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Dative Directing Group Effects in Ti-Catalyzed [2+2+1] Pyrrole Synthesis: Chemo- and Regioselective Alkyne Heterocoupling

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Supporting Information Placeholder

ABSTRACT: Transient dative substrate-Ti interactions have been found to play a key role in controlling the regioselectivity of alkyne insertion and [2+2] cycloaddition in Ti-catalyzed [2+2+1] pyrrole synthesis and Ti-catalyzed alkyne hydroamination. TMS-protected alkynes with pendent Lewis basic groups can invert the regioselectivity of TMS-protected alkyne insertion, leading to the selective formation of highly substituted 3-TMS pyrroles. The competency of various potential directing groups was investigated, and it was found that the directing group effect can be tuned by modifying the catalyst Lewis acidity, the directing group basicity, or the directing group tether length. Dative directing group effects are unexplored with Ti catalysts, and this study demonstrates the potential power of dative substrate-Ti interactions in tuning selectivity.

KEYWORDS: *directing group effects, multicomponent reactions, pyrroles, titanium, alkynes*

Introduction

Highly substituted pyrroles are important components of many bioactive natural products, drug candidates, and FDA-approved drugs.[1-4] Recently, we have reported several multicomponent formal [2+2+1] pyrrole syntheses from alkynes and diazenes or azides (Figure 1).[5-9] These methods provide facile, modular access to highly substituted pyrrole cores that are otherwise challenging to synthesize.

Attaining regio- and chemoselectivity can be inherently difficult [2+2+1] cycloaddition reactions such as our Ti-catalyzed pyrrole synthesis or the Pauson-Khand reaction.[10-11] Previous studies demonstrated that the selectivity of Ti-catalyzed alkyne coupling is driven by intrinsic alkyne stereoelectronic properties, and this substrate-driven selectivity results in a statistical mixture of regioisomers.[5] More recently we discovered that the heterocoupling of TMS-protected alkynes can occur with exceptional regioselectivity, yielding 2-TMS pyrroles (Figure 1, top).[8] These reactions are highly selective due to the electronic properties of the TMS-protected alkynes: they do not easily undergo the [2+2] cycloadditions with Ti=NR imidos, but rapidly (because of their electron-richness) and regioselectively (because of the thermodynamic α-Si effect[8, 12-19]) insert into azatitanacyclobutenes. This protocol can access all possible penta- and tetrasubstituted pyrrole substitution patterns except for 1,2,3,5-tetrasubstitution.

An alternative strategy for regiocontrol is to use heteroatom-based directing groups to enforce selectivity. For example, sulfur and nitrogen-substituted alkenes have been used in the cobalt catalyzed [2+2+1] Pauson-Khand reaction to direct the product regioselectivity.[20-22] This method has further been applied to the formal synthesis of Prostaglandin A2.[23] Removable directing groups have also been used in the Pauson-Khand reaction, notably by using silicon-tethered pyridinyl vinyl silanes which could go through facile hydrolytic desilylation.[24-25]

Pendent alkoxide directing groups have been used extensively in Ti-catalyzed and mediated reactions to engender regio-, chemo- and enantioselective transformations.[26] For example, Sharpless' catalytic asymmetric alkene epoxidation relies on alkoxide directing groups to engender enantiofacial selectivity,[27] while more recently Micalizio has used alkoxides to direct alkyne insertion regioselectivity in Ti-mediated reductive coupling reactions (Figure 1, middle)[18-19, 28-31] and Burns has used alkoxides to direct stereoselective alkene dihalogenation and haloazidation reactions.[32-35] Alkoxide-directed coupling reactions have also served as a platform for heterocycle syntheses, such as pyridines and indolizidines.[36-37]

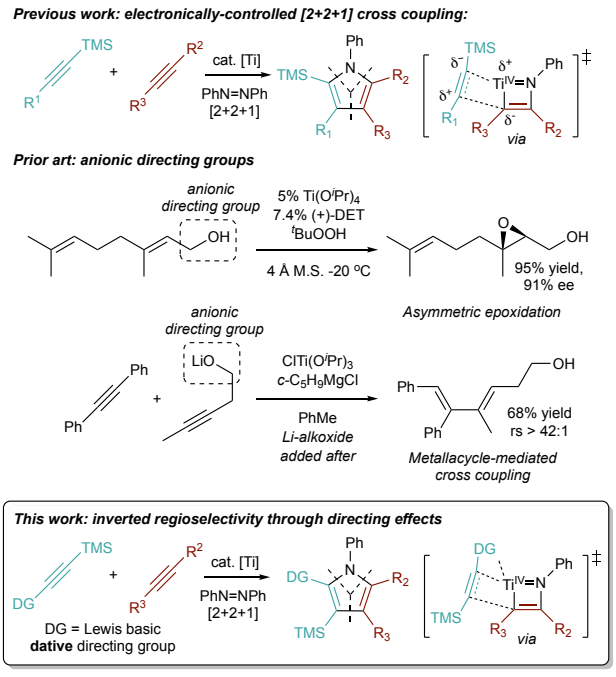


Figure 1. Top: general overview of directing groups in Ti catalyzed/mediated chemistry; Bottom: Ti-catalyzed [2+2+1] pyrrole synthesis and methods for chemo- and regioselective alkyne heterocoupling.

