C–C Bond-Forming Reactions

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C–C Bond-Forming Strategy by Manganese-Catalyzed Oxidative Ring-Opening Cyanation and Ethynylation of Cyclobutanol Derivatives

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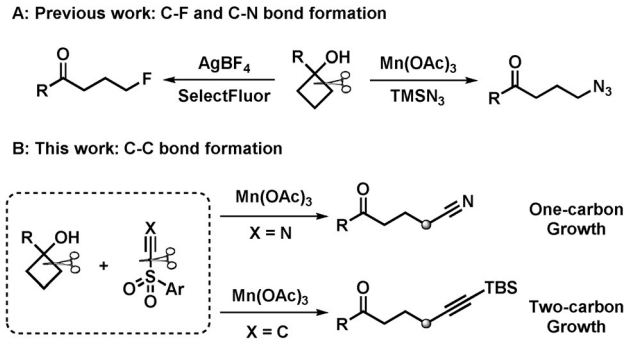
Abstract: *A novel C–C bond-forming strategy employing manganese-catalyzed ring-opening of cyclobutanol substrates, followed by cyanation or ethynylation, is described. A cyano C1 unit and ethynyl C2 unit are regiospecifically introduced to the γ-position of ketones at room temperature, providing a mild yet powerful method for production of elusive aliphatic nitriles and alkynes. All transformations described are based on a common sequence: 1) oxidative ring-opening of cyclobutanol substrates by C–C bond cleavage; 2) radical addition to triple bonds bearing an arylsulfonyl group; and 3) radical-mediated C–S bond cleavage.*

Tertiary cycloalkanols have proven to be privileged precursors for regiospecific synthesis of distally functionalized ketones by cleavage of the strained cyclic C–C bonds.[1] Compared to cyclopropanol, ring-opening of cyclobutanol is more challenging owing to a lower strain energy and an appreciable Thorpe–Ingold effect, which thus stabilizes cyclobutanol.[2] Methods for cleavage of the C–C bond of cyclobutanol include: a) transition-metal-catalyzed β-carbon elimination (for example, palladium or rhodium),[3] and b) single electron oxidation-triggered "radical clock" ring-opening;[4] the later pathway has been investigated to a lesser extent by comparison. Prompted by seminal work concerning the radical-mediated ring-opening of cyclobutanol, which employs stoichiometric amounts of oxidative metal reagents (for example, $Pb(OAc)_4$ and ceric ammonium nitrate),[5,6] we recently disclosed the first silver-catalyzed ring-opening fluorination of cyclobutanol-type molecules to generate γ-fluorinated ketones (Scheme 1 A, left).[7] However, it later transpired that silver-catalyzed ring-opening of cyclobutanol had limited applications. Studies revealed that silver catalyzed transformations favored intramolecular cyclization of the alkyl radical intermediate (the open-chain tautomer of cyclobutoxyl radical) rather than capture by extrinsic radical acceptors.[8] Consequently, a modified procedure was developed by which intramolecular cyclization was efficiently suppressed. The new method involved manganese-catalyzed ring-opening of cyclobutanol adducts to produce γ-azido ketones (Scheme 1 A, right).[9] To further demonstrate the utility and generality of the manganese-catalyzed method, herein we report a novel C–C bond-forming strategy by manganese-catalyzed oxidative ring-opening cyanation and ethynylation of cyclobutanol. At room temperature, the cyano and ethynyl groups are regioselectively introduced to the γ-position of ketones as a C1 and C2 unit, respectively, providing a mild but powerful method for production of diverse ketone derivatives, which are sometimes difficult to prepare. All of these transformations are based on a common sequence: a) oxidative ring-opening of cyclobutanol molecules by C–C bond cleavage; b) radical addition to triple bonds bearing an arylsulfonyl group; and c) radical-mediated C–S bond cleavage (Scheme 1 B).



Scheme 1. Manganese-catalyzed ring-opening functionalization of cyclobutanol substrates. TBS = *tert*-butyldimethylsilyl.

