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COMMUNICATION

Conia-ene annulation of the α-cyano β-TMS-capped alkynyl cycloalkanone system and its synthetic application†

Chih-Lung Chin,[a] Cheng-Feng Liao,[a] Hsing-Jang Liu,[a] Ying-Chieh Wong,[b] Ming-Tsang Hsieh,[b] Prashanth K. Amancha,[b] Chun-Ping Chang[b] and Kak-Shan Shia*[b]

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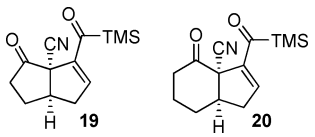
Under catalysis with ZnI_2, an effective annulation process of ω-silylacetylenic α-cyano ketones, leading to the formation of various bicyclic frameworks characterized with a TMS-containing methylenecyclopentane ring, has been developed.

The broad synthetic utility of the α-cyano ketone/ester system has been well documented, mainly depending on the fact that not only can the cyano group activate the α carbon to the ketone/ester carbonyl for condensation (*e.g.*, Knoevenagel condensation), but also it can serve as an effective directing group for consecutive alkylation to construct trisubstituted ketones/esters with complete regiocontrol.[1–6] Our long-lasting interest in the α-activated cross-conjugated cycloalkenone system in organic synthesis[7] has developed many synthetically useful α-cyano ketones/esters, part of which have been employed as key intermediates for the synthesis of naturally occurring products.[8–11] Along these lines, Conia-ene cyclization[12] for the titled system to generate a variety of bicyclic α-cyano ketones was then explored. Results and discussion are delineated as follows.

For the present studies, a series of structurally diverse ω-alkynyl α-cyano ketones **10–18**† (Table 1) were readily prepared *via* 1,4-conjugate addition of 1-(trimethylsilyl)-1-butyn-4-yl magnesium chloride to the corresponding 2-cyano-2-cycloalkenones **1–9** according to the synthetic procedures reported in the literature.[13–17] Most of 1,4-adducts thus obtained are quite stable and can be handled as usual with the exception of **10** and **11**. It was discovered that compounds **10** and **11** were quite sensitive to oxygen; upon exposure to air, the autoxidative annulation occurred rapidly to afford the corresponding cyclic acylsilanes **19** and **20**, respectively, in *ca.* 30 ~ 35% yield.[18,19] Thus, it is suggested that they be stored under inert gas atmosphere or used immediately after chromatographic purification.



With these substrates in hand,‡ Conia-ene reaction was attempted by the use of cyano ketone **11** as an initial model. Its cyclization was examined using a panel of Lewis acids and various reaction conditions. The particular Lewis acids (stannic chloride and zinc iodide) were chosen because they had been noted previously as appropriate catalysts for the related cyclization.[21,22] The results are summarized in Table 2. As indicated, the reaction system presented in Entry 5 (Table 2) appears superior to others in terms of the reaction rate and a high isolated yield of the desired product. As a typical experiment, upon treatment with 1 equiv. of ZnI_2 in refluxing toluene, compound **11** was found to undergo cyclization with complete regio- and stereocontrol to give product **21** in high yield (88%). The spectral data of **21** are in full agreement with the assigned structure, and the relative configuration is unambiguously identified by a single crystal X-ray analysis.[23]

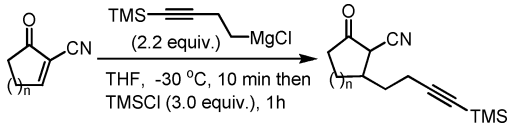
The above synthetic protocol was tentatively considered to be the method of choice and then applied to other substrates with various ring sizes.[24] The results are compiled in Table 3. The preferential formation of a TMS-appended methylenecyclopentane ring was observed for all substrates examined irrespective of the parent ring size. Moreover, a single stereoisomer was generated in all cases regarding the newly formed ring junction, with the unambiguous confirmation of the *cis*-arrangement for cyclization products **21** and **25**,[23,25] implying strongly that all 5/5 and other 5/6 fused products **23**, **24**, **26** and **27** are very likely to possess a *cis*-ring junction as well. The desired 5/7 and 5/12 fused products **28** and **30** were tentatively assigned to have a *cis*-and *trans*-ring junction, respectively, on the basis of the previous observation, wherein a similar cyclization process occurred starting with the same substrates.[18] The stereochemistry of the 5/8 fused product **29** was unambiguously determined based on the X-ray analysis of its corresponding alcohol **29a**,[26] readily produced by reduction of **29** with $NaBH_4$ at 0 °C in methanol as shown in Scheme 1.