To exert complete regiocontrol over multisubstituted pyrrole synthesis, we have undertaken a study of pendent directing group effects in Ti-catalyzed [2+2+1] pyrrole synthesis (Figure 1, bottom), envisioning that it would be possible to reverse the regiochemical course of the reaction. In contrast to anionic directing groups, the use of dative directing groups in titanium catalysis is unexplored. However, we envisioned that transient dative donor interactions could promote chemo- and regioselective reactions while also undergoing the facile ligand exchange needed for productive redox catalysis. We herein report that TMS-protected alkynes with pendent Lewis basic groups can invert the regioselectivity of TMS-protected alkyne insertion in Ti-catalyzed [2+2+1] pyrrole synthesis. This demonstrates that a dative directing group effect can override the substrate's intrinsic selectivity. These reactions lead to the formation of 3-TMS-substituted pyrroles, which can be used in complex molecule synthesis.

Results and Discussion

Unlike other TMS-protected alkynes, the [2+2+1] heterocouplng of ((2-methoxyphenyl)ethynyl)trimethylsilane (**1a**) with phenylpropyne (**2a**) was remarkably unselective for **4a-TMS**, giving a 1.1:1 ratio of **3a-TMS**:**4a-TMS** (Table 1, Entry 1).[8] We speculated that the increased yield of **3a-TMS** was a result of the *o*-OMe group precoordinating to Ti and directing 2nd alkyne insertion in a manner opposite the electronic properties of the alkyne (Figure 2).

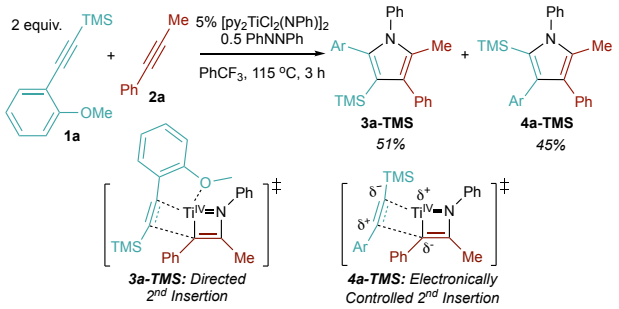
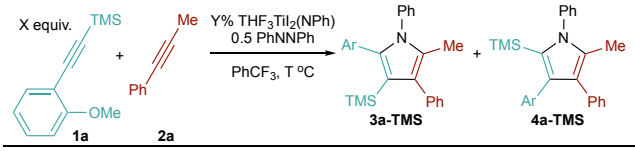


Figure 2. Initial observation of a directing group effect: *o*-Me substituted aryl alkynes (**1a**) have poor selectivity for electronically preferred 2nd insertion product **4a-TMS**.

Thus, we sought to find conditions that favored the directed 3-TMS product **3a-TMS**. First, $[py_2TiCl_2(NPh)]_2$ was replaced by the more Lewis acidic catalyst $THF_3TiI_2(NPh)$[38-39] to promote stronger coordination of the *o*-OMe group. This increased the **3a-TMS**:**4a-TMS** ratio to 5.5:1 (Table 1, Entry 2). Lowering the reaction temperature further improved the selectivity, giving regioisomeric ratios > 10.5:1 (Table 1, Entries 2-5). At lower temperatures dissociation of the *o*-OMe is likely slowed, resulting in formation of the kinetically preferred metallacycle leading to **3a-TMS** over **4a-TMS**.[8] In our previous studies of TMS-alkyne heterocouplings, chemoselectivities were good at a 1:1 ratio of the two alkynes, but from a practical perspective we found it better to use an excess of the TMS-alkyne in order to make product separations more simple. However, here reducing the equivalents of **1a** had little effect on yield or selectivity, indicating that the directing group effect can more effectively outcompete **2a** homocoupling (Entry 6). Thus, the conditions in entry 6 were deemed optimized.

The directing effect was explored on a range of TMS-protected alkynes with pendent Lewis basic functionality (Table 2). The optimized conditions from Table 1 were used (Condition A), along with the prior conditions for TMS-alkyne heterocoupling catalysis[8] (Condition B).

Table 1. Optimization of reaction conditions to promote directed alkyne insertion.[a]



Entry	T (°C)	X eq.	Time (h)	Y (%)	Yield of 3a[b] (%)	Ratio of 3a/4a[b]
1[c]	115	2	2	10	51	1.1
2	115	2	1	10	76	5.5
3	80	2	1	10	81	7.2
4	60	2	2	10	79	8.8
5	60	1	2	10	67	9.3
6	45	2	24	10	74	10.5
7	45	1	24	10	74	10.3

[a]A mixture of 0.1-0.2 mmol **1a**, 0.1 mmol **2a**, 0.225 mmol PhNNPh, 0.0025-0.01 mmol $(THF)_3TiI_2(NPh)$ and 0.01 Ph_3CH (internal standard) in 0.5 mL CF_3Ph were heated at desired temperature and time. [b]Yield and selectivity are determined by ^1H NMR and reported with respect to **2a**. [c]Reported in Ref 8 with $[py_2TiCl_2(NPh)]_2$ as catalyst.

