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Rapolu Kiran Kumar[a] and Xihe Bi*[a,b]

The majority reactions of alkynes in the literature are reported to proceed via either structural σ-activation or catalytic π-activation of C≡C bonds. We skilfully designed novel methods for catalytic σ-activation of C≡C bonds of alkynyl compounds. For terminal alkynyl compounds, σ-activation was achieved by silver(I)-catalyzed C-H functionalization. Whereas σ-activation of internal alkynes was accomplished by generation of propargylic cations from propargylic alcohols under Lewis-acid catalysis. These σ-activated species have successfully used for new C–C and C–hetero atom bonds formation reactions. Plausible reaction pathways were proposed based on typical control experiments to help the readers to gain insights into reactions and further discovery of new reactions based on this concept of catalytic σ-activation of C≡C bonds.

1. Introduction: Significance of alkyne functionalization reactions

Alkynes are one of the oldest known, structurally simple and unique chemicals. The alkyne (C≡C) functional group can be found in compounds derived from both living and non-living natural sources such as petroleum oil, coal, plants, small organisms, animals and human beings.[1] Alkyne functional group acts also as a motif of high significance in pharmaceutical[1b,c] and various potential applications.[2] The simplest alkyne i.e. acetylene is abundantly available from partial combustion of methane and cracking of hydrocarbons[3] and it can be converted into higher alkynes and alkynyl compounds via simple transformations.[4] Furthermore, alkynyl compounds can also be synthesized from other functional group chemicals.[5] Because of the synthesis of alkynes and conversion into other chemical assets were convenient, any new development in chemical reactions using alkynyl compounds was highly welcomed. Thereby, alkynyl compounds have become vital chemical reagents and the method of alkyne functionalization have been applied in a myriad of reactions both in intra- and intermolecular patterns.[6,7] Which has been witnessed through the development of a series of well-known reactions[8] that have become the foundation of organic chemistry. In addition to these, the use of alkyne functionalization reactions has been observed also in transition-metal-catalyzed recent highly advanced methodologies.[9,10]

2. Alkyne functionalization: Catalytic σ- or π-activation of C≡C bond

In our understanding, alkyne functionalization means activation of C≡C bond for subsequent transformations. Generally, activation of C-X multiple bonds i.e. C=X and C≡X (where X is C, N, O) bonds functionalization can be performed in two fundamental routes.[11] (1) σ-activation, in which activation takes place by interaction of activating species with C=X and C≡X bonds via σ-bond metathesis (if X is CH)[11c,d,f,g] or σ-coordination i.e. σ-complex formation (if X is hetero atom)[11a,b,e] (Figure 1a). (2) π-activation, in which activating species interacts with C=X and C≡X bonds via π-coordination i.e. π-complex formation (if X is CR, hetero atom) (Figure 1b).[9,10,11h-m]

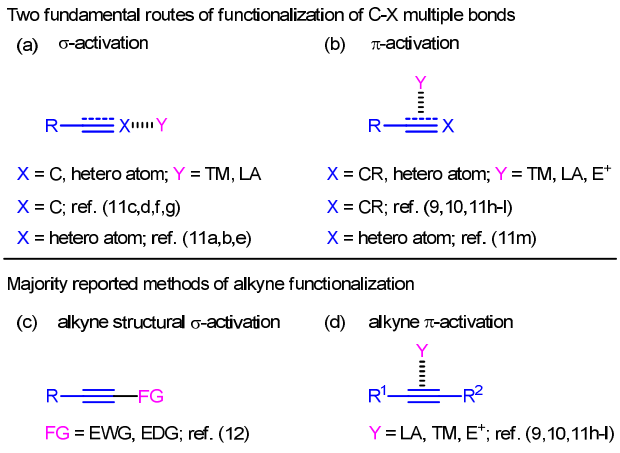
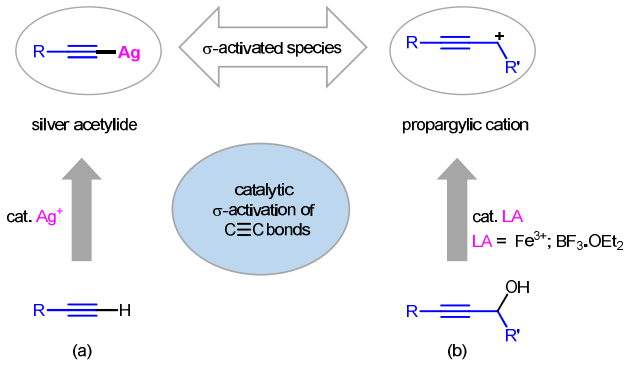


Figure 1 Routes of functionalization of C-X multiple bonds

[a] Department of Chemistry, Northeast Normal University
5268 Renmin Street, 130024 Changchun, P. R. CHINA
bixh507@nenu.edu.cn
[b] State Key Laboratory of Elemento-Organic Chemistry
Nankai University, 300071 Tianjin, P. R. CHINA

Regarding to alkynes, activation of C≡C bonds is possible by σ-bond metathesis (in case of terminal alkynes), π-coordination (in case of terminal and internal alkynes) and other routes.[12] Nevertheless, literature search revealed that, the reactions of terminal alkynes which need σ-activation for undergoing reactions, majority reports have used pre-activated alkynes as latent terminal alkynes. In other words, structural modification of terminal alkynes. Hence referred to as alkyne structural σ-activation (Figure 1c).[13] A serious drawback of alkyne structural σ-activation is, the need of an equivalent quantity of FG moiety. Whereas, the reactions of internal alkynes were reported to proceed via π-activation of C≡C bonds (Figure 1d).[9,10,11h-l]

Because of σ-activation of C≡C bonds is powerful mode of activation, we believed that, the catalytic version of σ-activation would be conceptually novel. Hence, we envisioned the catalytic σ-activation of C≡C bonds in the following two pathways (Scheme 1) while maintaining atom economical nature, efficiency in steps, cost effectiveness, environmental compliance and applicability to terminal and internal alkynes. (1) Catalytic ≡C-H activation in the case of terminal alkynes (Scheme 1a). 2) Catalytic generation of electrophilic centre at C≡C bonds i.e. C≡C-E^+ in case of internal alkynes (Scheme 1b).[14] We skilfully solved the above two challenges in the following two pathways. 1) The catalytic σ-activation via ≡C-H activation was achieved by silver(I)-catalyzed C-H σ-bond metathesis (Scheme 1a).[15] 2) The catalytic generation of electrophilic centre at C≡C bonds (i.e. C≡C-E^+) was performed by using propargylic alcohols under Lewis-acid (Fe^{3+} or $BF_3{\cdot}OEt_2$) catalysis (Scheme 1b).



Scheme 1 Our concept of catalytic σ-activation of C≡C bonds

The reason for selecting the propargylic alcohols as latent internal alkynes for σ-activation of C≡C bonds is the possibility of synthesis of propargylic alcohols from different functional group chemicals,[16] thereby applicable to large number of internal alkynes. Whereas, the reason for selective use of silver salts as catalysts include stability, availability of many varieties of silver(I) salts, non-toxicity and and low price.

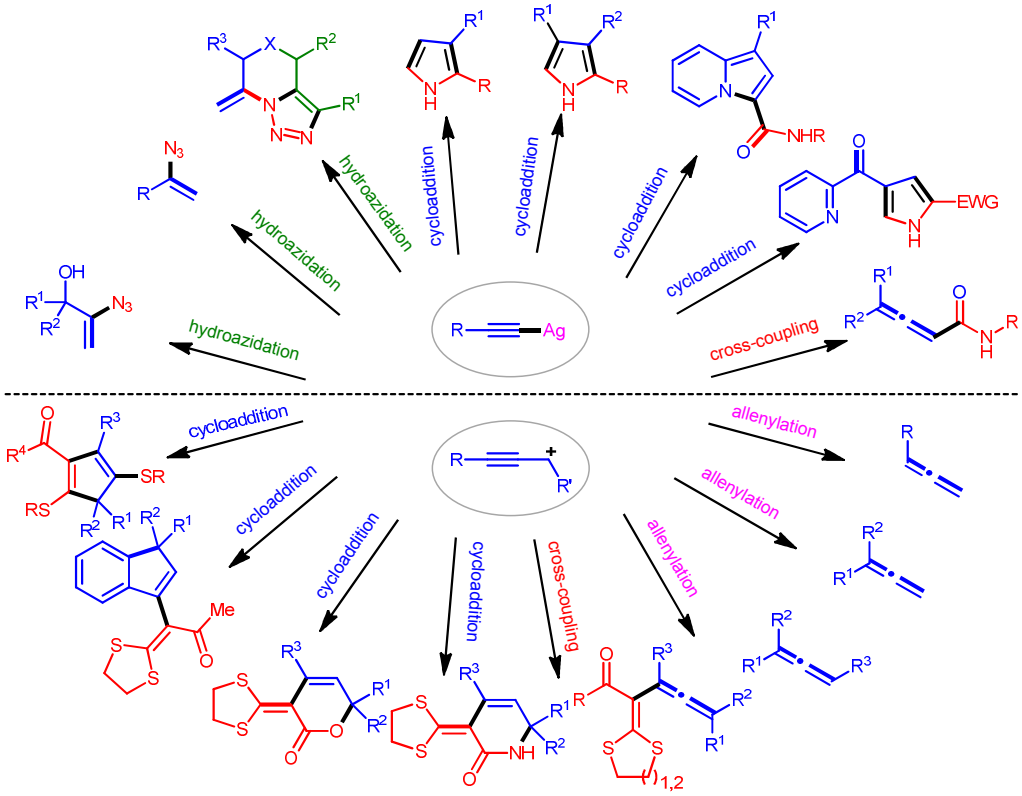


Figure 2 Chemistry of alkynes via catalytic σ-activation of C≡C bonds developed by our group

The following section discusses the advantages of our catalytic σ-activation over structural σ-activation and π-activation. 1) Catalytic σ-activation of C≡C bonds is a new path of alkyne functionalization compared to structural σ-activation and π-activation. Hence, it opens up a novel area of research in the chemistry of alkynes. 2) σ-Activation via C-H/C-OH bond cleavage made the protocols atom-economical compared with structural σ-activation. 3) The protocols were step-efficient because, the σ-activations were performed by C-H activation, which obviates the introduction of FGs over C≡C bonds and removal from the products. 4) In the case of propargylic alcohols as latent internal alkynes, cleavage of –OH motif during catalysis made the protocols step-efficient without the need to removal of –OH from the products. 5) Both terminal and internal alkynes were successfully activated. 6) The protocols work with catalytic amount of inexpensive silver salts and Lewis acids. 7) Because propargylic alcohols were used as precursors of internal alkynes for σ-activation, their easy access made this σ-activation highly favourable, whereas their divergent synthesis from many directions made the protocols quite general and applicable to different internal alkynes.

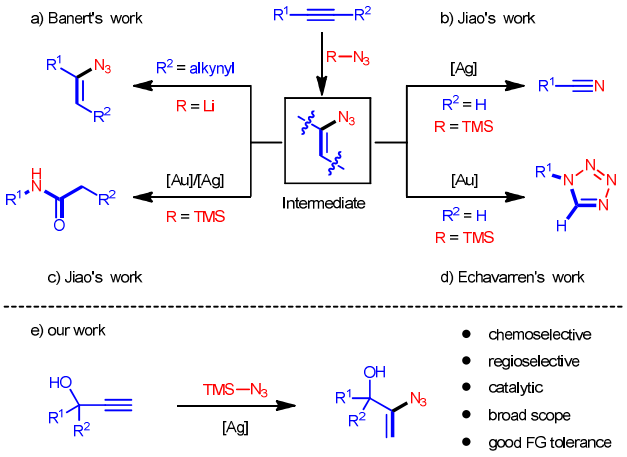
In this context, this review emphasized our group successfully developed alkyne functionalization reactions proceeded through catalytic σ-activation of C≡C bonds and their further applications in organic chemistry (Figure 2). An emphasis on reaction mechanistic aspects helps readers to further design new reactions based on this novel concept of catalytic σ-activation of C≡C bonds.

3. Silver(I)-catalyzed σ-activation of C≡C bonds in alkynyl compounds

3.1 Hydroazidation of ethynyl carbinols

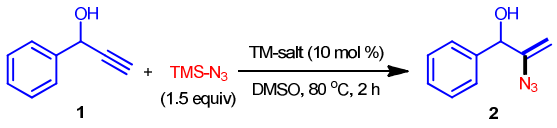
Since their discovery in 1910 by Foster and Newman, vinyl azides have been recognized as useful reagents and intermediates.[17,18] These compounds are particularly important in transition-metal-catalyzed azahetero cyclization reactions for the synthesis of *N*-heterocyclic compounds.[19] However, the synthetic potency of vinyl azides has not been fully explored because of the limited availability of methods for their large-scale synthesis.[20] Therefore, development of novel and more convenient methods for the large-scale synthesis of highly functionalized vinyl azides is urgently needed.

