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CAN-Mediated Highly Regio- and Stereoselective Oxidation of Vinylidenecyclopropanes: A Novel Method for the Synthesis of Unsymmetrical Divinyl Ketone and Functional Enone Derivatives

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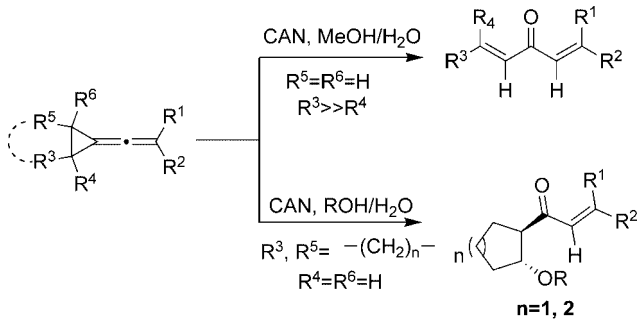

CAN-mediated oxidative rearrangement of various vinylidenecyclopropanes under mild conditions generates unsymmetrical divinyl ketone and functional enone derivatives in moderate to good yields with excellent regio- and stereoselectivities. The reaction mechanism was investigated on the basis of an oxygen-18 tracer experiment.

Vinylidenecyclopropanes (VCPs)[1] show unique reactivity in organic synthesis due to the presence of the cumulated C=C double bonds adjacent to the highly strained cyclopropyl ring, which might lead to several possible reactive positions. Therefore, controlling the regio- and stereoselective reactions of VCPs is a formidable challenge in organic synthesis.[2] Recently, much attention has been paid to the study of their reactivity, especially the control of the related selectivity and their potential synthetic utilities. Researchers have found that VCPs can be utilized as versatile starting materials to develop sequential reactions either employing metal catalysts or not, affording an efficient method for the preparation of many compounds with synthetic and biological importance.[3]

The previous investigations have shown that CAN was a useful reagent for oxidative single-electron transfer[4] processes leading to a number of novel carbon−carbon and carbon−heteroatom bond-forming reactions.[5,6] We, along with Nair, have reported several examples of CAN-mediated oxidation of methylenecyclopropanes (MCPs).[7] Recently, much attention has been paid to the radical reactions of VCPs.[8] To the best of our knowledge, reports on the metal salt mediated single-electron oxidation of VCPs are limited, probably due to the regioselectivity. Herein, we wish to report a CAN-mediated highly regio- and stereoselective oxidation of VCPs leading to unsymmetrical divinyl ketone and functional enone derivatives in moderate to good yields.

Initially, we examined the reaction of VCP (**1a**) with a solution of CAN (2.2 equiv) in methanol under an air atmosphere. After the solution was stirred for 6 h at room temperature, the unsymmetrical divinyl ketone (*E*)-**2a** was obtained in 48% yield along with the functional enone **3a** in 16% yield (entry 2, Table 1). With this result in hand, we assumed that the carbonyl oxygen might come from the oxygen in the air or the H_2O in the solvent. We then tried to confirm the origin of the carbonyl oxygen and optimize the reaction conditions. The experimental results showed that the oxygen was not necessary in this reaction; nevertheless the presence of H_2O in the solvent sharply improved the yield (entries 4−6, Table 1). We next found that the temperature effect was also important in improving the product yields. When the reaction was carried out under

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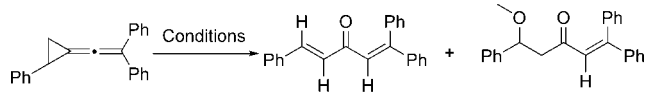
TABLE 1. Optimization of the Reaction Conditions for the Synthesis of Unsymmetrical Divinyl Ketone 2a[a]

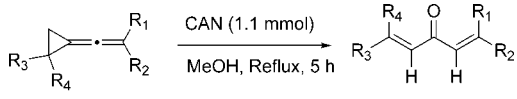


1a **2a** **3a**

entry	CAN (equiv)	solvent	*T* (°C)	time (h)	yield of **2a** (%)[b]	yield of **3a** (%)[b]
1	2.2	CH_3OH	0	6	31	26
2	2.2	CH_3OH	25	6	48	16
3	2.2	CH_3OH	50	5	66	8
4	2.2	CH_3OH/N_2[c]	50	5	67	9
5	2.2	CH_3OH[d]/N_2[c]	50	5	17	4
6	2.2	CH_3OH[d]/O_2	50	5	15	3
7	2.2	CH_3OH	reflux	1	58	12
8	**2.2**	**CH_3OH**	reflux	**5**	**72**	**trace**
9	2.2	CH_3OH[d]/H_2O(1.2 equiv)	reflux	5	69	trace
10	2.2	CH_3OH[d]/H_2O(5.5 equiv)	reflux	5	72	trace
11	2.2	CH_3OH[d]/H_2O(55.5 equiv)	reflux	5	71	trace

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.5 mmol) and commercial CAN in MeOH under an air atmosphere. [b] Isolated yield. [c] The reaction was carried out in glovebox: $O_2 \leq 10$ ppm. [d] Anhydrous CH_3OH was used: $H_2O \leq 0.05\%$, and CAN was dried over vacuo at 110 °C.

