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Communication

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Titanium Alkoxide-Based Regioselective Alkyne-Alkyne Reductive Coupling Mediated by in situ Generated Arylamidate

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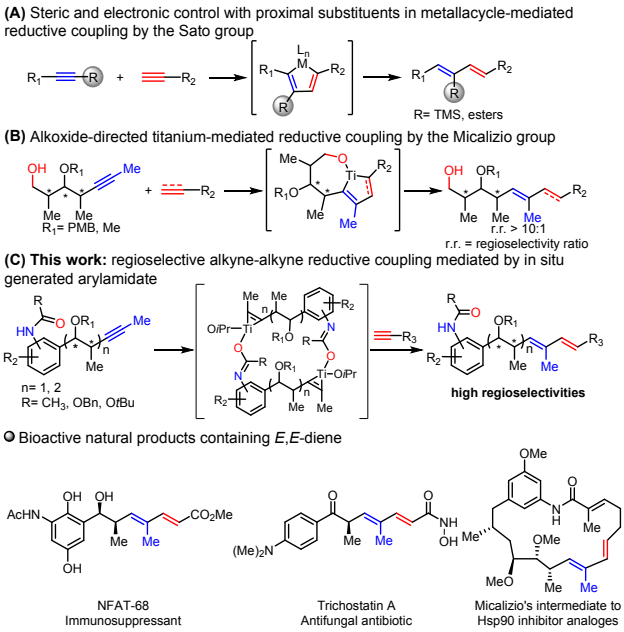
Supporting Information Placeholder

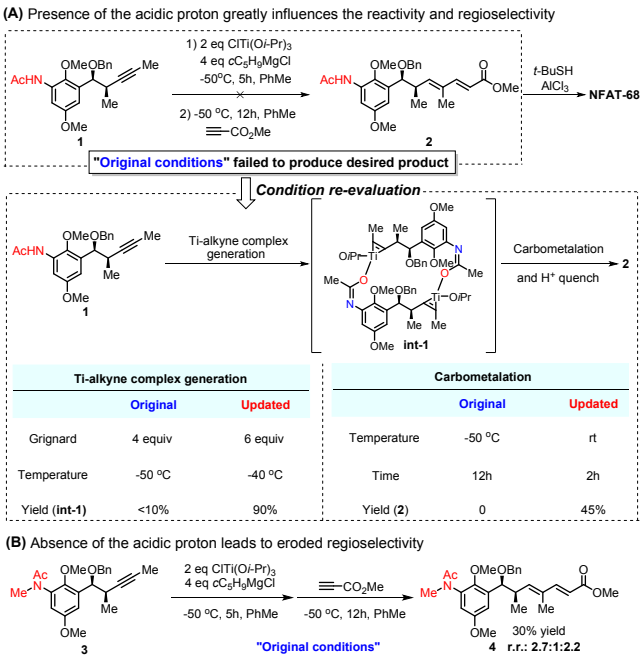
ABSTRACT: A titanium alkoxide-based alkyne-alkyne reductive coupling mediated by in situ generated arylamidate is described. High level of regioselectivity is achieved in 37 examples, where (*E*,*E*)-dienes are formed exclusively. To the best of our knowledge, this study represents the first example of an apparent amide and carbamate directing effect in metal-mediated reductive coupling.

Stereochemically well-defined, functionalized (*E*,*E*)-dienes are common structural features embedded in polyketide-derived natural products and related pharmaceutical agents.[1] In that context, transition-metal-mediated alkyne-alkyne reductive coupling reactions have recently emerged as step- and atom-economical carbon-carbon bond-forming reactions to access (*E*,*E*)-dienes by avoiding a prefunctionalization step. The principle challenges that lie within this strategy are the control of reactivity and olefin selectivity. In response to these challenges in the reductive coupling between internal alkynes and carbonyl-based π-systems or alkynes, useful strategies to control regioselection have been developed over the past decades. These strategies include steric differentiation,[2] π conjugation,[3] and directed carbometalation,[4] and have been actively implemented by research groups including Sato,[2,5] Buchwald,[6] Montgomery,[7] Krische,[8] Jamison,[3,9] and Micalizio[1f-h,4,10] (Scheme 1A and 1B). Among these strategies, substrate-directed transformations[11] enable the formation of highly organized transition states or intermediates through the association of a reagent with the substrate. The resulting conformationally rigid systems allow selective reactions, enabling useful levels of regioselectivity. The atom-economy and remarkable convergency provided by this strategy has been demonstrated by its application in several elegant total synthesis of natural products and complex molecules.[12] However, the use of in situ generated alkoxide was the only directing group strategy realized in the context of titanium-mediated reductive coupling. Underdevelopment limited the substrate scope for this transformation and subsequent applications, but allows for discovery and development of an alternative directing-group strategy.[4]

