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Cobalt(II)-Catalyzed Aerobic Oxidation of Terminal-capped Alkynyl α-Cyano Alkanone Systems. An Oxygen-mediated Radical Chain Reaction

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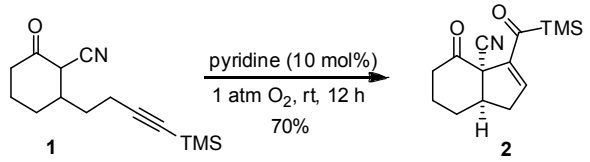
ABSTRACT: A new NHPI/Co(II)-catalyzed protocol, mechanistically involving a sequence of α-hydrogen abstraction, 5-*exo*-*dig* cyclization, oxygen capture, hydrogen transfer and 1,4-dehydration, has been developed to facilitate aerobic oxidation of aryl-, silyl- and alkyl-capped alkynyl α-cyano alkanone systems, respectively, to the corresponding highly functionalized products in an effective manner, thus turning this novel chain reaction, originally occurring spontaneously in low yields, into a practical methodology.

INTRODUCTION

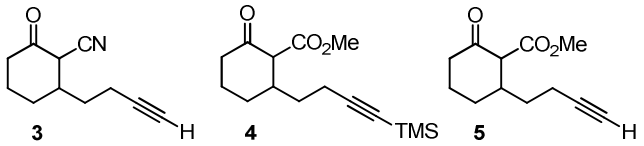
Since compound **1** was discovered to undergo aerobic oxidation spontaneously to afford α,β-unsaturated acylsilane **2** in ca. 30% yield upon exposure to air, attempts have been made to optimize reaction conditions, leading to findings that substrate **1** could convert to product **2** more effectively under catalysis with pyridine at one atmosphere of oxygen (Scheme 1).[1]

Scheme 1. Trimethylsilyl-capped Aerobic Oxidation.



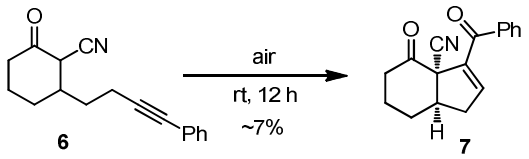
The generality of the autoxidative reaction has been verified by a variety of silyl-capped alkynyl α-cyano cycloalkanones as reported previously.[1] However, we found that the TMS-free α-cyano

cyclohexanone **3** and its α-ester counterparts **4** and **5** were rather stable under air, suggesting that both the α-cyano group and TMS functionality are required to induce the observed autoxidation. To expand the scope of this interesting type of reaction, attempts to cap the



terminal acetylene with various functionalities were then made. In one approach, when the acetylene was capped with a phenyl group, the expected transformation of substrate **6** to enone **7** was found to proceed spontaneously in ca. 7% yield under air (Scheme 2). Even if reactant **6** stood on bench or was dissolved in a commonly used solvent, including ethyl acetate, dichloromethane or dimethylformamide, for more than two days under air, its conversion rate into **7** maintained at this level and starting material was recovered intact by ca. 90%. When optimal reaction conditions developed previously (Scheme 1) were applied to substrate **6**, a complex mixture was obtained and the yield of product **7** was barely improved as analysed by ^{1}H NMR.

Scheme 2. Phenyl-capped Aerobic Oxidation.

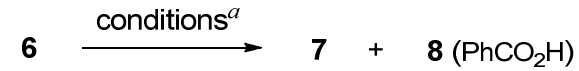


Screening of reaction conditions was then extensively carried out. Consequently, a commonly effective procedure was developed to realize the desired aerobic oxidation, wherein the terminal acetylene unit of the titled systems allowed to be capped with either an aryl, silyl or alkyl functionality. Results and discussion are presented as follows.

RESULTS AND DISCUSSION

Given that aforementioned aerobic reactions are triggered via a free radical cascade process, metal catalysts or oxidants reported to serve as useful radical initiators in air, including CuO/dibenzoyl peroxide (DBP), Mn(III)/Co(II)/O_2, di-t-butyl peroxide, TBAI/TBHP, CuI, $Mn(OAc)_3$, I_2, CAN, and *N*-hydroxyphthalimide (NHPI),[2-8] are first examined. Using substrate **6** as an initial model, screening results are listed in Table 1. Though the desired product **7**, except for treatment with $Mn(OAc)_3$ (entry 4), was mainly obtained in all cases examined, a side product, benzoic acid **8**, was accompanied in 17-45% yields. In fact, the direct oxidative cleavage of alkynes into carboxylic acids under metal catalysis has been well documented,[9] which might account for the low yield of product **7**. As indicated in entry 9, the reaction system (10 mol% $Co(OAc)_2$/20 mol% NHPI/PhH/air), giving rise to product **7** in 61% yield, is tentatively considered the system of choice and is applied to an array of substrates to verify its synthetic generality.

Table 1. Screening of Reaction Conditions.

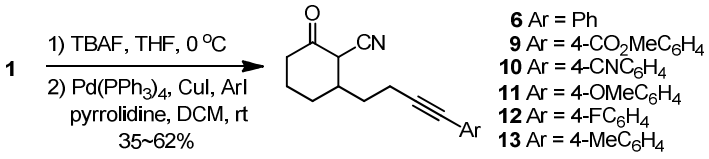


entry	reagent	solvent	time (h)	**7** / **8** yield (%)[b]
1	-	PhH	24	~7 / -
2	10% TBAI/1.0 equiv TBHP	PhH	48	51 / 45
3	20% CuI	DMF	12	20 / 17
4	2.0 equiv $Mn(OAc)_3$	PhH	12	27 / 37
5	10% I_2	PhH	48	9 / -
6	2.0 equiv CAN	MeOH	12	33 / 17
7	20% NHPI	PhH	40	50 / 35
8	10% $Cu(acac)_2$/20% NHPI	PhH	12	39 / 27
9	**10% $Co(OAc)_2$/20% NHPI**	**PhH**	**12**	**61 / 30**
10	10% $Co(OAc)_2$/20% NHPI	DMF	12	42 / 25

[a]All reactions were performed using substrate **6** (0.35 mmol) and 10~20 mol% catalyst in 1 mL of solvent as indicated above; the resulting mixture was vigorously stirred at room temperature under air. [b]Yields are for isolated, chromatographically pure products.

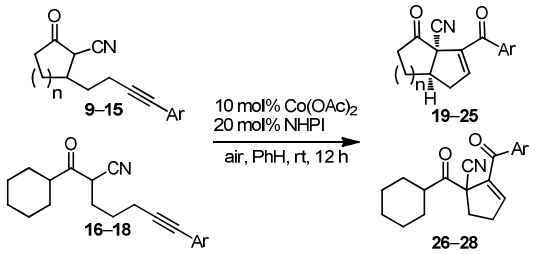
As shown in Scheme 3, compound **6** and various aryl-capped substrates **9**–**13** were readily prepared from compound **1** via a two-step sequence, involving deprotection of the trimethylsilyl group followed by Sonogashira coupling with an aryl iodide, in an overall yield of 35~62%.[10,11]

Scheme 3. Preparation of Aryl-capped Alkynes.



As compiled in Table 2, the present methodology is applicable for the acetylene unit capped with various aryls, irrespective of the stereoelectronic nature of the *para* substituent, affording the corresponding products in 35~61% yields (entries 1–7). Product **20** was unambiguously determined by the X-ray analysis,[12] lending strong support to the structural elucidation for this series of compounds by the use of conventional spectroscopic methods (^{1}H, ^{13}C, IR and HRMS). Similarly, acyclic substrates **16–18**, readily prepared in good to excellent yields according to synthetic procedures reported in the literature,[4b,5b,13] were also subjected to this newly developed protocol. As a result, desired products **26–28** were obtained in 28~40% yields, structures of which were fully confirmed by the X-ray analysis.[14,15] It is noteworthy that different from cyclic substrates (e.g. compound **1**), the spontaneous conversion rate of acyclic substrates **16–18** are thoroughly undetectable by ^{1}H NMR analysis. Though above autoxidative products seem to be isolated in low to moderate yields (28~61%) , however, unlike a regular reaction with a simple mechanistic insight, the inherent reactivity of this unique reaction comprises a five-step domino transformation, including α-hydrogen abstraction, 5-*exo*-*dig* cyclization, oxygen capture, hydrogen transfer and 1,4-dehydration. Even if 28% is the lowest reaction yield in all cases examined in Table 2, the average yield of each transformation is as high as 78%. In general, the corresponding side products, benzoic acids, were obtained in 25~ 40% for the current procedure.

Table 2. Autoxidation of Aryl-capped Alkynyl α-Cyano Alkanones.