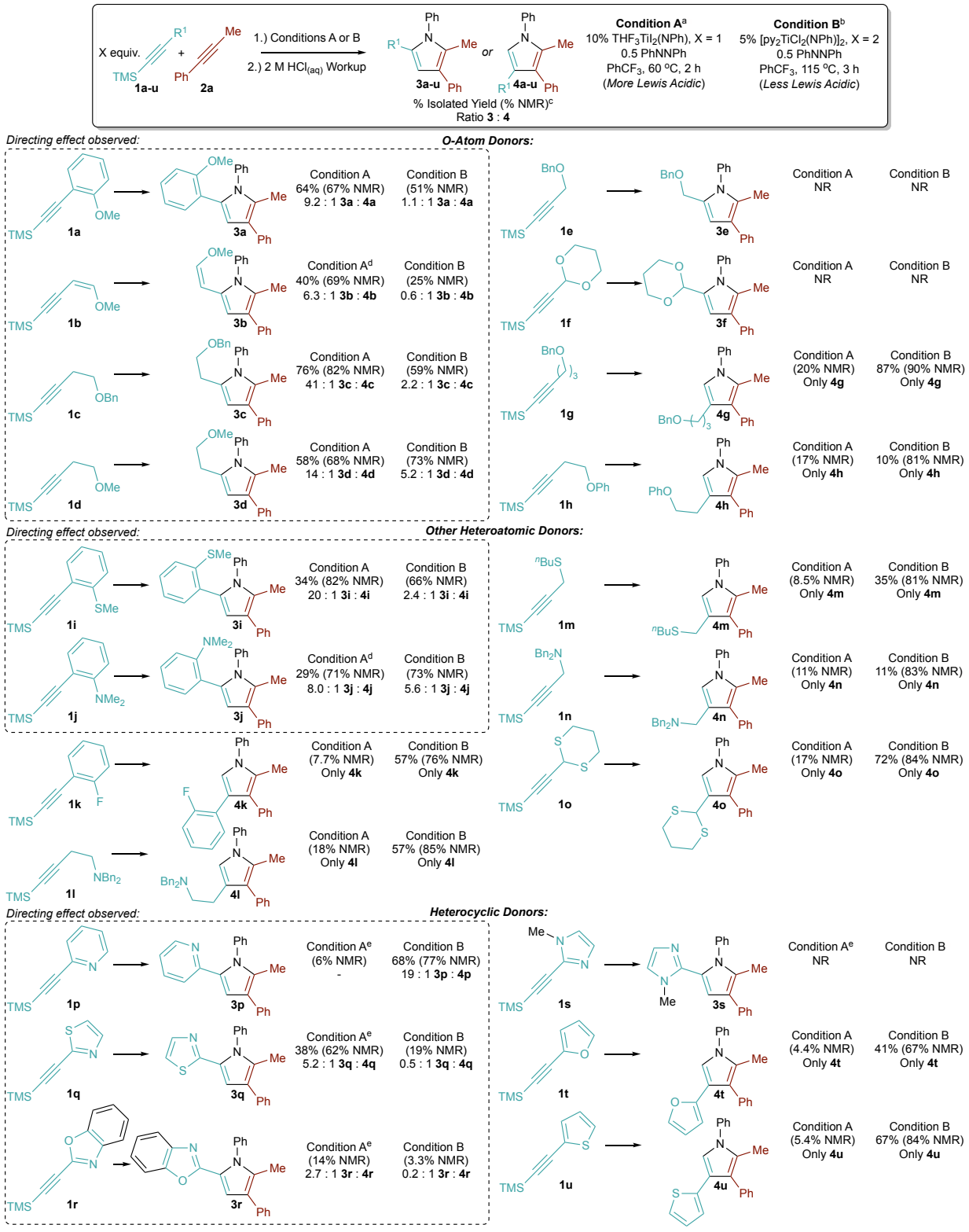
First, substrates containing O-atom donors (**1a**-**1h**) were tested. Substrates that can form 5 membered chelates upon 2nd insertion such as **1a**, vinyl methyl ether **1b**, and homopropargylic ethers **1c** and **1d** are excellent directing groups with the more Lewis acidic catalyst $THF_3TiI_2(NPh)$ (Condition A), giving high regioselectivity and yields of pyrroles **3a-3d**. Directing group effects are observed whether the 2-C linker is sp^2 (**1a**, **1b**) or sp^3 (**1c**, **1d**) hybridized. Substrates **1b**-**1d** are significantly less selective with the less Lewis acidic catalyst $[py_2TiCl_2(NPh)]_2$, although in the case of **1d** acceptable regioselectivity for **3d** is still obtained. Phenyl ether **1h**, which also contains a 2-C linker, manifests no directing group effect—presumably due to a combination of the weaker aryl ether donor O and increased rotational degrees of freedom.