Scheme 1. Alkyne-Alkyne Reductive Coupling for the Selective Synthesis of (*E*,*E*)-Dienes



Scheme 2. Arylacetamide Directing Effect in Alkyne-Alkyne Reductive Coupling

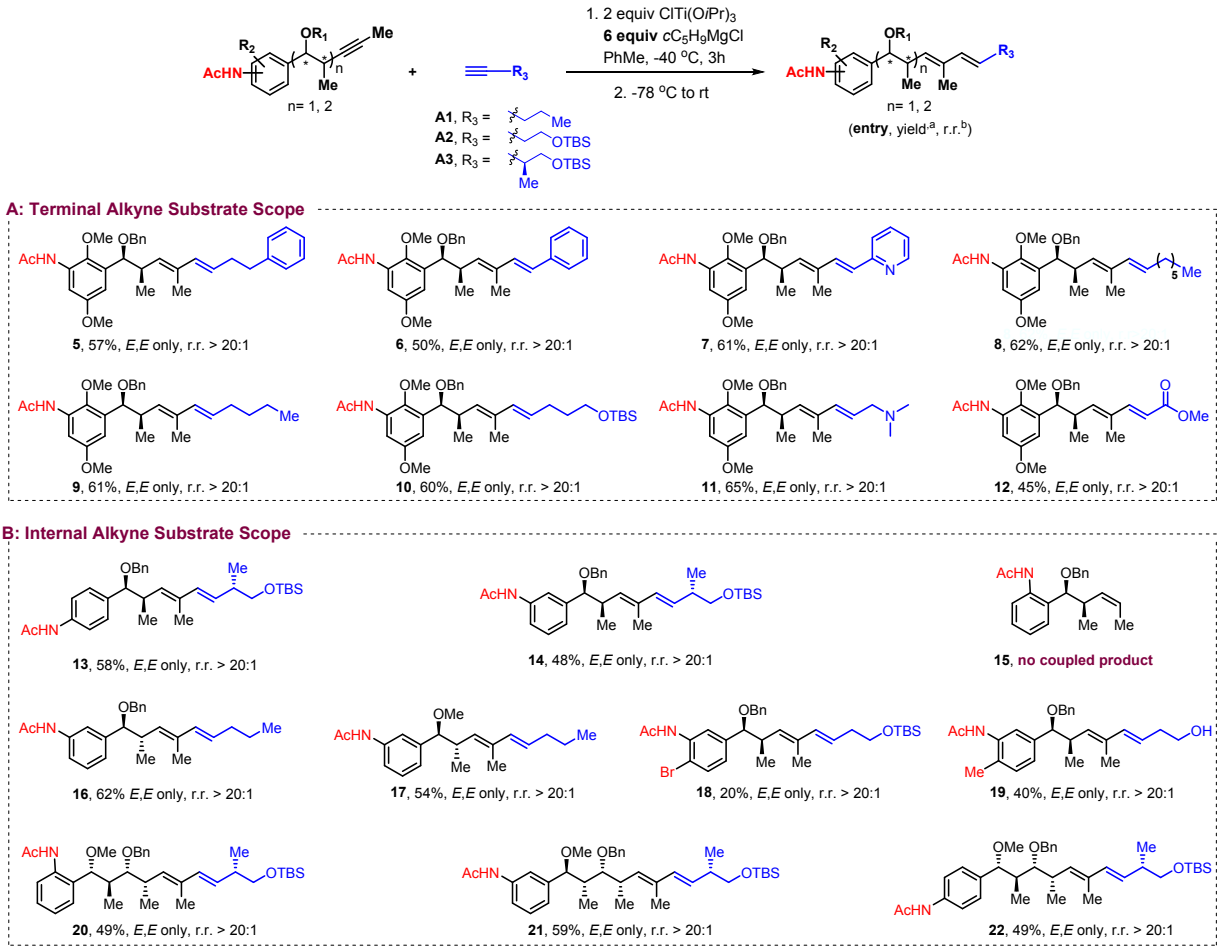


Alkyne Reductive Coupling

In line with our previous studies on reductive couplings[12n] and inspired by Micalizio[4] and Schafer's work,[13] we report a highly

regiocontrolled synthesis of (*E*,*E*)-dienes mediated by in situ generated arylamidate (Scheme 1C). This strategy takes advantage of

