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CuI-catalyzed Intramolecular Aminocyanation of Terminal Alkynes in *N*-(2-Ethynylphenyl)-*N*-sulfonylcyanamides *via* Cu-vinylidene Intermediates

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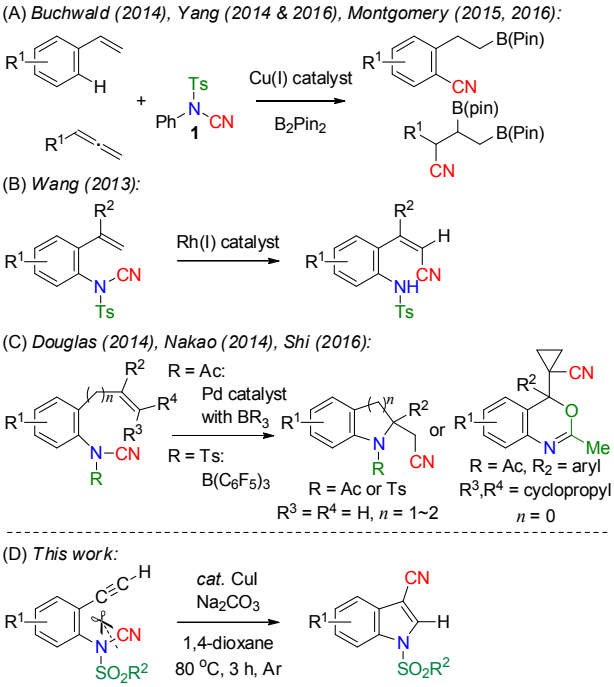
CuI-catalyzed Intramolecular aminocyanation of terminal alkynes in *N*-(2-ethynylphenyl)-*N*-sulfonylcyanamides was initiated by the formation of Cu-acetylide to trigger N-CN bond cleavage of the *N*-sulfonylcyanamide moiety followed by CN migration to form β-cyano Cu-vinylidene intermediate. Subsequently, the indole ring closure furnished the corresponding 1-sulfonyl-3-cyanoindoles.

Cyanamide derivatives have been extensively used as reactive N-C-N building blocks in organic synthesis,[1] and as ambidentate ligands in coordination chemistry.[2] Recently, the use of *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS, **1**) and its derivatives as organic cyanating reagents has received considerable attention, of which the N-CN bond cleavage provided reactive CN species for expeditious synthesis of a variety of cyano-containing organic molecules.[3]

NCTS (**1**) can react with various nucleophiles or organometallic reagents to form the corresponding X-CN bonds (X = C, N or O), including: (1) organozinc reagents,[4] aryl halides[5] or aryl/vinyl boronic acids[6] under transition-metal catalysis; (2) π-electron rich (hetero)arenes with $BF_3{\cdot}OEt_2$;[7] and (3) Grignard reagents,[8] boron enolates,[9] or deprotonated X-H nucleophiles (X = N or O).[10] NCTS (**1**) was also used as the CN source for direct cyanation of (hetero)arenes or alkenes *via* the transition-metal catalyzed C(sp^2)-H bond activation in the presence of miscellaneous neighboring directing groups.[11] Zeng reported that *ortho*-aminobenzonitriles were obtained by aminocyanation of arynes through the direct addition of *N*-arylcyanamides, which is an exception for the N-CN bond dissociation of cyanamides that did not possess electron-withdrawing substituents.[12]

The intermolecular reactions of NCTS (**1**) with unsaturated C-C bonds have also been studied. Buchwald and Yang demonstrated that bis-functionalization of vinylarenes was achieved by the reaction with NCTS (**1**) and $(Bpin)_2$ under Cu(I) catalysis. The vinyl group played the role of a directing group for the *ortho*-C(sp^2)-H cyanation and itself was simultaneously hydroborated.[13,14] Montgomery further adopted a similar reaction protocol for a cascade C(sp^2)-cyanation/diborylation of terminal allenes (**Scheme 1** (A)).[15]