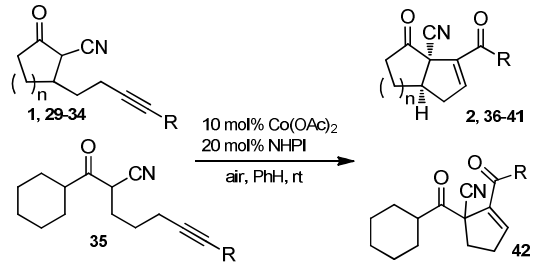


entry	substrate	product	yield (%)[a]
1	**9** n = 2 Ar = 4-$CO_2MeC_6H_4$	**19**	61
2	**10** n = 2 Ar = 4-CNC_6H_4	**20**	50[b]
3	**11** n = 2 Ar = 4-$OMeC_6H_4$	**21**	42
4	**12** n = 2 Ar = 4-FC_6H_4	**22**	40
5	**13** n = 2 Ar = 4-MeC_6H_4	**23**	40
6	**14** n = 1 Ar = Ph	**24**	38
7	**15** n = 1 Ar = 4-$OMeC_6H_4$	**25**	35
8	**16** Ar = Ph	**26**	40
9	**17** Ar = 4-$MeCO_2C_6H_4$	**27**	36[b]
10	**18** Ar = 4-$MeOC_6H_4$	**28**	28[b]

[a]Yields were for isolated, chromatographically pure products. [b]The structure was confirmed by X-ray crystallographic analysis.

Since the acetylene unit capped with an aryl group was found prone to oxidative cleavage, we assumed that a trialkylsilyl group providing more steric hindrance might retard the approach of active oxygen radical species (e.g., M–O-O·) to lessen the side effect. As such, this newly developed protocol was also employed to reinvestigate trialkylsilyl-capped counterparts containing a TMS,[1] TES or TBDMS functionality. Results are listed in Table 3. As TMS-capped α-cyano ketones **1**, **29**, **30,** and **35** were treated with Co(II)-catalyzed conditions, corresponding acylsilanes **2** (entry 2; 68% *vs*. 70%), **36** (entry 1; 55% *vs*. 59%), **37a**/**37b** (entry 3; 46% *vs*. 28%) and **42** (entry 8; 44% *vs*. 21%) were produced in almost equal or better yields as compared to those obtained by previous reaction conditions (10 mol% pyridine/1 atm O_2/rt), thus demonstrating that this newly developed method is more efficient and practical. Moreover, when the TMS group of substrate **1** was replaced with a bulkier TES or TBDMS group, the similar aerobic oxidation could proceed with equal facility, affording the corresponding products **39** (entry 5; 73%) and **41** (entry 7; 75%), respectively, in a slightly higher yields than their TMS counterpart **2** (entry 2; 68%). These results seem to reflect our argument that the steric hindrance of the terminal silyl group might hamper active oxygen radicals to access the acetylene unit, thus lessening its oxidative cleavage and resulting in higher yields. In addition, acylsilane products containing a bulkier TES or TBDMS group are much more stable than those containing a TMS group in that upon long-term exposure to light, the former remain intact but the latter are slowly decomposed to the corresponding α,β-unsaturated aldehydes, presumably due to Norrish Type I cleavage.[1,16]

Table 3. Autoxidation of Silyl-capped Alkynyl α-Cyano Alkanones.

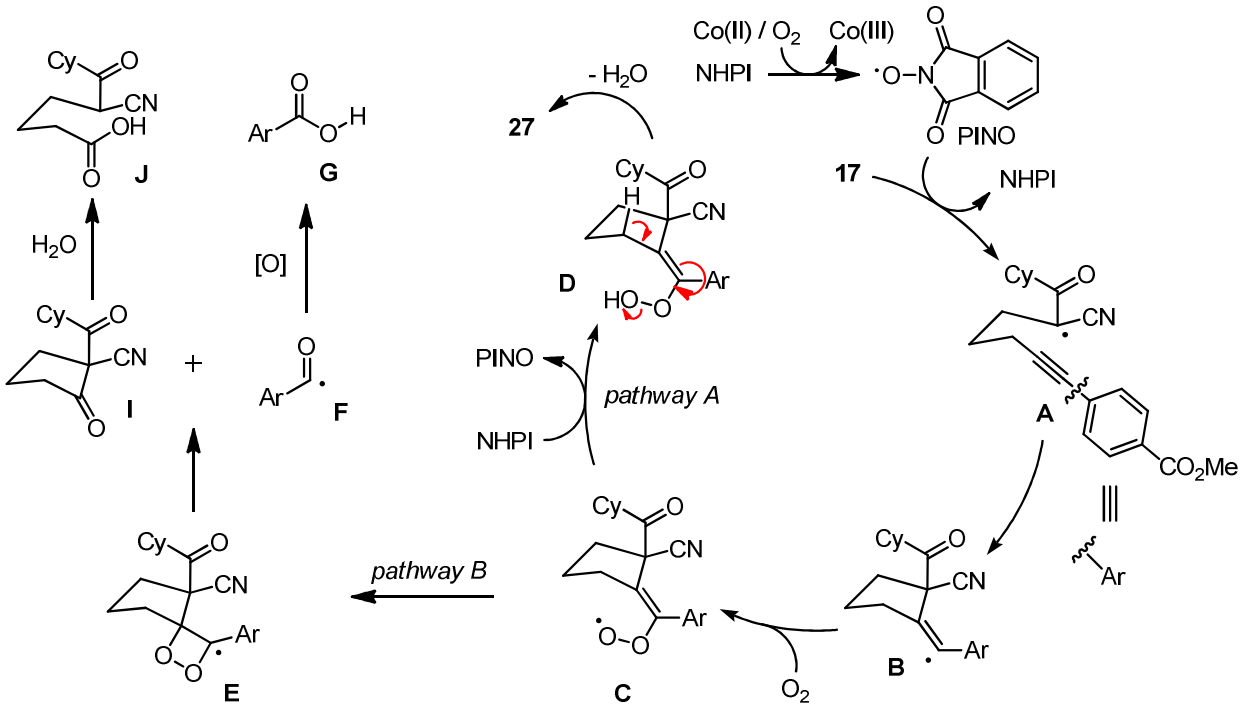


entry	substrate	product	t (h)	yield (%)[a]
1	**29** n = 1 R = TMS	**36**	12	55(59)[b]
2	**1** n = 2 R = TMS	**2**	18	68(70)[b]
3	**30** n = 3 R = TMS	**37a** + **37b**	48	**37a/37b** 46(28)[b]
4	**31** n = 1 R = TES	**38**	6	62
5	**32** n = 2 R = TES	**39**	12	73[c]
6	**33** n = 1 R = TBDMS	**40**	12	69[c]
7	**34** n = 2 R = TBDMS	**41**	24	75[c]
8	**35** R = TMS	**42**	48	44(21)[b]

[a]Yields were for isolated, chromatographically pure products. [b]The yields in the parenthesis are those of the reaction carried out under previous conditions in ref. 1 (10 mol% pyridine/1 atm O_2/rt).[c]The structure was confirmed by X-ray crystallographic analysis.[20,21,22]

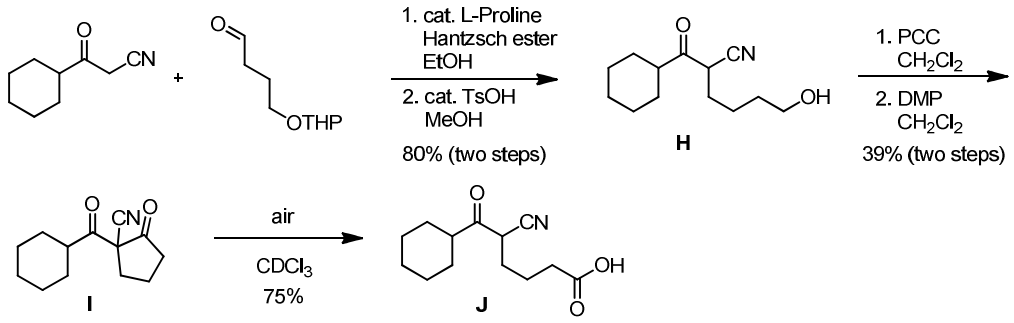
Using the transformation of compound **17** into **27** as a typical example, the proposed mechanism is depicted in Scheme 4. The chain reaction is initiated by abstracting hydrogen α to the cyano and ketone group of **17** *via* phthalimide *N*-oxyl (PINO) radical, generated under catalysis with Co(II)/NHPI in the presence of oxygen,[8a] to form radical intermediate **A**, which could immediately undergo 5-*exo-dig* addition to produce vinyl radical **B**.[17,18,19] Subsequently, an oxygen molecule is captured by vinyl radical **B** to provide vinyl peroxyl radical **C** by which the hydrogen of NHPI is abstracted to form hydroperoxide **D** followed by 1,4-dehydration to give product **27** and restart the catalytic cycle (*pathway A*). Alternatively, radical **C** might take *pathway B* to form dioxetane radical **E** which could decompose to furnish 1,3-diketone **I**, leading to carboxylic acid **J** via hydrolysis, and acyl radical **F**, leading to benzoic acid **G** via oxygenation.[6,9,23] 2-cyano-1,3-diketone **I**, a co-product of benzoic acid **G**, appeared unstable and prone to hydrolysis in the presence of moisture to afford the corresponding acid **J** as detected by LC-Mass (see S37-S38 in Supporting Information).

Scheme 4. Proposed Mechanism for Aerobic Oxidation with NHPI/Co(II) Acetate.



