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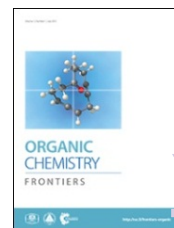
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4 **Titanium-Mediated Cross-Coupling Reactions of 1,3-Butadiynes with**  
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6  **$\alpha$ -Iminonitriles to 3-Aminopyrroles: Observation of an Imino Aza-Nazarov**  
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8 **Cyclization**  
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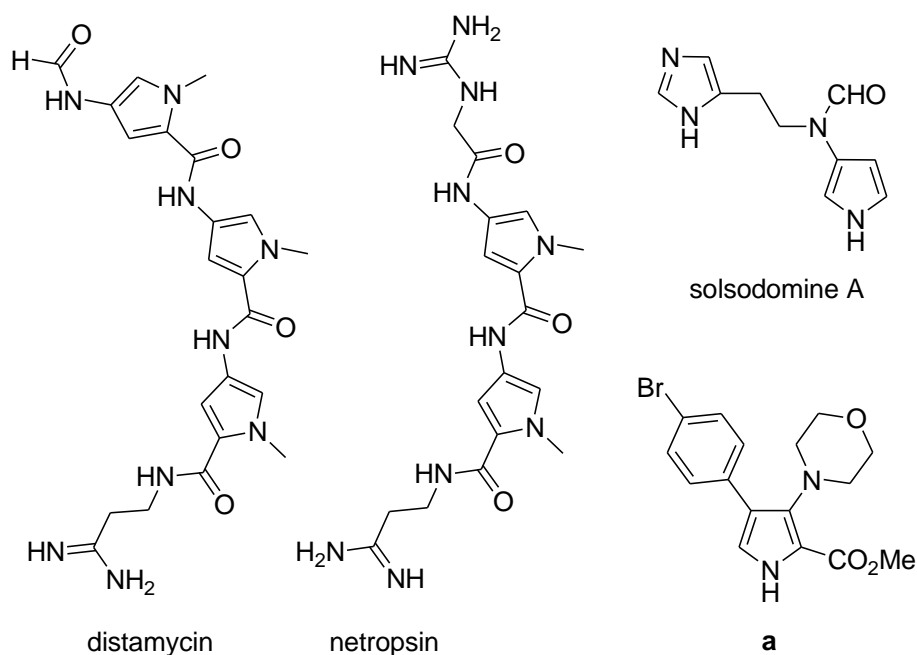
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30 **Abstract:**  $\text{Ti}(\text{O}^i\text{Pr})_4/2$   $n\text{BuLi}$ -mediated highly efficient cross-coupling reactions of  
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32 1,3-butadiynes with  $\alpha$ -iminonitriles are described. The method provides a convenient  
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34 access to functionalized 3-aminopyrroles with a wide diversity of substituents in a highly  
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36 regioselective manner. When optically pure  $\alpha$ -iminonitrile is employed in this reaction,  
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38 chiral pyrrole derivative is obtained without loss of the enantiopurity. Mechanistic study  
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40 indicates that the 3-aminopyrroles are formed upon treatment of the crude hydrolysis  
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42 products with silica gel or Lewis acid. A novel imino aza-Nazarov cyclization reaction is  
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44 proposed to account for the formation of the pyrrole products. Employing  
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46 titanium-monoyne complex in this reaction resulted in the homo-coupling of  
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48  $\alpha$ -iminonitriles, leading to the formation of 1,2-diimines.  
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60 3-Aminopyrroles are found in a variety of biologically active substances or natural