The hydroelementation of alkynes is a straightforward reliable pathway for synthesizing highly functionalized alkenes[9e-g] and furthermore alkynes are easily accessible chemicals. Therefore, we believed that the hydroazidation of alkynes will become an ideal method to synthesize vinyl azides (Scheme 2). But, such reactions are limited to electron-deficient alkynes.[20] Regarding to unactivated alkynes, only two individual examples were available (Scheme 2a and 2b).[20d,21a] In other cases, vinyl azides were formed as intermediates during the conversion of alkynes into amides (Scheme 2c)[21b] or tetrazoles (Scheme 2d).[21c] Inspired by Jiao's pioneering works (Scheme 2b and 2c), we focused on hydroazidation of ethynyl carbinols with $TMSN_3$ using our concept of catalytic σ-activation under silver catalysis. This investigation led us to the discovery of hydroxy-directed unprecedented chemo- and regioselective hydroazidation of ethynyl carbinols to afford 2-azidoallyl alcohols (Scheme 2e).[22]



Scheme 2 Unique reactions of alkynes with azides

As the start-up of investigation, when 1-phenylprop-2-yn-1-ol (**1**) was treated with TMS-N_3 in the presence catalytic amount of silver(I) salts like AgF, $AgNO_3$ or Ag_2CO_3 in DMSO solvent, it underwent regioselective hydroazidation to afford 2-azido-1-phenylprop-2-en-1-ol (**2**) in isolated yields of 62-85% (Scheme 3). It is noteworthy that, only the hydroazidation reaction took place and formation of nitrile product like Jiao's work (Scheme 2b) was not observed. Through this finding we discovered the special ability of –OH group of propargylic alcohols to stabilize vinyl azides. Reactions with other metal salts such as $Pd(OAc)_2$ or CuI were ineffective. The optimum reaction conditions used are TMS-N_3 (1.5 equiv) and Ag_2CO_3 (10 mol %) in DMSO at 80°C.

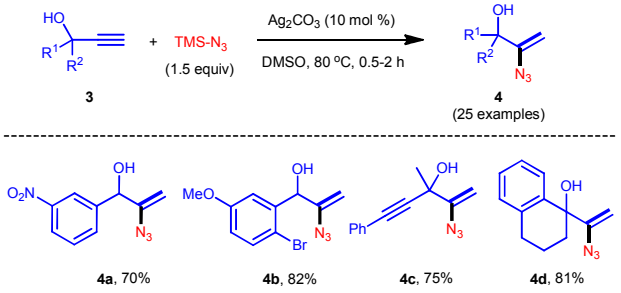


TM-salt : % yield = AgF : 62; $AgNO_3$: 75; **Ag_2CO_3 : 85**; $Pd(OAc)_2$: 0; CuI : 0

Scheme 3 TM-catalyzed hydroazidation of 1-phenylprop-2-yn-ol

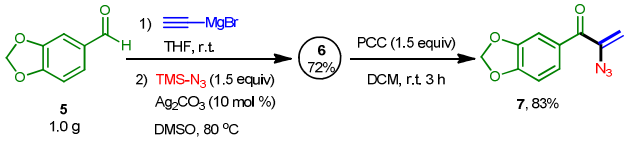
With the optimized conditions, we explored the scope of the reaction for different ethynyl carbinols (Scheme 4). The substrate scope was remarkable, a wide range of 2°- and 3°-ethynyl carbinols (**3**) substituted with alkyl, alkenyl, alkynyl, aryl, heteroaryl and cycloalkyl groups underwent hydroazidation reaction in a short reaction time (0.5–2 h), thereby afforded corresponding 2-azidoallyl alcohols (**4**) in good to excellent yields. The dense arrangement of different functional groups in one molecular scaffold renders 2-azidoallyl alcohols highly useful synthetic chemicals. Furthermore, because only one report by Trofimov and co-

workers is available to date on the synthesis of 2-azidoallyl alcohols by hydrazoic acid addition to acetylenic hydroxy acid nitriles,[23] we developed an efficient route for this type of compounds having great synthetic potential.



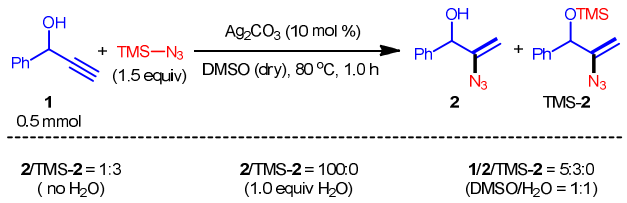
Scheme 4 Ag_2CO_3-catalyzed hydroazidation of ethynyl carbinols

The practicality of the Ag_2CO_3-catalyzed hydroazidation of ethynyl carbinols was demonstrated by gram-scale, one-pot synthesis of vinyl azide (**6**) starting from piperonyl aldehyde (**5**) and ethynylmagnesium bromide without isolating the carbinol product. Later vinyl azide (**6**) was oxidized to a carbonyl vinyl azide (**7**) in a yield of 83% (Scheme 5).



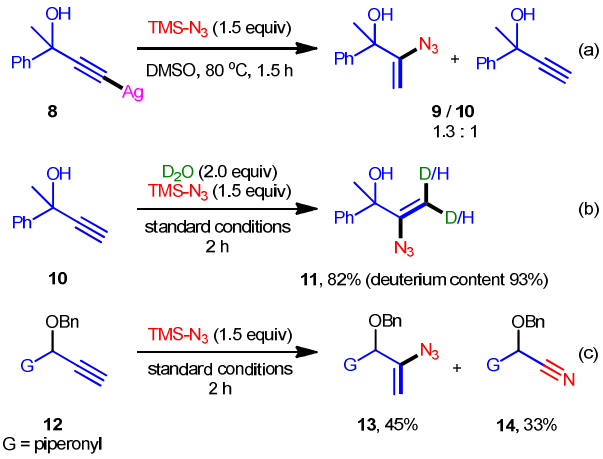
Scheme 5 One-pot, gram-scale synthesis of vinyl azide from piperonyl aldehyde

Subsequently, an investigation was carried out to determine reaction mechanism. Initially, reactions were performed to determine effect of residual water in DMSO solvent on reaction outcome (Scheme 6). A reaction in dry DMSO (2.0 mL) afforded a mixture of target vinyl azide **2** and O-trimethylsilylated vinyl azide (TMS-**2**) in 1:3 ratio. While performing the reaction in presence of H_2O (1.0 equiv), afforded only **2** and prevented the formation of TMS-**2**. A reaction with this TMS-**2** and H_2O (1.0 equiv) in the presence of Ag_2CO_3 (10 mol %) in DMSO at 80°C, TMS-moiety was remained intact. This reaction excluded the possibility of initial formation of TMS-**2** followed by hydrolysis into **2**. Finally, performing the reaction with mixed solvents of DMSO (1.0 mL) and H_2O (1.0 mL) caused a large amount of **1** to remain in the reaction mixture.



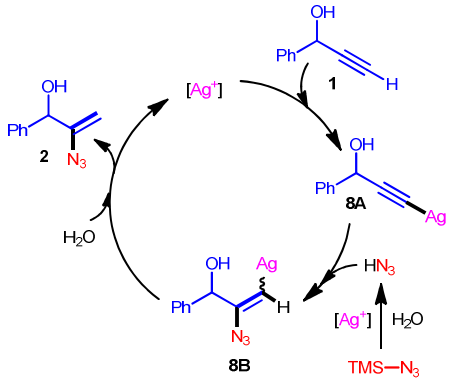
Scheme 6 Effect of water on reaction outcome

Next, control experiments were performed to gain further insights into the reaction pathway (Scheme 7). We synthesized silver acetylide (**8**) and reacted with TMS-N_3 under optimum reaction conditions without Ag_2CO_3 (Scheme 7a). This reaction afforded target vinyl azide (**9**) and ethynyl carbinol (**10**) in 1.3:1 ratio. The feasibility of hydroazidation reaction with silver substituted propargylic alcohol (**8**) without addition of Ag_2CO_3, implied silver-catalyzed hydroazidation of propargylic alcohols proceeded through the pathway involving silver acetylide intermediate **8**. Formation of deuterated product (**11**), when the reaction was performed in the presence of D_2O (2.0 equiv) under optimum reaction conditions confirmed that water was the hydrogen source of reaction (Scheme 7b). Silver acetylide (**8**) as the reaction intermediate was further supported by no reaction with internal alkynyl carbinol. The reaction of benzyl-protected substrate (**12**) with TMS-N_3 generated mixture of benzyl-protected vinyl azide (**13**) and nitrile product (**14**) (Scheme 7c). This reaction demonstrated the crucial role of hydroxyl moiety in stabilizing vinyl azide product. A radical process was excluded because of successful formation of vinyl azide (**9**) from ethynyl carbinol (**10**) in 77% yield in the presence of 2,2,6,6-tetramethylpiperidinyloxy (TEMPO).



Scheme 7 Experiments conducted to determine reaction mechanism

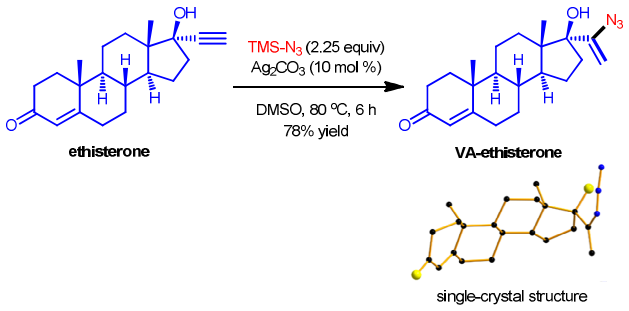
Catalytic cycle of the protocol was proposed based on above mechanistic studies (Scheme 8). Interaction of propargylic alcohol (**1**) with silver salt initiates the reaction by generation



Scheme 8 Postulated catalytic cycle of the protocol

of silver acetylide (**8A**). Simultaneously, silver-catalyzed in situ hydrolysis of TMS-N_3 generates hydrazoic acid (HN_3) and adds to silver acetylide (**8A**). This leads to formation of vinyl silver intermediate (**8B**).[15] Protonation of **8B** by trace amount of H_2O present in DMSO solvent liberates **2** as final product. This completes the catalytic cycle with regeneration of silver catalyst.

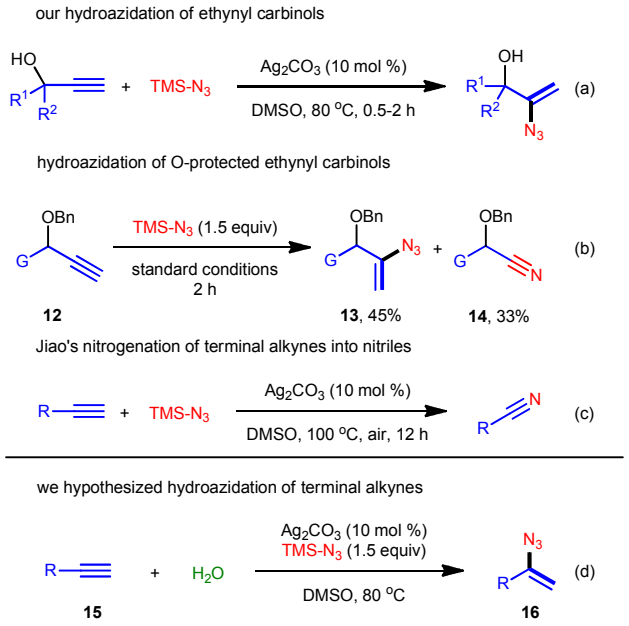
The application of the protocol was demonstrated through derivatization of ethisterone (the first oral active progestin)[24] into vinyl-azide-modified ethisterone (VA-ethisterone) without affecting its chiral centres (Scheme 9). This structural modification will be useful to medicinal chemists for structure-activity-relationship (SAR) studies.[25]



Scheme 9 Hydroazidation of ethisterone

3.2 Hydroazidation of terminal alkynes

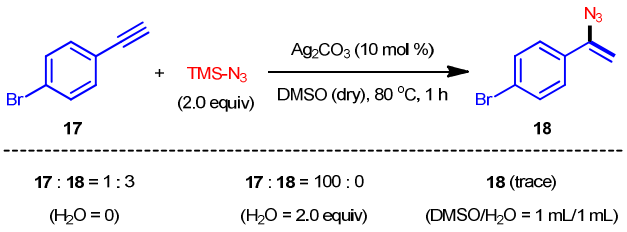
After comparing the results of the hydroazidation of ethynyl carbinols (Scheme 10a) and the controlled experiment



Scheme 10 Background for the hydroazidation of terminal alkynes

(Scheme 10b) with Jiao's silver-catalyzed nitrogenation of terminal alkynes into nitriles (Scheme 10c), we realized that the hydroxyl group either in the form of residual water in DMSO solvent or in the form of –OH moiety in ethynyl carbinols played a decisive role in stabilizing the vinyl azide during the reaction. In other words, either hydroxyl group protection or removal of residual water from solvent initiates the formation of nitriles from propargylic alcohols as in Jiao's work. From these, we hypothesized that the addition of an appropriate amount of H_2O to the reaction mixture would avoid the dependence on hydroxyl group, thereby can be established a general hydroazidation reaction of non-activated terminal alkynes (**15**) in a real sense (Scheme 10d).