In contrast to 2-C linkers, shorter (1-C) linkers such as propargylic ethers (**1e**) and acetals (**1f**) do not yield productive reactivity due to C-O bond decomposition.[40] Longer (3-C) linkers (**1g**) display no directing group effect, but are still competent for heterocoupling to the 2-unsubstituted pyrrole (**4g**).

Next, other Lewis basic heteroatom donors were examined. Arenes with an *ortho* –SMe (**1i**) or $–NMe_2$ (**1j**) couple with high regioselectivity to the directed products **3i** and **3j**. The less basic and softer –SMe group (**1i**) directed to higher regioselectivity (20:1) than harder –OMe (**1a**, 9.3:1) and $–NMe_2$ (**1j**, 8.0:1), which is unexpected due to the preference of Ti^{IV} for harder ligands. Given the sensitivity to chelate size observed with O-atom donors, the increased regioselectivity in **1i** may be a function of the S atomic size and resulting chelate angles of the S-containing ring.

Tertiary aryl amine **1j** displays good directing ability, although aliphatic pendent tertiary amines (**1l**, **1n**) do not. This may be due to an increase in tether flexibility coupled with the sterics of the 3° amine. Nonetheless, these substrates do not inhibit catalysis and are selective for heterocoupling to products **4l** and **4n**. Aryl fluorides (**1k**), alkyl thioethers (**1m**), and thioacetals (**1o**) give high yields of the non-directed products **4k**, **4m**, and **4o** with $[py_2TiCl_2(NPh)]_2$, which is more functional group tolerant than $THF_3TiI_2(NPh)$ owing to reduced Lewis acidity.

Table 2. Scope of directing group effects in Ti-catalyzed [2+2+1] pyrrole synthesis.



[a]Condition A: A mixture of 0.5 mmol **1** (1.1 eq.), 0.5 mmol **2** (1.1 eq), 0.225 mmol PhNNPh (0.5 eq.) and 0.05 mmol $THF_3I_2Ti(NPh)$ (0.1 eq.) in 2.5 mL CF_3Ph was heated for 2 hours. Reactions were quenched with 2 M HCl in MeOH; [b]Condition B: A mixture of 1.0 mmol **1** (2.2 eq.), 0.5 mmol **2** (1.1 eq), 0.225 mmol PhNNPh (0.5 eq.) and 0.025 mmol $[py_2Cl_2TiNPh]_2$ (0.05 eq.) in 2.5 mL CF_3Ph was heated for 3 hours. Reactions were quenched with 2 M HCl in MeOH; [c]Isolated and/or NMR yield of major regioisomer drawn and are reported with respect to **2a.** [d]Reaction run at 80 °C; [e]Reaction run at 115 °C.

Heterocyclic substituent reactivity is strongly dependent on the heterocycle basicity.[41] *N*-methylimidazole (**1s**) is too basic and inhibits catalysis for both $THF_3TiI_2(NPh)$ and $[py_2TiCl_2(NPh)]_2$ reactions through coordination to Ti. Pyridine (**1p**), which is a reasonably strong heterocyclic base but less basic than **1s**, inhibits catalysis with the more Lewis acidic $THF_3TiI_2(NPh)$, but acts as a directing group and yields high regioselectivity (19:1) with $[py_2TiCl_2(NPh)]_2$. Thiazole (**1q**), which is less basic than pyridine, acts as a selective directing group (5.2:1) with $THF_3TiI_2(NPh)$, but not with the less Lewis-acidic $[py_2TiCl_2(NPh)]_2$ (0.5:1). Benzoxazole (**1r**), which is similar to thiazole **1q** in basicity, yields similar selectivities but poor yields due to C-O bond cleavage, similar to other propargylic O-functional groups (**1e**, **1f**). Very weakly basic furan (**1t**) and thiophene (**1u**) pendants are not strong enough to serve as directing groups with either catalyst but still yield normal heterocoupled products **4t** and **4u**.

Internal alkyne **1w** is also suitable for directed heterocoupling, giving **3w** in moderate yield (Figure 3). This takes advantage of the extreme sensitivity of [2+2] cycloaddition to substrate sterics as well as the directing group effect in 2nd alkyne insertion. However, the window for success is narrow: less sterically encumbered alkynes (**1v**) predominantly homocouple due to their higher reactivity, while more sterically encumbered internal alkynes (**1x**) are too hindered even for 2nd insertion, and thus yield mainly pyrrole products of PhCCMe homocoupling.

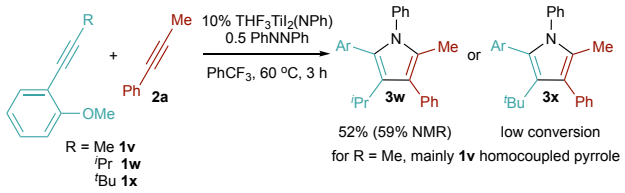


Figure 3. Directing group effects on internal alkyne heterocoupling.