TABLE 2. Synthesis of Various Unsymmetrical Divinyl Ketones 2[a]



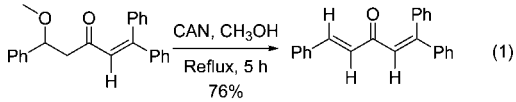
1 (0.5 mmol) **2**

entry	R^1/R^2	R^3	R^4	**1**	yield of **2** (%)[b]
1	Ph/Ph	Ph	H	**1a**	**2a**, 72
2	Ph/Ph	*p*-ClC_6H_4	H	**1b**	**2b**, 73
3	Ph/Ph	*p*-MeC_6H_4	H	**1c**	**2c**, 65
4	*p*-ClC_6H_4/*p*-ClC_6H_4	Ph	H	**1d**	**2d**, 61
5	Ph/Ph	*n*-C_4H_9	H	**1e**	**2e**, 70
6	Ph/Ph	Ph	Me	**1f**	**2f**, 51
7	Ph/Me	Ph	H	**1g**	**2g**, 53[c]

[a] Unless otherwise specified, the reaction was carried out with **1** (0.5 mmol) and commercial CAN (1.1 mmol) in MeOH. [b] Isolated yields. [c] **2g** was not very stable, and the reaction was completed in 2 h.

reflux, the yield of product **2a** was improved to 72% and **3a** was obtained in trace amount (entry 8, Table 1). Further investigations disclosed that the reaction in the presence of an excess amount of H_2O had little effect on the yield of **2a** (entries 8−11, Table 1).

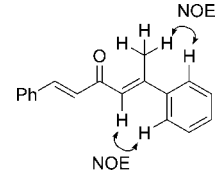
We also found that **2a** could be produced in 76% yield via elimination of one MeOH molecule when **3a** was heated for 5 h under reflux (eq 1).



3a **2a** (1)

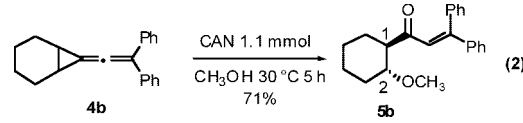
With the optimized conditions in hand, we next examined the reaction of various arylvinylidenecyclopropanes (ACPs) under identical conditions. The results are summarized in Table 2. When R^4 = H, $R^1 = R^2$ = Ar, the reaction proceeded smoothly to give the unsymmetrical divinyl ketones in good yields (entries 1−5, Table 2). A slightly lower yield was observed when R^4 = Me, $R^1 = R^2$ = Ph (entry 6, Table 2). Moreover, when the unsymmetrical VCP **1g** (*Z*:*E* = 1:1) was employed, only the thermodynamically stable product (1*E*,4*E*)-1,5-diphenylhexa-1,4-dien-3-one, **2g**, was observed in 53% yield (entry 7, Table 2). The configuration was established by the

SCHEME 1. Configuration of 2g



NOESY studies (Scheme 1). These unsymmetrical divinyl ketones are valuable building blocks for organic synthesis, which have been utilized in Diels−Alder reactions,[9] Michael reactions,[10] and conjugate addition reactions to prepare various ring systems.[11] The characteristic reaction of divinyl ketones is their acid-catalyzed Nazarov cyclization leading to cyclopentenones.[12]

Interestingly, when bicyclic VCP (**4b**) was employed, no divinyl ketone product was observed. Instead, the functional enone **5b**[13] was obtained in 53% yield. After a variety of reaction conditions were examined, we fortunately found the yield of **5b** could be improved to 71% when the reaction was carried out in MeOH at 30 °C for 5 h (eq 2).



4b **5b** (2)

Synthesis of functional enone compounds **5** with high stereoselectivity is of high chemical and biochemical importance.

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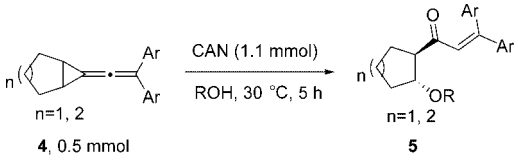
(13) The structure was confirmed by X-ray crystallographic analysis of the (2,4-dinitrophenyl)hydrazine derivative of **5b** (see the Supporting Information).

