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Acceleration of metallacycle-mediated alkyne–alkyne cross-coupling with TMSCl

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Abstract

Investigation of titanium-centered metallacycle-mediated cross-coupling between unsymmetrical internal alkynes has led to the discovery that TMSCl significantly accelerates the C–C bond forming event. We report a collection of results that compare the efficiency of this reaction employing $\text{Ti}(\text{O}i\text{-Pr})_4/2n\text{-BuLi}$ in PhMe with and without TMSCl, demonstrating in every case that the presence of TMSCl has a profound impact on efficiency. While relevant in the context of developing this fundamental bond-forming process as an entry to more complex organometallic transformations, these modified reaction conditions allow coupling processes to be run at > 10 times the concentrations previously possible [in 2.4M $n\text{-BuLi}$ (hexanes)], without the requirement of additional solvent. Finally, we demonstrate the effectiveness of these modified reaction conditions for the annulative cross-coupling between TMS-alkynes and 1,6-enynes leading to the formation of angularly substituted hydrindanes with, now well appreciated, high levels of regio- and stereoselection.

Graphical Abstract

Keywords

Titanium isopropoxide; Directed reactions; Metallacycle-mediated cross-coupling; 1,3-Dienes

Metallacycle-mediated cross-coupling of alkynes is growing as a powerful means of accessing stereodefined 1,3-dienes – functional groups with broad utility in stereoselective synthesis.¹ While originally discovered in the context of Reppe’s Nicatalyzed alkyne trimerization for the synthesis of benzenes,² recent advances in Group IV metal-centered coupling chemistry have resulted in methods suitable for regioselective and stereospecific

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cross-coupling of alkynes.³ In 1999, Sato reported the ability to employ $\text{Ti}(\text{O}i\text{-Pr})_4/2i\text{-PrMgX}$ in coupling reactions between polarized internal alkynes and terminal alkynes,⁴ and subsequent studies have culminated in the establishment of methods that have proven quite useful in natural product synthesis.⁵ While coupling of an internal alkyne with a terminal alkyne is now relatively straightforward, the related metallacycle-mediated union of two internal alkynes has proven to be substantially more challenging due to low levels of reactivity that routinely thwart attempts at cross-coupling, and difficulties controlling regioselectivity with respect to both participating π -systems. In studies aimed at rendering metallacycle-mediated cross-coupling alkoxide-directed, we discovered an important role of homopropargylic and bis-homopropargylic alcohols in these processes (Figure 1A).⁶ We reported that exposure of a Ti-alkyne complex (generated from treating an alkyne with the reagent combination of $\text{Ti}(\text{O}i\text{-Pr})_4/2\text{RMgX}$),⁷ to a homo- or bishomopropargylic alkoxide results in highly regioselective and stereospecific cross-coupling, presumably by way of a new alkoxide-directed organometallic transformation. This early success marked the beginning of a program to explore what we later termed “Class II”¹ alkoxide-directed metallacycle-mediated cross-coupling, led to a process for alkene-alkyne coupling (Figure 1B),⁸ and ultimately to a Ti-centered annulative cross-coupling (alkyne + alkyne + alkene) for the stereoselective synthesis of angularly substituted hydrindanes (Figure 1C).⁹ While successful, we have on occasion had difficulties optimizing reaction conditions for coupling, being limited by the concentration and quality of the commercial Grignard reagents employed in initial alkyne activation, physical properties associated with the ethereal solvent that the Grignard is in, and the relatively low concentrations that are required when employing this reagent combination (initial Ti-alkyne complex formation is typically carried out at $\sim 0.1\text{M}$ – higher concentrations often result in heterogeneous solutions).¹⁰ In recent studies, we have turned to the reagent combination of $\text{Ti}(\text{O}i\text{-Pr})_4/2n\text{-BuLi}$ in toluene as a suitable alternative to $\text{Ti}(\text{O}i\text{-Pr})_4/2\text{RMgX}$, and have observed success in annulative coupling processes¹¹ and imine-allylic alcohol coupling reactions.¹⁰ Here, we describe our efforts to employ such reaction conditions for hydroxyl-directed alkyne-alkyne coupling and report a dramatic rate enhancement for cross-coupling with the addition of TMSCl .

As illustrated in Figure 2A, we began our study by exploring the reaction between TMS-alkyne **1** and homopropargylic alcohol **2** promoted by the reagent combination of $\text{Ti}(\text{O}i\text{-Pr})_4/2n\text{-BuLi}$. To our surprise and disappointment, the efficiency of this process was quite poor, producing after 1h at -20°C the tetrasubstituted 1,3-diene in only 20% yield (albeit as a single isomer). Attempts to increase the yield of this process by prolonged stirring or increasing the reaction temperature were met with the observation of complex product mixtures, indicating what we believe to be a metastable nature of the metallacycleopentadiene intermediate. In cases where this intermediate is trapped in a fast intramolecular process (i.e. [2+2+2] annulation *en route* to hydrindanes), the instability of the metallacyclopentadiene intermediate does not surface as an issue that impacts reaction efficiency.⁹

Moving forward with an attempt to optimize the simple alkyne-alkyne cross-coupling process, we considered the four transformations that are critical for success (Figure 2B): (i) formation of a titanacyclopentene, (ii) ligand exchange, (iii) coordination, and (iv)

intramolecular carbometalation. Assuming that titanium must have an open coordination site for carbometallation to occur, we speculated that superstoichiometric quantities of LiO*i*-Pr (present from step (i)) may inhibit the desired C–C bond forming event by association with titanium. With this idea in mind we sought an additive that would intercept LiO*i*-Pr, moderating its propensity to form titanium-ate complexes and to potentially inhibit the desired reaction path.