Other internal alkynes can also serve as [2+2] partners along with directing group-tethered TMS alkynes. For example, reaction of 3-hexyne (**2b**) maintains good chemo- and regioselectivity to form **3ab**, albeit with a longer reaction time (Figure 4, top). Additionally, internal alkynes with appended directing groups such as **1v**—which typically would undergo rapid homocoupling (*vide supra*)—can be heterocoupled with TMS alkynes with pendent strong directing groups such as **1p** to form products such as **3pv** (Figure 4, bottom). Unfortunately, all heterocoupling attempts with terminal alkynes have failed; these alkynes appear to be too reactive and instead undergo either alkyne trimerization or pyrrole formation via homocoupling.

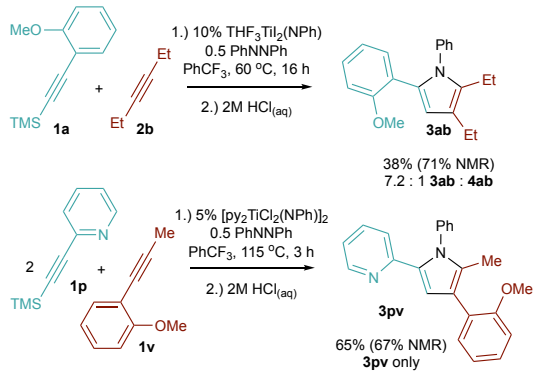


Figure 4. Directed heterocoupling with other internal alkyne [2+2] partners.

[2+2+1] directed heterocoupling can enable facile synthesis of pyrrole-containing EP_1 antagonist derivatives (Figure 5).[3, 42-44] These moieties are typically synthesized through classical Paal-Knorr syntheses, and require multistep pyrrole construction followed by post-functionalization of the pyrrole core to introduce more intricate substitution patterns[42-43] such as the 2-methyl-1,3,5-triaryl core of **5y**. Benzyl aryl ethers like that in **5y** do not serve as directing groups in the [2+2+1] reaction, but *o*-Me derivative **1y** is a deprotectable surrogate. Directed [2+2+1] heterocoupling of **1y** with **2a** and $(p\text{-BrPh})_2N_2$ gives methoxy-protected **3y**, which can be deprotected to phenol **4y** prior to benzylation to **5y** in 22% overall yield (Figure 5). The advantage of this protocol is that the [2+2+1] reaction is widely tolerant of substitution on both azobenzene[7] and alkyne[8] fragments, allowing access to diverse structures with relative ease.

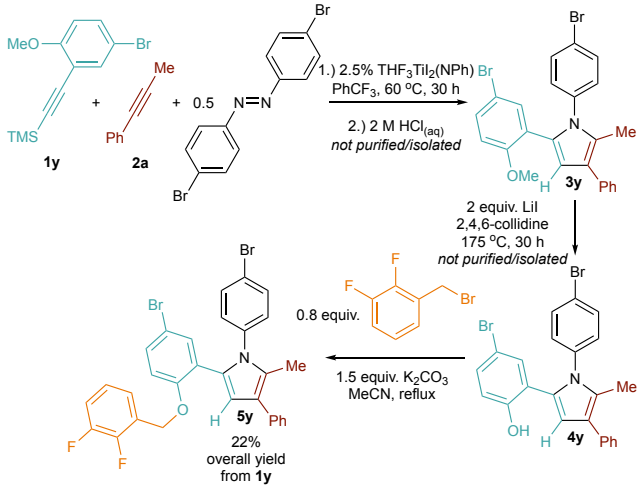


Figure 5. Synthesis of an EP_1 antagonist derivative **5y**.

In addition to alkyne insertion, directing group effects can also be seen during the [2+2] cycloaddition step (Figure 6). For example, reaction of **1z** under catalytic conditions results in exclusive formation of **6z**. In contrast, the reaction of 1-phenylpropyne gives a mixture of all 3 possible regioisomers.[5,7, 45-47] Since **1z** has little steric or electronic bias for [2+2] cycloaddition or insertion, it is likely that the –OMe group directs the [2+2] cycloaddition. Similarly, reaction of **1v** results exclusively in formation of **6v**.

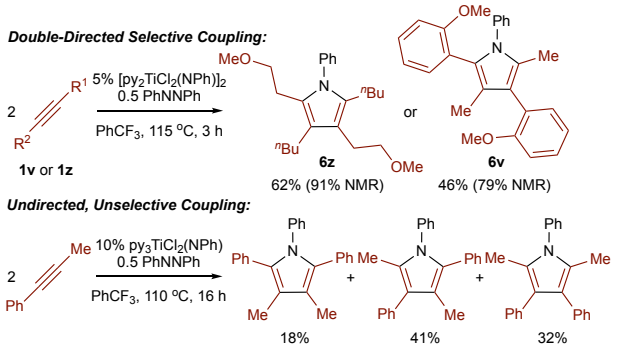


Figure 6. Substrate-directed regioselective pyrrole formation via alkyne homocoupling.