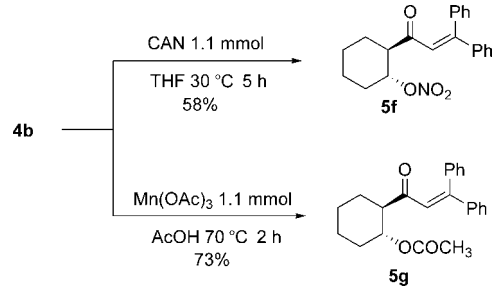
TABLE 3. Synthesis of Various Functional Enones 5 with High Stereoselectivity[a]



entry	Ar	n, 4	ROH[b]	yield of 5 (%)[c]
1	Ph	1, **4a**	MeOH	**5a**, 59
2	Ph	2, **4b**	MeOH	**5b**, 71
3	Ph	2, **4b**	EtOH	**5c**, 68
4	Ph	2, **4b**	CH_2=$CHCH_2OH$	**5d**, 55
5	*p*-ClC_6H_4	2, **4c**	MeOH	**5e**, 61
6	Ph	3, **4d**	MeOH	*d*

[a] Unless otherwise specified, the reaction was carried out with **4** (0.5 mmol) and commercial CAN (1.1 mmol) in ROH. [b] ROH in the reactions was also worked as solvent. [c] Isolated yields. [d] The reaction was complex.

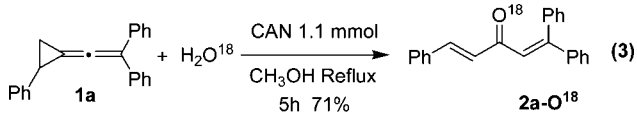
SCHEME 2. Reaction of 4b with the Nucleophiles from CAN and $Mn(OAc)_3$



In fact, these moieties are part of biologically important natural and unnatural compounds.[14] Therefore, under the optimized conditions, a series of bicyclic VCPs were employed to give the corresponding functional enone derivatives with high stereoselectivity (entries 1−5, Table 3).

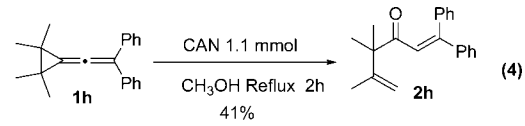
When THF was employed as solvent, treatment of **4b** with CAN afforded **5f** in 58% yield. Apparently, the NO_3 group in **5f** comes from CAN dissolving in the weakly nucleophilic solvent THF. Moreover, when $Mn(OAc)_3$ was employed instead of CAN and AcOH was chosen as the solvent, the reaction could smoothly proceed to produce the corresponding functional enone **5g** in 73% yield as a result of trapping AcO^- (Scheme 2).

To clarify the mechanism of this reaction, we carried out the reaction of **1a** with CAN in the presence of H_2O^{18}. As a result, we found that **2a**-O^{18} was formed in 71% yield with 87.5% O^{18} content in the oxygen atom of carbonyl group. This result clearly indicates that the oxygen atom of the carbonyl group in product **2** comes from the H_2O in the reaction system (eq 3).



On the basis of the above results, a plausible mechanism of the CAN-mediated oxidation reaction is shown in Scheme 3. The initial event is likely to be a single-electron oxidation of VCPs by CAN to furnish radical cation **A**.[7] The following nucleophilic attack of the solvent such as MeOH at the cyclopropane moiety may cause the rearrangement to produce the ring-opened radical intermediate **B**.[15] B can be further oxidized by a second equivalent of CAN to give cation **C**, which is quenched by water in the solvent to produce **D**. For VCPs **1**, a subsequent enol arrangement of the corresponding intermediate **D** and further elimination of MeOH may occur to furnish the product **2**. For bicyclic VCPs **4**, the key point is that the intermediate **B** is selectively attacked by the nucleophile from the less sterically hindered position to afford **C**. In this case, the trans isomer of functional enones **5** could not progress to the corresponding divinyl ketones (Scheme 3).

Moreover, when VCP (**1h**) with four methyl groups at the cyclopropane moiety was employed, the interesting product **2h** was observed in 41% yield (eq 4).



In conclusion, we have disclosed the CAN-mediated oxidative reactions of various VCPs with high regio- and stereoselectivity and developed a convenient approach to the synthesis of unsymmetrical divinyl ketone and functional enone derivatives. These novel compounds bearing unsaturated ketone skeletons would be useful in organic synthesis. On the basis of the oxygen-18 tracer experiment, we clarified that the oxygen atom of the products arises from the H_2O in the reaction system, and a plausible reaction mechanism was proposed. Hence, the reaction may be of interest from both the mechanistic and synthetic standpoints. Further studies to expand the scope and synthetic utility of the method are underway.