The versatile cyano functional group is used extensively for preparation of amines, amides, aldehydes, and carboxylic acids.[10] Owing to its robust transformable properties, nitrile synthesis is of great significance in both academia and industry.[11] With this in mind, we commenced our investigations into manganese-catalyzed ring-opening cyanation of cyclobutanol-type molecules using tosyl cyanide.[12] After considerable efforts, the reaction parameters were defined (Table 1; for details see the Supporting Information). We found that 1) manganese acetate was superior to other common manganese catalysts; 2) use of *N*,*N*-bidentate ligand 2,2′-bipyridine (bipy) significantly improved product yields; 3) hypervalent iodine oxidant was crucial to the reaction outcome; and 4) TMSCN used in lieu of TsCN did not enable the cyanation reaction.

With the optimized reaction conditions in hand, we set out to evaluate the substrate scope of the cyanation reaction (Scheme 2). Both electron-rich and deficient substrates

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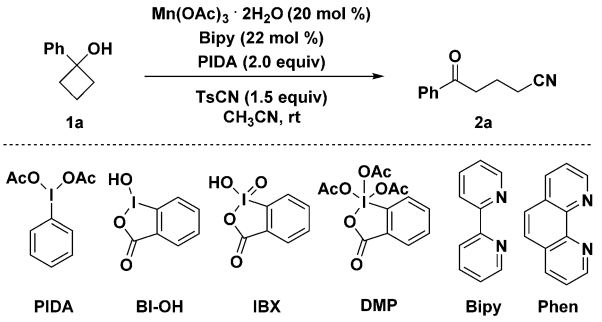
Table 1: Effect of ligand and oxidant.