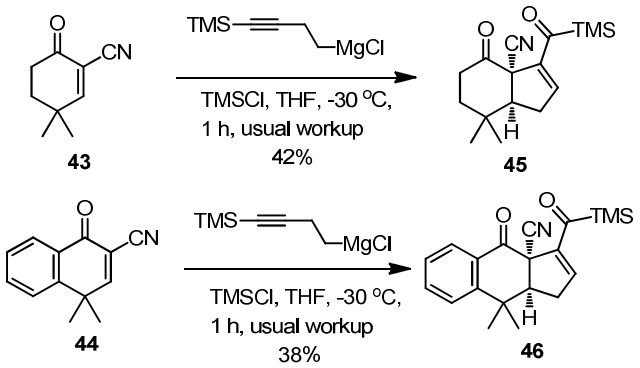
To confirm the mechanism, authentic sample **I** was then prepared according to Scheme 5. Intermediate **H** was synthesized via a modified procedure of Knoevenagel condensation followed by deprotection with TsOH in 80% over two steps.[4b,5b] Hydroxyl **H** was then oxidized with PCC to afford cyclic β-hydroxyl ketone, which without purification was further oxidized with DMP to afford the desired 2-cyano-1,3-diketone **I** in 39% over two steps. Compound **I** thus obtained was found to be hydrolysed in $CDCl_3$ in a couple of hours to form the corresponding carboxylic acid **J** as verified by ^1H and ^{13}C spectra shown in Figure S1 in Supporting Information. Neverthless, the clean ^1H and ^{13}C spectrum of **I** could be timely recorded (see S34 in Supporting Information). The above results lend strong support to the mechanism proposed in Scheme 4.

Scheme 5. Preparation of Authentic Sample 2-Cyano-1,3-diketone I.



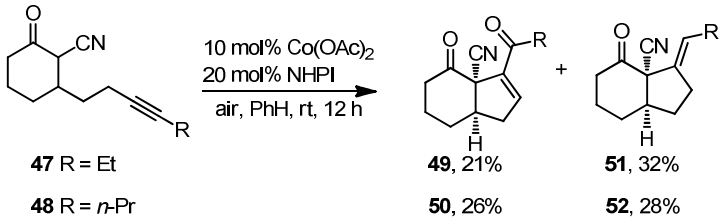
More intriguingly, when substrates **43** and **44** (Scheme 6) were designed to make the pendant acetylene unit get closer to the reacting α-carbon center via the Thorpe-Ingold effect, the expected chain reaction occurred almost instantly after an usual workup of 1,4-conjugate addition of the Grignard reagent, furnishing desired products **45** and **46** in 42% and 38% yields in one pot, respectively, structures of which were unambiguously confirmed by the X-ray crystallographic analysis.[24,25] Obviously, a gem-dimethyl group installed at the γ position could force the acetylene-containing linker to adopt a constrained conformation like intermediate **A** (Scheme 4), thus accelerating the chain reaction in an efficient fashion.

Scheme 6. Reaction Rate Enhanced by Thorpe-Ingold Effect.



When the above optimal reaction system was further extended to substrates capped with an alkyl group such as **47** and **48** (Scheme 7), readily prepared by 1,4-conjugate addition of an appropriate Grignard reagent to 2-cyano-2-cyclohexenone in good yields,[26] the corresponding products **49** and **50** were obtained in 21% and 26% yields, respectively. Also emphasized is the fact that upon exposure to air over two days, not a trace of substrates **47** and **48** was spontaneously converted into products **49** and **50** as determined by ^{1}H NMR analysis. These results suggest that the new methodology is synthetically more useful than the previous one in that it can activate the latent autoxidative reaction rather than just enhance it. However, the formation of products **51** and **52** is somewhat unexpected because similar products are not observed in both silyl-capped and aryl-capped series. In light of stereochemistry, they are tentatively assigned as *trans* isomers based on our previous studies on Conia-ene reactions with the same substrates in the presence of Lewis acids such as ZnI_2.[26b]

Scheme 7. Unexpected Conia-ene Reactions in Alkyl-capped Series.



Above outcomes might be rationalized as follows. As illustrated in Figure 1 base on Hartree-Fock quantum mechanic calculation (see S39 in Supporting Information),[27] vinyl radical **I** with

the relatively highest energy is supposed to be more reactive than its counterparts **II** and **III**, and thus could randomly capture either an oxygen molecule to continue the chain reaction or abstract a hydrogen atom from the reaction environment to terminate it.

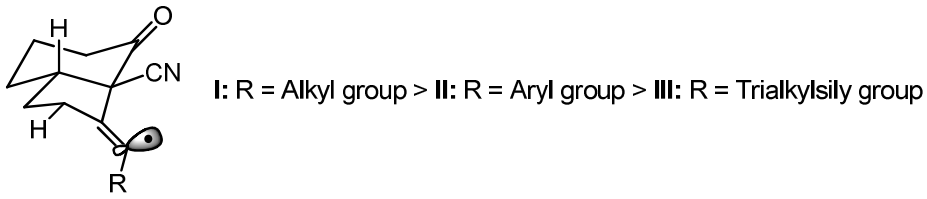


Figure 1. Relative energy of vinyl radicals **I**, **II** and **III** base on Hartree-Fock quantum mechanic calculation.

We also observed that the trialkylsilyl-capped series usually afforded the corresponding products in higher yields than their aryl- and alkyl-capped counterparts. An explanation could be that in addition to the steric hindrance of the silyl group making oxidative cleavage of the alkyne unit more difficult, a unique stabilizing force provided by the Si element through delocalization with its *d* orbital or low-lying σ* (Si-C) anti-bonding orbital might render trialkylsilyl vinyl radicals existing longer, thus trapping oxygen more efficiently.[1,18,23] For comparison purposes, α-cyano ester **53** and β-keto ester **54**, structurally analogous to α-cyano ketone **35** (Table 3, entry 8, 44%), were also synthesized and subjected to the same reaction conditions. As a result, both substrates **53** and **54** (Figure 2) were recovered intact over a period of 24 h at room temperature or under heating in refluxing benzene for 10 h, the poor reactivity of which might be ascribed to higher bond dissociation energy (BDE) as compared with substrate **35**.

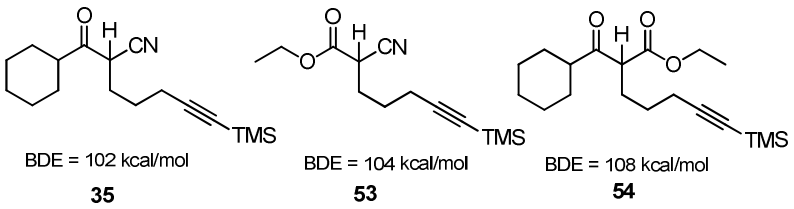


Figure 2. Bond dissociation energy of substrates **35**, **53** and **54**.

CONCLUSION

Our continued investigation on terminal-capped alkynyl α-cyano alkanone systems has culminated in a legitimate protocol (10 mol% $Co(OAc)_2$/20 mol% NHPI/PhH/air), by which an aerobic chain reaction, regardless of whether its spontaneous conversion rate is detectable, can be promoted in an effective fashion. Also demonstrated is the fact that the substituent capped on the terminal acetylene of the titled systems is structurally variable and not restricted to the trialkylsilyl group, originally recognized to be one of essential elements. Nevertheless, there is no doubt that the Si element of the trialkylsilyl group may play an extraordinary role in inducing the radical chain reaction although the underlying cause remains to be determined.

EXPERIMENTAL SECTION

General Experimental Procedure. All reactions were performed under air unless otherwise stated. All solvents and reagents were employed as received without further purification. Analytical thin layer chromatography was performed on SiO_2 60 F-254 plates and flash column chromatography was carried out using SiO_2 60 (particle size 0.040-0.055 mm, 230–400 mesh). Visualization was performed under UV irradiation at 254 nm followed by staining with aqueous potassium permanganate ($KMnO_4$ (3 g) and K_2CO_3 (20 g) in 300 mL of H_2O containing 5 mL of an aqueous solution of NaOH (5%, w/v)) and charring by heat gun. Infrared spectra (IR) were recorded on a FT-IR spectrometer and expressed in cm^{-1}. ^1H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz. Chloroform-*d* were used as the solvent and TMS (δ = 0.00 ppm) as an internal standard. Chemical shifts are reported as δ values in ppm as referenced to TMS. Multiplicities are recorded as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), qd (quartet of doubles), tt (triplet of triplets), ddd (doublet of doublet of doublets), m (multiplet), br (broad). Coupling constants (*J*) are expressed in Hz. HRMS was obtained on a triple quadrupole mass analysis using electrospray ionization (ESI) source or a double quadrupole mass analysis using electron impact (EI) source, and spectral data were recorded as *m/z* values. Melting points were measured using an Electrothermal instrument.