As illustrated in Figure 2C, treatment of TMS-alkyne **1** with Ti(O*i*-Pr)₄ and 2 equivalents of *n*-BuLi at –78 °C was followed by heating to 50 °C (to form the initial Ti-alkyne complex). Next, TMSCl was added to intercept the resulting LiO*i*-Pr. Cooling of the reaction mixture was then followed by addition of the second alkyne (**2**) as its corresponding Li-alkoxide. The resulting reaction mixture was stirred at –20 °C for 1h and quenched by protonation of the presumed metallacyclopentadiene intermediate. To our delight, the conjugated diene **3** was obtained in 72% isolated yield (without TMSCl, only 20% yield was observed; Figure 2A) – as experienced during our earlier study of this basic class of metallacycle-mediated cross-coupling, no evidence was found for the production of isomeric products.

TMSCl-induced acceleration in cross-coupling was observed with all substrates explored. As illustrated in Figure 3, TMS-alkynes possessing cyclopropane, hydrocinnamyl, *i*-Pr, and Ph substituents were all competent substrates for the reaction. Similarly, the other alkyne coupling partner could contain a primary or secondary hydroxyl directing group as well as a propargylic ether. Notably, a substrate bearing a tertiary alcohol directing group was not highly effective in this type of coupling reaction (with or without the addition of TMSCl).

Use of these *n*-BuLi/TMSCl-modified reaction conditions enables this class of metallacycle-mediated cross-coupling to be conducted at much higher concentrations than previously possible. For example, coupling of TMS-alkyne **1** with homopropargylic alcohol **2** was successful without adding toluene as solvent. This reaction was run in a 2.4M solution of *n*-BuLi in hexanes as the solvent, and delivered the 1,3-diene product **3** in 61% isolated yield (Figure 4; see Supporting Information for additional details).

Given that the first step in Ti-mediated annulative cross-coupling for the synthesis of hydrindanes is an alkoxide-directed alkyne–alkyne coupling, we explored if the current procedure would be useful for this more complex tandem reaction. As depicted in Figure 5, coupling of TMS-alkyne **1** with 1,6-enyne **13** proceeded with outstanding levels of regio- and stereocontrol, delivering the angularly substituted hydrindane **14** in 62% isolated yield.

Overall, we report a new procedure for metallacycle-mediated cross-coupling of internal alkynes. The use of TMSCl in Ti(O*i*-Pr)₄/2*n*-BuLi-promoted coupling results in a substantial increase in the rate of reaction and consistently delivers 1,3-diene-containing products in markedly increased yield in comparison to procedures lacking TMSCl. These modified reaction conditions can be employed with minimal solvent, enabling the coupling process to proceed in 2.4M *n*-BuLi, and have proven effective for hydroxyl-directed annulative crosscoupling *en route* to angularly substituted hydrindanes. We look forward to further exploring the potential impact of these new reaction conditions in other metallacycle-mediated cross-coupling processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Procedure for accomplishing regioselective and stereospecific reductive cross-coupling of internal alkynes.
- Use of $\text{Ti}(\text{O}i\text{-Pr})_4/2n\text{-BuLi}$ in metallacycle-mediated cross-coupling.
- Rate acceleration of cross-coupling by addition of TMSCl .
- Procedure to run cross-coupling in 2.4M BuLi in hexanes – this is by far the most concentrated any reaction of this type has been conducted. Use of $\text{Ti}(\text{O}i\text{-Pr})_4/2\text{RMgX}$ results in substantial limitation in the concentration at which such reactions can be conducted - - they typically become heterogeneous at concentrations $>0.2\text{ M}$ (ether).

A. Alkoxide-directed metallacycle-mediated cross-coupling between internal alkynes:

B. Alkoxide-directed metallacycle-mediated alkene-alkyne cross-coupling:

C. Annulative cross-coupling reaction between alkynes and 1,6-enynes:

^a = via intramolecular [4+2] of intermediate titanacyclopentadiene.

Figure 1.

Introduction to alkoxide-directed metallacycle-mediated cross-coupling with $\text{Ti}(\text{O}i\text{-Pr})_4/2\text{RMgX}$.

A. BuLi as a reductant in cross-coupling of disubstituted alkynes: **B. Considering a potential role of LiO*i*-Pr in dissuading the coupling reaction:** **C. Addition of TMSCl to the initial Ti-alkyne complex greatly accelerates coupling:** **Figure 2.**

Alkyne-alkyne coupling reactions with Ti(O*i*-Pr)₄/*n*-BuLi and the discovery of an acceleration induced by TMSCl.

Figure 3. Comparison of Ti-mediated alkyne-alkyne coupling reactions with and without the addition of TMSCl .

Figure 4.

Reaction can be run “neat” - 2.4 M $n\text{-BuLi}$ in hexanes was used as the solvent.

Figure 5.
 Use of TMSCl in the annulative cross-coupling reaction between TMS-alkynes and 1,6-enynes.