Having established that directing groups can influence the regiochemistry of [2+2] cycloaddition, the possibility of performing substrate-directed Ti-catalyzed alkyne hydroamination was explored.[48] Reaction of electronically unbiased substrate **1z** with aniline resulted in selective formation of **7z**, after directed [2+2] cycloaddition and protonolysis of the metallacycle by aniline (Figure 7). This reaction represents the first example of Ti-catalyzed directed alkyne hydroamination, and yields electronically unbiased dissymmetric ketones that are difficult to synthesize selectively *via* Wacker oxidation of internal alkenes.[49-54] It is notable that weakly Lewis-basic dialkyl ether of **1z** is capable of directing selective alkyne [2+2] cycloaddition despite stoichiometric quantities of aniline.

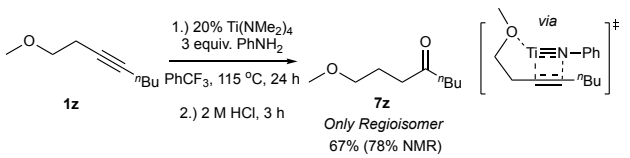


Figure 7. Substrate-directed regioselective alkyne hydroamination.

Conclusions

In summary, we have shown that TMS-protected alkynes with pendent Lewis basic groups can invert the regioselectivity of TMS-protected alkyne insertion, leading to selective formation of highly substituted 3-TMS pyrroles. This method provides a complementary approach to regioselective [2+2+1] pyrrole formation and also demonstrates how dative substrate-Ti interactions can influence—and, importantly, tune—regioselectivity through directing group effects, which was previously unexplored in Ti catalysis.

The inverse regioselectivity highly depends on the coordinating strength of the functional groups, the tether length, and the Lewis acidity of the Ti catalyst. These effects work in concert, providing a high degree of tunability of the pyrrole regiochemistry. Balancing the directing group Lewis basicity with the catalyst Lewis acidity is critical for catalysis: too strong of an acid-base pairing inhibits catalysis, while too weak of a pairing results in formation of 2-TMS pyrrole **4** instead of the 3-TMS pyrrole **3**. Further, we have shown that dative directing group effects can also play a role in other Ti-catalyzed reactions such as alkyne hydroamination, which leads to the selective formation of electronically unbiased imines/ketones *via* directed [2+2] alkyne/Ti=NR cycloaddition. This work will provide a basis for the development of other, selective Ti-catalyzed reactions that can exploit transient dative interactions, expanding directed Ti catalysis beyond classical alkoxide directing groups.

Experimental Section

General Considerations.

All air- and moisture-sensitive compounds were manipulated in a glovebox under a nitrogen atmosphere. The solvent, $PhCF_3$, was predried in a Pure Process Technology Solvent System and passed through activated basic alumina before being used. All high-boiling liquid reagents were freeze pump-thawed three times, brought into the glovebox, diluted in hexanes or diethyl ether, passed through activated basic alumina, pumped dry *in vacuo* and checked by ^{1}H NMR in $CDCl_3$ to ensure the dryness. $[(py)_2TiCl_2(NPh)]_2$[55], $(THF)_3TiI_2(NPh)$[8], ((2-methoxyphenyl)ethynyl)trimethylsilane (**1a**), 2-((trimethylsilyl)ethynyl)pyridine (**1p**)[8], trimethyl(thiophen-2-ylethynyl)silane (**1u**)[8], 1-methoxy-2-(prop-1-yn-1-yl)benzene (**1v**)[8], and (E)-1,2-bis(4-bromophenyl)diazene[5] were prepared according to reported procedure. 1-Phenyl-1-propyne (**2a**) and 3-hexyne (**2b**) were purchased from Sigma-Aldrich. Azobenzene was purchased from TCI Chemicals and purified by dissolving it in hexanes and washing with water. The organic layer was collected, dried over Na_2SO_4, and the solvent was removed *in vacuo*.

^{1}H, ^{13}C, ^{1}H-^{13}C and ^{1}H-^{15}N HMBC, NOESY, and No-D ^{1}H NMR spectra were collected on Bruker Avance III HD NanoBay 400 MHz, Bruker Avance III HD 500 MHz, or Varian Inova 500 MHz spectrometers. High-resolution mass spectra were collected on Agilent 7200 GC/QTOF-MS, Bruker BioTOF II ESI/TOF-MS, or AB-Sciex 4800 MALDI/TOF-MS. Chemical shifts are reported with references of residual protio-solvent impurity: ^{1}H (s, 7.16 ppm for C_6D_5H; s, 7.27 for ppm $CHCl_3$), ^{13}C (t, 128.39 ppm for C_6D_6; t, 77.23 ppm for $CDCl_3$). No-D NMR spectrum were referenced to the proton signal of the internal standard triphenylmethane (Ph_3CH, ppm = 5.0) at a delay time = 30 seconds and acquisition time = 5 seconds.

Example Reaction Condition Optimization (Table 1).