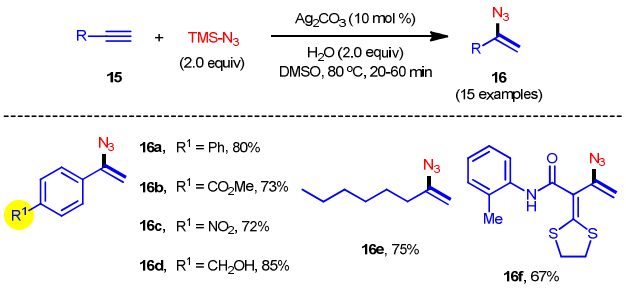
To assess the correctness of our assumption, we initially investigated the effect of H_2O by varying its relative quantity (Scheme 11). When a set of three reactions were performed using 4-bromophenylacetylene (**17**) and TMS-N_3 in dry DMSO (2.0 mL), DMSO (2.0 mL) with 2.0 equiv of H_2O and DMSO (1.0 mL) with H_2O (1.0 mL) to afford 4-bromophenyl vinylazide (**18**) in the substrate ratios shown in Scheme 11. This result not only confirmed our hypothesis but also revealed that an appropriate amount of H_2O was essential for hydroazidation of terminal alkynes and sliver-catalyzed hydrolysis of TMS-N_3 to generate N_3H.[22,26] With this, we established a powerful method for the hydroazidation of non-activated terminal alkynes into vinyl azides.[27]



Scheme 11 Effect of water on Ag_2CO_3-catalyzed hydroazidation of terminal alkynes

^{1}H NMR studies on the conversion of **17** into **18** over a time course were performed by analysing an aliquot of the reaction mixture at regular intervals (ca. 10 min). This clearly proved the clean formation of **17** with parallel consumption of **18** and also illustrated the necessity of strict control of reaction time to avoid further conversion of vinyl azides into nitriles as in Jiao's report.[21a]

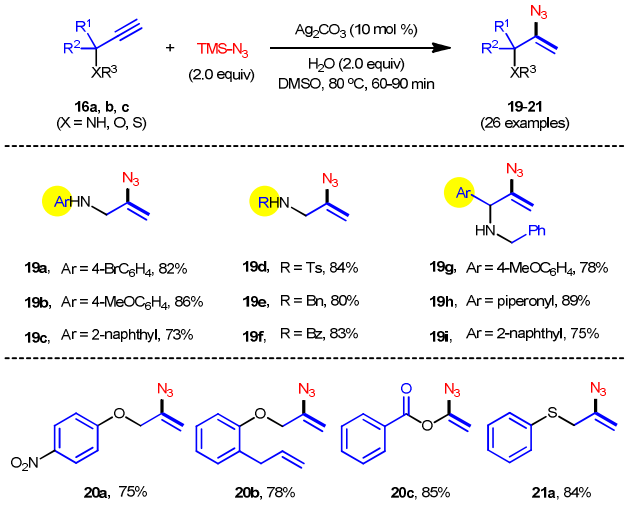
Later, we investigated the substrate scope of the protocol by using the optimized conditions of TMS-N_3 (2.0 equiv) and Ag_2CO_3 (10 mol %) in DMSO at 80°C (Scheme 12).



Scheme 12 Substrate scope of the Ag(I)-catalyzed hydroazidation of 1-alkynes

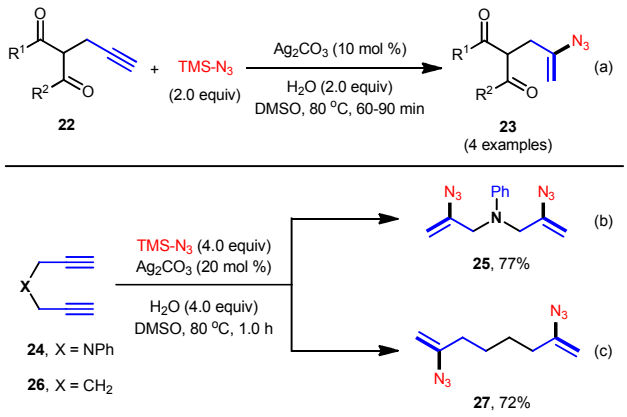
The substrate scope was quite general and broad. A range of aryl, alkyl and alkenyl alkynes (**15**) were compatible for the chemo-selective synthesis of corresponding vinyl azides (**16**) in excellent yields within 20–60 min.

Later, we checked the substrate scope of this Ag_2CO_3-catalyzed hydroazidation in case of propargylic amines, ethers and thioethers (Scheme 13). All these compounds efficiently underwent hydroazidation to afford corresponding vinyl azides (**19**-**21**). To the best of our knowledge, such functionalized compounds are new to organic chemistry.[28]



Scheme 13 Hydroazidation of propargylic amines, ethers and thioethers

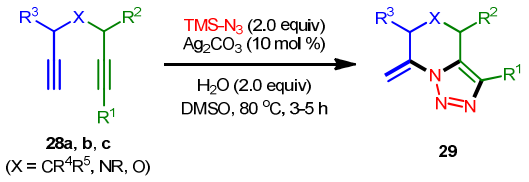
Subsequently, hydroazidation was extended to other alkynyl compounds like 4-alkynones (**22**), *N*,*N*-di(prop-2-yn-1-yl)aniline (**24**) and 1,7-octadiyne (**26**) (Scheme 14).



Scheme 14 Ag_2CO_3-catalyzed hydroazidation of other alkynyl compounds

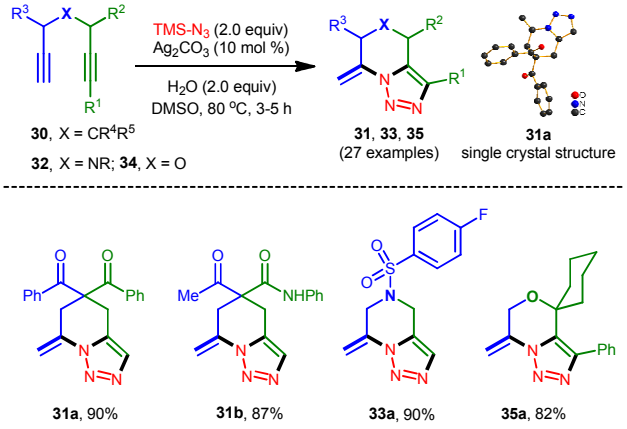
3.3 Tandem hydroazidation/cycloaddition of diynes

From the hydroazidation of 1-alkynes (Scheme 12) and double-hydroazidation of diynes (Scheme 14b, 14c), we assumed that performing mono-hydroazidation of diynes (**28**) would easily leads to tandem mono-hydroazidation followed by alkyne-azide cycloaddition, thereby formation of 1,5-fused 1,2,3-triazole frameworks (**29**) (Scheme 15).



Scheme 15 Envisioned tandem hydroazidation/cycloaddition of diynes

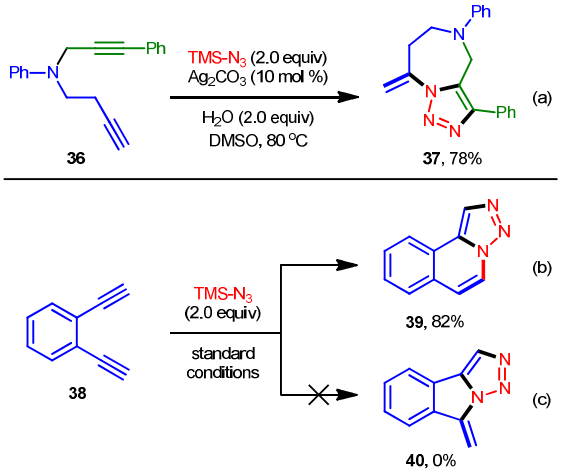
To check correctness of our assumption, a reaction was performed between 1,3-diphenyl-2,2-di(prop-2-yn-1-yl)propane-1,3-dione (**30a**) and TMS-N_3 (2.0 equiv) in the presence of Ag_2CO_3 (10 mol %) in DMSO with H_2O (2.0 equiv) at 80°C (Scheme 16). This reaction afforded piperidine-fused 1,2,3-triazole **31a** in 90% isolated yields. The structure of **31a** was confirmed also with single-crystal X-ray analysis. To the best of our knowledge, this was the first example of a transition-metal-catalyzed tandem hydroazidation/alkyne-azide cycloaddition of diynes. Later, substrate scope of this protocol was checked with a wide range of 1,6-diynes with X = CR^4R^5 (**30**), X = NR (i.e. *N*-protected-*N*,*N*-dipropargyl amines) (**32**) and X = O (i.e. dipropargyl ethers) (**34**). By these reactions we have synthesized a variety of piperidine-fused 1,2,3-triazoles (**31**),[29] piperazine-fused 1,2,3-triazoles (**33**)[30] and morpholine-fused 1,2,3-triazoles (**35**)[31] in moderate to high yields. Electron-donating (alkyl and aryl) and electron-withdrawing groups (*p*-toluenesulfonyl and *p*-fluorobenzenesulfonyl) on the nitrogen atom of propargylic amines were well tolerated during the reaction.



Scheme 16 Ag_2CO_3-catalyzed tandem hydroazidation/cyclo-addition of 1,6-diynes

Later, this Ag_2CO_3-catalyzed hydroazidation was applied to unsymmetrical diyne **36** and *o*-diethynylbenzene **38** to synthesize 1,2,3-triazoles with more fused rings with respect to size and number of fused rings (Scheme 17). Diyne **36** underwent expected hydroazidation at terminal alkynyl moiety followed by alkyne-azide-1,2,3-cycloaddition reaction with the internal alkyne moiety, leading to formation of 1,4-diazepine-fused 1,2,3-triazole (**37**) in 78% yields (Scheme 17a). With this, we constituted an extremely convenient way to construct such type of fused heterocyclic frameworks.[32] These triazolobenzodiazepines have emerged as powerful

pharmacophores.[33] Whereas, *o*-ethynylbenzene (**38**) underwent hydroazidation at terminal position of C≡C bond unexpectedly, followed by alkyne-azide cycloaddition (Scheme 17b) instead of expected internal hydroazidation followed by alkyne-azide cycloaddition (Scheme 17c). This reaction afforded triazolo isoquinoline (**39**)[34] in 82% isolated yields. This unexpected terminal hydroazidation of C≡C bond might be due to steric hindrance effect.



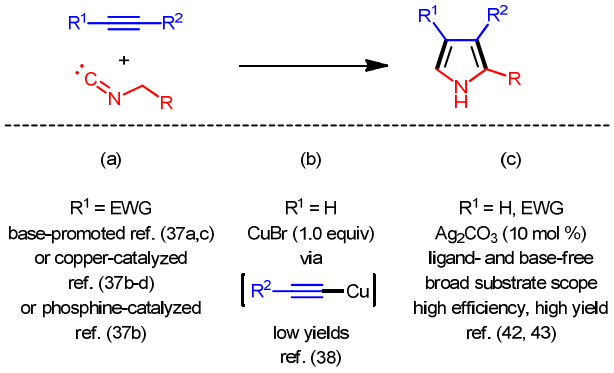
Scheme 17 Synthesis of highly fused 1,2,3-triazoles

3.4 Synthesis of oligo-substituted pyrroles

Heterocyclic molecules such as "pyrroles" were prominent as an essential part of many pharmaceuticals, biologically active ingredients and functional materials. Pyrroles serve also as intermediates in organic synthesis. Hence, the synthesis of oligosubstituted pyrroles had attained great importance. Despite the traditional metal-free methods and transition-metal-catalyzed advanced methods[11a,35] were available, methods that can able to synthesize pyrroles from basic chemicals were an important research objective.[36] Because of alkynes and nitriles were one such readily available basis chemicals, the atom-economical intermolecular cycloaddition of alkynes and isocyanides has become an ideal representative route for the synthesis of oligosubstituted pyrroles (Scheme 18).

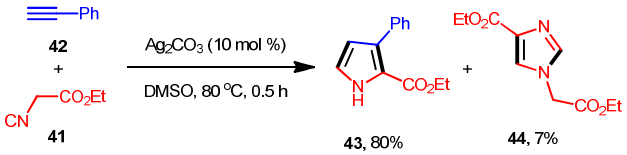
But, the available methods for the synthesis of pyrroles in this route were restricted to electron-deficient alkynes (structural σ-activation) and π-activation of C≡C bonds under base-promoted[37a,c] or copper-[37b-d] or phosphine-catalyzed[37b] conditions (Scheme 18a). The sole method that proceeds via σ-activated copper alkynylide species requires stoichiometric quantity of Cu(I) salt. Hence, we termed it as the method of structural σ-activation (Scheme 18b).[38] Hence, development of new methods involving catalytic σ-activation of alkynes was greatly needed.

The reason for selecting the silver salts as catalysts for cycloaddition of alkynes and isocyanides is that the silver catalysis[39] avoid the dimerization of isocyanides into imidazoles[40] and alkynes[41] in to 1,3-diynes. With this, our group[42] and Lei group[43] individually and simultaneously reported silver(I)-catalyzed cycloaddition of unactivated alkynes and isocyanides for the efficient synthesis of oligosubstituted pyrroles (Scheme 18c).



Scheme 18 Alkyne-isocyanide cycloaddition strategies for the synthesis of pyrroles

From our previous experience of Ag_2CO_3-catalyzed σ-activation of alkynes, we performed the start-up reaction between ethyl-isocyanoacetate (**41**) and phenylacetylene (**42**) using catalytic amount of Ag_2CO_3 in DMF at 80°C. This reaction afforded 2,3-disubstituted pyrrole (**43**) and trace amount of imidazole derivative (**44**) (Scheme 19).



Scheme 19 Ag_2CO_3-catalyzed alkyne-isocyanide cycloaddition for pyrrole synthesis

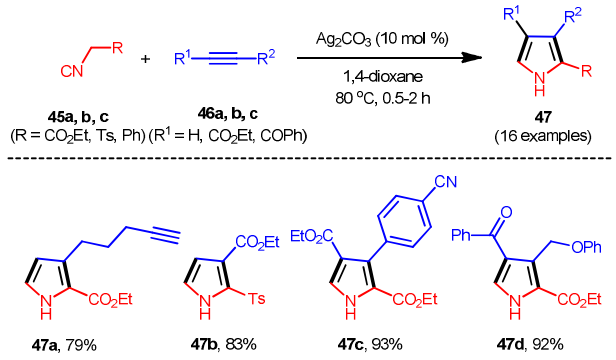
After this delighted result, standardization of the protocol was performed (Table 1). This demonstrated the decisive role played by counter anion of silver salt, type of solvent and reaction temperature on reaction efficiency as well as pyrrole (**43**) and imidazole (**44**) products distribution. The reaction conditions of Ag_2CO_3 (10 mol %) in 1,4-dioxane at 80 °C were finalized as the protocol optimal reaction conditions (Table 1, Entry 13).