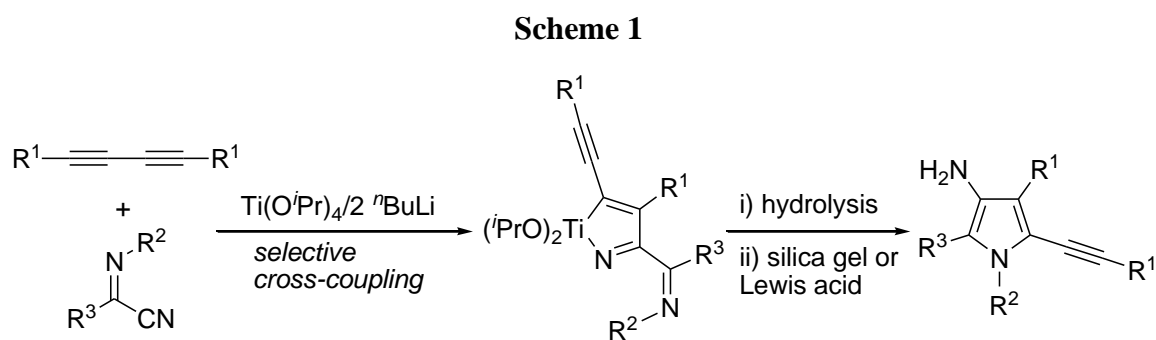
products,<sup>1</sup> and are also useful building blocks in synthetic chemistry.<sup>2</sup> For example, as shown in Figure 1, natural products such as distamycin and netropsin with 3-aminopyrrole skeletons are well-known DNA-minor groove binding agents with strong preference for adenine/thymine-rich sequences.<sup>3</sup> The 3-aminopyrrole alkaloid solso domine A, isolated from the fresh berries of solanum sodomaeum L., shows activity against *Mycobacterium intracellulare*.<sup>4</sup> 3-Aminopyrrole-2-carboxylates, such as “a”, is identified as a common pharmacophore which exhibits potent anticonvulsant activity by blocking sodium channels in a frequency-dependent manner.<sup>5</sup> Although a large number of pyrrole syntheses have been reported in recent years, the efficient synthetic routes to 3-aminopyrroles are quite



**Figure 1.** Representative examples of bioactive 3-aminopyrrole derivatives

limited.<sup>6-9</sup> General synthetic methods include: functional group transformation of pyrrole derivatives such as 3-nitropyrrole,<sup>6a-d</sup> 3-arylazopyrroles,<sup>6e</sup> pyrrol-3-carboxylic acids<sup>6f</sup> etc.,<sup>7</sup>

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4 intramolecular cyclization of enamionitrile derivatives<sup>8</sup> such as Thorpe-Ziegler type  
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6 cyclization<sup>8e-j</sup> *etc.*<sup>9</sup> However, these methods usually restrict to special substituted substrates.  
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9 Thus, the development of new methodologies using readily available starting materials is  
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11 highly desired. On the other hand, titanium-mediated cross-coupling reactions have been  
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13 proved to be highly efficient for the construction of carbon-carbon or carbon-heteroatom  
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15 bonds, and the thus generated titanacycles are important intermediates for further selective  
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17 transformations.<sup>10</sup> During our continued studies on the chemistry of titanium-butadiyne  
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19 complexes,<sup>11</sup> we have developed the coupling reactions of titanium-butadiyne complexes  
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21 with aldehydes or ketones, leading to the selective synthesis of stereodefined  
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23 *trans*-enynols<sup>11a</sup> or trisubstituted [3]cumulenols.<sup>11b</sup> Inspired by these results, we are next  
24  
25 interested in the potential coupling reactions of titanium-butadiyne complexes with  
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27 functionalized nitriles. In this paper, we report titanium-mediated cross-coupling reactions  
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29 of 1,3-butadiynes with  $\alpha$ -iminonitriles, which provide a convenient one-pot synthesis of  
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31 functionalized 3-aminopyrroles upon treatment of the crude hydrolysis products with silica  
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33 gel or Lewis acid (Scheme 1). Interestingly, 3-aminopyrroles were formed likely *via* a rare  
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35 imino aza-Nazarov cyclization of the diimines produced by hydrolysis of the *in situ*  
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37 generated azatitanacycles.  
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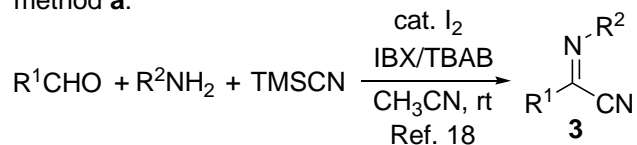