Scheme 1. Reactions of unsaturated C-C bonds with NCTS (**1**) or its derivatives

Our attention was attracted by the intramolecular CN migration reaction of *ortho*-alkenyl substituted NCTS derivatives, wherein the NCTS portion served as an internal cyano donor for intramolecular cyanation of alkenes. Wang found that the Rh(I)-catalyzed reactions of *ortho*-vinyl substituted NCTS derivatives resulted in the intramolecular alkene-cyanation (**Scheme 1** (B)).[16] Douglas,[17] Nakao[18] and Shi,[19] independently reported that *ortho*-allyl or homoallyl

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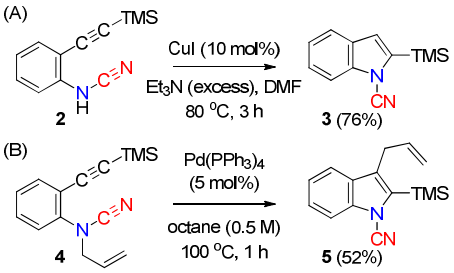
substituted NCTS derivatives or the *N*-acyl-*N*-phenylcyanamide congeners underwent intramolecular aminocyanation in the presence of boranes as activators, in which the N-CN bond dissociation took place accompanied by the simultaneous addition of the N-CN bond to alkenes (**Scheme 1** (C)).

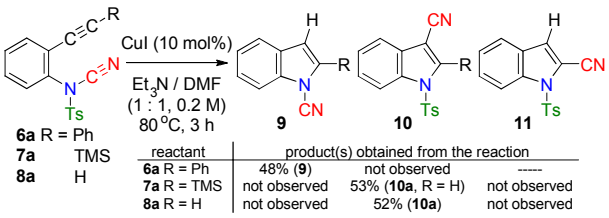
The above mentioned works indicated that Lewis acid or transition metal promoted N-CN bond cleavage of NCTS derivatives is an effective approach to provide reactive CN species for versatile cyanation applications. Nevertheless, the present C-CN bond formation with NCTS derivatives was limited only to sp^2-hybridized carbon centers.[3] The inter- and intramolecular reactions of NCTS-derived cyanating reagents with *sp*-hybridized carbon centers still remain unexploited.



Scheme 2. Literature-reported reactions

Literature survey revealed that the reactions of *N*-(2-alkynylphenyl)cyanamide derivatives have rarely been studied. Yamamoto reported that CuI-catalyzed reaction of *N*-(2-(2-(trimethylsilyl)ethynyl)phenyl)cyanamide (**2**) gave 2-trimethylsilyl-1-cyanoindole (**3**) in 76% yield.[20] In addition, the reaction of *N*-allyl-*N*-(2-(2-(trimethylsilyl)ethynyl)phenyl)cyanamide (**4**) under $Pd(PPh_3)_4$ catalysis afforded 3-allyl-2-trimethylsilyl-1-cyanoindole (**5**) in 52% yield (**Scheme 2**).[21] Both reactions resulted in the *N*-cyanoindole derivatives, which showed that the N-CN bond without an electron-withdrawing group is substantially stable under catalytic conditions. Even in the presence of an electron-withdrawing group, Saá demonstrated that *N*-(2-(phenylethynyl)phenyl)-*N*-tosylcyanamide (**6a**) is thermally stable at 150 °C and distinctive from the corresponding ynamide analogs that can undergo thermal cyclization to form benzo[*b*]carbazole.[22] Therefore, we were prompted to investigate the unexploited reactivity whether the N-CN bond cleavage followed by intramolecular electrophilic cyanation of *N*-(2-ethynylphenyl)-*N*-sulfonylcyanamides could be achieved under catalytic condition.