Table 1 Optimization of protocol reaction conditions

Entry	Condition	% Yield (**43**:**44**)	Entry	Condition	% Yield (**43**:**44**)
1	**Ag_2CO_3**	**80:7**	8	$AgBF_4$	0:0
2	AgOAc	0:80	9	$AgClO_4$	0:0
3	AgOTf	0:84	10	DMSO	trace:78
4	Ag_2O	trace:86	11	acetonitrile	trace:87
5	AgF	trace:82	12	DCM	78:13
6	$AgNO_2$	trace:81	**13**	**1,4-dioxane**	**90:trace**
7	$AgNO_3$	0:0	14	at 40°C	trace:88

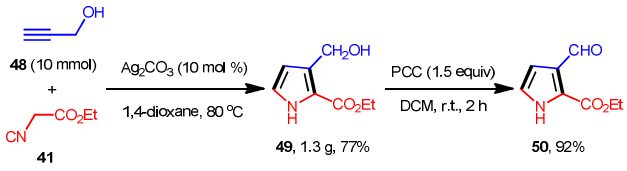
Later, substrate scope of the protocol was checked with a wide range of terminal alkynes (**46a**) bearing –OH, ketone and ester functional groups, aliphatic, alicyclic, aryl and hetero aryl moieties with electron-deficient and electron-rich substituents

and isocyanides like ethyl-isocyanoacetate (**45a**), *p*-toluene-sulfonyl-methyl-isocyanide (**45b**) and benzyl isocyanide (**45c**). This Ag_2CO_3-catalyzed methodology was also compatible for catalytic π-activation of C≡C bonds in structural σ-activated internal alkynes (**46b**, **46c**) for the synthesis of 2,3,4-tri-substituted pyrroles (**47c**, **47d**) (Scheme 20). With this, we developed a powerful method for the synthesis of 2,3-di-substituted and 2,3,4-tri-substituted pyrroles (**47a**, **47b**).



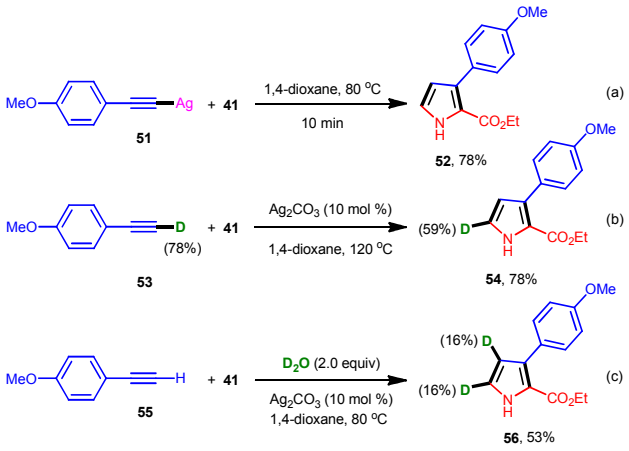
Scheme 20 Scope of the Ag_2CO_3-catalyzed synthesis of pyrroles from alkynes

Pyrrole derivatives like **47a**, **47c** and **47d** with an ester group at 2-position and an unoccupied 5-position i.e. α-free-pyrrole-2-carboxylates have been widely utilized in synthesis of pyrrole alkaloids, porphyrins, polypyrroles and BODIPY dyes.[44] This protocol can also afford functionalized pyrroles that were difficult to realize through classical and known reactions. For example, 1*H*-pyrrole-3-carbaldehyde (**50**)[45] was difficult to realize by Vilsmeier-Haack pyrrole formylation reaction, which preferentially introduce formyl group at 2-position rather than 3-position (Scheme 21).[46]



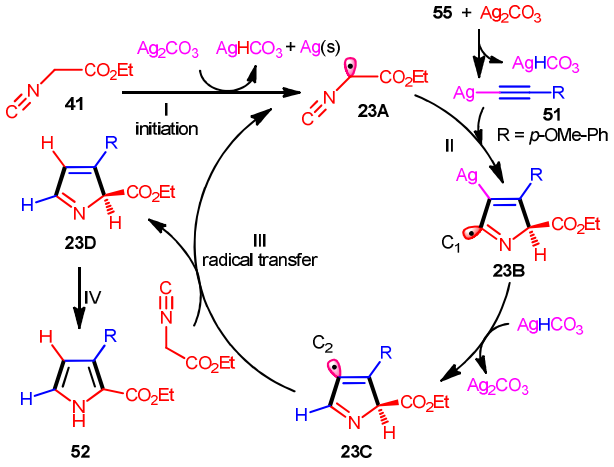
Scheme 21 Application of the protocol

Typical experimental investigation was carried out to determine the reaction's most plausible pathway (Scheme 22). The success of the reaction by silver acetylide (**51**) and ethyl-isocyanoacetate (**41**) revealed that silver acetylide was the reaction intermediate (Scheme 22a). The reaction with deuterated acetylene **53** clearly suggested acetylenic hydrogen as the source of α-hydrogen of pyrroles (**47**) (Scheme 22b). Whereas, necessity of elevated temperature (120°C) indicated that, the cleavage of C-H bond as the rate-limiting step. The reaction in the presence of D_2O suggested the source of β-hydrogen in pyrroles (Scheme 22c).



Scheme 22 Experiments conducted to determine the reaction mechanism

Based on these experimental results and literature precedents,[47] the most plausible pathway of the reaction was proposed by taking ethyl-isocyanoacetate (**41**) and *p*-methoxy phenylacetylene (**55**) as examples (Scheme 23). This silver-catalyzed alkyne-isocyanide cycloaddition reaction takes place in a stepwise manner involving; (I) Deprotonation and subsequent oxidation of isocyanide (**41**) with Ag_2CO_3 to form an isocyanide radical (**23A**). (II) Generation of **23B** by an intermolecular cycloaddition between **23A** and silver acetylide (**51**). (III) Concerted protonation of **23B** into **23C** and **23C** into **23D** along with regeneration of isocyanide radical (**23A**). (IV) Intramolecular H-shift leading to conversion of **23D** into pyrrole (**52**) as final product.[47b]

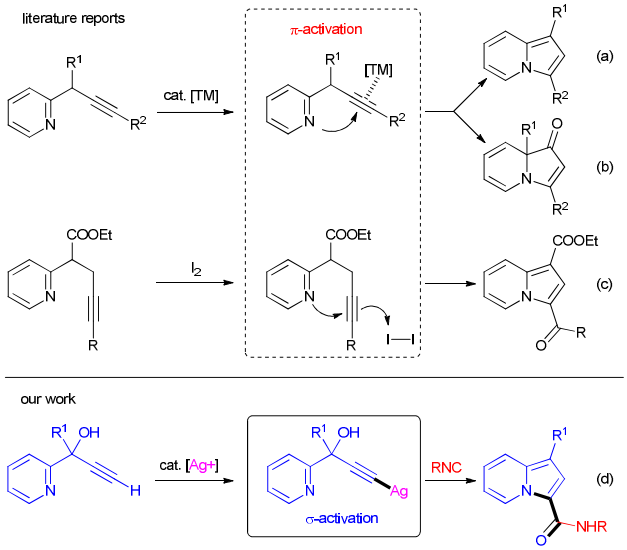


Scheme 23 Postulated catalytic cycle of the protocol

3.5 Synthesis of indolizines

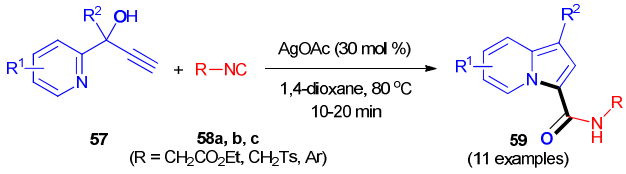
Indolizines are another significant class of nitrogen-containing fused heterocyclic molecules found in variety of natural and synthetic compounds displaying medicinal properties.[48] Among all the available methods of synthesis of indolizines,[49-54] cycloisomerization of propargylic pyridines was the straightforward pathway (Scheme 24).[50-54] Nevertheless, in such route, the transition-metal-catalyzed (Scheme 24a,

24b)[50-53] and I_2-mediated (Scheme 24c)[54] methods proceed via π-activation of C≡C bonds. To the best of our knowledge, no method was available to proceed via catalytic σ-activation of C≡C bonds of propargylic pyridines. Hence, we thought that designing a method involving catalytic σ-activation of C≡C bonds of propargylic pyridines followed by strategic insertion of isocyanide molecule into in situ generated silver acetylide for the synthesis of indolizine core would be more attractive (Scheme 24d).[55]



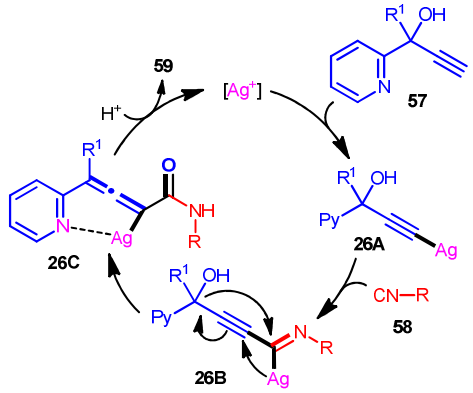
Scheme 24 Methods of synthesis of Indolizines from propargylic pyridines

This protocol involved reaction of 2-pyridine-substituted terminal 3°-propargylic alcohols (**57**) with isocyanides (**58**) in the presence of AgOAc (30 mol %) in 1,4-dioxane at 80°C. The products were *N*-substituted indolizine-3-carboxamide (**59**) derivatives (Scheme 25). This protocol was applicable to a series of 2-pyridyl-3°-terminal-propargylic alcohols (**57**) and different isocyanides like ethyl-isocyanoacetate (**58a**), TosMIC (**58b**) and aryl-isocyanides (**58c**).



Scheme 25 AgOAc-catalyzed synthesis of indolizine-3-carboxamides

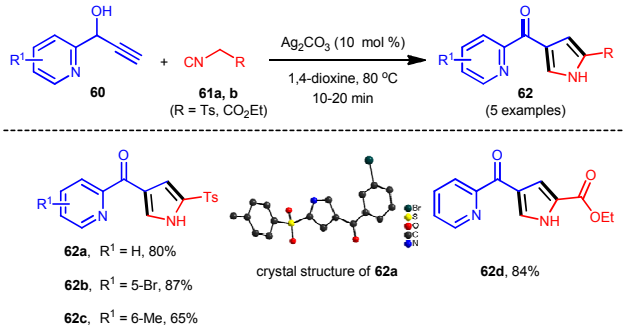
A plausible catalytic cycle for the formation indolizine-3-carboxamides was proposed with the help of previous related reports[50-52] and our research experience on silver-catalyzed reactions of isocyanides and terminal alkynes[42] (Scheme 26).



Scheme 26 Proposed catalytic cycle for the formation of indolizines

3.6 Synthesis of 2,4-disubstituted pyrroles

Interestingly, in the case of 2-pyridine-substituted terminal 2°-propargylic alcohols (**60**), under above reaction conditions (Scheme 25), a intermolecular [3+2]-cycloaddition reaction took place leading to formation of 2,4-disubstituted pyrroles (**62**). Later, the reaction conditions were optimized to Ag_2CO_3 (10 mol %) in 1,4-dioxane at 80°C (Scheme 27).



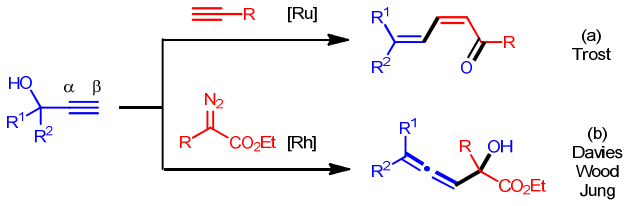
Scheme 27 Synthesis of 2,4-disubstituted pyrroles

It is important to note that, this [3+2]-cycloaddition between alkyne and isocyanide took place in the opposite direction to the [3+2]-cycloaddition reaction between terminal alkynes (**42**) and isocyanides (**41**) mentioned in Scheme 19.[42] This difference in reaction is due to the directing effect of 2-pyridyl moiety. The special importance of this type of cycloaddition reaction is the formation of 2,4-disubstituted pyrroles, which is in contrast to the reaction of terminal alkynes (**46a**) and isocyanides (**45**) reported by our group[42] and Lei group,[43] in which the products were 2,3-disubstituted pyrroles. To the best of our knowledge, this type of synthesis of 2,4-disubstituted pyrroles[56] from isocyanides and alkynes has not been reported to date.