Preparation of Substrates. The general procedure for 1,4-conjugate addition in the synthesis of compounds **1**, **31**–**34**, **45** and **46** is demonstrated as follows using **1** as a typical example.[1]

2-Oxo-6-(4-(trimethylsilyl)but-3-ynyl)-cyclohexanecarbonitrile (1): To a stirred solution of α-cyano-2-cyclohexenone (302 mg, 2.50 mmol) in THF (5 mL) was added freshly prepared (4-buty-1-nyl)trimethylsilane magnesium chloride solution (6.0 mL, 0.92 M in THF, 5.50 mmol) dropwise at –30 ^{o}C. After stirring for 10 min at the same temperature, TMSCl (0.95 mL, 7.50 mmol) was introduced in one portion. The resulting mixture was stirred for another 1 h at –30 ^{o}C. Saturated NH_4Cl solution (8 mL) was added to quench the reaction. The aqueous layer was separated and extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by flash chromatography on silica gel using EtOAc/*n*-hexane (1:9) as eluant to afford substrate **1** (476 mg, 77% yield, a mixture of keto isomers in a ratio of 1:2 (*cis* : *trans*)) as a yellowish oil. ^{1}H NMR (600 MHz, $CDCl_3$) major isomer: δ 3.33 (d, J = 11.6 Hz, 1H), 2.56–2.52 (m, 1H), 2.38–1.80 (m, 6H), 1.74–1.33 (m, 4 H), 0.08 (s, 9H); minor isomer: δ 3.52 (d, J = 4.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) major isomer: δ 200.0, 115.7, 105.1, 86.0, 49.6, 42.2, 40.3, 32.9, 27.0, 22.7, 16.8, -0.1 (3C); minor isomer: δ 200.9, 115.4, 104.7, 86.2, 47.5, 40.9, 38.8, 30.4, 28.8, 22.6, 17.0, –0.3 (3C); IR (neat): 2249, 2174, 1728 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{14}H_{21}NOSi$: 247.1392 $[M]^+$; found: 247.1391.

2-Oxo-5-(4-(triethylsilyl)but-3-ynyl)-cyclopentanecarbonitrile (31): A mixture of keto isomers in a ratio of 1:5 (*cis* : *trans*) was obtained as a yellowish oil; 372 mg, 54% yield; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 2.93 (d, J = 12.4 Hz, 1H), 2.58–2.27 (m, 4H), 2.17–1.86 (m, 2H), 1.73–1.64 (m, 2H), 1.59–1.49 (m, 1H), 0.94 (t, J = 8.0 Hz, 9H), 0.54 (q, J = 8.0 Hz, 6H); minor isomer: δ 3.38 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer : δ 205.9, 116.0, 106.1, 83.3, 45.9, 41.7, 37.1, 32.7, 27.0, 17.5, 7.4 (3C), 4.3 (3C); minor isomer: δ 206.3, 114.2, 105.9, 83.8, 44.2, 38.4, 36.1, 29.6, 26.4, 17.9, 7.3 (3C), 4.2 (3C); IR (neat): 2955, 2875, 2245, 2173, 1759, 1459, 726; HRMS (EI): *m/z* calcd for $C_{16}H_{25}NOSi$: 275.1705 $[M]^+$; found: 275.1709.

2-Oxo-6-(4-(triethylsilyl)but-3-ynyl)-cyclohexanecarbonitrile (32): A mixture of keto isomers in a ratio of 1:1.5 (*cis* : *trans*) was obtained as a yellowish oil; 441 mg, 61% yield; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 3.32 (d, J = 11.2 Hz, 1H), 2.76–2.68 (m, 1H), 2.63–2.57 (m, 1H), 2.46–1.99 (m, 5H), 1.90–1.55 (m, 4H), 0.95 (t, J = 8.0 Hz, 9H), 0.55 (q, J = 8.0 Hz, 6H); minor isomer: δ 3.51 (d, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: δ 200.0, 115.7, 106.0, 83.3, 49.6, 42.2, 40.3, 33.0, 28.8, 24.7, 16.9, 7.3 (3C), 4.3 (3C); minor isomer: δ 200.8,

115.4, 105.7, 83.4, 47.5, 40.8, 38.8, 30.5, 27.0, 24.6, 17.0, 7.3 (3C), 4.3 (3C); IR (neat): 2955, 2877, 2241, 2173, 1728, 1458, 1239, 740 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{15}H_{22}NOSi$: 260.1471 $[M–Et]^+$; found: 260.1477.

2-(4-(*tert*-Butyldimethylsilyl)but-3-ynyl)-5-oxocyclopentanecarbonitrile (33): A mixture of keto isomers in a ratio of 1:4 (*cis* : *trans*) was obtained as a yellowish oil; 241 mg, 35% yield; ^1H NMR (400 MHz, $CDCl_3$) major isomer: δ 2.92 (d, J = 12.4 Hz, 1H), 2.60–2.30 (m, 4H), 2.06–1.83 (m, 2H), 1.74–1.64 (m, 2H), 1.59–1.49 (m, 1H), 0.89 (s, 9H), 0.05 (s, 6H); minor isomer: δ 3.38 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: δ 205.9, 116.0, 105.6, 84.2, 45.9, 41.7, 37.1, 32.7, 27.0, 25.9 (3C), 17.4, 16.3, -4.6 (2C); minor isomer: δ 206.2, 114.2, 105.5, 83.8, 44.2, 40.5, 36.1, 29.6, 26.4, 25.9 (3C), 17.8, 16.6, –4.6 (2C); IR (neat): 2954, 2858, 2242, 2173, 1759, 1463, 776; HRMS (EI): *m/z* calcd for $C_{12}H_{16}NOSi$: 218.1001 $[M–^tBu]^+$; found: 218.0991.

2-(4-(*tert*-Butyldimethylsilyl)but-3-ynyl)-6-oxocyclohexanecarbonitrile (34): A mixture of keto isomers in a ratio of 1:3 (*cis* : *trans*) was obtained as a yellowish oil; 239 mg, 33% yield; ^1H NMR (400 MHz, $CDCl_3$) major isomer: δ 3.31 (d, J = 11.2 Hz, 1H), 2.68–2.56 (m, 2H), 2.46–1.99 (m, 5H), 1.90–1.55 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H); minor isomer: δ 3.51 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: δ 199.9, 115.7, 105.6, 84.4, 49.7, 42.3, 40.4, 33.0, 28.9, 26.0 (3C), 24.8, 17.0, 16.4, –5.7 (2C); minor isomer: δ 200.8, 115.5, 105.2, 84.5, 47.5, 41.0, 38.9, 30.7, 27.1, 26.0 (3C), 24.9, 17.1, 16.2, –5.3 (2C); IR (neat): 2952, 2858, 2248, 2173, 1730, 1463, 1251, 776 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{13}H_{18}NOSi$: 232.1158 $[M–^tBu]^+$; found: 232.1148.

7,7-Dimethyl-4-oxo-3-((trimethylsilyl)carbonyl)-3a,4,5,6,7,7a-hexahydro-1*H*-indene-3a-carbonitrile (45): Compound **45** was obtained directly after an usual work up of 1,4-conjugate addition. Yellow soild; 304 mg, 42% yield; m.p. 95–96 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 6.93 (t, J = 2.4 Hz, 1H), 3.02 (m, 1H), 2.89 (ddd, J = 10.0, 8.0, 1.6 Hz, 1H), 2.72 (ddd, J = 18.4, 8.0, 3.2 Hz, 1H), 2.42–2.30 (m, 2H), 1.94–1.81 (m, 2H), 1.47 (s, 3H), 0.98 (s, 3H), 0.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 229.7, 201.7, 146.2, 145.7, 118.8, 59.5, 54.5, 36.5, 34.8, 34.6, 32.4, 28.4, 27.9, –1.9 (3C); IR (CH_2Cl_2): 2962, 2240, 1731, 1595, 1250, 848 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{16}H_{23}NO_2Si$: 289.1498 $[M]^+$; found: 289.1489.

9,9-Dimethyl-4-oxo-3-((trimethylsilyl)carbonyl)-3a,4,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalene-3a-carbonitrile (46): Compound **46** was obtained directly after an

usual work up of 1,4-conjugate addition. Yellow solid; 321 mg, 38% yield; m.p. 136–137 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (dd, J = 7.6, 1.2 Hz, 1H), 7.56 (td, J = 7.6, 1.2 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.30 (td, J = 7.6, 1.2 Hz, 1H), 6.81 (dd, J = 3.2, 2.4 Hz, 1H), 3.22 (t, J = 9.0 Hz, 1H), 2.88 (ddd, J = 19.2, 9.2, 3.2 Hz, 1H), 2.19 (ddd, J = 19.2, 9.2, 2.4 Hz, 1H), 1.48 (s, 6H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 229.3, 187.2, 149.2, 148.7, 144.3, 134.5, 132.2, 129.2, 127.0, 125.3, 120.0, 56.0, 55.0, 37.0, 36.8, 33.6, 25.4, –2.0 (3C); IR (CH_2Cl_2): 2966, 2903, 2239, 1685, 1599, 1377, 1250, 849 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{20}H_{23}NO_2Si$: 337.1498 $[M]^+$; found: 337.1499.

The general procedure for Sonogashira coupling in the synthesis of substrates **6** and **9**–**15** is demonstrated as follows using **9** as a typical example.