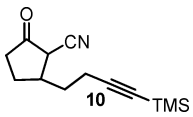
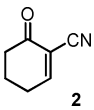
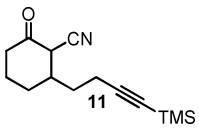
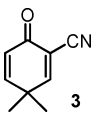
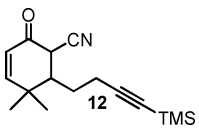
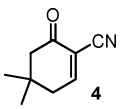
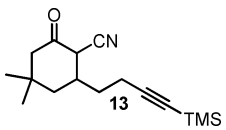
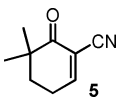
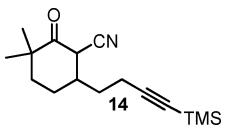
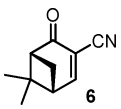
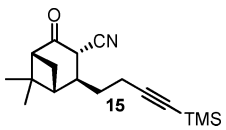
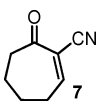
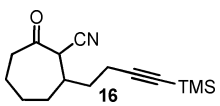
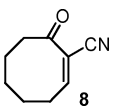
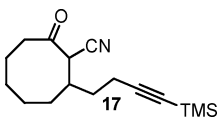
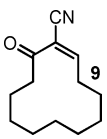
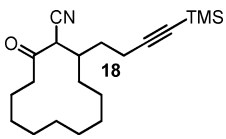
The proposed mechanism for the formation of 5/5, 5/6 and 5/7 fused products is illustrated in Scheme 2 using substrate **11** as a specific example. Accordingly, the aforementioned ZnI_2-mediated

[a]*Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan, 30013, ROC*
[b]*Institute of Biotechnology and Pharmaceutical Research, National Health Research Institutes, Miaoli County, 35053, Taiwan, ROC. E-mail: ksshia@nhri.org.tw; Fax: +886-37-586-456; Tel: +886-37-246-166*

† Electronic supplementary information (ESI) available: Experimental details and analytical data (^1H, ^{13}C and HRMS/ESMS) for all new compounds; the X-ray crystallographic pictures for **21**, **25** and **29a**. CCDC reference numbers 765388–765390. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05591g

Table 1 1,4-Addition of (4-buty-1-nyl)trimethylsilane magnesium chloride to 2-cyano-2-cycloalkenones

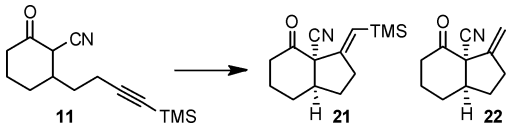


Substrate	Product	Yield (%)[a]
		68[b] (*cis*:*trans* = 1 : 3)
		77[b] (*cis*:*trans* = 1 : 2)
		40[b] (*cis*:*trans* = 3 : 2)
		75[b] (*cis*:*trans* = 1 : 1)
		72[b] (*cis*:*trans* = 2 : 5)
		74[c,d]
		72[b] (*cis*:*trans* = 3 : 1)
		71[d]
		69[d]

[a] Yields are for isolated, chromatographically pure products. [b] The ratio of the keto:keto diastereomeric forms. [c] The stereochemistry was confirmed by NOE experiments. [d] A single set of ^{1}H and ^{13}C NMR spectrum, respectively, was obtained.