3.7 Cross-coupling reactions with isocyanides

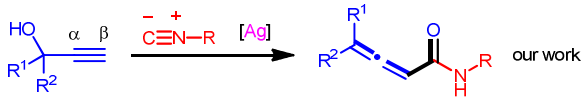
Among the transition-metal-catalyzed C–C bond formation reactions, distinguishing reactions such as C–C bond formation at α- or β-carbon of propargylic alcohols accompanying oxygen transposition onto cross-coupling partner are particularly striking because they constitute a convenient strategy to synthesize oxygen-functionalized unsaturated compounds.[57-59]

Several varieties of α-C–C coupling/1,3-oxygen transposition of propargylic alcohols with coupling partners, such as aldehydes, imines, allyl carbonates and diaryliodonium salts have been reported by Trost and Gaunt research groups.[57] But, the reports regarding the β-C–C coupling/oxygen transposition of propargylic alcohols were scarce, limited to (1) Ruthenium-catalyzed cross-coupling of propargylic alcohols with alkynes or alkenes to synthesize enones (Scheme 28a).[58] (2) Rhodium-catalyzed coupling of propargylic alcohols with diazoacetates to afford α-hydroxy allenes (Scheme 28b).[59]



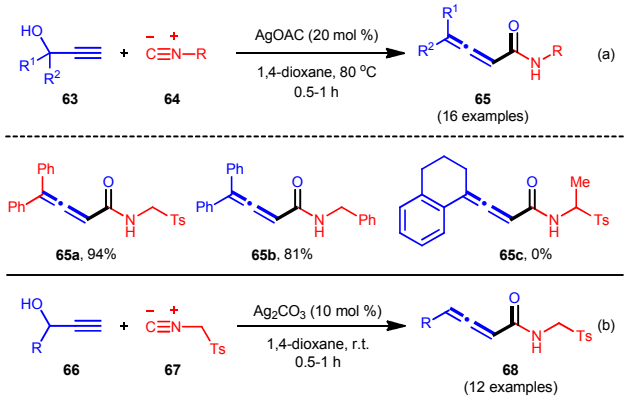
Scheme 28 β-C-C Coupling/oxygen transposition reactions of propargylic alcohols

Because the isocyanide functional group itself acts as a carbene species[60] we envisaged that organic isocyanides could react in the same manner as carbene species generated in situ from alkynes (Scheme 28a) and diazoesters (Scheme 28b), which may lead to formation of 2,3-allenamides[61] via tandem β-C–C coupling/oxygen transposition reaction (Scheme 29).



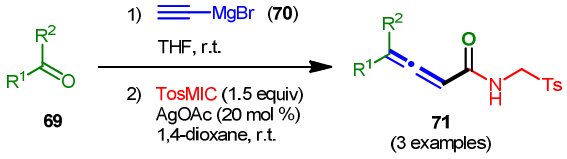
Scheme 29 We assumed tandem β-C-C coupling/oxygen transposition reaction

The experimental results confirmed this hypothesis and disclosed an unprecedented tandem β-C–C coupling/oxygen transposition reaction of propargylic alcohols with isocyanides for the synthesis of 2,3-allenamides (Scheme 30).[62] The optimal reaction conditions were AgOAc (20 mol %) in 1,4-dioxane at 80°C incase of 3°-propargylic alcohols (**63**) (Scheme 30a) and Ag_2CO_3 (10 mol %) in 1,4-dioxane at room temperature for 2°-propargylic alcohols (**66**) (Scheme 30b). In the case of α-tosylethyl isocyanide, no **65c** was observed.



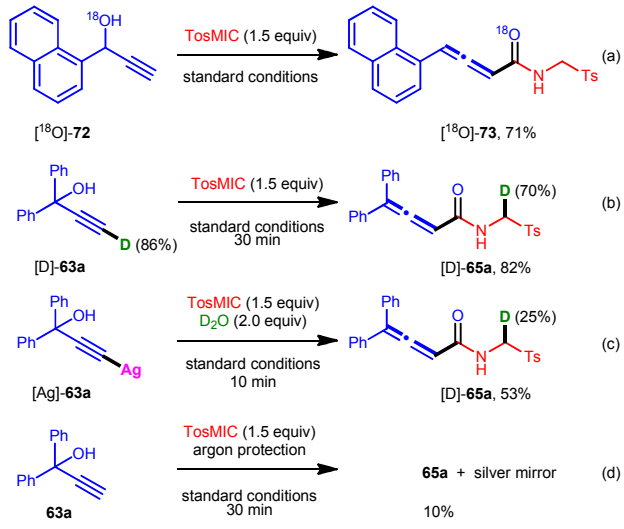
Scheme 30 Silver(I)-catalyzed coupling of propargylic alcohols with isocyanides

This novel methodology was also successful in a one-pot manner of synthesis of 2,3-allenamides directly from aldehydes/ketones (**69**) and alkynyl Grignard reagents (**70**) without isolation and purification of intermediate propargylic alcohols (Scheme 31). This process sharply reduced cost and waste, thus suitable for industrial implementation.



Scheme 31 One-pot synthesis of 2,3-allenamides from carbonyl compounds

Control experiments were performed to check the fate of propargylic alcohol –OH group, acetylenic hydrogen atom and other factors affecting the reaction (Scheme 32). The propargylic alcohol –OH moiety as the source of oxygen atom was verified by performing a reaction with ^{18}O-labelled propargylic alcohol [^{18}O]-**72**. Which led to formation of ^{18}O-labelled 2,3-allenamide (^{18}O-**73**) (Scheme 32a). The fate of acetylenic hydrogen was assessed by the reaction of deuterated **63a** (D-**63a**), which afforded deuterated 2,3-allenamide (D-**65a**), thereby indicated the source of hydrogen on α-carbon atom of 2,3-allenamide (Scheme 32b). This was further supported by lack of reaction with α-tosylethyl isocyanide for the synthesis of **65c**. The success of the reaction with silver acetylide (Ag-**63a**) under standard conditions in the absence of silver catalyst revealed silver acetylide as the reaction intermediate (Scheme 32c). The sharp decrease in the yield of **65a** under argon atmosphere revealed the significance of oxygen atmosphere (Scheme 32d). These experimental results demonstrated that the reaction mechanism involved a tandem carbon-carbon coupling/isomerization pathway. Investigation to reveal a more detailed mechanism is in progress.



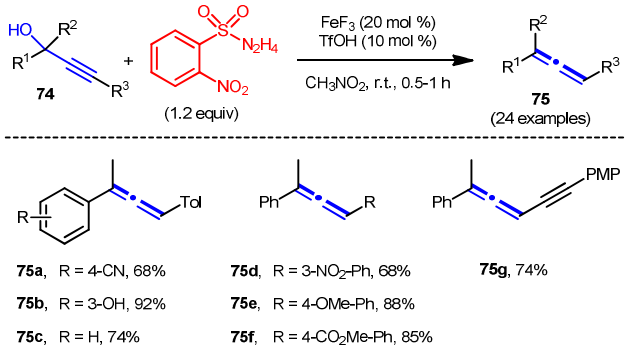
Scheme 32 Control experiments

4. Iron(III)-catalyzed σ-activation of C≡C bonds in propargylic alcohols

As mentioned earlier in scheme 1b, we investigated the catalytic σ-activation of C≡C bonds of propargylic alcohols under Iron(III)-catalysis. The σ-activation of C≡C bonds under Fe(III)-catalysis was attributed via formation of electrophilic centre at propargylic carbon atom.

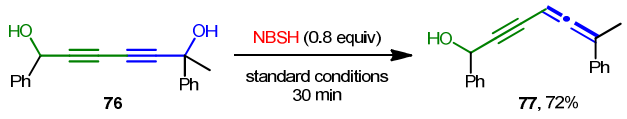
4.1 Reductive deoxyallenylation: synthesis of allenes

Iron(III)-catalyzed reductive deoxyallenylation[63] of internal propargylic alcohols (**74**) into allenes (**75**) was carried out with 2-nitrobenzenesulfonylhydrazide (NBSH)[64] in the presence of FeF_3 (20 mol %) and TfOH (10 mol %) in nitromethane solvent at ambient temperatures (Scheme 33).[65] This method represents an extremely convenient approach to allenes (**75**) over other reports on reductive deoxyallenylation of propargylic alcohols.[63,64] A wide variety of 2°- and 3°-propargylic alcohols (**74**) underwent reductive deoxyallenylation into di- and tri-substituted allenes (**75**).[66] The alkynyl allene **75g** indicated the importance of catalytic σ-activation of C≡C bonds via generation of propargylic cation over the π-activation.



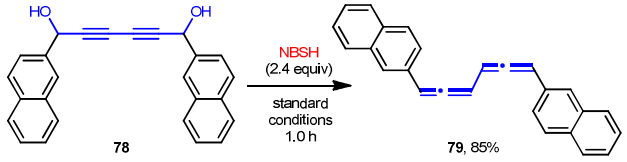
Scheme 33 Iron(III)-catalyzed deoxyallenylation of propargylic alcohols

Using this protocol, we performed selective reductive deoxyallenylation of 3°-propargylic alcohol moiety into allene moiety over 2°-propargylic alcohol moiety (Scheme 34).



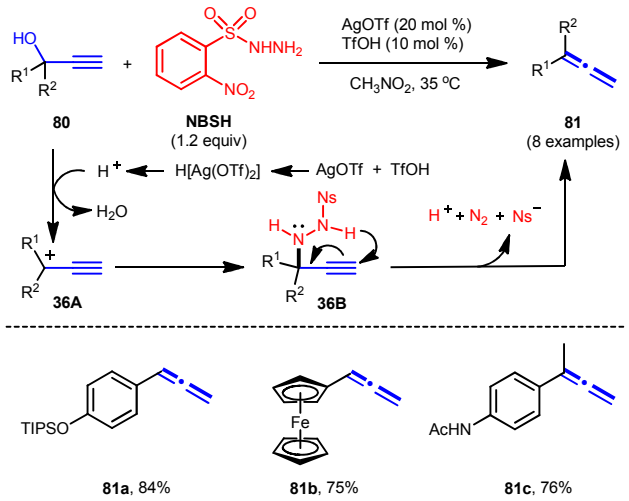
Scheme 34 Selective reductive deoxyallenylation of 3°-propargylic alcohol moiety

We subsequently applied this methodology for conversion of bis-propargylic alcohols (**78**) into diallenes (**79**)[67] (Scheme 35).



Scheme 35 Complete reductive deoxyallenylation of bis-propargylic alcohols

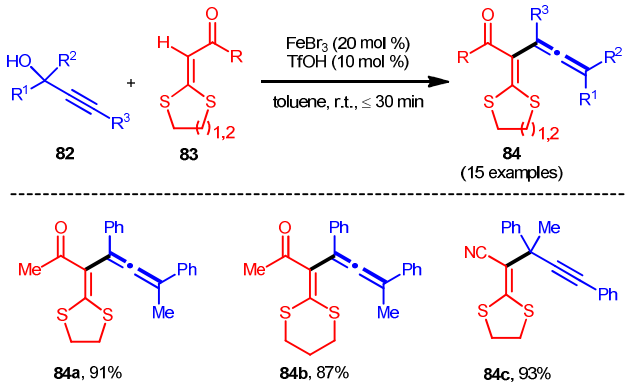
But, terminal propargylic alcohols (**80**) gave better results under optimized conditions of AgOTf (20 mol %) and TfOH (10 mol %) in nitromethane solvent at 35°C (Scheme 36).[65] With this we reported, the most powerful method for the synthesis of terminal allenes.[68]



Scheme 36 AgOTf-catalyzed conversion of terminal propargylic alcohols into allenes

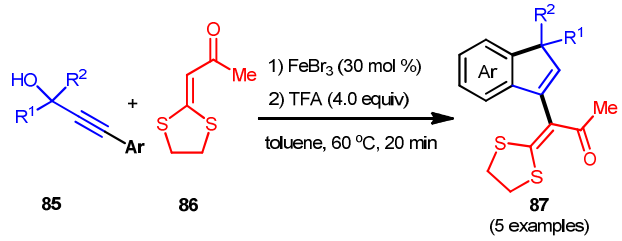
4.2 Coupling with α-oxo-ketene-dithioacetals

From the first report by Kelber in 1910,[69] α-oxo-ketene-dithioacetals have been recognized as versatile synthons in organic syntheses. They have also been considered as polar functionalized alkenes in two-carbon fragment reactions. Using the strategy of σ-activation of C≡C bonds via propargylic cation, we have developed a deoxyallenylative coupling of propargylic alcohols (**82**) with α-oxo-ketene-dithioacetals (**83**) for new and facile synthesis of gem-bis(alkylthio)vinyl-allenes (**84**).[70] The reaction optimal conditions were $FeBr_3$ (20 mol %) and TfOH (10 mol %) in toluene at ambient temperatures (Scheme 37).[71] The reaction with α-cyano-ketene-dithioacetal afforded 1,1-bis(alkylthio)penten-4-yne (**84c**). We exploited the regulatory effect of alkylthio group of these gem-bis(alkylthio)vinyl-allenes (**84**), by using these as reagents for synthesis of fully substituted pyrroles.[72]



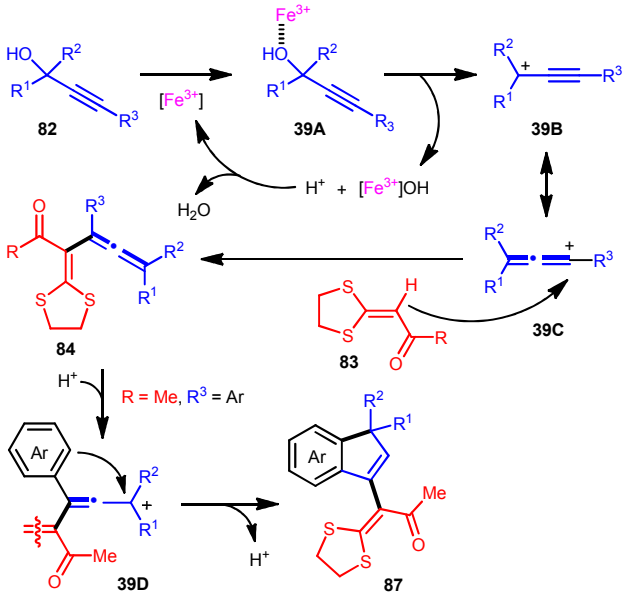
Scheme 37 Coupling of propargylic alcohols with α-oxo ketene dithioacetals

Further studies revealed that, the reaction between 3°-propargylic alcohols (**82**) with R^3 = Ar i.e. **85** and α-acetyl-ketene-dithioacetal (**86**) under $FeBr_3$ catalysis, rapidly produced *gem*-dialkylthio-vinylallenes (**84**).[71] Furthermore, when TFA was added to this reaction mixture and stirred, generated indene derivatives (**87**) in moderate to good yields (Scheme 38).