Example for Entry 2: In a glovebox, to an NMR tube was added PhNNPh (8.2 mg, 0.045 mmol, 0.5 eq.), $(THF)_3I_2TiNPh$ (6.1 mg, 0.01 mmol, 0.11 eq.), ((2-methoxyphenyl)ethynyl)trimethylsilane (**1a**) (20.4 mg, 0.1 mmol, 1.1 eq.), phenylpropyne (**2a**) (11.6 mg, 0.1 mmol, 1.1 eq.), triphenylmethane (4.9 mg, 0.02 mmol, 0.22 eq.) as the internal standard, and 0.5 mL $PhCF_3$. The NMR tube was sealed and brought out of the glovebox, and a t = 0 h No-D ^{1}H NMR spectrum was taken. The NMR tube was heated at 115 °C in an oil bath. No-D ^{1}H NMR spectra were taken every 15 minutes until the full consumption of PhNNPh. Yields are reported with respect to **2a**.

Example Synthesis and Isolation of Multisubstituted Pyrroles via Heterocoupling Reactions (Table 2, Condition A).

*Example for ((2-methoxyphenyl)ethynyl)trimethylsilane (**1a**):* In a glovebox, to a 7 mL vial was added PhNNPh (41.0 mg, 0.225 mmol, 0.5 eq.), $(THF)_3I_2TiNPh$ (30.5 mg, 0.05 mmol, 0.11 eq.), ((2-methoxyphenyl)ethynyl)trimethylsilane (**1a**) (102 mg, 0.5 mmol, 1.1 eq.), phenylpropyne (**2a**) (58.0 mg, 0.5 mmol, 1.1 eq.), and 2.5 mL $PhCF_3$. The reaction was then sealed with a Teflon screw cap and heated at 60 °C outside of the glovebox in an oil bath for 2 hours. The reaction was diluted by 2 mL ethyl acetate, quenched by 2 mL 2M HCl in methanol for 1 hour, washed with DI water, dried over Na_2SO_4 and concentrated prior to purification. The product **3a** was isolated by silica gel chromatography using 5% EA/Hex eluent to give a pale-yellow oil. (120 mg, 64% corrected yield). Yields are reported with respect to **2a**.

Example Synthesis and Isolation of Multisubstituted Pyrroles via Heterocoupling Reactions (Table 2, Condition B).

*Example for (5-(benzyloxy)pent-1-yn-1-yl)trimethylsilane (**1g**):* In a glovebox, to a 7 mL vial was added PhNNPh (41.0 mg, 0.225 mmol, 0.5 eq.), $[(py)_2Cl_2TiNPh]_2$ (18.4 mg, 0.025 mmol, 0.055 eq.), (5-(benzyloxy)pent-1-yn-1-yl)trimethylsilane (**1g**) (246 mg, 0.1 mmol, 2.2 eq.), phenylpropyne (**2a**) (58.0 mg, 0.5 mmol, 1.1 eq.), and 2.5 mL $PhCF_3$. The reaction was then sealed with a Teflon screw cap and heated at 115 °C outside of the glovebox in an oil bath for 3 hours. The reaction was diluted by 2 mL ethyl acetate, quenched by 2 mL 2M HCl in methanol for 1 hour, washed with DI water, dried over Na_2SO_4 and concentrated prior to the purification. The product **4g** was isolated by silica gel chromatography using 2% EA/Hex eluent to give a colorless oil (166 mg, 87% yield). Yields are reported with respect to **2a**.

Example No-D ^{1}H NMR Determination of Pyrrole Regioisomeric Ratios (Table 2, Condition A).

*Example for ((2-methoxyphenyl)ethynyl)trimethylsilane (**1a**):* In a glovebox, to an NMR tube was added PhNNPh (8.2 mg, 0.045 mmol, 0.5 eq.), $(THF)_3I_2TiNPh$ (6.1 mg, 0.01 mmol, 0.11 eq.), ((2-methoxyphenyl)ethynyl)trimethylsilane (**1a**) (20.4 mg, 0.1 mmol, 1.1 eq.), phenylpropyne (**2a**) (11.6 mg, 0.1 mmol, 1.1 eq.), triphenylmethane (4.9 mg, 0.02 mmol, 0.22 eq.) as the internal standard, and 0.5 mL $PhCF_3$. The NMR tube was sealed and brought out of the glovebox, and a t = 0 h No-D ^{1}H NMR spectrum was taken. The NMR tube was heated at 60 °C in an oil bath for 2 h. The NMR tube was then cooled to ambient temperature, and a t = 2 h No-D ^{1}H NMR spectrum was taken. Yields are reported with respect to **2a**.

Example No-D ^{1}H NMR Determination of Pyrrole Regioisomeric Ratios (Table 2, Condition B).

*Example for (5-(benzyloxy)pent-1-yn-1-yl)trimethylsilane (**1g**):* In a glovebox, to an NMR tube was added PhNNPh (8.2 mg, 0.045 mmol, 0.5 eq.), $[(py)_2Cl_2TiNPh]_2$ (6.1 mg, 0.005 mmol, 0.055 eq.), (5-(benzyloxy)pent-1-yn-1-yl)trimethylsilane (**1g**) (49.2 mg, 0.2 mmol, 2.2 eq.), phenylpropyne (**2a**) (11.6 mg, 0.1 mmol, 1.1 eq.), triphenylmethane (4.9 mg, 0.02 mmol, 0.22 eq.) as the internal standard, and 0.5 mL $PhCF_3$. The NMR tube was sealed and brought out of the glovebox, and a t = 0 h No-D ^{1}H NMR spectrum was taken. The NMR tube was heated at 115 °C in an oil bath for 3 h. The NMR tube was then cooled to ambient temperature, and a t = 3 h No-D ^{1}H NMR spectrum was taken. Yields are reported with respect to **2a**.