Table 1. Arylacetamide Directing Effect in Alkyne-Alkyne Reductive Coupling



[a]Isolated yield after chromatographic purification over silica gel. [b]Regioselectivity was based on the analysis of the ^{1}H NMR spectra of the crude products; r.r. = regioselectivity ratio.

the commonly used amine protecting groups, acetyl (Ac), *tert*-butyloxycarbonyl (Boc), and carboxybenzyl (Cbz) groups, to render the directing effects and achieves useful levels of regioselectivity. This protocol represents the first examples of apparent amide and carbamate directing effects in metal-mediated reductive coupling.

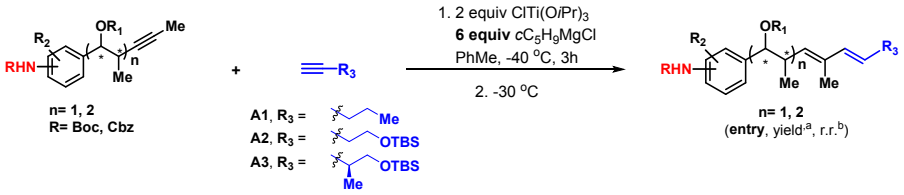
The development of this methodology originated from our previous investigation concerning the reductive coupling between internal alkynes obtained from asymmetric propargylation reactions and acetylenic esters (Scheme 2).[12n] In an effort to apply this strategy to the total synthesis of NFAT-68,[12n] we were surprised to find that previous reaction conditions ("original conditions") for the reductive coupling failed to produce the desired diene **2** using alkynyl acetamide **1** and methyl propiolate, requiring reinvestigation of the reaction conditions (Scheme 2A). *For the generation of the presumed titanacyclopropene complex*, (1) two additional equivalents (six vs four) of the Grignard reagent were required to achieve full conversion, indicating that an excess amount of Grignard reagent was necessary for the deprotonation of the acetamide proton; (2) a higher reaction temperature was required to initiate the formation of **int-1**, where the thermodynamic effect of the deprotonated amide on the successful generation of Ti-alkyne complex has not been previously described in reductive coupling reactions. *For the intermolecular carbometalation process*, elevated coupling temperature was needed for complete consumption of **int-1**, producing **2** as a single regioisomer. Collectively, the presence of an acetamide on the aryl ring had a pronounced impact on the reactivity and selectivity of the reaction. Interestingly, the *N*-methylated counterpart **3** (Scheme 2B) produced diene **4** with significantly eroded regioselectivity under the "original conditions" and led to decomposition under the updated conditions. This control experiment provided evidence that the in situ generated amidate anion may have played an important role on the selectivity of this coupling reaction. Enlightened by Schafer's work[13] on employing monoanionic *N*,*O*-chelating ligands with a tight bite angle including amidates in titanium-catalyzed reactions, we hypothesized that the in situ generated arylamidate might associate with the titanium center to direct the coupling reaction.

On that basis, we surveyed the coupling of alkynyl acetamide **1** with a range of terminal alkynes bearing diverse functionality (Table 1). To our delight, (*E*,*E*)-diene products (**5**-**12**) were formed with excellent regioselectivity in all cases. Aryl, pyridyl (**5**-**7**), silyl ether (**10**), alkyl amine (**11**) ,and ester (**12**) were all well-tolerated, demonstrating the broad functional group tolerance of this coupling reaction.

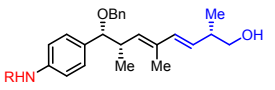
The alkyne substrate scope was evaluated subsequently, where the variation of acetamide substitution pattern, stereochemistry, electronics on the aryl ring, hydroxyl protecting groups, and tether length was investigated (Table 1). While *meta*- and *para*-substituted arenes delivered dienes (**13** and **14**) with good

reactivity and excellent selectivity, the *ortho*-substitution failed to give a coupled product, but gave only alkyne reduction (**15**).