Methyl 4-(4-(2-cyano-3-oxocyclohexyl)but-1-ynyl)benzoate (9): A mixture of 2-oxo-6-(4-(trimethylsilyl)but-3-ynyl)cyclohexanecarbonitrile **1** (1.0 g, 4.0 mmol) was treated with TBAF (4.8 mL, 1M in THF) in THF (20 mL) at 0 ^{o}C for 1 h and then cooled to room temperature and quenched with water. The aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude residue, which without purification, was further treated with methyl 4-iodobenzoate (1.25 g, 4.8 mmol), CuI (76 mg, 0.40 mmol), $Pd(PPh_3)_4$ (462 mg, 0.40 mmol) and pyrrolidine (0.67 ml, 8.0 mmol) in CH_2Cl_2 (15 mL) under nitrogen at room temperature for 6 h. The mixture was filtered through a pad of celite and slica gel followed by washing with CH_2Cl_2 (50 mL). The organic solution was concentrated under reduced pressure to give the crude residue, which was subjected to purification by flash chromatography on silica gel using 30% EtOAc in *n*-hexane as eluant to afford a mixture of keto isomers in a ratio of 1: 3 (*cis* : *trans*) as a yellowish oil (630 mg, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) major isomer: δ 7.93 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 3.88 (s, 3H), 3.32 (d, J = 11.6 Hz, 1H), 2.64–2.47 (m, 2H), 2.33–2.03 (m, 4H), 1.90–1.67 (m, 5H); minor isomer: δ 3.55 (d, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: δ 200.0, 166.4, 131.3 (2C), 129.2 (2C), 128.9, 128.0, 115.7, 91.4, 81.0, 52.0, 49.6, 42.1, 40.1, 33.1, 28.8, 24.6, 16.4; IR (neat): 2950, 2248, 1721, 1606, 1437, 1279, 1110 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{20}NO_3$: 310.1443 $[M+H]^+$; found: 310.1438.

The general procedure for Knoevenagel condensation using Hantzsch ester as a reducing agent in the synthesis of substrates **16**–**18** and **35** is demonstrated as follows using **16** as a typical example.[13]

2-(Cyclohexanecarbonyl)-7-phenylhept-6-ynenitrile (16): To a stirred solution of 3-oxohexanenitrile (755 mg, 6.8 mmol) and 5-phenylpent-4-ynal (1.3 g, 8.2 mmol) in EtOH (100 mL) was added L-proline (312 mg, 2.7 mmol) and Hantzsch ester (1.7 g, 6.8 mmol) sequentially in one portion. The resulting mixture was stirred at 25 ^{o}C for 16 h. The reaction solution was concentrated under reduced pressure, which was purified by flash chromatography on silica gel using 33% CH_2Cl_2 in *n*-hexane as eluant to afford substrate **16** as a pale-yellow oil; 1.40 g, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.36 (m, 2H), 7.27–7.25 (m, 3H), 3.60 (dd, J = 8.4, 5.6 Hz, 1H), 2.73 (tt, J = 11.2, 3.6 Hz, 1H), 2.48 (t, J = 6.8 Hz, 2H), 2.13–1.65 (m, 8H), 1.42–1.17 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.5, 131.4, 128.2, 127.7, 123.4, 117.3, 88.2, 81.7, 49.1, 41.7, 28.5, 28.3, 27.8, 25.7, 25.4, 25.2, 25.1, 18.7; IR (neat): 2934, 2242, 1722, 1450 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{20}H_{24}NO$: 294.1858 $[M+H]^+$; found: 294.1845.

Methyl 4-(6-cyano-7-cyclohexyl-7-oxohept-1-ynyl)benzoate (17): Yellow oil; 1.39 g, 58% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H), 3.58 (dd, J = 8.4, 6.0 Hz, 1H), 2.74 (tt, J = 10.8, 3.2 Hz, 1H), 2.50 (t, J = 6.8 Hz, 2H), 2.12–1.65 (m, 8H), 1.43–1.17 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.3, 166.4, 131.3, 129.3, 129.0, 128.1, 117.2, 91.6, 81.1, 52.0, 49.1, 41.6, 28.4, 28.2, 27.7, 25.5, 25.3, 25.2, 25.1, 18.8; IR (neat): 2934, 2241, 1731, 1715, 1607, 1436, 1308, 1109 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{22}H_{25}NO_3$: 351.1834 $[M]^+$; found: 351.1830.

2-(Cyclohexanecarbonyl)-7-(4-methoxyphenyl)hept-6-ynenitrile (18): Yellow oil; 1.21 g, 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8, Hz, 2H), 3.77 (s, 3H), 3.60 (dd, J = 8.4, 5.6 Hz, 1H), 2.72 (tt, J = 10.8, 3.2 Hz, 1H), 2.45 (t, J = 6.8 Hz, 2H), 2.10–1.93 (m, 2H), 1.89–1.86 (m, 2H), 1.79–1.63 (m, 4H), 1.41–1.15 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.5, 159.1, 132.8, 117.3, 115.5, 113.8, 81.5, 56.6, 55.1, 49.1, 41.7, 28.5, 28.3, 27.8, 25.7, 25.4, 25.2, 25.1, 18.7; IR (neat): 2934, 2241, 1720, 1606, 1510, 1450, 1247, 834 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{26}NO_2$: 324.1958 $[M+H]^+$; found: 324.1952.

2-(Cyclohexanecarbonyl)-7-(trimethylsilyl)hept-6-ynenitrile (35): Colorless oil; 1.42g, 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.57 (dd, J = 8.8, 5.6 Hz, 1H), 2.72 (tt, J = 11.2, 3.6 Hz, 1H), 2.28 (t, J = 6.8 Hz, 2H), 2.01–1.86 (m, 4H), 1.81–1.61 (m, 4H), 1.41–1.18 (m, 6H), 0.12

ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.5, 117.3, 105.3, 86.0, 49.2, 41.8, 28.6, 28.4, 27.7, 25.5, 25.3, 25.2, 19.1, 0.0; IR (neat): 2935, 2176, 1723, 1451, 1250, 844 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{17}H_{27}NOSi$: 289.1862 $[M]^+$; found: 289.1867.

Synthesis of Products. The general procedure for autoxidative annulation in the synthesis of products **7**, **19**–**28**, **38**–**42** and **49**–**52** was demonstrated as follows using **7** as a typical example.

3-Benzoyl-4-oxo-3a,4,5,6,7,7a-hexahydro-1*H*-indene-3a-carbonitrile (7): A mixture of 2-oxo-6-(4-phenylbut-3-ynyl)cyclohexanecarbonitrile **6** (125 mg, 0.50 mmol), $Co(OAc)_2$ (7 mg, 0.04 mmol) and *N*-hydroxyphthalimide (13 mg, 0.08 mmol) in benzene (1 mL) was stirred under air at room temperature for 12 h. The mixture was filtered through a pad of celite and slica gel followed by washing with CH_2Cl_2 (2 × 20 mL). The organic layer was concentrated under reduced pressure to give the residue, which was subjected to purification by flash chromatography on silica gel using EtOAc/*n*-hexane = 2/5 as eluant to afford product **7** (81 mg, 61% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.2 Hz, 2H), 6.83 (t, J = 2.8 Hz, 1H), 3.29–3.23 (m, 1H), 2.98 (ddd, J = 18.4, 6.8, 2.8 Hz, 1H), 2.77 (dt, J = 13.6, 6.0 Hz, 1H), 2.48–2.40 (m, 2H), 2.14–2.06 (m, 1H), 2.02–1.94 (m, 2H), 1.68–1.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 190.2, 149.1, 140.0, 137.2, 132.7, 128.9, 128.4, 117.8, 59.7, 50.4, 38.4, 38.2, 27.0, 24.0; IR (neat): 2929, 2238, 1726, 1646, 1343 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{17}H_{15}NO_2$: 265.1103 $[M]^+$; found: 265.1098.

Methyl 4-(3a-cyano-4-oxo-3a,4,5,6,7,7a-hexahydro-1*H*-indene-3-carbonyl)benzoate (19): Colorless oil; 99 mg, 61% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 6.81 (t, J = 2.8 Hz, 1H), 3.93 (s, 3H), 3.28 (quint, J = 6.4 Hz, 1H), 2.97–2.90 (m, 1H), 2.86–2.78 (m, 1H), 2.48–2.39 (m, 2H) 2.19–1.92 (m, 3H), 1.69–1.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 189.7, 166.0, 150.1, 140.8, 140.0, 133.4, 129.6, 128.7, 117.7, 59.1, 52.4, 50.5, 38.2, 38.1, 26.6, 23.9; IR (neat): 2953, 2234, 1725, 1651, 1282, 1109 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{18}NO_4$: 324.1236 $[M+H]^+$; found: 324.1227.