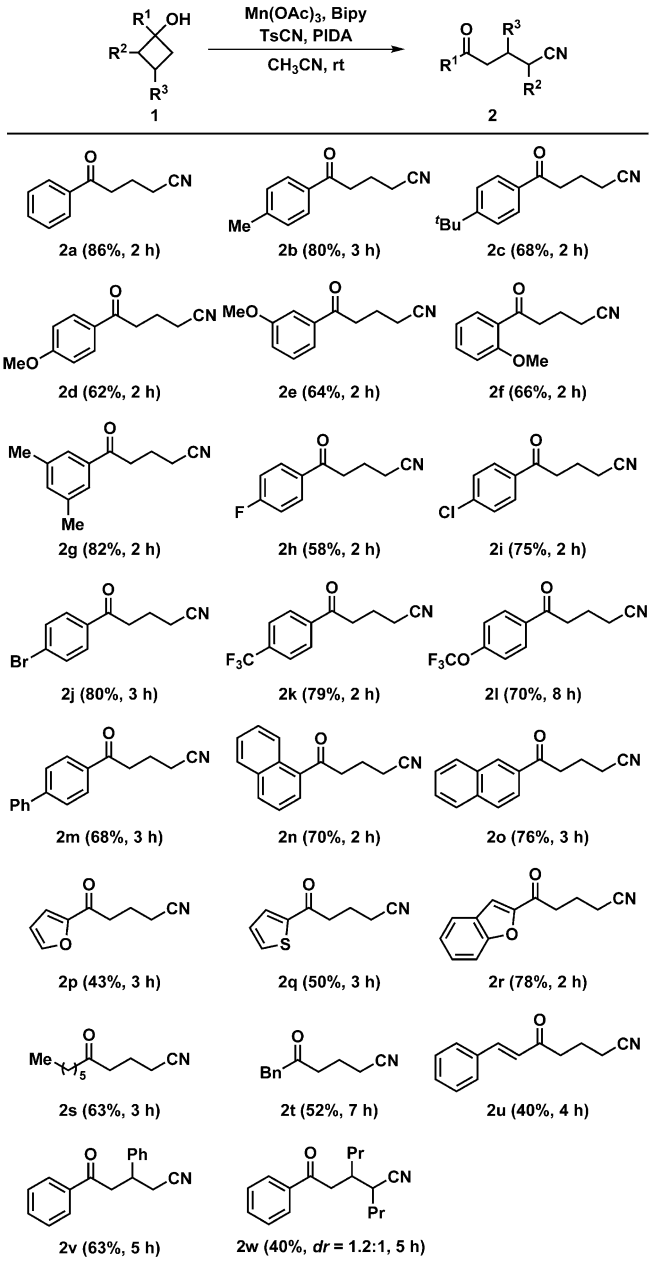


Entry	Variation of reaction conditions	Yield [%][a]
1	none	86
2	no bipy	30
3	Phen instead of bipy	66
4	Py instead of bipy	<10
5	BI-OH instead of PIDA	56
6	IBX instead of PIDA	49
7	DMP instead of PIDA	68
8	TMSCN instead of TsCN	0

[a] Yields of isolated products.

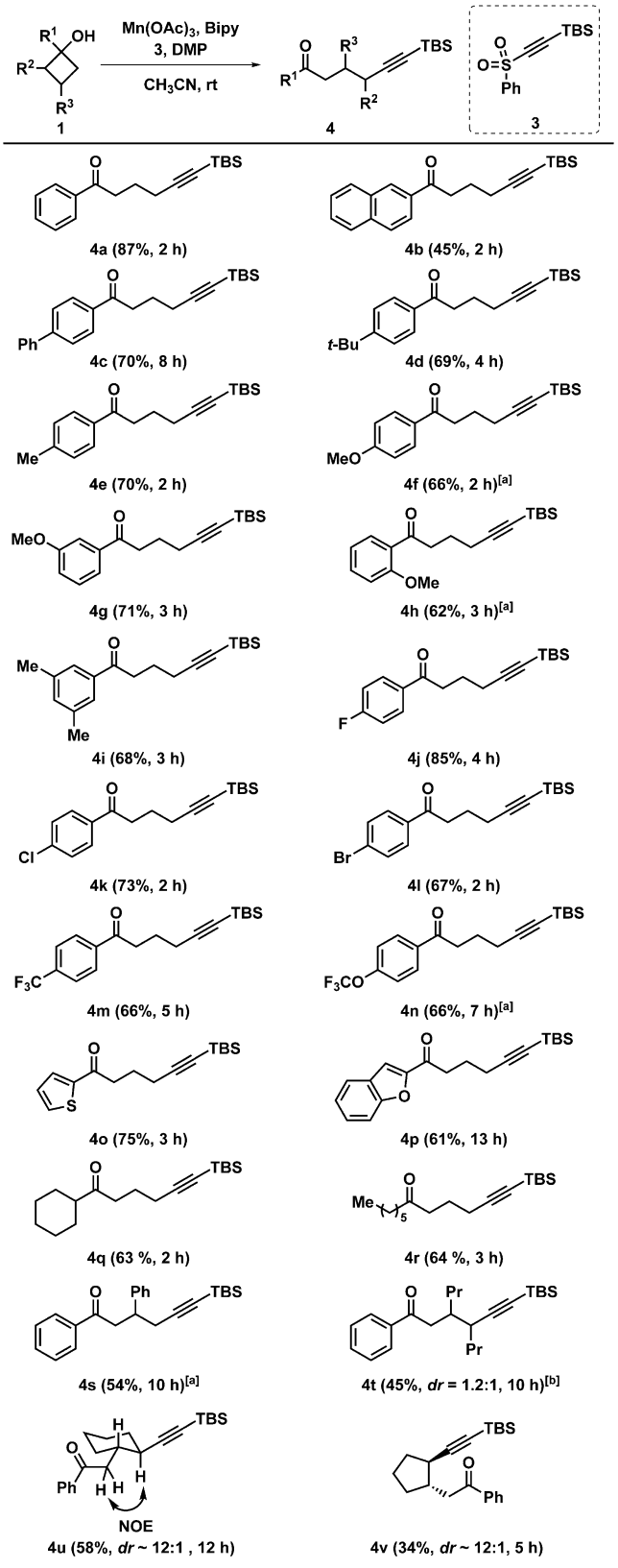
afforded the γ-cyanated ketones in synthetically useful yields. It seemed that steric hindrance had little impact on the reaction, as all *ortho*-, *meta*-, and *para*-substituted substrates led to similar yields (**2d**–**2f**). The presence of halide, such as chloride or bromide, was valuable in the product (**2i** and **2j**) because it provided a platform for further product manipulation during cross-coupling reactions. Besides phenyl adducts, cyanation of polyaryl cyclobutanol molecules also delivered good yields (**2n**–**2o**). Heteroaryl and alkyl cyclobutanol substrates were also suitable substrates for production of the corresponding γ-cyanated ketones (**2p**–**2s**). The transformation of susceptible alkenyl cyclobutanol was noteworthy, though the material yielded a reasonably low product yield (**2u**). Moreover, cyanation of less reactive substrates bearing multiple substituents on the cyclobutyl ring still proceeded smoothly to give the desired cyanation products (**2v** and **2w**).