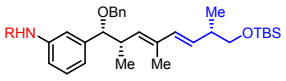
Table 2. Arylcarbamate Directing Effect in Alkyne-Alkyne Reductive Coupling



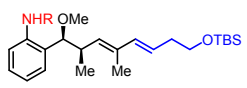
Internal Alkyne Substrate Scope



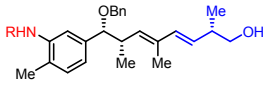
R= Boc, 23a, 65%, *E,E* only, r.r. > 20:1
R= Cbz, 23b, 61%, *E,E* only, r.r. > 20:1



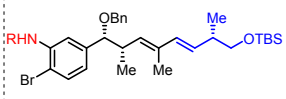
R= Boc, 24a, 62%, *E,E* only, r.r. > 20:1
R= Cbz, 24b, 52%, *E,E* only, r.r. > 20:1



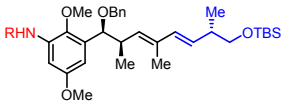
R= Boc, 25a, 56%, *E,E* only, r.r. > 20:1
R= Cbz, 25b, 51%, *E,E* only, r.r. > 20:1



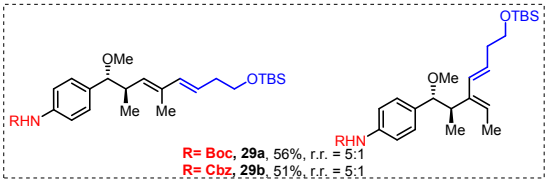
R= Boc, 26a, 58%, *E,E* only, r.r. > 20:1
R= Cbz, 26b, 50%, *E,E* only, r.r. > 20:1



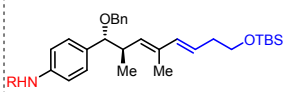
R= Boc, 27a, 58%, *E,E* only, r.r. > 20:1
R= Cbz, 27b, 67%, *E,E* only, r.r. > 20:1



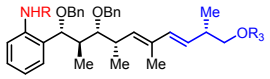
R= Boc, 28a, 66%, *E,E* only, r.r. > 20:1
R= Cbz, 28b, 63%, *E,E* only, r.r. > 20:1



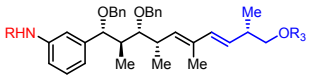
R= Boc, 29a, 56%, r.r. = 5:1
R= Cbz, 29b, 51%, r.r. = 5:1



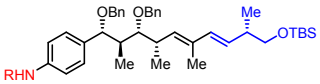
R= Boc, 30a, 56%, *E,E* only, r.r. > 20:1
R= Cbz, 30b, 51%, *E,E* only, r.r. > 20:1



R= Boc, R_3= TBS, 31a, 51%, *E,E* only, r.r. > 20:1
R= Cbz, R_3= H, 31b, 45%, *E,E* only, r.r. > 20:1