R<sup>1</sup> = silyl, aryl, alkyl; R<sup>2</sup>, R<sup>3</sup> = aryl or alkyl

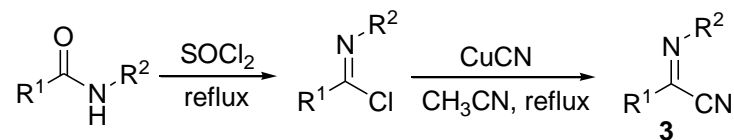
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4 The reactivity of nitriles with group 4 metal complexes has been intensively studied  
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6 during the last decades, in which C≡N insertion into a metal-carbon bond<sup>12</sup> or a  
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8 heterobimetallic complex,<sup>13</sup> and formation of metal-ketenimate species<sup>14</sup> have been  
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10 observed. However, so far only one report by Sato *et al.* related to titanium-mediated  
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12 cross-coupling reactions of nitriles (restrict to  $\alpha$ -heterofunctionalized nitriles) with alkynes  
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14 is preceded.<sup>15</sup> They demonstrated that azatitanacyclopentadienes formed by  
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16 cross-coupling reactions of alkynes with  $\alpha$ -methoxyacetonitriles could react with  
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18 aldehydes, sulfonylacetylenes or second  $\alpha$ -methoxyacetonitrile to afford furans, pyridines  
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20 and pyrroles, respectively.<sup>15</sup> The  $\alpha$ -iminonitriles (imidoyl cyanides) are important synthetic  
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22 precursors for the synthesis of  $\alpha$ -keto acids, diimines, amides, amidines *etc.*,<sup>16</sup> and also  
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24 serve as effective components in various cycloaddition reactions.<sup>17</sup> Due to the enhanced  
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26 reactivities of C=N and C≡N bond, both of these two unsaturated moieties in  
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28  $\alpha$ -iminonitriles might couple with alkynes in the presence of low-valent titanium species.  
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30 We are therefore quite interested in exploring new reaction patterns using these substrates.  
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32  $\alpha$ -Iminonitriles can be readily prepared by the following two methods (Scheme 2):  
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34 IBX/TBAB-mediated oxidative Strecker reaction (method a)<sup>18</sup> and the reactions of imidoyl  
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36 chlorides with CuCN (method b). Initially, we investigated the titanium-mediated coupling  
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38 reactions of 1,4-bis(*tert*-butyldimethylsilyl)buta-1,3-diyne **1a** with  
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40 (*Z*)-*N*-(4-methoxyphenyl)benzimidoyl cyanide **3a**. The results are shown in Table 1. Based  
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42 on our previous studies,<sup>11</sup> titanium-butadiyne complex **2a** (also referred to as  
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44 alkynyltitanacyclopropene) was prepared *in situ* by the reaction of diyne **1a** with 1.3 equiv  
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46 of Ti(O<sup>*i*</sup>Pr)<sub>4</sub>/2 <sup>*n*</sup>BuLi reagent in THF. Addition of 1.1 equiv of **3a** to the mixture containing  
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## Scheme 2

