,2-triarylvinyl)pyridines[9] as well as **3b**[10].

In conclusion, a titanacyclopropane-based complex has been characterized as a key reaction intermediate in the synthesis of a variety of diarylated 1,2-di(pyridin-2-yl)ethanes, 2-(1,2,2-triarylvinyl)pyridines and derivatives, along with V-shaped 2,6-bis(1,2,2-triarylvinyl)pyridines. The double nucleophilic addition to pyridylalkynes described in this work represents a new reactivity pattern complementing the carbometallation/electrophilic addition strategy commonly used for the 1,2-functionalization of alkynes.[11]

Conflicts of interest

There are no conflicts of interest to declare.

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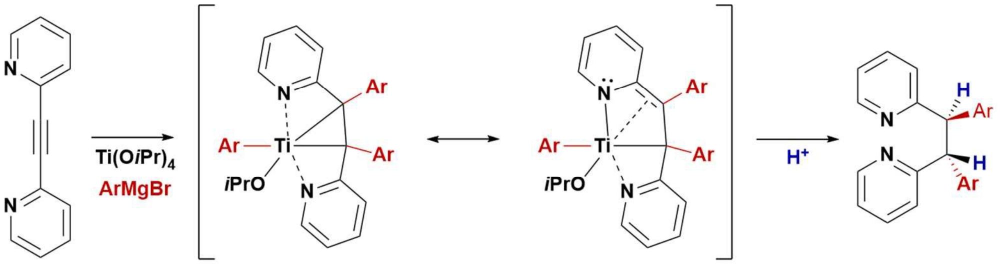

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