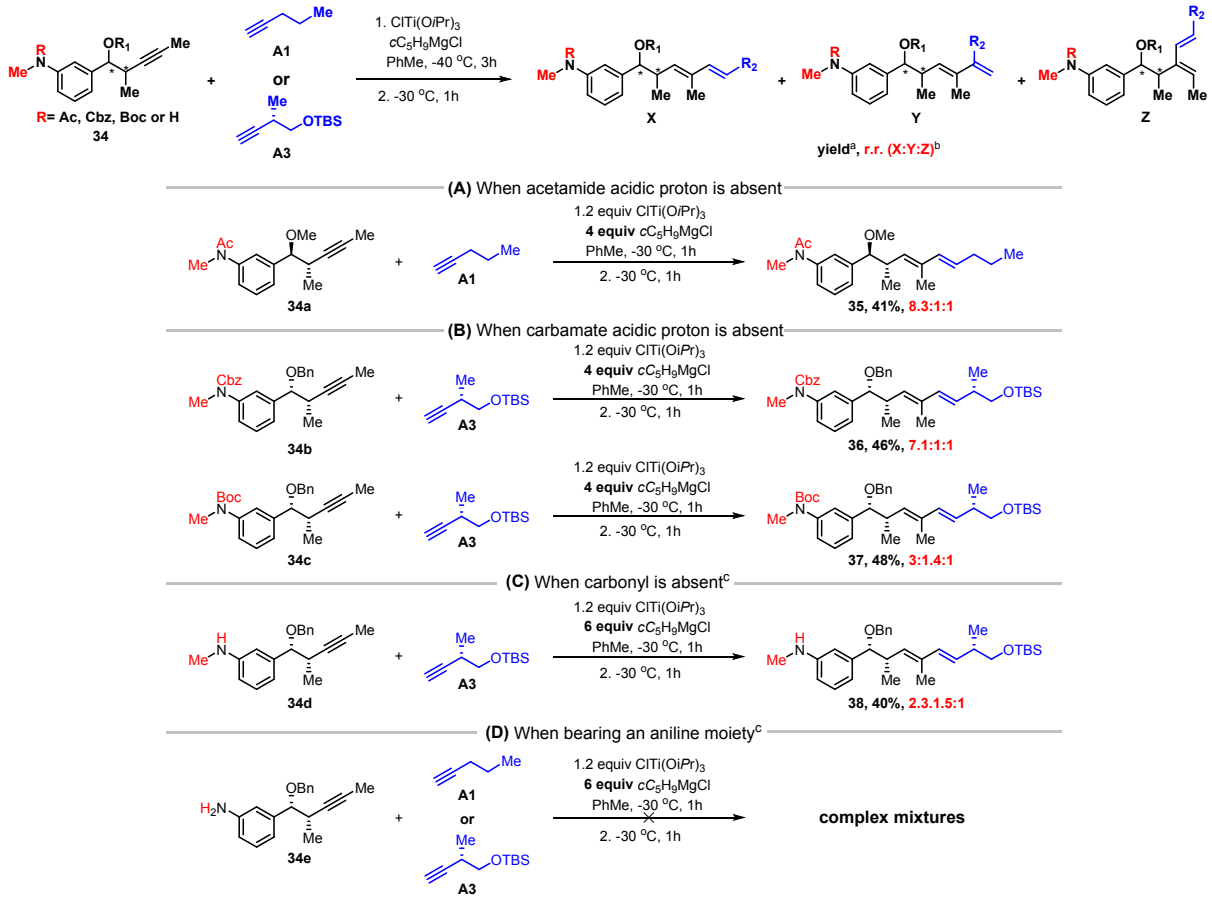
R= Boc, R_3= TBS, 32a, 60%, *E,E* only, r.r. > 20:1
R= Cbz, R_3= H, 32b, 54%, *E,E* only, r.r. > 20:1



R= Boc, 33a, 47%, *E,E* only, r.r. > 20:1
R= Cbz, 33b, 50%, *E,E* only, r.r. > 20:1

[a]Isolated yield after chromatographic purification over silica gel. [b]Regioselectivity was based on the analysis of the ^{1}H NMR spectra of the crude products; r.r. = regioselectivity ratio.

Scheme 3. Control Experiments



[a]Combined yields of all regioisomers after chromatographic purification over silica gel. [b]Regioselectivity was based on the analysis of the ^{1}H NMR spectra of the crude products; r.r. = regioselectivity ratio. [c]6 equivalents of cC$_5$H$_9$MgCl was used.