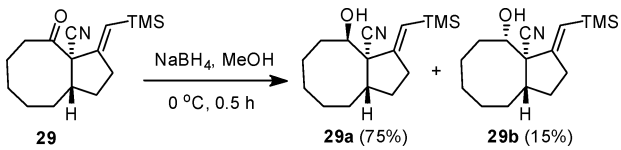
Conia-ene cyclization should proceed through intramolecular addition of the metal enolate to the acetylenic moiety with the trimethylsilyl group pointing outward to relieve 1,3-allylic strain,

Table 2 Optimization of Conia-ene cyclization with an initial model **11**

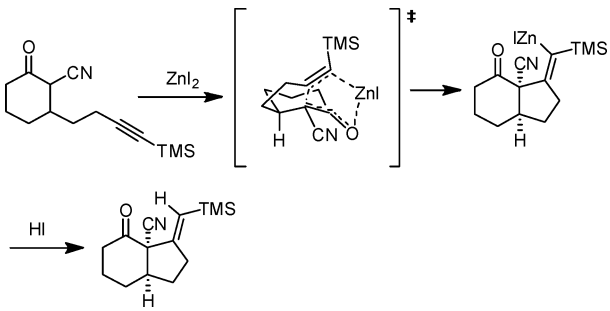


Entry	Conditions	Product (s)	(Yield%)[a]
1	$TiCl_4$ (1.8 eq.) CH_2Cl_2, rt, 23 h	**21** (13%)	
2	$SnCl_4$ (1.0 eq.) CH_2Cl_2, rt, 16 h		**22** (34%)
3	$ZnCl_2$ (1.0 eq.) Toluene, reflux, 48h	**21** (61%)	**22** (7%)
4	ZnI_2 (1.0 eq.) Toluene, reflux, 48h	**21** (80%)	**22** (6%)
5	ZnI_2 (1.0 eq.) Toluene, reflux, 3h	**21** (88%)	

[a] Yields are for isolated, chromatogrphically pure products.



Scheme 1



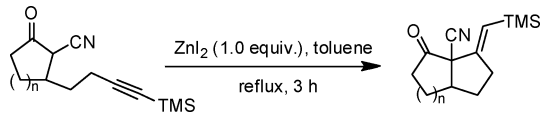
Scheme 2

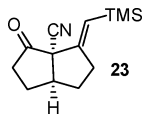
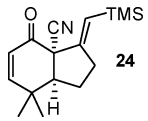
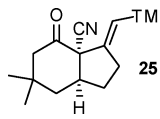
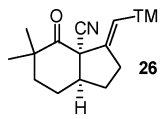
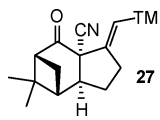
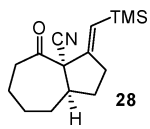
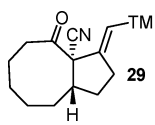
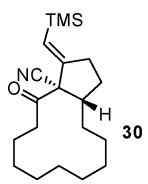
leading to the observed bicyclic products after protonation with hydriodic acid. As for the medium- and large-membered ring systems, the most favourable transition state might fit into a *trans* conformation due to a lower activation energy, thus resulting in *trans*-fused products instead (*e.g.* **29**).

To clarify the role of the TMS group, representative substrates **10**, **11** and **16** were further subjected to deprotection under standard conditions[27] to afford the corresponding acetylene compounds **31–33**. Under similar reaction conditions (Scheme 3), these TMS-removed compounds were found to undergo the desired cyclization as efficiently as or even slightly more efficient than their TMS-containing analogues, suggesting that the TMS functionality appears not to be essential for the title system to effect Conia-ene reaction.

For comparison, α-ester counterparts **37** and **38** were also prepared,[28] and treated with the same reaction conditions. As illustrated in Scheme 4,[12,21] the expected cyclization did occur to afford products **39** (77%) and **40** (71%), but yields were inferior to the corresponding α-cyano products **21** (88%) and **35** (90%), respectively, by 11% and 19% (*vide supra*).

Table 3 ZnI_2 mediated Conia-ene reaction of various ω-silylalkynyl-α-cyano ketones

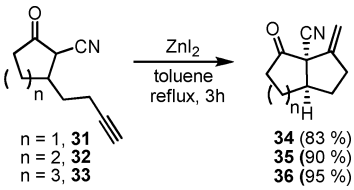


Substrate	Product	Yield (%)[a]
10	 **23**	85
12	 **24**	77
13	 **25**	86
14	 **26**	83
15	 **27**	85
16	 **28**	80
17	 **29**	81
18	 **30**	78

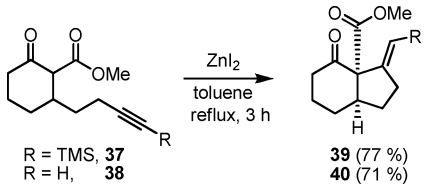
[a] Yields are for isolated, chromatographically pure products.