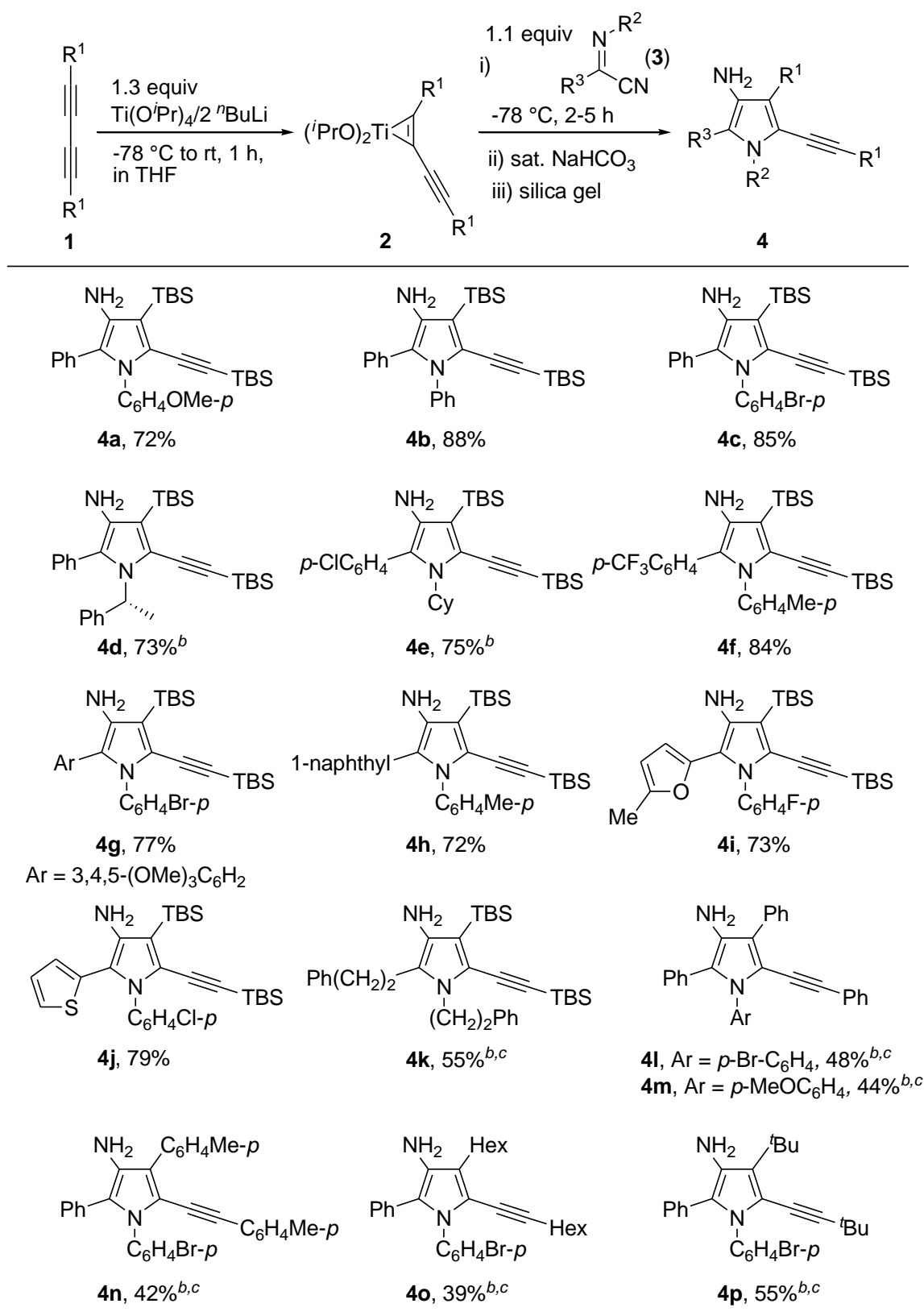
method a:



method b:



**2a** at  $-78\text{ }^\circ\text{C}$  and stirred for 2 h resulted in the formation of 5-alkynyl-3-aminopyrrole **4a** in 47% yield after quenching the mixture with 3 M HCl followed by silica gel purification. To our delight, the yield of **4a** could be improved to 72% by quenching the reaction mixture with saturated aqueous  $\text{NaHCO}_3$  solution. It was noted that in this case, in addition to **4a**, one more byproduct could be detected in the crude reaction mixture. However, after the crude material was dissolved in  $\text{CH}_2\text{Cl}_2$ <sup>19</sup> followed by addition of silica gel and evaporation of the solvent, TLC analysis showed that only **4a** remained. The results indicated that the observed byproduct converted to **4a** on the silica gel. This conclusion was also confirmed by control experiments (*vide infra*). With the optimized reaction conditions in hand, substrate scope of this reaction was examined (Table 1). We first investigated the effect of the substituents on  $\alpha$ -iminonitriles. When *N*-phenyl- or *N*-(*p*-bromophenyl)-substituted iminonitriles were employed, the corresponding 3-aminopyrroles **4b** and **4c** were obtained in 88% and 85% yields, respectively. The results indicated that the presence of electron-neutral or withdrawing *N*-aryl group on iminonitrile afforded higher product yields. *N*-alkyl-substituted iminonitriles such as *N*-(*R*)-(1-phenylethyl) or *N*-cyclohexyl-substituted one were also examined. Although the