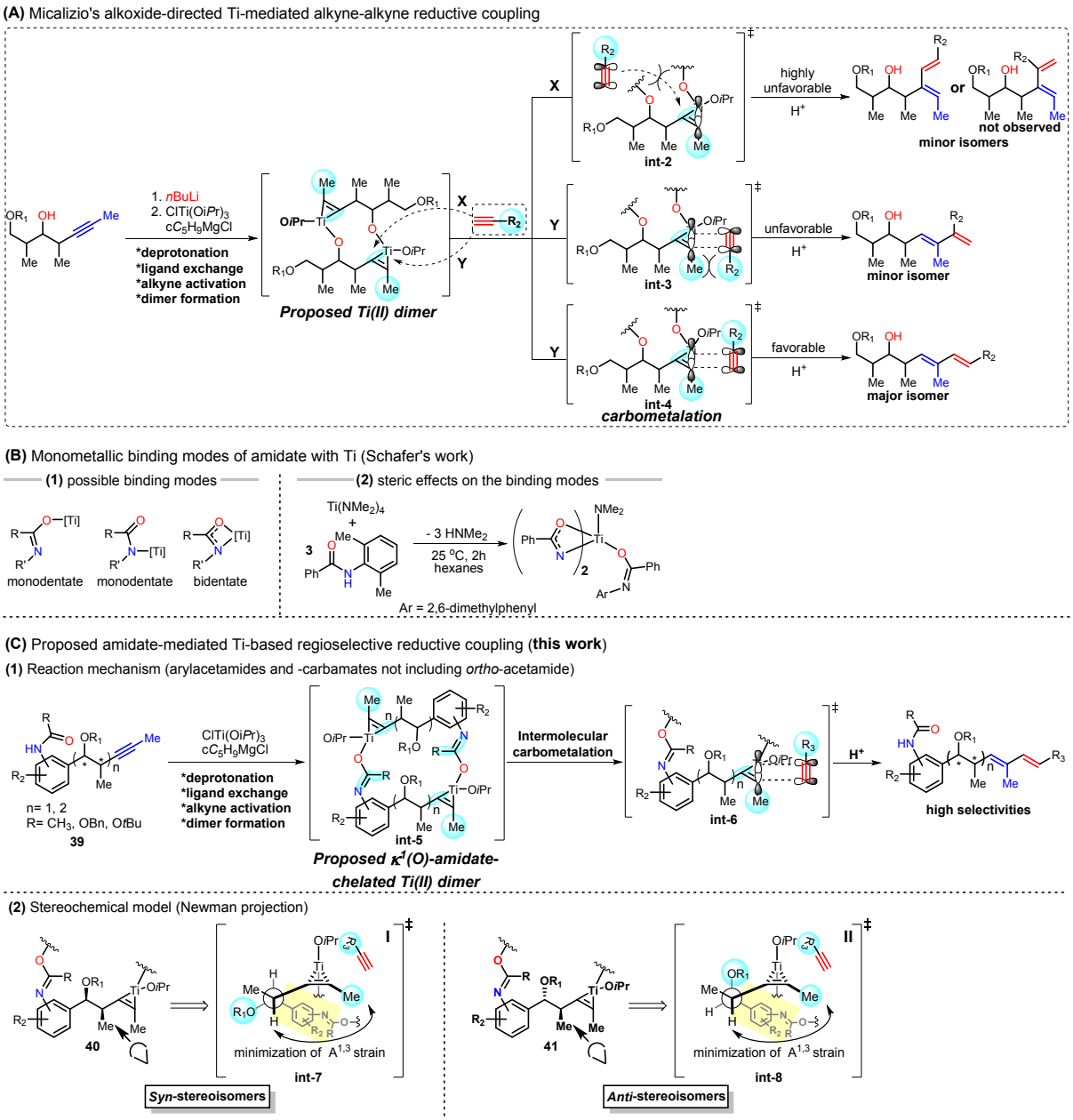


Figure 1. Proposed Reaction Mechanism

Contrary to Micalizio's study, substrate stereochemistry had little or no impact on reaction selectivity (**16** and **17**).[1h] Additionally, placement of an electron-withdrawing group or electron-donating group *ortho* to the acetamide did not alter the selectivity, furnishing **18** and **19** as the only isomers. The yield of **18** was diminished presumably due to the metal/halogen exchange of Grignard reagent with arylbromide. Importantly, substrates with extended tether length also proved to be viable for the coupling to obtain products (**20**-**22**) with excellent regioselectivity. Given that excellent regiocontrol was achieved in complex molecular settings, we expect this methodology will find wide application in natural product and complex molecule synthesis. Accordingly, these results suggest that arylacetamides have a strong directing group effect on titanium alkoxide-mediated reductive couplings.

Encouraged by the success with acetamide bearing substrates, we investigated carbamates (Boc and Cbz) to determine if they would display a similar directing effect as the amides (Table 2). Gratifyingly, with a lower reaction temperature, (*E*,*E*)-dienes (20 examples) were obtained as the exclusive regioisomers in moderate yields. In an analogous fashion, factors such as substitution pattern (**23**-**25**), electronic contributions on the aryl ring (**26**-**28**), stereochemistry and hydroxyl protecting groups (**25** and **29**), and tether length (**31**-**33**) were evaluated. All products were obtained with useful levels of regioselectivity. A decreased selectivity (**29**) was observed, when the arene substrate was *para*-substituted and an *anti*-stereochemical relationship between benzylic methyl ether and homobenzylic methyl group was present. Accordingly, carbamates (Boc and Cbz) also displayed an apparent directing effect to render (*E*,*E*)-dienes with excellent levels of selectivity.

Control experiments were conducted to demonstrate the importance of the directing effect of acetamide[14] or carbamate[15] through in situ formation of arylamidate.[16] As depicted in Scheme 3A and 3B, when the N-H proton was replaced with a methyl group on acetamide or carbamate, the reaction selectivity was significantly decreased along with the production of the other two regioisomers (**35**-**37**).[12n] Additionally, removal of the carbonyl functionality from the arylamine (Scheme 3C and 3D) led to a

complex product mixture. Two additional equivalents of Grignard reagent were added for deprotonation of the acidic amine hydrogen, which excluded the possibility that the transformation was mediated by a deprotonated arylamine.