Synthesis of 5-(5-bromo-2-((2,3-difluorobenzyl)oxy)phenyl)-1-(4-bromophenyl)-2-methyl-3-phenyl-1*H*-pyrrole (5y).

Reaction of 1y with 2a to form 3y. In a glovebox, to a 20 mL vial was added 283 mg **1y** (1 eq., 1 mmol), 116 mg **2a** (1 eq., 1 mmol), 166 mg (*E*)-1,2-bis(4-bromophenyl)diazene (0.5 eq., 0.5 mmol), 15 mg $(THF)_3I_2TiNPh$ (2.5 %, 0.025 mmol) and 5 mL $PhCF_3$. The reaction was then sealed with a Teflon screw cap and heated in the glovebox for 30 hours at 60 °C. After being cooled down to ambient temperature, the reaction was removed from the glovebox, 10 mL hexanes was added to the reaction, and the mixture was filtered through a fine frit. The filtrate was concentrated *in vacuo* and mixed with 10 mL 2M HCl in methanol. After 2-hour stirring, the mixture was diluted by 20 mL DI water and extracted by hexanes (15 mL x 3). The organic layer was washed with brine, dried by $MgSO_4$ and concentrated in vacuo to get a yellow solid, **3y**, that was carried on in the reaction as-is.

Deprotection of 3y to 4y. In a glovebox, the entirety of **3y** was dissolved in 2 mL of 2,4,6-collidine and transferred to a 7 mL vial, followed by the addition of 266 mg LiI (2 eq., 2 mmol). The vial was sealed and heated outside of the glovebox at 175 °C for 30 hours. The reaction was diluted by 20 mL methanol and 20 mL DI water and then acidified by 20 mL 2M HCl in methanol. The mixture was extracted by hexanes (15 mL x 6) and the organic layer was washed with brine and dried by $MgSO_4$. Removal of the volatiles yielded the crude oily product **4y**, which was directly used in the next step.

Benzylation of 4y to 5y. Next, 0.2 g K_2CO_3 (1.44 eq., 1.44 mmol), 0.1 mL 2,3-difluorobenzyl bromide (0.78 eq., 0.78 mmol) and 3 mL MeCN were added. The mixture was stirred at reflux for 3 hours. The mixture was diluted by 10 mL DI water and extracted by hexanes (20 mL x 3). The collected organic layer was washed with brine, dried by $MgSO_4$, and concentrated. The only purification of the final product was carried out via silica gel chromatography using 12% DCM/Hex eluent to give a white solid **5y** (135 mg, 22% overall yield with respect to **1y**). ^{1}H NMR (400 MHz, C_6D_6): δ 7.62-7.60 (m, 2H), 7.35 (t, $^3J_{HH}$ = 7.8 Hz, 2H), 7.24 (dd, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.7 Hz, 1H), 7.18-7.15 (m, 1H), 6.97-6.93 (m, 2H), 6.90 (td, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.7 Hz, 1H), 6.77-6.71 (m ,3H), 6.65-6.58 (m, 3H), 6.54 (tdd, $^3J_{HH}$ = 7.9, 5.0 Hz, $^4J_{HH}$ = 1.4 Hz, 1H), 6.39 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 4.57 (s, 2H, -O-CH_2-Ar), 2.08 (s, 3H, 2-NC$_4$-CH_3) ppm. ^{13}C NMR (101 MHz, C_6D_6): δ 156.0, 150.7 (dd, $^1J_{CF}$ = 249 Hz, $^2J_{CF}$ = 12.4 Hz), 148.3 (dd, $^1J_{CF}$ = 249 Hz, $^2J_{CF}$ = 13.2 Hz), 138.9, 137.8, 132.3, 131.9, 130.3, 129.8, 128.9, 128.9, 128.6, 127.5 (d, $^3J_{CF}$ = 10.9 Hz), 126.6, 125.9, 124.4 (dd, $^2J_{CF}$ = 6.7 Hz, $^3J_{CF}$ = 4.7 Hz), 124.0 (app t, $^{2,3}J_{CF}$ = 3.1 Hz), 123.8 (d, $^3J_{CF}$ = 1.1 Hz), 121.5, 120.8, 116.6, 116.4, 113.2, 111.8, 63.6 (dd, $^3J_{CF}$ = 4.5 Hz, $^4J_{CF}$ = 3.0 Hz), 12.7 ppm. MALDI-HRMS: Calc for $C_{30}H_{21}NOBr_2F_2$ [M-Br$^+$] 528.0775; found 528.0305.

ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, characterization data and NMR spectra (PDF)

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Notes

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selective pyrrole synthesis via directed TMS-alkyne insertion
tunable through directing group/catalyst matching