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A High-Yield Regiospecific Synthesis of Keto Oximes from Aryl-Conjugated Ethylenes and Ethyl Nitrite in the Presence of Cobalt Complex and BH_4^- Ion

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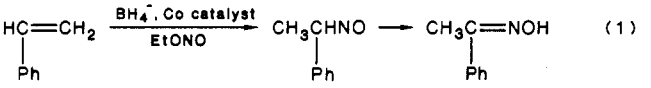
The title reaction of substituted styrenes, 1-phenyl-1,3-butadiene, and some cyclic aryl-conjugated ethylenes proceeds smoothly at room temperature, affording the corresponding oximes in moderate to nearly quantitative yields. The reaction mechanism is discussed on the basis of the formation of an alkylcobalt intermediate and its subsequent reaction with ethyl nitrite.

Alkyl nitrite is an easily available nitrogen source that has been used for the synthesis of carbon–nitrogen bonds. However, its use for this purpose has been limited to reactions under strongly acidic or basic conditions.[1] We report here a new catalytic reaction using this reagent, which proceeds smoothly under mild reaction conditions: the reaction of using alkyl nitrite with aryl-conjugated ethylenes in the presence of cobalt complex and tetrahydroborate ion. The reaction proceeds at room temperature to yield oximes of acetophenone derivatives regioselectively in moderate to quantitative yields (eq 1).



(1)

The involvement of NO^+ at the intermediate stage of the reaction is not plausible because the addition of NO^+ to substituted ethylenes proceeds according to the Markownikoff rule,[2] whereas exclusively anti-Markownikoff-type products were formed in this cobalt-catalyzed reaction. Deuterium labeling experiments and the control reactions of alkyl nitrite with independently prepared alkylcobalt complex suggested that the alkylcobalt complex is a key compound in the catalytic process.

When a catalytic amount of $Co(DH)_2Cl(py)$[3] and R_4NBH_4 were stirred in benzene under Ar atmosphere, a green suspension indicative of reduced cobalt species was obtained. The addition of ethyl nitrite and styrene to the suspension produced a brown homogenous solution. After the mixture was stirred at room temperature, the product was collected by extraction with ether and purified on a silica gel column. The results of various ring-substituted styrenes are summarized in Table I. The isolated yields of oximes were nearly quantitative except for *m*-nitrostyrene. The low yield observed with this substrate may be due to the instability of the nitro group under the reaction conditions:[4] In fact, unidentified brown precipitate separated out during the extraction process. Other functional groups such as Cl, Br, ether, and alkoxycarbonyl were intact during the reaction. The catalytic process was completely chemo- and regioselective, producing acetophenone oxime derivatives exclusively. In the case of *o*-allylstyrene, which has both aryl-conjugated and -nonconjugated carbon–carbon double bonds within the mol-

Table I. Nitrosation of Ring-Substituted Styrenes with Ethyl Nitrite[a]

R in substrate ($RC_6H_4CH=CH_2$)	reaction time, h	isolated yield of oxime [$RC_6H_4C(CH_3)=NOH$], %
H	25	94
p-Cl	22	97[b]
p-CH_3	27	96
p-CH_3O	27	94
m-NO_2	25	33
o-Br	25	93
o-Cl	23	99
o-CH_3	28	96
o-CH_2=$CHCH_2O$	28	98
o-CH_2=$CHCH_2O$	27	72[c]

[a] Reaction conditions: $ClCo(DH)_2py$/styrene/Et_4NBH_4/EtONO = 0.1/1/1.5/2.5. Reaction at room temperature under Ar in benzene. [b] Reaction in the dark. [c] Reaction was carried out at 60 °C by using isopentyl nitrite (3 equiv per substrate) instead of EtONO.

