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Trimethylsilyl-Protected Alkynes as Selective Cross Coupling Partners in Ti-Catalyzed [2+2+1] Pyrrole Synthesis

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Abstract

Trimethylsilyl (TMS)-protected alkynes serve as selective alkyne cross coupling partners in Ti-catalyzed [2+2+1] pyrrole synthesis. Reactions of TMS-protected alkynes with internal alkynes and azobenzene catalyzed by Ti imido catalysts yield pentasubstituted 2-TMS-pyrroles with greater than 90% selectivity over the other 9 possible pyrrole products. The steric and electronic effects of the TMS group have both been identified to play key roles in this highly selective pyrrole synthesis. This strategy provides a convenient methodology to synthesize multisubstituted pyrroles as well as an entry point into further pyrrole diversification through facile modification of the resulting 2-silylpyrrole products, as demonstrated through a short formal synthesis of the marine natural product Lamellarin R.

E Pluribus Unum

Trialkylsilyl-protected alkynes enable highly chemo- and regioselective reactions in Ti-catalyzed [2+2+1] multicomponent pyrrole synthesis. The resulting pentasubstituted 2-SiR₃ pyrroles are formed with up to 99% selectivity over the other 9 possible pyrrole products.

Keywords

Pyrrole; Titanium; Cycloaddition; Alkyne; Selectivity

Pyrroles are molecules of interest in a variety of fields, including pharmaceuticals,^[1] natural products,^[2] dyes^[3] and materials.^[4] Even though there are many well-developed methods for the synthesis of pyrroles, the efficient synthesis of multisubstituted pyrroles is still challenging. For example the Paal-Knorr condensation of primary amines with 1,4-diketones and related cyclization reactions require extensive preconstruction of the carbon backbone and often have limited substitution patterns.^[1, 5] Multicomponent reactions that can

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circumvent complex precursor synthesis typically require very specific functional groups or substitution patterns.^[6] For example, many formal [3+2], [2+2+1], and related multicomponent cycloadditions necessitate electron-withdrawing substituents on the pyrrole, [6–7] or are limited to the synthesis of mono-, di-, or trisubstituted pyrrole products.^[6a, 8]

Recently, we demonstrated an atom economical method to synthesize pentasubstituted pyrroles from simple alkynes and azobenzene via a Ti-catalyzed formal [2+2+1] reaction (Figure 1, top).^[9] However, our initial report was limited to the homocoupling of alkynes, and unsymmetric alkynes yielded poor, substrate-controlled regioselectivity. Regioselectivity in other intermolecular [2+2+1] reactions such as the Pauson-Khand reaction is often difficult to achieve in the absence of clear stereoelectronic differentiation of alkyne substituents, and remains a significant synthetic challenge.^[10] In an effort to design more useful and practical pyrrole syntheses, we have explored several routes to the chemo- and regioselective heterocoupling of alkynes in the [2+2+1] reaction to yield highly substituted pyrroles. Herein, we report that silyl-protected alkynes serve as excellent heterocoupling partners, yielding pentasubstituted N-aryl pyrroles in high chemo- and regioselectivity (Figure 1, bottom). This reaction provides a versatile and simple platform for the construction of highly substituted pyrroles, as well as an entrypoint into further pyrrole diversification through facile modification of the resulting 2-silylpyrrole products.

In the course of our studies, we have found that TMS-phenylacetylene (**1a**) is incapable of productive [2+2+1] reactivity. Attempted hydroamination of **1a** with [(py₂TiCl₂NPh)₂ and PhNH₂, which should proceed through [2+2] cycloaddition of the alkyne to the Ti=NPh imido, resulted in no product formation indicating that **1a** is incapable of facile [2+2] addition with simple Ti imido halides (Figure 2, top). Thus, we hypothesized that they may be suitable cross-coupling partners with other alkynes that are capable of [2+2] cycloaddition. To test this hypothesis, we ran the reaction of **1a** with 1-phenyl-1-propyne (**2a**), and found that it gave remarkably chemo- and regioselective cross coupling of the two alkyne partners (Figure 2, bottom). This model reaction was optimized to achieve the highest yield of the crossover pyrrole and its overall selectivity among all homocoupled and crossover products (Table S1). Selectivities are fairly good with a 1:1 ratio of **1a:2a**, but we chose to use 2 equivalents of **1a** in order to simplify byproduct separation.

Under the optimized reaction conditions, the substrate scope was investigated. First, a suite of TMS-protected aryl alkynes was reacted with **2a** (Table 1). All pyrroles were isolated after hydrolysis of the TMS group, giving **3aa-3ra** as the major regioisomer in almost all cases. Most aryl TMS acetylenes give exceptionally high yields and selectivities, typically above 90%. There is no electronic effect on yield or selectivity (**3aa-3fa**, **3ja-3la**), while sterically encumbered substrates such as **1i** are more difficult to insert, leading to more homocoupling of **2a** and slightly lowered yield/selectivity of the desired **3ia**. The reaction shows reasonably broad functional group tolerance, including aryl halides (**3ca**, **3da**) and some Lewis basic groups (**3ea-3ga**; **3la**, **3ma'**), although aryl nitriles and carbonyl derivatives arrest catalysis (See SI).