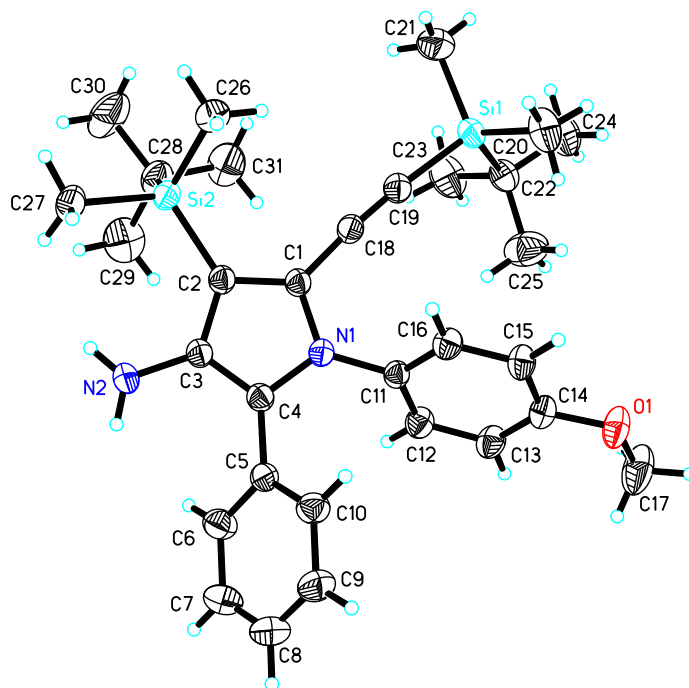
**Table 1.** Synthesis of 3-aminopyrroles from 1,3-butadiynes and  $\alpha$ -iminonitriles.<sup>a</sup>

<sup>a</sup> Isolated yields. <sup>b</sup> The crude products were treated with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ . <sup>c</sup>  $-78^\circ\text{C}$  to  $0^\circ\text{C}$ , 3-5 h.



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4 substrates with iminonitriles could occur at  $-78\text{ }^{\circ}\text{C}$ , the desired products were not observed  
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7 after silica gel purification. The results suggested that the silica gel was not effective in  
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10 promoting the transformations to pyrroles in these cases. To our delight, further  
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12 optimizations indicated that when the crude products obtained by quenching with saturated  
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14 aqueous  $\text{NaHCO}_3$  solution followed by normal work-up was stirred at  $50\text{ }^{\circ}\text{C}$  in THF for 1 h  
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16  
17 in the presence of 4.0 equiv of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , the desired products **4d** and **4e** could be obtained  
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20 in 73% and 75% yields, respectively. It was noted that the use of enantiomerically pure  
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22 *N*-(*R*)-(1-phenylethyl)-substituted iminonitrile gave **4d** without racemization, as  
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24 determined by chiral-column HPLC analysis of **4d** and ( $\pm$ )-**4d**. The iminonitriles bearing  
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26 *p*-Cl, *p*- $\text{CF}_3$ , 3,4,5-(MeO) $_3$  and 1-naphthyl substituents on the *C*-aryl rings ( $\text{R}^3$  group)  
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28 reacted smoothly with **1a** to afford **4e-4h** in 72-84% yields. *C*-Heteroaryl-substituted  
29  
30 iminonitriles such as (5-methyl-2-furanyl) or (2-thienyl)-substituted one were tolerated  
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32 well during the reaction to afford **4i** and **4j** in 73% and 79% yields, respectively. The  
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34 reaction was also compatible to *C*-alkyl substituted iminonitrile, furnishing **4k** in 55%  
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36 yield. Next, we made the effort to employ aryl- or alkyl-substituted 1,3-butadiynes as the  
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38 diyne substrates. As shown in Table 1, when phenyl or *p*-tolyl-substituted butadiynes were  
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40 used as the coupling components, the corresponding products **4l-4n** could be formed in  
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42 42-48% yields by treatment of the crude products with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in  $\text{CH}_2\text{Cl}_2$  at room  
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44 temperature. **4l-4n** could also be formed without the need to use Lewis acid. The use of  
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46 alkyl-substituted butadiynes such as Hex-C $\equiv$ C-C $\equiv$ C-Hex and  $t\text{BuC}\equiv\text{C}-\text{C}\equiv\text{C}'\text{Bu}$  were also  
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48 suited for this reaction, furnishing the pyrrole products **4o** and **4p** in 39% and 55% yields,  
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50 respectively. One of the reasons for the lower yields of **4l-4p** derived from aryl- or  
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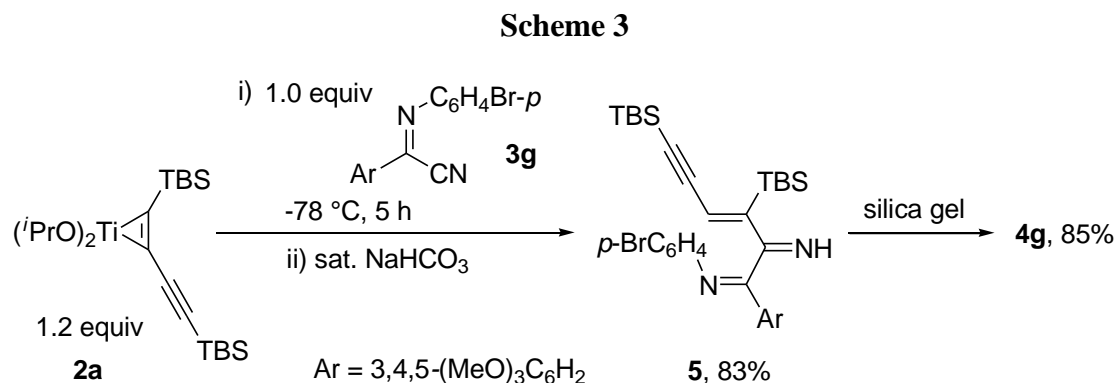
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4 alkyl-substituted butadiynes might be due to the lower yields of the first step for the  
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6 formation of the corresponding titanium-butadiyne complexes.<sup>11a</sup> The structure and the  
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8 regioselectivity of 3-aminopyrroles **4** were unambiguously confirmed by X-ray  
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10 crystallographic analyses of the product **4a** (Figure 1) and the *N*-tosylated derivatives of **4l**  
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12 and **4p**.<sup>20</sup>  
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**Figure 1.** X-ray crystal structure of 3-aminopyrrole **4a**