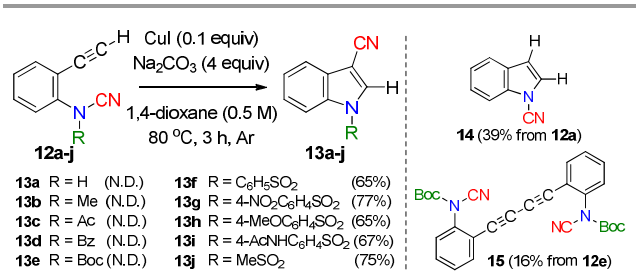
The *N*-phenylcyanamide derivatives used in our study were prepared by three different approaches, including dehydration of *N*-phenylureas by sulfonyl chlorides,[8] direct cyanation of *N*-sulfonylanilines with BrCN,[17,22] and Tiemann rearrangement of benzamidoximes.[23] In our initial trials, *N*-(2-alkynylphenyl)-*N*-tosylcyanamides (**6a**, **7a** and **8a**) were first subjected to Yamamoto's CuI and $Pd(PPh_3)_4$ conditions to explore the reaction outcomes. While the reactions of **6a-8a** did not proceed with $Pd(PPh_3)_4$, the reactions with CuI gave two different results, as shown in **Scheme 3**. Both the terminal and TMS-ethynyl derivatives (**8a** and **7a**) afforded 1-tosyl-3-cyanoindole[24] (**10a**) as the product, contrast to the 1-cyano-2-phenylindole[25] (**9**) obtained from the phenylethynyl derivative **6a**.



Scheme 3. Reactions of *N*-(2-alkynylphenyl)-*N*-tosylcyanamides (**6a**-**8a**) under literature condition

The formation of **10a** has particularly attracted our attention, in which the formal cleavage of the N-CN bond took place accompanied with intramolecular aminocyanation of the alkyne to furnish the 3-cyanoindole skeleton. It is noteworthy that the regiochemistry of our intramolecular aminocyanation of the alkyne is contrary to the intramolecular aminocyanation or cyanation of alkenes[16-19] (**Scheme 1**) and prompted us to further examine the reaction details.

Various conditions for the reaction of **8a**, including different bases, metal salts, ligands/additives, solvents, and temperature, were screened in order to optimize the formation of **10a**. The maximal yield was obtained when the reaction was carried out in 1,4-dioxane with CuI as the catalyst, and Na_2CO_3 as the base under argon at 80 °C, and the reaction could be completed within 3 hours. The CuI-catalyzed aminocyanation ring closure of **8a** afforded exclusively 1-tosyl-3-cyanoindole (**10a**) in an excellent yield. The survey of the conditions also concluded that both Cu catalyst and base are required, and reaction yields were presumably the same in open air and under an argon atmosphere.



Scheme 4. Reaction of *N*-substituted *N*-(2-ethynylphenyl)cyanamides (**12a**-**j**)

Subsequently, a series of *N*-(2-ethynylphenyl)cyanamides (**12a-j**) with different substituents at cyanamide were subjected to the optimized condition to screen for suitable *N*-substituents which could promote the N-CN bond cleavage and CN migration. 1-Cyanoindole[25] (**14**) was the only product isolated from the reaction of *N*-(2-ethynylphenyl)cyanamide (**12a**), which confirmed that cleavage of the unsubstituted N-CN bond cannot be achieved under CuI catalysis. The survey of the substituent effects showed that only the sulfonyl groups can proceed to the intramolecular aminocyanation to afford 1-sulfonyl-3-cyanoindole derivatives (**13f**-**j**) in good yields, while