Based on the above-described experiments, we proposed a likely mechanism (Figure 1C) for reductive coupling mediated by in situ generated arylamidate that builds on Micalizio's[1g], Shafer's[13] and our earlier work[12n] (Figure 1A and 1B). The Micalizio group has laid a solid foundation in the mechanistic interpretation of operational intermediates and transition states leading to selective reductive coupling in the field of directed-metalation mediated by titanium alkoxide. Specifically, in the case where the intramolecular coordination of homoallylic alkoxide with titanium is hampered by significant ring strain, a Ti (II) dimer is proposed to be the intermediate during the formation of titanacyclopropene complex. The selectivity of the subsequent carbometalation and formation of *E*,*E*-dienes can be rationalized by simple steric consideration, where the **int-4** has the least unfavorable steric interactions between Ti(II) dimer and the incoming terminal alkyne (Figure 1A). On the other hand, the Shafer group has established the coordination modes of amidates with Ti(IV) (Figure 1B). The amidates bind in either a bidentate or monodentate mode through either nitrogen or oxygen atom, where κ^1-(*O*) binding will be favored in a sterically congested environment. Given the considerations described above, we propose a κ^1-(*O*)-amidate-chelated Ti(II) dimer (**int-5**) that is responsible for the unprecedented selectivity and reactivity (Figure 1C). In comparison to Micalizio's strategic placement of an alkoxide as a directing group, the use of arylamidate in our case creates a more sterically crowed environment resulting in better selectivities and lower reactivities (transition states **I** and **II**, highlighted in yellow). Based on this proposal, as the *anti*-stereoisomers (**int-8**) have the ether group (OR_1) positioned closer to the titanium reacting center compared with the *syn*-stereoisomers (**int-7**), **int-8** is sterically more congested than **int-7**. The proposition is consistent with the observation that the *anti*-substrates were less reactive than their *syn*-counterparts (Table 1, **14** vs. **16**; Table 2, **23** vs. **29**, where both the *anti*-substrates did not couple with the most sterically hindered terminal alkyne (**A3**). Furthermore, different positions of the acetamide and carbamate functionality on the aryl ring might produce geometrically different arylamidate-associated intermediates that have distinct stabilities and steric environment. In particular for *para*-substituted carbamates (Table 2, **29**), the combination of the destabilization effect of a bulky carbamate and more sp^2 character of the dimer might lead to a weaker coordination of the amidate with Ti. This may allow for the terminal alkyne to approach from the inner sphere of the dimer (resembling to pathway **X** in Figure 1A), explaining the formation of the other regioisomer. In contrast, a substrate with an *ortho*-substituted acetamide (**15**) would likely to form a dimer featuring less steric interactions and sp^2 character, permitting the possibility of a bidentate *N*,*O*-chelation. The ensuing higher coordinated dimer might have the titanium center shielded by the steric bulk, decreasing its reactivity for the coupling reaction (Table 1, **15**).[13b]

In summary, a highly regioselective alkyne-alkyne reductive coupling mediated by in situ generated arylamidate is described to provide access to a synthetically useful class of (*E*,*E*)-dienes. Excellent regioselectivity is achieved in 37 examples. Factors such as acetamide and carbamate substitution pattern, electronics of the aryl ring, stereochemistry, hydroxyl protecting groups, and tether length were investigated. Transition state models are proposed to rationalize the experimental observations. The utility of this methodology was first demonstrated in our convergent synthesis of NFAT-68.[12n] The extension of this methodology and application in the total synthesis of natural products and pharmaceutical agents are underway in our laboratory and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, analytical data, and ^1H and ^{13}C NMR spectra

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Notes

The authors declare no competing financial interests.

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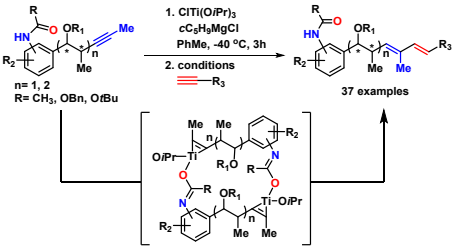

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- New amide and carbamate directing effects