To understand the reaction mechanism, we tried to isolate the possible intermediate before treating the crude products with silica gel. A diimine product **5**, derived from the coupling reaction of titanium-butadiyne complex **2a** with *N*-(4-bromophenyl)-3,4,5-trimethoxybenzimidoyl cyanide **3g**, was found to be stable upon isolation through neutral Al<sub>2</sub>O<sub>3</sub>. The structure of **5** was also confirmed by X-ray crystallographic analysis.<sup>20</sup> **5** converted to 3-aminopyrrole **4g** in high yield of 85% upon loading on silica gel followed by column chromatography. The results indicated that

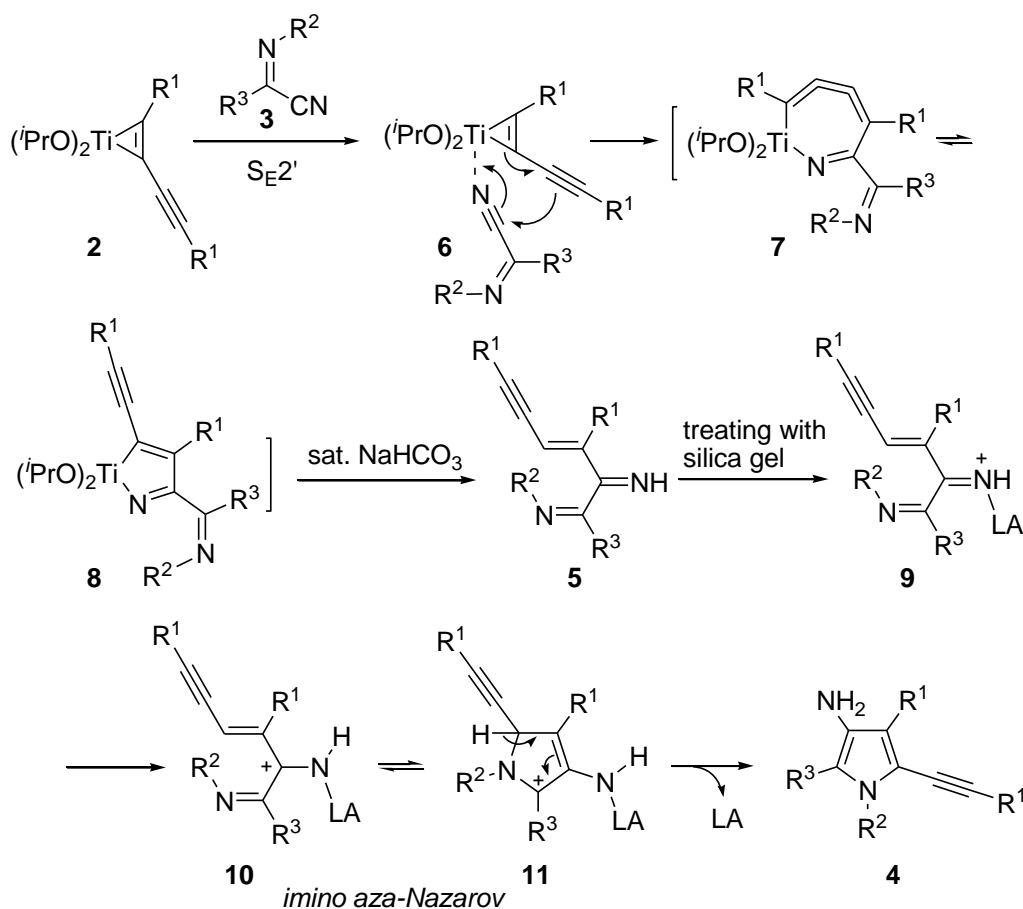
3-aminopyrrole **4** was formed during the silica gel purification process (Scheme 3).