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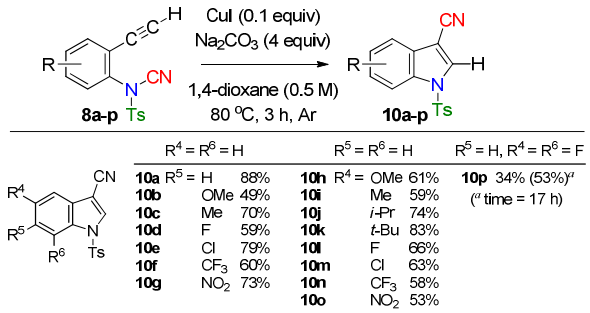
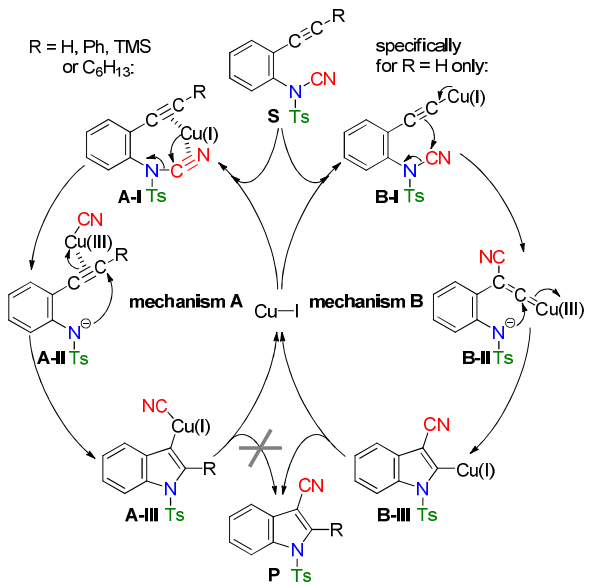
N-methyl- and *N*-acyl-substituted *N*-(2-ethynylphenyl)cyanamides (**12b-e**) gave no desired products but complicated results (**Scheme 4**).



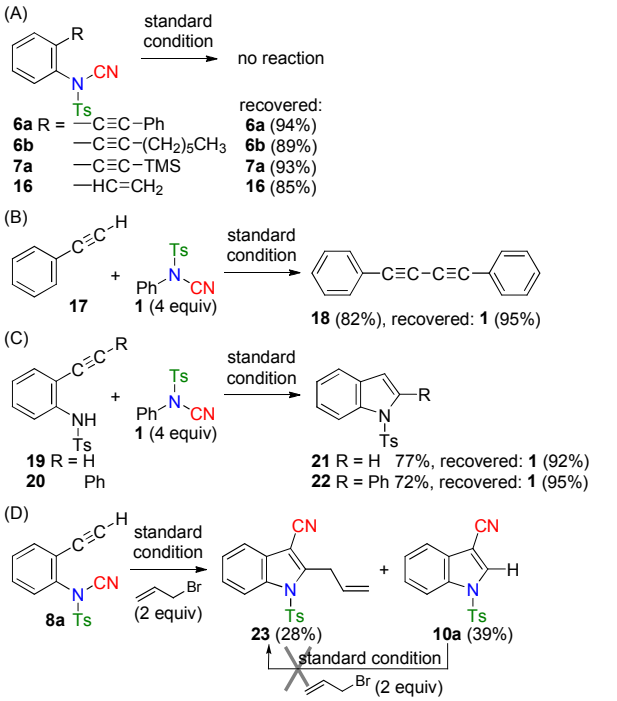
Scheme 5. Reaction of *N*-(2-ethynylphenyl)-*N*-tosylcyanamides **8a-p**

Meanwhile, a variety of *N*-tosyl-*N*-(2-ethynylphenyl)cyanamides (**8a-p**) were subjected to the optimized condition to explore the scope and generality of the intramolecular aminocyanation reaction. Our investigation showed that the reactions of all the substrates (**8a-p**) proceeded flawlessly under the optimized condition to form the corresponding 1-tosyl-3-cyanoindole derivatives (**10a-p**) in good yields (**Scheme 5**).