Encouraged by the cyanation reaction, we then investigated the ring-opening ethynylation of cyclobutanol substrates.[13] Although alkynylation reactions are achievable with costly palladium catalyst and perishable alkynylating reagents, alkynyl bromides or alkynyl hypervalent iodine for example,[14] a general method that uses inexpensive catalyst and routine reagents is still desired. Under the previously described reaction conditions, but employing TBS-protected phenylsulfonyl ethyne **3** as the alkynylating agent, cyclobutanol was readily converted into the γ-ethynylated ketone **4** (Scheme 3). Variation of oxidant from PIDA to DMP improved the yields of alkynylation reactions attempted, but in some cases PIDA produced better conversions (**4f**, **4h**, **4n**, and **4s**). Both electron-rich and deficient aryl substituted cyclobutanol adducts were tolerated during reaction, demonstrating the broad functional group compatibility of the method. While a variety of phenyl substituted substrates resulted in good product yields, the reaction of naphthyl



Scheme 2. Ring-opening cyanation of *tert*-cyclobutanol substrates. Reaction conditions: **1** (0.20 mmol), TsCN (0.30 mmol, 1.5 equiv), $Mn(OAc)_3 \cdot 2H_2O$ (0.04 mmol, 0.2 equiv), bipy (0.044 mmol, 0.22 equiv), and PIDA (0.40 mmol, 2.0 equiv) in CH_3CN (1.5 mL) at RT. Yields of isolated products are given.

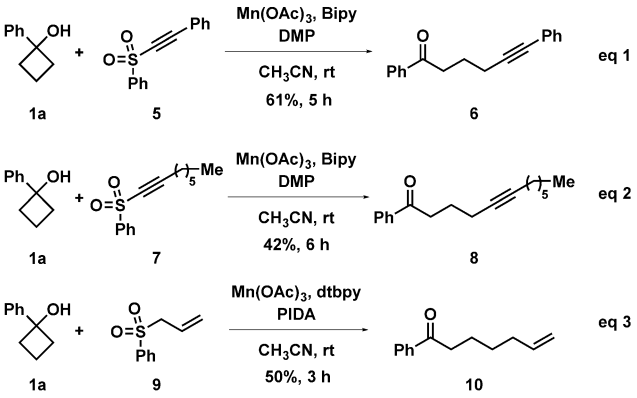
cyclobutanol gave a surprisingly low yield (**4b**). In contrast, yield did not drop significantly when a strong electron-withdrawing group, such as CF_3, was present in the substrate (**4m**). Heteroaryl and alkyl cyclobutanol substrates reacted readily to afford the corresponding alkynes in synthetically useful yields (**4o**–**4r**). Highly functionalized cyclobutanol substrates were also suitable (**4s** and **4t**), though less reactive. Notably, alkynylation of bicyclic tertiary alcohols predominantly furnished the thermodynamically favored *anti*-isomers, as determined by NOE experiments, which was supposed to be controlled by the steric congestion apparent at the reaction site (**4u** and **4v**). In this way, reaction of 1-