Cyclization products thus obtained, as exemplified by compounds **21**, **28**, **35** and **36** in Scheme 5, were subsequently applied to reductive alkylation, a two-step sequence involving decyanation with lithium naphthalenide (LN)[29] followed by alkylation in one pot. The reaction took place smoothly in a stereoselective manner at –45 °C in THF, leading to a single stereoisomer in all cases examined.

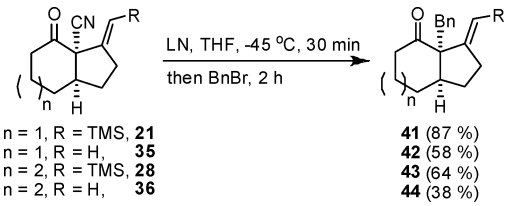
It was somewhat unexpected that the TMS functionality could survive the LN-induced reductive conditions. Also intriguing is the finding that TMS-containing reactants appear to give the



Scheme 3



Scheme 4



Scheme 5

corresponding alkylated products in much higher yields than their TMS-free counterparts (*i.e.*, **41** (87%) *vs.* **42** (58%) and **43** (64%) *vs.* **44** (38%)). Nevertheless, whether the TMS group accounts for such a distinct difference in yields in LN-induced alkylation still needs to be further studied before any conclusions can be derived.

The stereochemistry of products **41** and **42** possessing a *cis* ring junction was determined by NOE experiments (Fig. 1), as well as a chemical correlation[30,31] *via* removal of the TMS moiety; however, the *cis* configuration of products **43** and **44** are tentatively assigned based on previously structurally closely related compounds,[13] and remains to be determined.

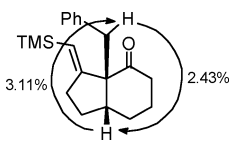


Fig. 1 NOE data of compound **41**.

As demonstrated above, though the title system just replaced a conventional α-ester with an α-cyano group to promote a known cyclization process under Lewis acid catalysis, it may complement inadequate functions of its ester counterpart, such as reductive alkylation, for more advanced synthetic elaboration and undergo a unique autoxidative cyclization, which is hitherto unknown,[18] and thus will be a valuable addition to the current synthetic chemistry.

In summary, under induction with ZnI_2, the Conia-ene annulation process for ω-silylalkynyl α-cyano ketones has been developed to effectively construct various bicyclic skeletons in moderate to good yields with complete stereo- and regioselectivity. It is conceivable that this newly developed methodology can be extended to the synthesis of other frequently encountered ring systems by suitable modifications of the starting material. As well, the angular cyano group thus formed in the cyclization products may allow for

facile access to the corresponding angularly substituted derivatives *via* a simple operation of LN-induced alkylation, which is difficult to achieve by the presence of any other functionalities.

Acknowledgements

We are grateful to the National Science Council and the National Health Research Institutes of the Republic of China for financial support.

Notes and references

‡ An isolated case of the β-alkynyl α-cyano ketone using copper/silver as co-catalyst to effect Conia-ene reaction was recently reported by Li and co-workers.[20]

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24 Transition metal catalysts, including $Pd(OAc)_2$, $CpCo(CO)_2$, $(PPh_3)AuCl$, $W(CO)_6$ and $Mo(CO)_6$ were also screened to facilitate Conia-ene cyclization. However, they are all inferior to ZnI_2, presumably due to the presence of the bulky TMS group disfavoring the formation of a metal-alkyne complex.
25 Crystal data for **25**: $C_{16}H_{25}NOSi$, $M = 275.46$; monoclinic, space group $P2_1/c$; $a = 11.914(4)$, $b = 11.740(4)$, $c = 12.726(4)$ Å, $\beta = 106.442(5)^\circ$, $V = 1707.1(9)$ Å^3, $T = 273(2)$K; $Z = 4$; $\mu = 0.132$ mm^{-1}; reflections: total = 19759, unique = 4247 ($R_{int} = 0.0866$); R indices (all data): $R_1 = 0.1543$, $wR2 = 0.1603$. CCDC 765388.
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