3-(4-Cyanobenzoyl)-4-oxo-3a,4,5,6,7,7a-hexahydro-1*H*-indene-3a-carbo- nitrile (20): White solid; 73 mg, 50% yield; m.p. 149–150 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 6.80 (t, J = 2.8 Hz, 1H), 3.31 (quint, J = 6.4 Hz, 1H), 2.92 (ddd, J = 18.8, 7.6, 2.8 Hz, 1H), 2.87–2.80 (m, 1H), 2.49–2.39 (m, 2H), 2.23–2.16 (m, 1H), 2.15–2.06 (m, 1H), 2.00–1.92 (m, 1H), 1.71–1.63 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 188.8, 149.9, 140.8, 139.8, 132.3, 129.3, 117.8, 117.5, 115.9, 58.7, 50.6, 38.1, 37.8, 26.2, 23.9; IR

(CH_2Cl_2 cast): 2941, 2232, 1731, 1651, 1250 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{15}N_2O_2$: 291.1134 $[M+H]^+$; found: 291.1129.

3-(4-Methoxybenzoyl)-4-oxo-3a,4,5,6,7,7a-hexahydro-1*H*-indene-3a-carbonitrile (21): Colorless oil; 62 mg, 42% yield; ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.0 Hz, 2H), 6.78 (t, J = 2.8 Hz, 1H), 3.88 (s, 3H), 3.21 (quint, J = 6.4 Hz, 1H), 3.00 (ddd, J = 18.4, 7.2, 2.8 Hz, 1H), 2.71–2.64 (m, 1H), 2.47–2.40 (m, 2H), 2.05–1.81 (m, 3H), 1.64–1.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 188.7, 163.5, 147.2, 139.9, 131.5, 129.8, 117.9, 113.8, 60.3, 55.5, 50.4, 38.5, 38.4, 27.3, 24.0; IR (neat): 2960, 2239, 1727, 1599, 1261, 1026 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{18}NO_3$: 296.1287 $[M+H]^+$; found: 296.1281.

3-(4-Fluorobenzoyl)-4-oxo-3a,4,5,6,7,7a-hexahydro-1*H*-indene-3a-carbonitrile (22): Colorless oil; 57 mg, 40% yield; ^1H NMR (400 MHz, $CDCl_3$): δ 7.78 (dd, J = 8.8, 5.6 Hz, 2H), 7.12 (t, J = 8.8 Hz, 2H), 6.79 (t, J = 2.8 Hz, 1H), 3.26 (quint, J = 6.0 Hz, 1H), 2.96 (ddd, J = 18.4, 7.2, 2.8 Hz, 1H), 2.80–2.73 (m, 1H), 2.48–2.39 (m, 2H), 2.15–2.07 (m, 1H), 2.00–1.93 (m, 2H), 1.67–1.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 188.7, 165.5 (d, $^1J_{C\text{-}F}$ = 253.1 Hz), 148.8, 139.7, 133.4 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 131.6 (d, $^3J_{C\text{-}F}$ = 9.2 Hz), 117.8, 115.6 (d, $^2J_{C\text{-}F}$ = 22.2 Hz), 59.6, 50.4, 38.2 (2C), 26.8, 23.9; IR (neat): 2945, 2239, 1726, 1648, 1598, 1230 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{17}H_{14}FNO_2$: 283.1009 $[M]^+$; found: 283.1012.

3-(4-Methylbenzoyl)-4-oxo-3a,4,5,6,7,7a-hexahydro-1*H*-indene-3a-carbonitrile (23): Colorless oil; 56 mg, 40% yield; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H); 6.85 (t, J = 2.4 Hz, 1H), 3.28–3.22 (m, 1H), 3.02 (ddd, J = 18.4, 6.8, 2.4 Hz, 1H), 2.78–2.70 (m, 1H), 2.52–2.43 (m, 2H), 2.42 (s, 3H), 2.13–2.03 (m, 1H), 2.02–1.90 (m, 2H), 1.69–1.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 189.8, 148.4, 143.7, 140.0, 134.5, 129.2, 129.1, 117.9, 59.9, 50.4, 38.5, 38.3, 27.2, 24.0, 21.6 ; IR (neat): 2949, 2238, 1725, 1643 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{18}H_{17}NO_2$: 279.1259 $[M]^+$; found: 279.1261.

4-Benzoyl-3-oxo-1,2,3,3a,6,6a-hexahydropentalene-3a-carbonitrile (24): Colorless oil; 48 mg, 38% yield; ^1H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.2 Hz, 2H), 6.74 (t, J = 2.4 Hz, 1H), 3.51–3.45 (m, 1H), 3.21 (ddd, J = 19.6, 8.0, 2.4 Hz, 1H), 2.68 (dt, J = 19.6, 2.4 Hz, 1H), 2.62–2.48 (m, 2H), 2.46–2.37 (m, 1H), 1.85–1.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.1, 189.6, 148.8, 137.3, 137.1, 132.9, 128.9, 128.4, 117.4, 58.6, 46.3, 40.1, 36.3, 26.7; IR (neat): 2958, 2239, 1750, 1652 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{16}H_{13}NO_2$: 251.0946 $[M]^+$; found: 251.0948.

4-(4-Methoxybenzoyl)-3-oxo-1,2,3,3a,6,6a-hexahydropentalene-3a-carbonitrile (25): Colorless oil; 49 mg, 35% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 7.2 Hz, 2H), 6.93 (d, J = 7.2 Hz, 2H), 6.65 (t, J = 2.4 Hz, 1H), 3.86 (s, 3H), 3.48–3.43 (m, 1H), 3.20 (ddd, J = 19.2, 7.6, 2.4 Hz, 1H), 2.66 (dt, J = 19.2, 2.4 Hz, 1H), 2.64–2.36 (m, 3H), 1.83–1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.3, 188.2, 163.6, 146.3, 137.3, 131.5, 129.7, 117.4, 113.7, 59.1, 53.5, 46.3, 40.0, 36.4, 26.8; IR (neat): 2920, 2241, 1753, 1641 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{17}H_{16}NO_3$: 282.1152 $[M+H]^+$; found: 282.1125.

2-Benzoyl-1-(cyclohexanecarbonyl)cyclopent-2-enecarbonitrile (26): Colorless oil; 62 mg, 40% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 6.89 (t, J = 2.4 Hz, 1H), 3.36 (tt, J = 11.2, 3.2 Hz, 1H), 2.95–2.80 (m, 2H), 2.63–2.56 (m, 1H), 2.40–2.32 (m, 1H), 2.10–1.69 (m, 4H), 1.52–1.17 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 190.1, 150.1, 143.2, 137.0, 132.7, 128.8, 128.4, 120.1, 57.6, 48.7, 36.1, 33.5, 29.1, 28.7, 27.9, 25.6, 25.6, 24.9; IR (neat): 2933, 2856, 2237, 1719, 1643, 1449 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{20}H_{21}NO_2$: 307.1572 $[M]^+$; found: 307.1585.

Methyl 4-(5-cyano-5-(cyclohexanecarbonyl)cyclopent-1-enecarbonyl)benzoate (27): White solid; 66 mg, 36% yield; m.p. 124–126 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H), 6.86 (t, J = 2.8 Hz, 1H), 3.93 (s, 3H), 3.35 (tt, J = 11.2, 3.2 Hz, 1H), 2.95–2.82 (m, 2H), 2.65–2.59 (m, 1H), 2.41–2.34 (m, 1H), 2.10–2.04 (m, 2H), 1.84–1.70 (m, 3H), 1.49–1.20 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.3, 189.5, 166.0, 151.0, 143.1, 140.6, 133.5, 129.6, 128.7, 119.9, 57.5, 52.4, 48.7, 36.1, 33.6, 29.2, 27.9, 25.6, 25.6, 24.9; IR (CH_2Cl_2 cast): 2935, 2856, 2237, 1723, 1646, 1283, 1108 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{22}H_{23}NO_4$: 365.1627 $[M]^+$; found: 365.1643.

1-(Cyclohexanecarbonyl)-2-(4-methoxybenzoyl)cyclopent-2-enecarbonitrile (28): White solid; 47 mg, 28% yield; m.p. 118–120 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 9.2 Hz, 2H), 6.91 (d, J = 9.2 Hz, 2H), 6.81 (t, J = 2.4 Hz, 1H), 3.85 (s, 3H), 3.35 (tt, J = 10.8, 3.2 Hz, 1H), 2.89–2.84 (m, 2H), 2.61–2.54 (m, 1H), 2.39–2.32 (m, 1H), 2.11–2.02 (m, 2H), 1.83–1.69 (m, 4H), 1.49–1.19 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.6, 188.6, 163.4, 148.5, 143.3, 131.3, 129.7, 120.3, 113.7, 57.9, 55.5, 48.8, 36.1, 33.5, 29.2, 27.9, 25.7, 25.6, 24.9; IR (CH_2Cl_2 cast): 2934, 2855, 2237, 1720, 1634, 1600, 1259, 1028 cm^{-1}; HRMS (ESI): *m/z* calcd. for $C_{21}H_{24}NO_3$: 338.1756 $[M+H]^+$; found: 338.1746.