Experimental Section

General Procedure for Synthesis of Unsymmetrical Divinyl Ketones via a CAN-Mediated Oxidation of VCPs. To a stirred solution of VCP **1** (0.5 mmol) in MeOH (2 mL) was added a solution of CAN (1.1 mmol) in MeOH (2 mL). Then the mixture was refluxed. After being stirred for the specified time, the reaction mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$. After filtration and removal of the solvent in vacuo, the residue was purified with flash chromatography (silica/petroleum ether−ethyl acetate 15:1 to 10:1 v/v) to afford **2**. Spectral data for **2b**: yellow solid, mp 84−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.42 (m, 8H), 7.23−7.31 (m, 5H), 7.10−7.15 (m, 2H), 6.77 (s, 1H), 6.36 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.7, 127.4, 128.3, 128.4, 128.6, 128.9, 129.0, 129.1, 129.5, 130.2, 133.4, 135.8, 139.0, 140.0, 140.4, 154.0, 191.1; IR (KBr) 3026, 1645, 1589, 1489, 1331, 1195, 1089, 1030, 818, 766, 697 cm^{-1}; MS (70 eV, EI) *m*/*z* 346 (M^+ + 2), 344 (M^+); HRMS (EI) *m*/*z* calcd for $C_{23}H_{17}ClO$ (M^+) 344.0968, found 344.0969.

General Procedure for the Synthesis of Functional Enone Derivatives via a CAN-Mediated Oxidation of Bicyclic VCPs. To a stirred solution of bicyclic VCP **4** (0.5 mmol) in the appropriate solvent (2 mL) was added CAN (1.1 mmol) in the same solvent (2 mL). The reaction temperature was then increased to 30 °C. After being stirred for the specified time, the reaction mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$. After filtration and removal of

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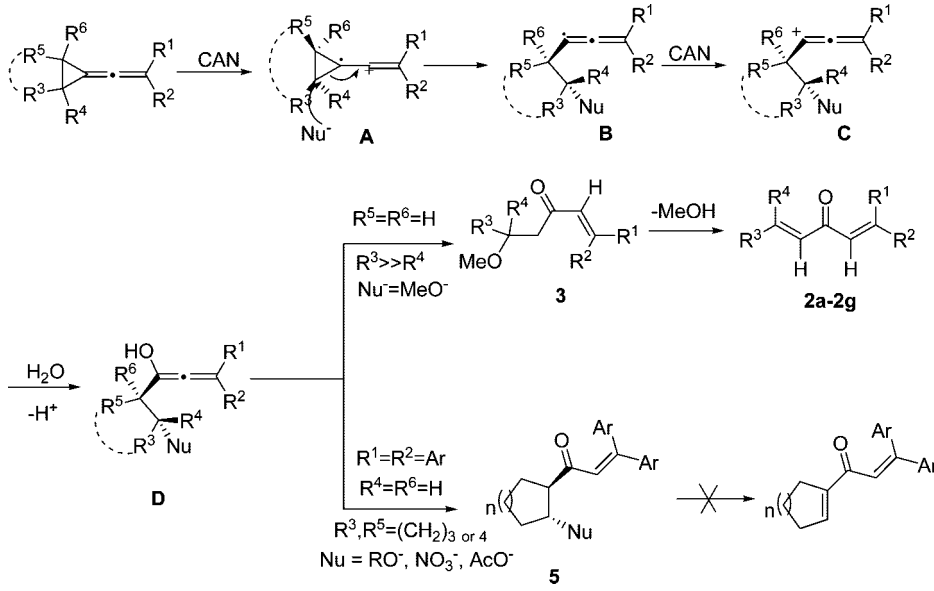
SCHEME 3. Proposed Mechanistic Pathway for the Reaction



the solvent in vacuo, the residue was purified with flash chromatography (silica/petroleum ether−ethyl acetate 15:1 to 10:1 v/v) to afford **5**. Spectral data for **5b**: yellow semisolid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.37 (m, 8H), 7.19−7.23 (m, 2H), 6.67 (s, 1H), 3.31−3.39 (m, 1H), 3.29−3.31 (s, 3H), 2.46−2.55 (m, 1H), 2.10−2.17 (m, 1H), 1.69−1.80 (m, 2H), 1.60−1.68 (m, 1H), 1.28−1.39 (m, 1H), 1.00−1.24 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 25.0, 28.6, 30.3, 56.5, 56.6, 80.8, 126.6, 128.0, 128.2, 128.3, 128.5, 129.2, 129.5, 139.1, 141.4, 153.5, 203.8; IR (KBr) 2931, 1686, 1589, 1445, 1361, 1189, 1097, 766, 696 cm^{-1}; MS (70 eV, EI) *m*/*z* 320 (M^+); HRMS (EI) *m*/*z* calcd for $C_{22}H_{24}O_2$ (M^+) 320.1776, found 320.1770.

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Supporting Information Available: General experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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