Scheme 38 Synthesis of indenes from propargylic alcohols and α-acetyl-ketene-dithioacetals

A plausible mechanism for the coupling reaction between propargylic alcohols (**82**) with α-oxo-ketene-dithioacetals (**83**) and rearrangement to indene derivatives (**87**) was proposed (Scheme 39). The reaction might initiated by formation of coordination complex **39A** between propagylic alcohol (**82**) and ferric ion (Fe^{3+}), thereby increases polarity of –OH group. Which is followed by generation of propargylic cation (**39B**) by releasing [Fe^{3+}]OH. This propargylic cation is responsible for coupling to α-oxo-ketene-dithioacetals (**83**) for the formation of *gem*-bis(alkylthio)vinyl-allenes (**84**) or 1,1-bis(alkylthio)penten-4-yne (**84c**). Whereas, rearrangement of *gem*-bis(alkylthio)vinyl-allenes (**84**) into indene derivatives (**87**) involve protonization of **84** followed by cyclization through electrophilic aromatic substitution.

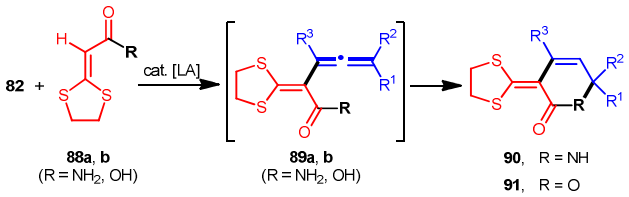


Scheme 39 Proposed mechanism

5 $BF_3{\cdot}OEt_2$-catalyzed σ-activation of C≡C bonds in propargylic alcohols

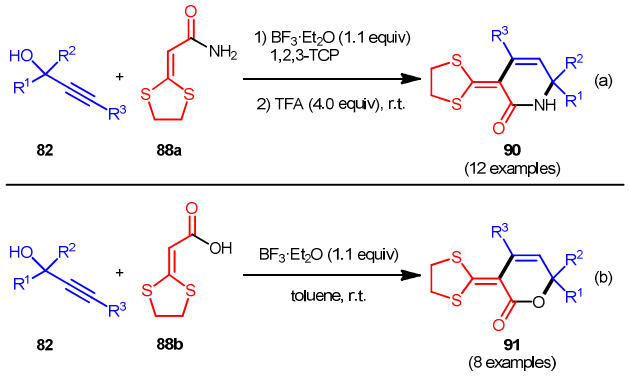
5.1 Tandem coupling and annulation with 3,4-dienamides/acids

From the reaction mechanism in scheme 39, we hypothesized that, the replacement of R-moiety of α-oxo-ketene-dithioacetals (**83**) with R = NH_2/OH (**88a**, **b**) will cause the products *gem*-bis(alkylthio)vinylallenes (**89**) to undergo intramolecular annulation between amide/acid moiety and allene part, thereby lead to formation of α-bis(alkylthio)-δ-lactams (**90**) and α-bis(alkylthio)-δ-lactones (**91**) (Scheme 40).



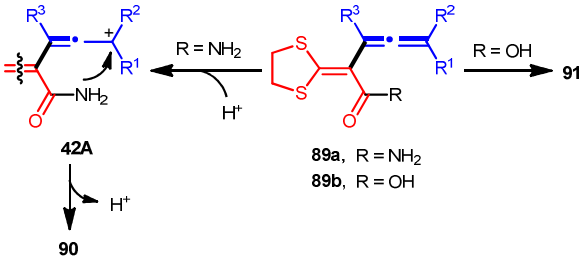
Scheme 40 Background on the synthesis of δ-lactams/δ-lactones

This assumption was realized for the synthesis of α-bis(alkylthio)-δ-lactams (**90**) and α-bis(alkylthio)-δ-lactones (**91**) (Scheme 41).[73] The reaction conditions for the synthesis of α-bis(alkylthio)-δ-lactams (**90**) were $BF_3{\cdot}OEt_2$ (1.1 equiv) in 1,2,3-trichoropropane followed by addition of trifluoroacetic acid (TFA) at room temperature (Scheme 41a). Incase of α-bis(alkylthio)-δ-lactones (**91**), tandem coupling/intramolecular annulation took place in toluene without addition of TFA (Scheme 41b).



Scheme 41 Synthesis of α-bis(alkylthio)-δ-lactams and α-bis(alkylthio)-δ-lactones

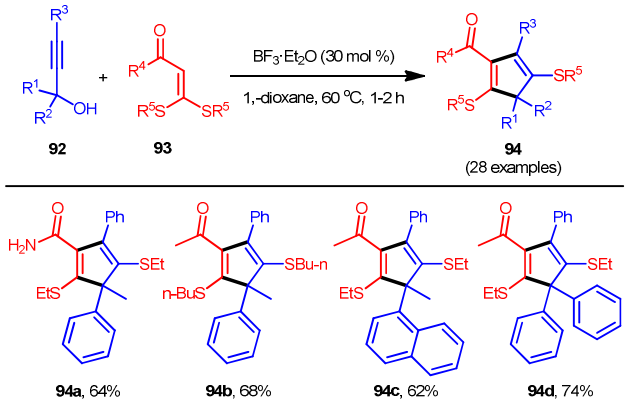
The reaction pathway for the synthesis of δ-lactams (**90**) and δ-lactones (**91**) involved coupling of α-oxo-ketene-dithioacetals (**88a**, **b**) with propargylic alcohols according to scheme 39, leading to formation of allenic amides (**89a**) and allenic acids (**89b**). After coupling, in case of allenic amides (**89a**), protonation of central carbon of allenic system and intramolecular nucleophilic addition of amino group to tertiary carbocation produces δ-lactams (**90**). Whereas in case of allenic acids (**89b**), the allene moiety is activated by Lewis acid, which is followed by intramolecular nucleophilic attack by hydroxyl motif leads to formation of δ-lactones (**91**) (Scheme 42).



Scheme 42 Reaction mechanism

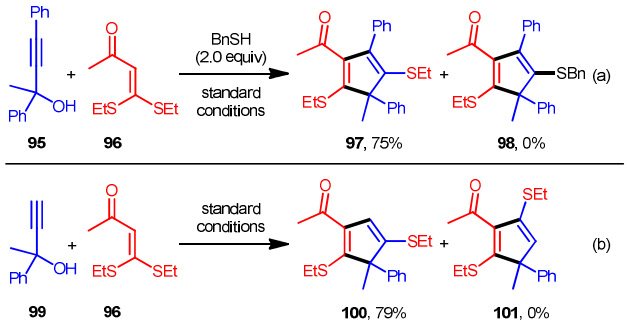
5.2 Coupling with α-oxo ketene dithioacetals

We have developed a [3+2]-cycloaddition reaction between propargylic alcohols (**92**) and α-oxo-ketene-dithioacetals (**93**) as two-carbon atom synthons for the first-time synthesis of 2,5-dialkylthio-cyclopentadienes (**94**)[74] (Scheme 43).[75] The optimal reaction conditions were $BF_3{\cdot}OEt_2$ (30 mol %) 1,4-dioxane at 60 °C.



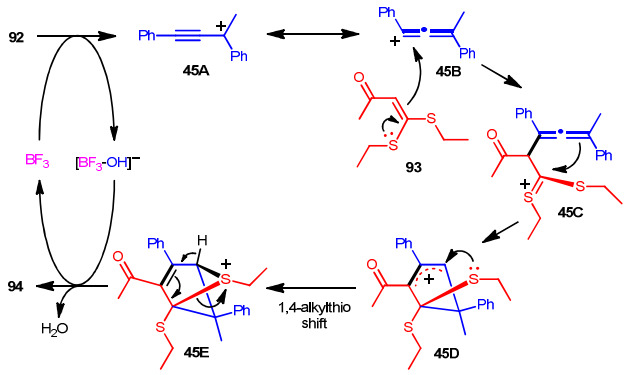
Scheme 43 Cycloaddition of propargylic alcohols with α-oxo-ketene-dithioacetals

The intramolecular pattern of the 1,4-alkylthio group migration was proven by cross-over experiment (Scheme 44a). Reaction of **95** with α-oxo-ketene-dithioacetal (**96**) under optimal reaction conditions in the presence of benzyl mercaptan (BnSH) formed non-cross-over product (**97**) without any cross-over product (**98**). The possibility of 1,3-alkylthio shift was ruled out by the reaction of terminal propargylic alcohol (**99**) with **96**. This reaction afforded **100** without 1,3-alkylthio migration product **101** (Scheme 44b).



Scheme 44 Experiments conducted to reveal reaction mechanism

Based on experimental investigation and literature reports,[76] we proposed an appropriate pathway of the protocol (Scheme 45). First, the propargyl cation (**45A**) might formed by loss of –OH group from propagylic alcohol **92** with the help of $BF_3{\cdot}OEt_2$. The propargylic cation (**45A**) is in resonance as allenic carbocation (**45B**). The preferential attack of α-oxo-ketene-dithioacetal (**93**) on allenic carbocation (**45B**) affords intermediate **45C**. This **45C** subsequently undergoes intramolecular cyclization to afford a five-membered carbocycle (**45D**). Later, **45D** undergoes 1,4-alkylthio shift to form **45E**. Finally, elimination of proton and cleavage of C-S bond produces 2,5-diethylthio cyclopentadiene (**94**).



Scheme 45 Reaction mechanism

Conclusions

We have successfully implemented the concept of catalytic σ-activation of C≡C bonds to both terminal and internal unactivated alkynes. In the case of terminal alkynes, σ-activation was achieved by silver-catalyzed C-H bond metathesis. Incase of internal alkynes, catalytic σ-activation was achieved via generation of a propargylic cation from corresponding propargylic alcohols under Lewis-acid catalysis. These σ-activated species were skilfully utilized for unprecedented hydroazidation, cycloaddition, cross-coupling, deoxyallenylation and annulation reactions in intramolecular, intermolecular and tandem manner. By these reactions we have synthesized highly functionalized vinyl azides, allenes, heterocyclic and carbocyclic compounds. Furthermore, our catalytic system for σ-activation was also applicable to π-activation of C≡C bonds.

Further research work in order to pursue catalytic σ-activation of C≡C bonds by using abundantly available metal, non-metal catalysts and other alkynyl compounds for the synthesis of biologically significant and commercially valuable chemicals is in progress in our research laboratory.

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Notes and references

1 (a) F. Bohlmann, H. Burkhardt and C. Zdero, In *Naturally Occurring Acetylenes*, Academic Press, New York, 1973; (b) A. L. K. Shi Shun and R. R. Tykwinski, *Angew. Chem. Int. Ed.*, 2006, **45**, 1034; (c) R. E. Minto and B. J. Blacklock, *Prog. Lipid Res.*, 2008, **47**, 233.

2 J. Barluenga, D. de Sáa, A. Gómez, A. Ballesteros, J. Santamaría, A. de Prado, M. Tomás and A. L. Suárez-Sobrino *Angew. Chem. Int. Ed.*, 2008, **47**, 6225.

3 (a) H. Schobert, *Chem. Rev.*, 2014, **114**, 1743; (b) A. Corma, *Chem. Rev.*, 2014, **114**, 1545.

4 (a) P. Siemsen, R. C. Livingston and F. Diederich, *Angew. Chem. Int. Ed.*, 2000, **39**, 2632; (b) J. P. Brand and J. Waser, *Chem. Soc. Rev.*, 2012, **41**, 4165; (c) U. H. F. Bunz, *Acc. Chem. Res.*, 2001, **34**, 998; (d) C.-H. Ding and X.-L. Hou, *Chem. Rev.*, 2011, **111**, 1914; (e) C.-J. Li, *Acc. Chem. Res.*, 2010, **43**, 581.

5 (a) D. Habrant, V. Rauhala and A. M. P. Koskinen, *Chem. Soc. Rev.*, 2010, **39**, 2007; (b) M. Zhang, T. Jia, C. Y. Wang and P. J. Walsh, *J. Am. Chem. Soc.*, 2015, **137**, 10346; (c) E. Quesada and R. J. K. Taylor, *Tetrahedron Lett.*, 2005, **46**, 6473; (d) M. Okutani and Y. Mori, *J. Org. Chem.*, 2009, **74**, 442.