3-Oxo-4-((triethylsilyl)carbonyl)-1,2,3,3a,6,6a-hexahydropentalene-3a-carbonitrile (38): Yellow oil; 90 mg, 62% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 (t, J = 2.8 Hz, 1H), 3.40–3.34 (m, 1H), 3.19 (ddd, J = 19.6, 8.4, 2.8 Hz, 1H), 2.59 (dt, J = 19.6, 2.8 Hz, 1H), 2.43–2.39 (m, 2H), 2.36–2.26 (m, 1H), 1.77–1.69 (m, 1H), 0.93 (t, J = 8.0 Hz, 9H), 0.77 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 230.1, 203.7, 148.1, 144.7, 117.3, 57.3, 45.8, 40.5, 35.7, 26.4, 7.2 (3C), 3.1 (3C); IR (neat): 2919, 2238, 1754, 1590, 1460, 737 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{16}H_{23}NO_2Si$: 289.1498 $[M]^+$; found: 289.1494.

4-Oxo-3-((triethylsilyl)carbonyl)-1,4,5,6,7,7a-hexahydroindene-3a-carbonitrile (39): Yellow solid; 111 mg, 73% yield; m.p. 59–60 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (t, J = 2.8 Hz, 1H), 3.13–3.06 (m, 1H), 2.96 (ddd, J = 18.8, 6.8, 2.8 Hz, 1H), 2.68–2.62 (m, 1H), 2.43 (ddd, J = 18.4, 4.8, 2.8 Hz, 1H), 2.23–2.16 (m, 1H), 2.06–2.00 (m, 1H), 1.92–1.85 (m, 2H), 1.56–1.50 (m, 1H), 0.96 (t, J = 8.0 Hz, 9H), 0.80 (q, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 230.3, 201.0, 148.0, 147.5, 117.8, 58.4, 49.9, 38.8, 38.1, 27.1, 24.3, 7.2 (3C), 3.1 (3C); IR (CH_2Cl_2 cast): 2955, 2875, 2235, 1733, 1576, 1457, 1239, 850 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{17}H_{25}NO_2Si$: 303.1655 $[M]^+$; found: 303.1644.

4-((*tert*-Butyldimethylsilyl)carbonyl)-3-oxo-1,2,3,3a,6,6a-hexahydropentalene-3a-carbonitrile (40): Yellow solid; 100 mg, 69% yield; m.p. 85–86 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (t, J = 2.8 Hz, 1H), 3.41–3.35 (m, 1H), 3.21 (ddd, J = 19.6, 8.4, 2.8 Hz, 1H), 2.62 (dt, J = 19.6, 2.8 Hz, 1H), 2.45–2.41 (m, 2H), 2.37–2.30 (m, 1H), 1.78–1.70 (m, 1H), 0.90 (s, 9H), 0.27 (s, 3H), 0.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 229.4, 203.6, 148.4, 145.1, 117.3, 57.4, 45.8, 40.5, 35.8, 26.5 (3C), 26.4, 16.8, –5.4, –5.7; IR (CH_2Cl_2 cast): 2954, 2858, 2242, 2174, 1759, 1589, 1251, 839 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{24}NO_2Si$: 290.1576 $[M+H]^+$; found: 290.1568.

3-((*tert*-Butyldimethylsilyl)carbonyl)-4-oxo-3a,4,5,6,7,7a-hexahydro-1*H*-indene-3a-carbonitrile (41): Yellow solid; 114 mg, 75% yield; m.p. 93–94 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (t, J = 2.8 Hz, 1H), 3.12–3.06 (m, 1H), 2.95 (ddd, J = 18.8, 6.8, 2.8 Hz, 1H), 2.67 (dt, J = 13.2, 6.4 Hz, 1H), 2.43 (ddd, J = 18.8, 5.2, 2.8 Hz, 1H), 2.24–2.17 (m, 1H), 2.07–2.00 (m, 1H), 1.93–1.87 (m, 2H), 1.57–1.48 (m, 1H), 0.93 (s, 9H), 0.29 (s, 3H), 0.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 229.6, 201.0, 148.6, 147.9, 117.9, 58.5, 49.9, 38.8, 38.1, 27.0, 26.4 (3C), 24.3, 16.7, –5.4, –5.7; IR (CH_2Cl_2 cast): 2931, 2239, 1728, 1583, 1251, 840 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{17}H_{25}NO_2Si$: 303.1655 $[M]^+$; found: 303.1643.

1-(Cyclohexanecarbonyl)-2-((trimethylsilyl)carbonyl)cyclopent-2-enecarbonitrile (42): Yellow oil; 67 mg, 44% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (t, J = 2.8 Hz, 1H), 3.34 (t, J = 10.8, 3.2 Hz, 1H), 2.94–2.81 (m, 2H), 2.52–2.45 (m, 1H), 2.30–2.22 (m, 1H), 2.19–1.97 (m, 2H), 1.83–1.73 (m, 4H), 1.54–1.36 (m, 4H), 0.28 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 229.7, 206.5, 150.0, 148.5, 120.3, 56.1, 48.70, 35.6, 33.7, 29.7, 29.3, 27.8, 25.7, 24.9, -2.05 (3C); IR (neat): 2935, 2235, 1719, 1585, 1250, 846 cm^{-1}; HRMS (EI): *m/z* calcd. for $C_{17}H_{25}NO_2Si$: 303.1655 $[M]^+$; found: 303.1650.

4-Oxo-3-propionyl-3a,4,5,6,7,7a-hexahydro-1*H*-indene-3a-carbonitrile (49): Colorless oil; 23 mg, 21% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (t, J = 2.4 Hz, 1H), 3.19 (quint., J = 6.8 Hz, 1H), 2.92 (ddd, J = 18.4, 7.2, 2.8 Hz, 1H), 2.80-2.67 (m, 3H), 2.45-2.38 (m, 1H), 2.35–2.28 (m, 1H), 2.12–2.04 (m, 1H), 2.02–1.92 (m, 2H), 1.65–1.56 (m, 1H), 1.13(t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.4, 196.1, 146.4, 141.5, 117.8, 58.5, 50.6, 38.0, 37.9, 31.8, 26.7, 24.2, 7.7; IR (neat): 2940, 2238, 1729, 1671, 1369 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{16}NO_2$: 218.1176 $[M+H]^+$; found: 218.1177.

3-Butyryl-4-oxo-3a,4,5,6,7,7a-hexahydro-1*H*-indene-3a-carbonitrile (50): Colorless oil; 30 mg, 26% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (t, J = 2.4 Hz, 1H), 3.19 (quint., J = 6.4 Hz, 1H), 2.92 (ddd, J = 18.4, 6.8, 2.4 Hz, 1H), 2.76-2.63 (m, 3H), 2.42 (ddd, J = 18.4, 5.6, 2.8 Hz, 1H), 2.35–2.28 (m, 1H), 2.12–2.01 (m, 1H), 1.98–1.92 (m, 2H), 1.73–1.56 (m, 3H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 195.7, 146.3, 141.9, 117.8, 50.6, 40.5, 38.1, 37.9, 26.7, 24.2, 17.5, 13.7; IR (neat): 2956, 2932, 2242, 1729, 1669, 1375 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{18}NO_2$: 232.1332 $[M+H]^+$; found: 232.1333.

***E*-4-Oxo-3-propylideneoctahydro-1*H*-indene-3a-carbonitrile (51):**[26b] Colorless oil; 33mg, 32% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65 (tt, J = 7.6, 20 Hz, 1H), 2.90–2.84 (m, 1H), 2.65–2.52 (m, 3H), 2.50–2.41 (m, 1H), 2.11 (quint., J =7.6 Hz, 1H), 2.03–1.94 (m, 3H), 1.93–1.84 (m, 2H), 1.69–1.55 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.4, 134.1, 133.0, 118.9, 57.3, 52.5, 38.5, 30.7, 28.7, 25.8, 24.9, 22.1, 13.4; IR (neat): 2940, 2234, 1714, 1458, 1240cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{18}NO$: 204.1383 $[M+H]^+$; found: 204.1384.

***E*-3-Butylidene-4-oxooctahydro-1*H*-indene-3a-carbonitrile (52):**[26b] Colorless oil; yield: 30 mg, 28%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.69 (tt, J = 7.6, 2.0 Hz, 1H), 2.90–2.84 (m, 1H), 2.65–2.49 (m, 3H), 2.48–2.41 (m, 1H), 2.11–1.84 (m, 6H), 1.68–1.55 (m, 2H), 1.43–1.35 (m, 2H),

0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.5, 134.7, 131.6, 118.9, 57.5, 52.6, 38.5, 30.8, 30.6, 28.8, 26.0, 25.0, 22.3, 13.7; IR (neat): 2960, 2932, 2234, 1716, 1453, 1235 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{20}NO$: 218.1539 $[M+H]^+$; found: 218.1540.

Synthesis of the authentic sample I .