In addition to aryl alkynes, TMS-protected alkyl alkynes (**3na-3pa**) all perform well in highly cross selective pyrrole formation (**3na-3op**), although sterically encumbered *tert*-

butyl groups (**3qa**) do not participate in catalysis and yield only homocoupled **2a**. Notably, conjugated enynes (**3pa**) are tolerated in catalysis, providing an additional functional handle on the resulting pyrrole. TMS₂C₂ (**1r**) is also a competent cross coupling partner, yielding **3aa** on workup.

Other silyl groups are also competent for heterocoupling. Silyloxy groups (**1t**) effectively yield cross product **3oa**. The slightly larger TBDMS-protected alkyne **1u** also couples effectively to form **3aa** upon workup, but the very bulky TIPS-protected alkyne **1v** fails to engage in cross coupling. The TBDMS group provides a more stable silylpyrrole than the TMS group, while the Si(OMe)₃ group provides additional synthetic versatility^[11] in Hiyama-type couplings.^[12]

The origins of regio- and chemoselectivity in these heterocoupling reactions are derived mainly from electronic factors of both alkyne partners (Figure 3). Regioselectivity in [2+2] cycloaddition of phenylpropyne derivatives with Ti=NPh is driven primarily by the electronics of the metallacyclic transition state (Figure 3, **TS1**) where the δ⁺ is better stabilized by CH₃. This electronically-driven regioselectivity is also seen in py₃TiCl₂(NPh)-catalyzed hydroamination, where *N*,1-diphenylpropan-2-imine is the sole product resulting from metallacycle **INT1**.^[13]

Chemoselectivity of alkyne insertion into the Ti-C bond of the azametallacyclobutadiene intermediate **INT1** is driven by alkyne coordination to Ti. Electron-rich alkynes are better ligands to Ti^{IV} Lewis acids, and as such the electron-rich TMS-alkynes effectively outcompete other alkynes in binding and subsequently inserting into the metallacycle via **TS2** (Figure 3). This can be observed in reactions of the series of *para*-substituted phenylpropynes (Table 2, **3ab-3ae**) where alkynes with more electron-donating groups competed more effectively with TMSCCR, resulting in more homocoupled arylpropyne products and thus overall lower selectivity. Further evidence for alkyne electronics/binding driving 2nd insertion selectivity can be seen in the competition experiment where the more electron rich *p*-substituted TMS aryl alkyne **1f** outcompetes the electron deficient alkyne **1b** by 2:1 (Figure 4). Regioselectivity of TMS-alkyne insertion is likely driven by the α-silyl effect, where the α-SiMe₃ moiety stabilizes δ⁻ buildup during insertion (Figure 3, **TS2**), favoring the metallacycle that places SiMe₃ on the α-C. Similar effects have been observed in the hydroboration of silyl alkynes^[14] and the reactivity of group 4 metal alkyne complexes.^[15]

Directing group effects are observable in reactions with (2-methoxy)phenyl-TMS-acetylene (**1g**) and pyridin-2-yl-TMS-acetylene (**1m**). **1g** gives significant amounts of the **3ga'** regioisomer, and for **1m**, **3ma'** is almost exclusively formed, likely because coordination of the TMS alkyne to Ti *via* the OMe or 2-pyridyl groups would enforce the opposite insertion of the TMS-alkyne into the azametallacyclobutene [2+2] intermediate. (Figure 5). Interestingly, the thiophenyl derivative **1l** does not show a directing effect, presumably due to the hard/soft Ti/S mismatch making thiophenes weaker donors to Ti.

Next, different [2+2] alkyne partners were tested with **1a** and **1o** (Table 2). Unlike modifications to the TMS-protected alkynes, electronic and steric modification of the [2+2]

alkyne partner alters the reaction selectivity. For example, electron-donating phenylpropyne derivatives (**3ad**, **3od**, **3ae**, **3oe**) decrease the yield and chemoselectivity of second insertion, resulting from an increase in the formation of homocoupled arylpropyne pyrroles. This highlights the importance of alkyne precoordination during the alkyne 1,2 insertion step, where now the electron-donating arylpropyne can more effectively compete with the electron-rich TMS-protected alkynes. Consistent with this, reaction of 2-methoxyphenyl propyne (**2f**), which can precoordinate to Ti through the ether moiety, leads predominantly to homocoupling of **2f** instead of heterocoupled **3af**. *Ortho*-steric hindrance on aryl propynes (**3ag-3ai**, **3og-3oi**) significantly lessens conversion and regioselectivity of [2+2] cycloaddition. Prolonged reaction time does not increase conversion, indicating catalyst death in these cases.