6 (a) S. Patai, In *The Carbon-Carbon Triple bond*, Ed.: Wiley-VCH, Germany, 1978, **1**, ISBN: 9780470771563; 9780471994978; (b) S. Patai, In *The Carbon-Carbon Triple bond*, Ed.: Wiley-VCH, Germany, 1978, **2**, ISBN: 9780470771570; 9780471994985; (c) F. Diederich, P. J. Stang and R. R. Tykwinski, In *Acetylene Chemistry*, Ed.: Wiley-VCH, Germany, 2005, ISBN: 3-527-30781-8; (d) P. J. Stang and F. Diederich, In *Modern Acetylene Chemistry*, Ed.: Wiley-VCH, Germany, 2008, ISBN: 3-527-29084-2; (e) B. M. Trost and C.-J. Li, In *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations*, Ed.: Wiley-VCH, Germany, 2014, ISBN: 3527677909; 9783527677900.

7 (a) I.-T. Trotuş, T. Zimmermann and F. Schüth, *Chem. Rev.*, 2014, **114**, 1761; (b) B. Godoi, R. F. Schumacher and G. Zeni, *Chem. Rev.*, 2011, **111**, 2937; (c) D. F. Harvey and D. M. Sigano, *Chem. Rev.*, 1996, **96**, 271; (d) C. Oger, L. Balas, T. Durand and J.-M. Galano *Chem. Rev.*, 2013, **113**, 1313; (e) K. Gilmore and I. V. Alabugin, *Chem. Rev.*, 2011, **111**, 6513.

8 (a) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrhedron Lett.*, 1975, **16**, 4467; (b) R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874; (c) P. Thirumurugan, D. Matosiuk and K. Jozwiak, *Chem. Rev.*, 2013, **113**, 4905; (d) R. F. Lockwood and K. M. Nicholas, *Tetrahedron Lett.*, 1977, **18**, 4163; (e) K. M. Nicholas, *Acc. Chem. Res.*, 1987, **20**, 207; (f) R. D. Stephens and C. E. Castro *J. Org. Chem.*, 1963, **28**, 3313; (g) C. Glaser, *Ber. Dtsch. Chem. Ges.*, 1869, **2**, 422; (h) A. S. Hay, *J. Org. Chem.*, 1962, **27**, 3320; (i) W. Chodkiewicz and P. C. R. Cadiot, *Hebd. Seances Acad. Sci.*, 1955, **241**, 1055; (j) W. Chodkiewicz, *Ann. Chim.*, 1957, **2**, 819; (k) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts and M. I. Foreman, *J. Chem. Soc. Perkin Trans., 1*, 1973, 977; (l) R. R. Jones and R. G. Bergman, *J. Am. Chem. Soc.*, 1972, **94**, 660; (m) A. G. Myers, E. Y. Kuo and N. S. Finney, *J. Am. Chem. Soc.*, 1989, **111**, 8057; (n) D. J. Gorin and F. D. Toste, *Nature*, 2007, **446**, 395; (o) R. Huisgen, *Angew. Chem. Int. Ed.*, 1963, **2**, 565; (p) M. Passerini, *Gazz. Chim. Ital.*, 1921, **51**, 126; (q) I. Ugi, K. Offermann, H. Herlinger and D. Marquarding, *Liebigs Ann. Chem.*, 1967, **709**, 1.

9 (a) Y. Yamamoto, *Chem. Soc. Rev.*, 2014, **43**, 1575; (b) F. Chen, T. Wang and N. Jiao, *Chem. Rev.*, 2014, **114**, 8613; (c) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731; (d) L. Huang, M. Arndt, K. Gooβen, H. Heydt and L. J. Gooβen, *Chem. Rev.*, 2015, **115**, 2596; (e) F. Alonso, I. P. Beletskaya and M. Yus, *Chem. Rev.*, 2004, **104**, 3079; (f) M. C. Willis, *Chem. Rev.* 2010, **110**, 725; (g) X. Zeng, *Chem. Rev.*, 2013, **113**, 6864; (h) M. Meldal and C. W. Tornøe, *Chem. Rev.*, 2008, **108**, 2952; (i) R. Dorel and A. M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028; (j) L.-N. Guo, X.-H. Duan and Y.-M. Liang, *Acc. Chem. Res.*, 2011, **44**, 111; (k) R. Chinchilla and C. Nájera, *Chem. Rev.*, 2014, **114**, 1783; (l) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285; (m) J. Tsuji and T. Mandai, *Angew. Chem. Intl. Ed.*, 1995, **34**, 2589; (n) A. Fürstner, *Acc. Chem. Res.*, 2014, **47**, 925; (o) L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281.

10 G. Fang and X. Bi, *Chem. Soc. Rev.*, 2015, **44**, 8124.

11 (a) Y. Yamamoto, I. D. Gridnev, N. T. Patil and T. Jin, *Chem. Commun.*, 2009, 5075; (b) Y. Yamamoto, *J. Org. Chem.*, 2007, **72**, 7817; (c) B. M. Trost, M. T. Sorum, C. Chan, A. E. Harms and G. Rühter, *J. Am. Chem. Soc.*, 1997, **119**, 698; (d) A. Gimeno, A. B. Cuenca, S. Suárez-Pantiga, C. R. de Arellano, M. Medio-Simón and G. Asensio, *Chem. Eur. J.*, 2014, **20**, 683; (e) N. Fujiwara and Y. Yamamoto, *J. Org. Chem.*, 1999, **64**, 4095; (f) T. Ren, *Organometallics*, 2005, **24**, 4854; (g) N. Ochi, Y. Nakao, H. Sato and S. Sakai, *J. Am. Chem. Soc.*, 2007, **129**, 8615; (h) N. Asao, K. Sato, Menggenbateer and Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 3682; (i) N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395; (j) N. T. Patil, N. K. Pahadi and Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 10096; (k) A. J. Pearson and R. A. Dubbert, *J. Chem. Soc., Chem. Commun.*, 1991, 202; (l) Z. Huo, I. D. Gridnev and Y. Yamamoto, *J. Org. Chem.*, 2010, **75**, 1266; (m) W. Guan, F. B. Sayyed, G. Zeng and S. Sakai, *Inorg. Chem.*, 2014, **53**, 6444.

12 C. Zhang, H. Zhang, L. Zhang, T. B. Wen, X. He and H, Xia, *Organometallics*, 2013, **32**, 3738.

13 (a) S. N. Karad, W.-K. Chung and R.-S. Liu, *Chem. Sci.*, 2015, **6**, 5964; (b) J. E. Davies, M. J. Mays, P. R. Raithby, K. Sarveswaran and G. A. Solan, *J. Chem. Soc., Dalton Trans.*, 2001, 1269; (c) Y. Sumida, T. Kato, S. Yoshida and T. Hosoya, *Org. Lett.*, 2012, **14**, 1552; (d) S. Kramer, K. Dooleweerdt, A. T. Lindhardt, M. Rottländer and T. Skrydstrup, *Org. Lett.*, 2009, **11**, 4208; (e) H. Yuan, K.-J. Bi, B. Li, R.-C. Yue, J. Ye, Y.-H. Shen, L. Shan, H.-Z. Jin, Q.-Y. Sun and W.-D. Zhang, *Org. Lett.*, 2013, **15**, 4742; (f) X. Xu, X. Zhang, Z. Wang and M. Kong, *RSC Advances*, 2015, **5**, 40950.

14 (a) K. M. Nicholas, *Acc. Chem. Res.*, 1987, **20**, 207; (b) B. J. Teobald, *Tetrahedron*, 2002, **58**, 4133.

15 (a) U. Halbes-Letinois, J.-M. Weibel and P. Pale, *Chem. Soc. Rev.*, 2007, **36**, 759; (b) U. Létinois-Halbes, P. Pale and S. Berger, *J. Org. Chem.*, 2005, **70**, 9185; (c) X. Zhang, B. Liu, X. Shu, Y. Gao, H. Lv and J. Zhu, *J. Org. Chem.*, 2012, **77**, 501; (d) M. Yu, R. Skouta, L. Zhou, H.-f. Jiang, X. Yao and C.-J. Li, *J. Org. Chem.*, 2009, **74**, 3378; (e) C. Wei, Z. Li and C.-J. Li, *Org. Lett.*, 2003, **5**, 4473.

16 S. K. Kundu, K. Mitra and A. Majee, *RSC Adv.*, 2015, **5**, 13220.

17 (a) M. O. Forster and S. H. Newman, *J. Chem. Soc.*, 1910, **97**, 2570; (b) M. O. Forster and S. H. Newman, *J. Chem. Soc.*, 1911, **99**, 1277.

18 K. Banert, in *Organic Azides*: *Syntheses and Applications* (Eds.: S. Bräse, K. Banert), Wiley, Chichester, 2010.

19 (a) Y.-F. Wang, K. K. Toh, J.-Y. Lee and S. Chiba, *Angew. Chem. Int. Ed.*, 2011, **50**, 5927; (b) Y.-F. Wang, K. K. Toh, E. P. J. Ng and S. Chiba, *J. Am. Chem. Soc.*, 2011, **133**, 6411; (c) Y.-F. Wang and S. Chiba, *J. Am. Chem. Soc.*, 2009, **131**, 12570; (d) B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey and T. G. Driver, *J. Am. Chem. Soc.*, 2007, **129**, 7500; (e) B. J. Stokes, C. V. Vogel, L. K. Urnezis, M. Pan and T. G. Driver, *Org. Lett.*, 2010, **12**, 2884; (f) Y.-F. Wang, K. K. Toh, S. Chiba and K. Narasaka, *Org. Lett.*, 2008, **10**, 5019.

20 (a) I. F. D. Hyatt and M. P. Croatt, *Angew. Chem. Int. Ed.*, 2012, **51**, 7511; (b) F. Palacios, D. Aparicio, J. M. de Los

Santos, I. Perez de Heredia and G. Rubiales, *Org*. *Prep*. *Proced*. *Int*., 1995, **27**, 171; (c) M. Haddach, R. Pastor and J. G. Riess, *Tetrahedron*, 1993, **49**, 4627; (d) K. Banert, *Chem*. *Ber*., 1989, **122**, 1175; (e) T. Kitamura and P. J. Stang, *Tetrahedron Lett*., 1988, **29**, 1887. (f) M. Ochiai, M. Kunishima, K. Fuji and Y. Nagao, *J. Org*. *Chem*., 1988, **53**, 6144; (g) V. G. Ostroverkhov and E. A. Shilov, *Ukr*. *Khim*. *Zh*., 1957, **23**, 615.

21 (a) T. Shen, T. Wang, C. Qin and N. Jiao, *Angew*. *Chem*. *Int*. *Ed*., 2013, **52**, 6677; (b) C. Qin, P. Feng, Y. Ou, T. Shen, T. Wang and N. Jiao, *Angew*. *Chem*. *Int*. *Ed*., 2013, **52**, 7850; (c) M. Gaydou and A. M. Echavarren, *Angew*. *Chem*. *Int*. *Ed*., 2013, **52**, 13468.

22 Z. Liu, J. Liu, L. Zhang, P. Liao, J. Song and X. Bi, *Angew*. *Chem*. *Int*. *Ed*., 2014, **53**, 5305.

23 B. A. Trofimov, A. G. Mal'kina and R. N. Kudyakova, *Zh*. *Org*. *Khim*. 1993, **29**, 1942.

24 A. B. Forinash and S. L. Evans, *Pharmacotherapy*, 2003, **23**, 1573.

25 P. M. Levine, K. Imberg, M. J. Garabedian and K. Kirshenbaum, *J. Am*. *Chem*. *Soc*., 2012, **134**, 6912.

26 (a) T. Jin, S. Kamijo and Y. Yamamoto, *Tetrahedron Lett*., 2004, **45**, 9435; (b) T. Jin, S. Kamijo, and Y. Yamamoto, *Eur*. *J. Org*. *Chem*., 2004, 3789.

27 Z. Liu, P. Liao and X. Bi, *Org*. *Lett*., 2014, **16**, 3668.

28 M. Alajarín, A. Vidal, and R.-A. Orenes, *Eur*. *J*. *Org*. *Chem*., 2002, 4222.

29 (a) Z. Liu, D. Zhu, B. Luo, N. Zhang, Q. Liu, Y. Hu, R. Pi, P. Huang and S. Wen, *Org*. *Lett*., 2014, **16**, 5600; (b) H. Yanai, and T. Taguchi, *Tetrahedron Lett*., 2005, **46**, 8639; (c) T. M. Krtille, C. de la Fuente, L. Pickering, R. T. Aplin, K. E. Tsitsanou, S. E. Zographos, N. G. Oikonomakos, R. J. Nash, R. C. Griffiths and G. W. J. Fleet, *Tetrahedron*: *Asymmetry*, 1997, **8**, 380.

30 (a) S. Bera and G. Panda, *Org*. *Biomol*. *Chem*., 2014, **12**, 3976; (b) D. K. Mohapatra, P. K. Maity, R. J. Gonnade, M. S. Chorghade and M. K. Gurjar, *Synlett*, 2007, 1893; (c) V. S. Sudhir, N. Y. P. Kumar, R. B. N. Baig and S. Chandrasekaran, *J. Org*. *Chem*., 2009, **74**, 7588; (d) C. Chowdhury, S. Mukherjee, B. Chakraborty and B. Achari, *Org*. *Biomol*. *Chem*., 2011, **9**, 5856; (e) I. Akritopoulou-Zanze, V. Gracias and S. W. Djuric, *Tetrahedron Lett*., 2004, **45**, 8439; (f) V. S. Sudhir, R. B. N. Baig and S. Chandrasekaran, *Eur*. *J*. *Org*. *Chem*., 2008, 2423.