2-(cyclohexanecarbonyl)-6-hydroxyhexanenitrile (H): To a stirred solution of 3-cyclohexyl-3-oxopropanenitrile (1.51 g, 10 mmol) and 4-((tetrahydro-2H-pyran-2-yl)oxy)butanal (1.72 g, 10 mmol) in EtOH (50 mL) was added L-proline (230 mg, 2 mmol) and Hantzsch ester (2.54 g, 10 mmol) sequentially in one portion. The resulting mixture was stirred at 25 ^{o}C for 16 h. The reaction solution was concentrated under reduced pressure followed by rapid chromatography on silical gel (CH_2Cl_2) to afford the crude product. To a stirred solution of the crude product in methanol (50 mL) was added *p*-TsOH (380 mg, 2 mmol) in one portion. The resulting mixture was stirred at 25 ^{o}C for 10 h. The reaction solution was concentrated under reduced pressure to give the crude residue, which was purified by chromatography on silica gel using EtOAc/n-Hexane = 1/3 to 1/1 as eluant to afford compound **H** (1.78 g, 80% yield over 2 steps) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68 (t, J = 6.0 Hz, 2H), 3.52 (dd, J = 8.0, 6.0 Hz, 1H), 2.75 (tt, J = 10.8, 3.2 Hz, 1H), 1.95–1.15 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.8, 117.3, 61.4, 48.8, 41.9, 31.4, 28.1, 28.0, 25.2, 24.9, 23.1; IR (neat): 3422, 2934, 2858, 2243, 2198, 1719, 1450 cm^{-1}; LRMS (ESI): m/z = 224 $[M+H]^+$, 246 $[M+Na]^+$, 469 $[2M+Na]^+$; HRMS (ESI): *m/z* calcd for $C_{13}H_{22}NO_2$: 224.1645 $[M+H]^+$; found: 224.1651.

1-(cyclohexanecarbonyl)-2-oxocyclopentanecarbonitrile (I): To a stirred solution of 2-(cyclohexanecarbonyl)-6-hydroxyhexanenitrile **H** (447 mg, 2 mmol)in dry CH_2Cl_2 (20 mL) were added celite (2 g) and PCC (1.08 g, 5 mmol) sequentially in one portion at 0 ^{o}C. The resulting mixture was stirred at 25 ^{o}C for 3 h. The reaction mixture was filtrated with a pad of silica gel and then the filtrate was concentrated under reduced pressure to give the crude β-hydroxy ketone. To the solution of the β-hydroxy ketone in dry CH_2Cl_2 (20 mL) was added DMP (848 mg, 2 mmol) in one portion at 0 ^{o}C. The resulting mixture was stirred at 25 ^{o}C for 1 h. The reaction mixture was quenched with 10% $Na_2S_2O_{3(aq)}$ solution (10 mL) at 0 ^{o}C for 30 min. The organic layer was washed with saturated $NaHCO_{3(aq)}$ solution and brine, dried over $MgSO_{4(s)}$, filtered and concentrated to give the crude residue, which was purified by chromatography on silica gel using EtOAc/n-hexane (3/20) as eluant to afford 2-cyano-1,3-diketone **I** (171 mg, 39% yield over 2 steps) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.15 (tt, J = 10.8, 3.6 Hz, 1H), 2.74

(quint, J = 6.8 Hz, 1H), 2.47 (t, J = 7.6 Hz, 2H), 2.43 (quint, J = 6.8 Hz, 1H); 2.19–2.06 (m, 2H), 2.04–1.96 (m, 1H), 1.87–1.69 (m, 4H), 1.45–1.16 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.1, 201.3, 116.5, 60.3, 48.9, 36.9, 32.9, 29.2, 28.1, 25.2, 25.0, 24.8, 19.6; IR (neat): 2934, 2857, 2239, 1761, 1715, 1450 cm^{-1}; LRMS (ESI): m/z = 220 $[M+H]^+$, 242 $[M+Na]^+$.

5-cyano-6-cyclohexyl-6-oxohexanoic acid (J): 2-cyano-1,3-diketone **I** (22 mg, 0.1 mmol) was hydrolysed to acid **J** upon exposure to air in $CDCl_3$ over 48 h at roon temperature. The solution was concentrated to give the crude residue which was purified by chromatography on silica gel using EtOAc as eluant to afford acid **J** (18 mg, 75% yield) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.54 (dd, J = 8.0, 6.0 Hz, 1H), 2.49 (tt, J = 10.8, 3.2 Hz, 1H), 2.44 (t, J = 6.8 Hz, 2H) 2.15–1.69 (m, 8H), 1.49–1.16 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.3, 178.6, 117.2, 49.2, 41.8, 33.0, 28.5, 28.3, 27.8, 25.4, 25.3, 25.1, 21.9; LRMS (ESI): m/z = 260 $[M+Na]^+$; HRMS (ESI): *m/z* calcd for $C_{13}H_{18}NO_3$: 236.1292 $[M-H]^-$; found: 236.1284.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds including compounds **I** and **J**, X-ray crystallographic analysis of products **20**, **27**, **28**, **39**-**41**, **45** and **46**, geometries of vinyl radicals **I**, **II**, **III** and compounds **35**, **53** and **54** along with Cartesian atom coordinates, absolute energies, and BDE are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) Crystallographic data for **20** (CCDC 971512): $C_{18}H_{14}N_2O_2$, M_w = 290.31, triclinic, a = 7.729(15) Å, b = 7.756(14) Å, c = 12.50(3) Å, V = 730(2) Å^3, space group P -1, Z = 2, a total of 4725 reflections were collected in the range 1.67 to 25.03^o. Of these, 2465 were independent; for the observed data, wR2 = 0.2474, R1 = 0.1106.

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(14) Crystallographic data for **27** (CCDC 962910): $C_{22}H_{23}NO_4$, M_w = 365.41, triclinic, a = 19.901(11) Å, b = 9.308(5) Å, c = 10.561(6) Å, V = 1907.7(19) Å^3, space group P 21/c, Z = 4, a total of 9435 reflections were collected in the range 2.43 to 25.14^o. Of these, 3383 were independent; for the observed data, wR2 = 0.2170, R1 = 0.0972.

(15) Crystallographic data for **28** (CCDC 968701): $C_{21}H_{23}NO_3$, M_w = 337.40, triclinic, a = 7.7230(3) Å, b = 21.7910(10) Å, c = 10.8617(4) Å, V = 1809.62(13) Å^3, space group P 21/n, Z = 4, a total of 12081 reflections were collected in the range 2.82 to 25.03^o. Of these, 3183 were independent; for the observed data, wR2 = 0.0952, R1 = 0.0381.

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(20) Crystallographic data for **39** (CCDC 883936): $C_{17}H_{25}NO_2Si$, M_w = 303.47, triclinic, a = 17.6278(10) Å, b = 8.0278(5) Å, c = 12.3398(7) Å, V = 1693.79(17) Å^3, space group P 21/c, Z = 4, a total of 11381 reflections were collected in the range 2.80 to 25.24^o. Of these, 3008 were independent; for the observed data, wR2 = 0.1027, R1 = 0.0579.

(21) Crystallographic data for **40** (CCDC 971513): $C_{16}H_{23}NO_2Si$, M_w = 289.44, triclinic, a = 7.1377(10) Å, b = 12.3260(18) Å, c = 18.630(3) Å, V = 1634.6(4) Å^3, space group P 21/n, Z = 4, a total of 8759 reflections were collected in the range 1.98 to 25.15^o. Of these, 2915 were independent; for the observed data, wR2 = 0.1830, R1 = 0.0815.

(22) Crystallographic data for **41** (CCDC 966268): $C_{17}H_{25}NO_2Si$, M_w = 303.47, triclinic, a = 19.146(14) Å, b = 7.452(6) Å, c = 12.716(9) Å, V = 1755(2) Å^3, space group C c, Z = 4, a total of 4110 reflections were collected in the range 2.95 to 25.02^o. Of these, 2443 were independent; for the observed data, wR2 = 0.0922, R1 = 0.0564.

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(25) Crystallographic data for **46** (CCDC 886563): $C_{20}H_{23}NO_2Si$, M_w = 337.48, triclinic, a = 26.426(12) Å, b = 26.426(12) Å, c = 7.039(4) Å, V = 7.039(4) Å^3, space group R 3, Z = 9, a total of 8174 reflections were collected in the range 1.54 to 25.00^o. Of these, 2311 were independent; for the observed data, wR2 = 0.0799, R1 = 0.0744.

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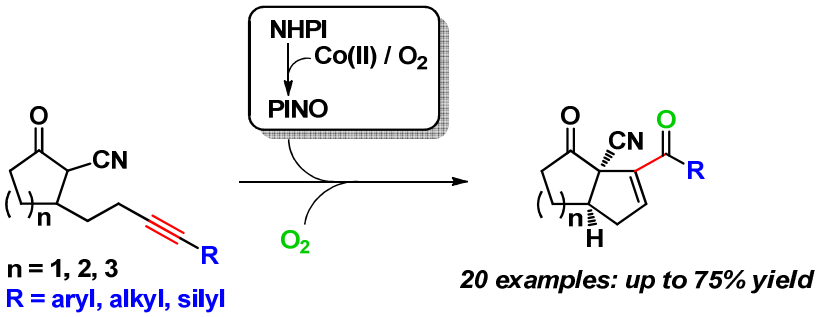
Graphic


NHPI
Co(II) / O2
PINO
O
CN
n
R
O2
O
CN
O
R
n
H
n = 1, 2, 3
R = aryl, alkyl, silyl
20 examples: up to 75% yield