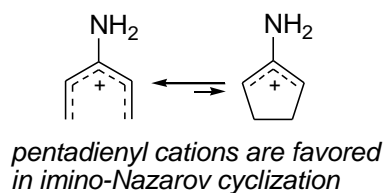
Based on the above results, we propose the following reaction mechanism for this novel transformation using butadiyne as the substrates (Scheme 4): First, addition of the  $\text{C}\equiv\text{N}$  moiety of iminonitrile to the less hindered propargyl titanium moiety in complex **2** via  $\text{S}_{\text{E}}2'$ -type<sup>21-22</sup> reaction gives an azatitanacyclocumulene **7**, which might isomerize to azatitanacyclopentadiene **8**. **8** might also be formed by direct insertion of CN bond into the  $\text{Ti}-\text{C}(\text{sp}^2)$  bond close to  $\text{R}^1$  group of **2**. However, the attack of the nitrile from this side may encounter large steric hindrance. Hydrolysis of **8** affords the diimine product **5**. Further transformation of **5** to 3-aminopyrroles **4** might proceed via an interesting imino aza-Nazarov cyclization promoted by silica gel due to its weak Lewis acidity.<sup>23</sup> As we know, imino<sup>24</sup> and aza-Nazarov<sup>25</sup> cyclizations are variations of the classical Nazarov reaction involving  $4\pi$  electrocyclizations. Until now, the reports for imino-type Nazarov cyclizations are quite limited.<sup>24</sup> Calculations by Smith *et al.* indicated that the 3-imino-type Nazarov reaction is energetically disfavored due to the stabilization of 3-aminopentadienyl cation over the cyclic allylic cation by conjugation with the lone pair electrons on the nitrogen atom (Scheme 5).<sup>26</sup> To the best of our knowledge, the imino aza-Nazarov

cyclization has only been reported as a postulated reaction step in a diamine monotriflate-catalyzed asymmetric cyclization of ketoazirines.<sup>27</sup> In our case, the allylic cation **11** could be more favored due to the stronger stabilization by an adjacent nitrogen atom on NR<sup>2</sup> group.