31 (a) N. S. Mani and A. E. Fitzgerald, *J. Org*. *Chem*., 2014, **79**, 8889; (b) K. B. Mishra and V. K. Tiwari, *J. Org*. *Chem*., 2014, **79**, 5752; (c) R. H. Vekariya, R. Liu and J. Aubé, *Org*. *Lett*., 2014, **16**, 1844; (d) R. Li, D. J. Jansen and A. Datta, *Org*. *Biomol*. *Chem*., 2009, **7**, 1921; (e) Y. S. Reddy, A. P. J. Pal, P. Gupta, A. A. Ansari and Y. D. Vankar, *J. Org*. *Chem*., 2011, **76**, 5972; (f) E. Balducci, L. Bellucci, E. Petricci, M. Taddei and A. Tafi, *J. Org*. *Chem*., 2009, **74**, 1314; (g) M. R. Lambu, A. Hussain, D. K. Sharma, S. K. Yousuf, B. Singh, A. K. Tripathi and D. Mukherjee, *RSC Adv*., 2014, **4**, 11023; (h) A. I. Oliva, U. Christmann, D. Font, F. Cuevas, P. Ballester, H. Buschmann, A. Torrens, S. Yenes and M. A. Pericàs, *Org*. *Lett*., 2008, **10**, 1617.

32 M. Sau, C. Rodríguez-Escrich and M. A. Pericàs, *Org*. *Lett*., 2011, **13**, 5044.

33 L. Bertelli, G. Biagi, I. Giorgi, O. Livi, C. Manera, V. Scartoni, C. Martini, G. Giannaccini, L. Trincavelli and P. L. Barili, *Farmaco*, 1998, **53**, 305.

34 (a) Y. Hu, J. Hu, X. Wang, L. Guo, X. Shu, Y. Niu and Y. Liang, *Tetrahedron*, 2010, **66**, 80; (b) R. K. Arigela, S. Samala, R. Mahar, S. K. Shukla and B. Kundu, *J. Org*. *Chem*., 2013, **78**, 10476.

35 (a) N. T. Patil and Y. Yamamoto, *Arkivoc*, 2007, **10**, 121; (b) I. Nakamura and Y. Yamamoto, *Chem*. *Rev*., 2004, **104**, 2127.

36 (a) S. Michlik and R. Kempe, *Nat*. *Chem*., 2013, **5**, 140; (b) D. Srimani, Y. Ben-David, D. Milstein, *Angew*. *Chem*. *Int*. *Ed*., 2013, **52**, 4012.

37 (a) H. Saikachi, T. Kitagawa and H. Sasaki, *Chem*. *Pharm*. *Bull*., 1979, **27**, 2857; (b) S. Kamijo, C. Kanazawa and Y. Yamamoto, *J. Am*. *Chem*. *Soc*., 2005, **127**, 9260; (c) O. V. Larionov and A. de Meijere, *Angew*. *Chem*. *Int*. *Ed*., 2005, **44**, 5664; (d) Q. Cai, F. Zhou, T. Xu, L. Fu and K. Ding, *Org*. *Lett*., 2011, **13**, 340.

38 A. V. Lygin, O. V. Larionov, V. S. Korotkov and A. de Meijere, *Chem*. *Eur*. *J*., 2009, **15**, 227.

39 T. Hayashi, Y. Uozumi, A. Yamazaki, M. Sawamura, H. Hamashima and Y. Ito, *Tetrahedron Lett*., 1991, **32**, 2799.

40 (a) C. Kanazawa, S. Kamijo and Y. Yamamoto, *J. Am*. *Chem*. *Soc*., 2006, **128**, 10662; (b) R. Grigg, M. I. Lansdell and M. Thornton-Pett, *Tetrahedron*, 1999, **55**, 2025.

41 (a) C. He, S. Guo, J. Ke, J. Hao, H. Xu, H. Chen and A. Lei, *J. Am*. *Chem*. *Soc*., 2012, **134**, 5766; (b) C. He, J. Hao, H. Xu, Y. Mo, H. Liu, J. Han and A. Lei, *Chem*. *Commun*., 2012, **48**, 11073.

42 J. Liu, Z. Fang, Q. Zhang, Q. Liu and X. Bi, *Angew*. *Chem*. *Int*. *Ed*., 2013, **52**, 6953.

43 M. Gao, C. He, H. Chen, R. Bai, B. Cheng and A. Lei, *Angew*. *Chem*. *Int*. *Ed*., 2013, **52**, 6958.

44 N. Ono and T. Okujima In *Isocyanide Chemistry*: *Applications in Synthesis and Material Science First Edition* (Ed.: V. G. Nenajdenko), Wiley-VCH, Weinheim, 2012, p. 385.

45 A. R. Kelly, M. H. Kerrigan and P. J. Walsh, *J. Am*. *Chem*. *Soc*., 2008, **130**, 4097.

46 J. R. Garabatos-Perera, B. H. Rotstein and A. Thompson, *J. Org*. *Chem*., 2007, **72**, 7382.

47 J. Daru, Z. Benda, A. Póti, Z. Novác and A. Stirling, *Chem*. *Eur*. *J*., 2014, **20**, 15395.

48 (a) J. P. Michael, *Alkaloids*, 2001, **55**, 91; (b) C. Bailly, *Curr*. *Med*. *Chem*.: *Anti-Cancer Agents*, 2004, **4**, 363; (c) J. P. Michael, *Nat*. *Prod*. *Rep*., 2008, **25**, 139.

49 (a) U. Bora, A. Saikia and R. C. Boruah, *Org*. *Lett*., 2003, **5**, 435; (b) D. Basavaiah and A. J. Rao, *Chem*. *Commun*., 2003, 604; (c) V. Specowius, F. Bendrath, M. Winterberg, A. Khurshid and P. Langer, *Adv*. *Synth*. *Catal*., 2012, **354**, 1163; (d) E. L. Kostik, A. Abiko and A. Oku, *J. Org*. *Chem*., 2001, **66**, 2618.

50 (a) I.V.Seregin and V.Gevorgyan, *J. Am*. *Chem*. *Soc*., 2006, *128*, 12050; (b) Z.Li, D. Chernyak and V. Gevorgyan, *Org*. *Lett*., 2012, **14**, 6056; (c) I. V. Seregin, A. W. Schammel and V. Gevorgyan, *Org*. *Lett*., 2007, **9**, 3433; (d) D. Chernyak, C. Skontos and V. Gevorgyan, *Org*. *Lett*., 2010, **12**, 3242.

51 (a) C. R. Smith, E. M. Bunnelle, A. J. Rhodes and R. Sarpong, *Org*. *Lett*., 2007, **9**, 1169; (b) A. R. Hardin and R. Sarpong, *Org*. *Lett*., 2007, **9**, 4547.

52 B. Yan, Y. Zhou, H. Zhang, J. Chen and Y. Liu, *J. Org*. *Chem*., 2007, **72**, 7783.

53 (a) C. H. Zhang, H. Zhang, L. Y. Zhang, T. B. Wen, X. M. He and H. P. Xia, *Organometallics*, 2013, **32**, 3738; (b) L.-H. Chung and C.-Y. Wong, *Organometallics*, 2013, **32**, 3583.

54 (a) I. Kim, J. Choi, H. K. Won and G. H. Lee, *Tetrahedron Lett*., 2007, **48**, 6863; (b) I. Kim, H. K. Won, J. Choi and G. H. Lee, *Tetrahedron*, 2007, **63**, 12954.

55 X. Meng, P. Liao, J. Liu and X. Bi, *Chem*. *Commun*., 2014, **50**, 11837.

56 (a) L. Meng, K. Wu, C. Liu and A. Lei, *Chem*. *Commun*., 2013, **49**, 5853; (b) Z. Shi, M. Suri and F. Glorius, *Angew*. *Chem*. *Int*. *Ed*., 2013, **52**, 4892; (c) Q. Zeng, L. Zhang, J. Yang, B. Xu, Y. Xiao and J. Zhang, *Chem*. *Commun*., 2014, **50**, 4203.

57 (a) B. M. Trost, X. Luan and Y. Miller, *J. Am*. *Chem*. *Soc*., 2011, **133**, 12824; (b) B. S. L. Collins, M. G. Suero and M. J. Gaunt, *Angew*. *Chem*. *Int*. *Ed*., 2013, **52**, 5799; (c) M. Kalek and F. Himo, *J. Am*. *Chem*. *Soc*., 2012, **134**, 19159.

58 (a) B. M. Trost and J. A. Flygare, *J. Am*. *Chem*. *Soc*., 1992, **114**,

5476; (b) B. M. Trost and M. T. Rudd, *J. Am. Chem. Soc.*, 2005, **127**, 4763; (c) B. M. Trost and A. C. Gutierrez, *Org. Lett.*, 2007, **9**, 1473; (d) B. M. Trost, N. Maulide and M. T. Rudd, *J. Am. Chem. Soc.*, 2009, **131**, 420.

59 (a) Z. Li, V. Boyarskikh, J. H. Hansen, J. Autschbach, D. G. Musaev and H. M. L. Davies, *J. Am. Chem. Soc.*, 2012, **134**, 15497; (b) G. A. Moniz and J. L. Wood, *J. Am. Chem. Soc.*, 2001, **123**, 5095; (c) M. E. Jung and J. Pontillo, *Org. Lett.*, 1999, **1**, 367.

60 *Isocyanide Chemistry*: *Applications in Synthesis and Material Science*, 1st ed., (Ed.: V. G. Nenajdenko), Wiley-VCH, Weinheim, 2012.

61 (a) S. Ma and H. Xie, *Tetrahedron*, 2005, **61**, 251. (b) S. Ma and H. Xie, *J. Org. Chem.*, 2002, **67**, 6575; (c) S. Ma and H. Xie, *Org. Lett.*, 2000, **2**, 3801; (d) G. Chen, C. Fu and S. Ma, *Org. Lett.*, 2009, **11**, 2900; (e) W. Yuan, X. Zhang, Y. Yu and S. Ma, *Chem. Eur. J.*, 2013, **19**, 7193.

62 J. Liu, Z. Liu, N. Wu, P. Liao and X. Bi, *Chem. Eur. J.*, 2014, **20**, 2154.

63 (a) X. Pu and J. M. Ready, *J. Am. Chem. Soc.*, 2008, **130**, 10874; (b) A. Claesson and L.-I. Olsson, *J. Am. Chem. Soc.*, 1979, **101**, 7302; (c) H. Jiang, W. Wang, B. Yin and W. Liu, *Eur. J. Org. Chem.*, 2010, 4450.

64 (a) A. G. Myers and B. Zheng, *J. Am. Chem. Soc.*, 1996, **118**, 4492; (b) M. Movassaghi and O. K. Ahmad, *J. Org. Chem.*, 2007, **72**, 1838.

65 Z. Liu, P. Liao and X. Bi, *Chem. Eur. J.*, 2014, **20**, 17277.

66 (a) X. Tang, C. Zhu, T. Cao, J. Kuang, W. Lin, S. Ni, J. Zhang and S. Ma, *Nat. Commun.*, 2013, **4**, 2450; (b) Q. Xiao, Y. Xia, H. Li, Y. Zhang and J. Wang, *Angew. Chem. Int. Ed.*, 2011, **50**, 1114.

67 (a) N. D. Paul, S. Mandal, M. Otte, X. Cui, X. P. Zhang and B. de Bruin, *J. Am. Chem. Soc.*, 2014, **136**, 1090; (b) T. J. A. Graham and A. G. Doyle, *Org. Lett.*, 2012, **14**, 1616.

68 (a) P. Rona, P. Crabbé, *J. Am. Chem. Soc.*, 1969, **91**, 3289; (b) J. Kuang, S. Ma, *J. Org. Chem.*, 2009, **74**, 1763; (c) H. Nakamura, T. Kamakura, M. Ishikura, J.-F. Biellmann, *J. Am. Chem. Soc.*, 2004, **126**, 5958.

69 C. Kelber, *Ber. Dtsch. Chem. Ges.*, 1910, **43**, 1252.

70 J. Song, Z. Fang, Y. Liu, R. Li, L. Xu, B.-D. Barry, Q. Liu and X. Bi, *Synlett*, 2011, 2551.

71 Q. Li, Y. Wang, Z. Fang, P. Liao, B.-D. Barry, G. Che and X. Bi, *Synthesis*, 2013, **45**, 0609.

72 Z. Fang, H. Yuan, Y. Liu, Z. Tong, H. Li, J. Yang, B.-D. Barry, J. Liu, P. Liao, J. Zhang, Q. Liu and X. Bi, *Chem. Commun.*, 2012, **48**, 8802.

73 Y. Liu, B.-D. Barry, H. Yu, J. Liu, P. Liao, and X. Bi, *Org. Lett.*, 2013, **15**, 2608.

74 (a) M. Wang, F. Han, H. Yuan and Q. Liu, *Chem. Commun.*, 2010, **46**, 2247; (b) K. Hartke and K.-H. Lee, *Liebigs Ann. Chem.* 1992, 413.

75 Z. Fang, J. Liu, Q. Liu and X. Bi, *Angew. Chem. Int. Ed.*, 2014, **53**, 7209.

76 (a) L. Pan, X. Bi and Q. Liu, *Chem. Soc. Rev.*, 2013, **42**, 1251; (b) X. Zhang, W. T. Teo and P.W. H. Chan, *Org. Lett.*, 2009, **11**, 4990; (c) Y. Zhu, G. Yin, D. Hong, P. Lu and Y. Wang, *Org. Lett.*, 2011, **13**, 1024; (d) W. Zhao and E. M. Carreira, *Org. Lett.*, 2003, **5**, 4153.