Scheme 3. Ring-opening ethynylation of *tert*-cyclobutanol substrates. Reaction conditions: **1** (0.20 mmol), **3** (0.30 mmol, 1.5 equiv), $Mn(OAc)_3 \cdot 2H_2O$ (0.04 mmol, 0.2 equiv), bipy (0.044 mmol, 0.22 equiv), and DMP (0.40 mmol, 2.0 equiv) in CH_3CN (1.5 mL) at RT. Yields of isolated products are given. [a] PIDA (2.0 equiv) was used instead of DMP. [b] $Mn(OAc)_3 \cdot H_2O$ (1.5 equiv) was used instead of the combination of $Mn(OAc)_3 \cdot H_2O$, bipy, and DMP.

phenylcyclopropanol also led to the corresponding β-alkynylated ketone in 65% isolated yield, whereas cyclopentanol substrates were incompatible with the reaction conditions. The TBS group present in the products is easily removed by fluoride reagent, delivering carbonyl-containing terminal alkynes.

The alkynylation method could be applied to preparation of internal alkynes. For example, reaction of cyclobutanol **1a** with phenylsulfonyl alkyne **5** or **7** readily generated the corresponding alkyne **6** or **8**, respectively [Scheme 4, Eq. (1) and (2)]. Remarkably, synthesis of the asymmetric dialkyl alkyne **8** is challenging and has not been accessed by previously reported procedures.[14] Moreover, preliminary results indicated that this method could be harnessed for allylation of cyclobutanol substrates, affording elusive carbonyl-containing linear alkenes by three-carbon growth [Scheme 4, Eq. (3)].



Scheme 4. Other examples of ring-opening C–C bond formation.

Based on the experimental observations, a mechanistic pathway was postulated (Figure 1). Initially, interaction between a Mn^{III} salt and hypervalent iodine generates an oxidized Mn^{V} species **a**.[15] Subsequently, **a** incorporates cyclobutanol **1** to form complex **b**, which undergoes a simultaneous single-electron transfer (SET) process to give cyclobutyloxy radical **d**. Radical **d** can tautomerize into an alkyl carbon radical **e** after ring-opening. The interaction between radical **e** and arylsulfone results in cleavage of the C–S bond, which eventually gives rise to cyanation product **2** or alkynylation product **4**.

In summary, we described a novel and general C–C bond-forming strategy by the manganese-catalyzed ring-opening cyanation and ethynylation of cyclobutanol-type substrates. A variety of γ-cyanated and alkynylated alkyl ketones were regioselectively synthesized at room temperature, providing mild but powerful methods for production of elusive aliphatic nitriles and alkynes. The procedure could be further applied to ring-opening allylation. Other applications are under investigation in our laboratory.

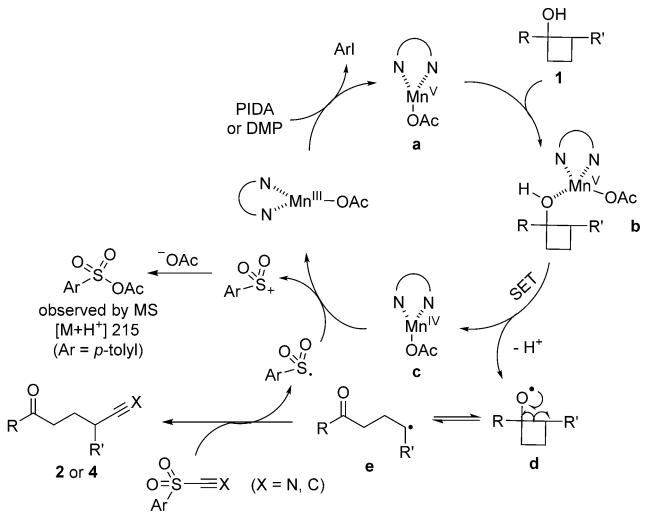


Figure 1. Plausible mechanistic pathway.

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Keywords: alkynylation · cyanation · cyclobutanol · manganese catalysis · ring-opening

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