## Scheme 4

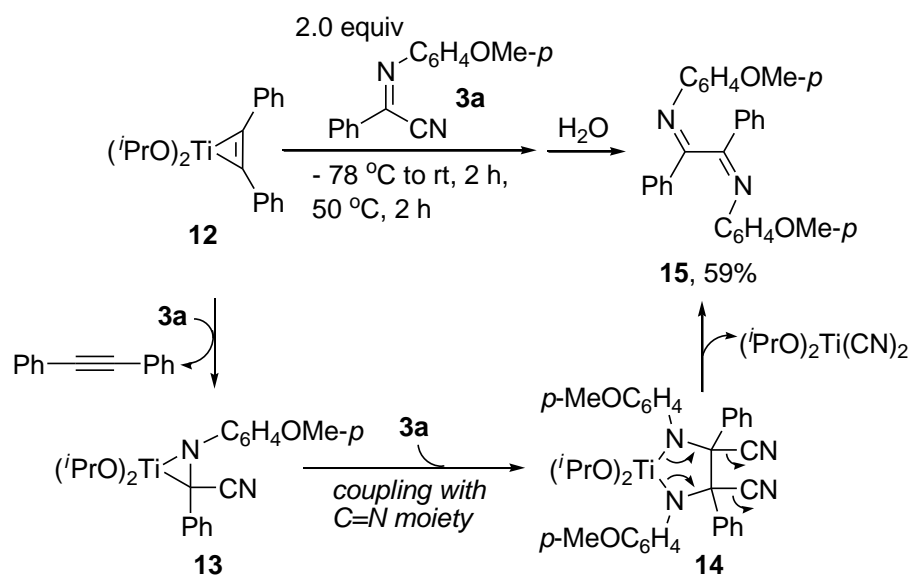


## Scheme 5



We also investigated the reactions of titanium-monoyne complexes with  $\alpha$ -iminonitriles (Scheme 6). Interestingly, the expected 3-aminopyrroles were not obtained, instead, the diimine **15** was obtained in 59% yield, along with 74% of diphenylacetylene, after quenching the reaction mixture by water. In addition, one more byproduct was also observed, the structure of which was not defined yet. The reaction might proceed by first ligand exchange to give a titanium-imine complex **13**, which undergoes homo-coupling with another  $\alpha$ -iminonitrile to give **14** by insertion of C=N moiety to azatitanacycle **13**. This is followed by elimination of CN groups to deliver the desired product **15**. Diimines are valuable ligands in transition-metal chemistry,<sup>28</sup> for example, the diimine-Ni complex shows high catalytic activity in olefin polymerization.<sup>28b-c</sup> Our reaction provides a simple and efficient method for the synthesis of diimines.

Scheme 6



In summary, we have developed a titanium-mediated regioselective cross-coupling reaction of 1,3-butadiynes with  $\alpha$ -iminonitriles. Functionalized 3-aminopyrroles were

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4 efficiently constructed upon treatment of the crude hydrolysis products with silica gel or  
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6 Lewis acid. The reaction likely proceeds *via* a novel imino aza-Nazarov type cyclization of  
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8 the diimines produced by hydrolysis of the *in situ* generated azatitanacycles. Employing  
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10 titanium-monoyne complex in this reaction resulted in homo-coupling of  $\alpha$ -iminonitriles,  
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12 leading to the formation of 1,2-diimines. Further studies to expand the reaction scope are in  
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14 progress.  
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23 **Electronic supplementary information (ESI) available:** Experimental details,  
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25 spectroscopic characterization of all new compounds, X-ray crystallography of compounds  
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27 **3b, 4a**, *N*-tosylated derivatives of **4l, 4p, 5, 15** and CIF files giving crystal data are given in  
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29 the Supporting Information file.  
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38 Research Development Program (Grant No. 2011CB808700) for financial support.  
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#### 44 **Notes and references**

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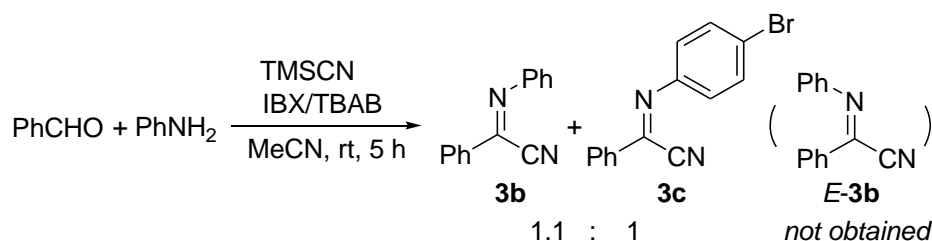


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- (19) The use of  $\text{CH}_2\text{Cl}_2$  as the solvent enables an efficient transformation to pyrrole on

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4 silica gel.  
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7 (20) The X-ray crystal structures of compounds **3b**, **4a**, *N*-tosylated derivatives of **4l** and  
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9 **4p**, **5** and **15** are shown in supporting information. CCDC-988139 (**3b**),  
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11 CCDC-988138 (**4a**), CCDC-988137 (*N*-tosylated derivative of **4l**), CCDC-988141  
12  
13 (*N*-tosylated derivative of **4p**), CCDC-988140 (**5**) and CCDC-988142 (**15**) contain  
14  
15 the supplementary crystallographic data for this paper. These data can be obtained  
16  
17 free of charge from The Cambridge Crystallographic Data Centre via  
18  
19 [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).  
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