Scheme 6. Proposed mechanism

A tentative mechanism was first sketched in accordance to the conventional 3-substituted indole formation from 2-alkynylaniline derivatives *via* indol-3-yl metal intermediates (**mechanism A** in **Scheme 6**).[26] The reaction was proposed to start with the formation of substrate-copper complex (**A-I**) by π-coordination of alkyne and nitrile moieties to the copper center. Subsequently, the heterolytic cleavage of N-CN bond accompanied by migration of the electrophilic cyano group to the copper center resulted in the *N*-tosyl-2-alkynylanilide cyano-copper complex **A-II**. Intermediate **A-II** then underwent *trans*-aminometalation across the alkyne followed by cyanation to give 1-tosyl-3-cyanoindoles (**P**) *via* the intermediacy of 1-tosylindol-3-yl cyano-copper complex (**A-III**) (**mechanism A** in **Scheme 6**).



Scheme 7. Control experiments

A series of control experiments were conducted in order to gain insight into the mechanistic details. *ortho*-Vinyl- and internal alkynyl-tethered NCTS derivatives (**16**, **6a-b** and **7a**) were first subjected to the standard condition to explore the limitation of the unsaturated C-C components. The results indicated that the intramolecular aminocyanation of alkenes or internal alkynes did not take place under CuI catalysis (**Scheme 7** (A)).

In an effort to investigate whether the intermolecular aminocyanation or cyanation of phenylacetylenes could occur, an excess amount of NCTS (**1**) was used as an external CN source to react with phenylacetylene (**17**) or *N*-tosyl-2-alkynylanilines (**19** and **20**) under the standard condition. The reaction of phenylacetylene gave only the homocoupling adduct **18** and intact NCTS (**1**) was recovered, while the reactions of *N*-tosyl-2-ethynylanilines (**19** and **20**) afforded exclusively the corresponding 1-tosylindoles (**21** and **22**, respectively) and the recovered NCTS (**1**) (**Scheme 7** (B)(C)). The results revealed that NCTS (**1**) is stable under the standard condition and the subsequent electrophilic addition of cyano group to phenylacetylenes was infeasible. As a result, **mechanism A** (**Scheme 6**) was negligible since it failed to account for the fact that the intramolecular aminocyanation reaction is only applicable to terminal alkynes and the heterolytic cleavage of N-CN bond of NCTS derivatives cannot be triggered under copper catalysis.

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Notably, only terminal alkynes underwent the intramolecular aminocyanation reaction, which led to the assumption that the formation of Cu-acetylide complex plays a key role in the reaction. In an attempt to trap the transient indolyl-Cu complex, the addition of allyl bromide to the reaction of **8a** under the standard condition was carried out. The reaction afforded the aminocyanation adduct **10a** accompanied with 1-tosyl-2-allyl-3-cyanoindole (**23**). Since **23** cannot be obtained from the reaction of **10a** under the same condition, the result suggested that 1-tosylindol-2-yl-Cu complex (**B-III**) was formed in the reaction (**Scheme 7** (D)).

On the basis of the control experiments, the plausible mechanism was proposed to start with the formation of Cu-acetylide **B-I** with the increase of π-electron density at the β-carbon. Intramolecular nucleophilic attack of the β-carbon to the electrophilic cyanamide carbon accompanied with the N-CN bond cleavage resulted in the β-cyano Cu-vinylidene complex **B-II**.[27] Subsequent intramolecular nucleophilic attack of the remaining tosylamide at the α-carbon of the Cu-vinylidene complex (**B-II**) afforded 1-tosylindol-2-yl-Cu complex **B-III**. Protonation of **B-III** furnished the product **10a** and regained the Cu(I) catalyst to continue the catalytic cycle (**mechanism B** in **Scheme 6**).

In summary, we disclosed the CuI-catalyzed intramolecular aminocyanation of *ortho*-(*N*-tosyl-*N*-cyanoamino)-substituted phenylacetylene derivatives. The mechanistic investigation suggested that the transformation proceeded through a cyanation-amination sequence involving both Cu-acetylide and Cu-vinylidene intermediates to account for the regiochemical course. The N-CN bond cleavage was triggered solely by the neighboring Cu-acetylide, which enlightens that the intramolecular β-electrophilic addition of Cu-acetylide complex would be feasible for further synthetic applications.

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