Differing aromatic substituents (**3ai**, **3oi**, **3ak**, **3ok**) are also tolerated, although now pyridine substitution (**3al** and **3ol**) completely inhibits catalysis through coordination to Ti. Longer alkyl substituents (**3am**, **3om**) also work well, but bulkier isopropyl substituents (**3an**, **3on**) do not undergo facile [2+2] cycloaddition. Reactions of unactivated dialkyl/diaryl internal alkynes (**3ao-3ar**, **3oo-3or**) require the more Lewis acidic (THF)₃I₂TiNPh. However, alkynes with little electronic differentiation, like 4-methyl-2-pentyne (**3ar**, **3or**), yield products of unselective [2+2] cycloaddition, and bulky internal alkynes (**3as**, **3os**) are unreactive.

The advantage of the silyl directing group is its ability to be functionalized after reaction. Although poor partners for cross coupling reactions, 2-TMS pyrroles can undergo facile electrophilic aromatic substitution. For example, NBS substitution of the TMS group yields bromopyrroles in high yield, which provides a versatile handle for further pyrrole functionalization (Figure 6, top).

Furthermore, this alkyne heterocoupling strategy can provide facile access to the pyrrole core of lamellarins, a class of marine natural products. We have completed a short formal synthesis of lamellarin R. *In situ* benzylic oxidation of **6wd** with 2-iodoxybenzoic acid (IBX) (**6wd** was generated from the [2+2+1] coupling of **1w**, **2d** and 4,4'-azodanisole) yields **7wd**, which can then be deprotected by tetrabutylammonium fluoride and water to the aldehyde **8wd**, intersecting a previous synthesis reported by Jia^[16] (Figure 6, bottom).

In summary, we have found that we can exploit the electronic properties of silyl-substituted alkynes to perform highly chemo- and regioselective [2+2+1] heterocouplings to form pyrroles. The products, 2-silyl-pyrroles, can be further functionalized and provide access to a large range of tetra- and pentasubstituted pyrroles, yielding diverse N-arylated pyrroles that map onto several natural product cores. Going forward, we plan on exploiting this and related types of electronic control to further advance chemo- regioselective Ti-catalyzed oxidative amination reactions beyond pyrrole synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Previous work:

statistical mixtures of homocoupled alkyne pyrroles

This work: regio- and chemo-selective
alkyne heterocoupling

Figure 1.
General equations of Ti-catalyzed pyrrole formation.

Figure 2.

Failed [2+2] cycloaddition of **1a** (top) led to the exploration of its use as a partner in selective heterocoupling reactions (bottom).

Figure 3. General mechanism and proposed origins of selectivity in cross-selective [2+2+1] pyrrole synthesis.

Figure 4.

Competition between electronically differentiated TMS-protected alkynes favors reaction of electron rich alkynes.

Figure 5.
Lewis basic groups change the selectivity of 2nd alkyne insertion through directing effects.

In-situ bromination of TMS pyrroles: **[2+2+1] strategy in the formal synthesis of Lamellarin R:** **Figure 6.**

Further elaboration of TMS pyrroles. Top: bromination of 2-TMS-pyrroles. Bottom: formal synthesis of lamellarin R.

Table 1

Scope of coupling partners with 1-phenyl-1-propyne (**2a**)^a

^a 0.5 mmol (1.1 eq) 1-phenyl-1-propyne (**2a**), 1.0 mmol **1** (2.2 eq.), 0.225 mmol PhNNPh (0.5 eq.) and 0.025 mmol [py₂Cl₂TiNPh]₂ (0.05 eq.) in 2.5 mL CF₃Ph heated for 3 hours. Reactions were quenched with 2M HCl in MeOH to remove the silyl group.

^b Isolated yield of **3** based on PhNNPh.

^c Selectivity against all possible pyrroles;

^d 1.5 h.

^e 1 equiv. of **1**.

^f 4 h.

^g 24 h.

^h 5 h.

Table 2

Scope of coupling partners with **1a** and **1o**.^a

^a 0.5 mmol (1.1 eq) **2**, 1.0 mmol **1a** or **1o** (2.2 eq.), 0.225 mmol PhNNPh (0.5 eq.) and 0.025 mmol [py₂Cl₂TiNPh]₂ (0.05 eq.) in 2.5 mL CF₃Ph heated for 1.5 or 3 hours.

^b Isolated yield of **3** based on PhNNPh. GC yields in parenthesis.

^c Selectivity against all possible pyrroles.

^d 48 h.

^e 24 h.

^f 6 h.

^g (THF)₃I₂TiNPh (10 mol %) used as catalyst.

^h 4 h.