(1) Sandler, S. R.; Karo, W. *Organic Functional Group Preparations*; Academic: New York, 1972; Vol. III, p 315.
(2) Meinwald, J.; Meinwald, Y. G.; Barker, T. N. *J. Am. Chem. Soc.* **1964**, *86*, 4074.
(3) Abbreviations: DH, monoanion of dimethylglyoxime; py, pyridine; salpro, *N,N'*-disalicylidene-1,2-propanediamine; TPP, *meso*-tetraphenylporphyrin.
(4) Wade, R. C. *J. Mol. Catal.* **1983**, *18*, 273.

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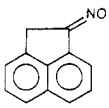
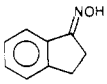
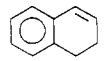
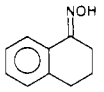
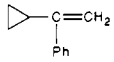
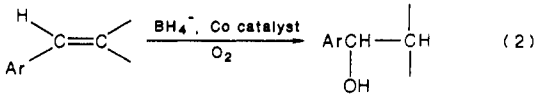
Table II. Nitrosation of 1,2-Disubstituted Aryl-Conjugated Ethylenes with EtONO[a]

substrate	reaction time, h	product	isolated yield, %[b]
PhCH=CHCH=CH_2	28	PhCH=CHC(CH_3)=NOH	87[c]
PhCH=$CHCH_2OH$	54	PhC(=NOH)-CH_2CH_2OH	33 (63)
PhCH=$CHCH_2OCH_3$	47	PhC(=NOH)-$CH_2CH_2OCH_3$	16 (72)
PhCH=$CHCH_3$	72	PhC(=NOH)-CH_2CH_3	8 (–)[d]
PhCH=$CHCOOCH_2CH_3$	72		0 (–)[d]
	48		79[e] (–)[d]
	54		16 (–)[f]
	38		24[g] (–)[d]
	48		38 (61)
	36		65[h] (34)
	27		0 (–)[d]
	25		0[i] (0)[j]

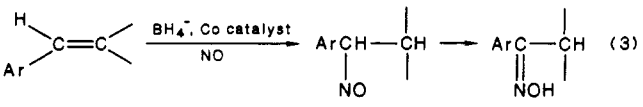
[a] Reaction conditions were the same as in Table I. [b] Values in parentheses indicate yields of recovered starting materials. [c] Ratio (syn:anti) = 4.2:1. [d] Other compound identified on TLC was only the starting material. [e] Ratio (syn:anti) = 4.0:1. [f] Not determined. [g] $NaBH_4$ (3 equiv per substrate) was used instead of Et_4NBH_4. [h] $NaBH_4$ (2 equiv per substrate) was used instead of Et_4NBH_4. [i] No oxime was isolated after the reaction. [j] No starting material remained.

ecule, the reaction occurred selectively at the aryl-conjugated bond. Ring closure forming derivatives of 3,4-dihydrobenzopyran did not occur.

Cyclic as well as acyclic 1,2-disubstituted aryl-conjugated olefins were similarly converted to the conjugated oximes regioselectively, although the yields were moderate to poor in contrast to those of terminal olefins (Table II). Nevertheless, it is notable that in the previously reported cobalt-catalyzed reaction of styrenes with molecular oxygen[5] (eq 2) or nitrogen oxide[6] (eq 3), these substrates were



(2)



(3)

unreactive or hardly reactive. Yields of oximes are high for all the substrates examined in this study (Table I and II) compared with yields of the reactions with NO, the maximum yield of which was less than 70%. In this respect, the reaction with alkyl nitrite is the most reactive one in the related cobalt-catalyzed reactions. However, the reactivity was still insufficient for synthetic purposes with some 1,2-disubstituted ethylenes, especially with those having trans substitutents as shown in Table II. An attempt at this type of reaction with aliphatic olefins was also unsuccessful so far. In the runs of poor yields of oximes listed in Table II, substrates were mostly recovered unreacted, indicating that the rates of reaction of these substrates were slow. The yields were not increased even when the stirring of the reaction mixture was continued for longer periods, because the products themselves were not completely stable during a prolonged reaction time when the reactivity of the substrate was low.[7] A slow supply of BH_4^- may be better for a substrate of reduced reactivity, because $NaBH_4$, which is not completely soluble in the reaction medium, gave a better yield of oxime than completely soluble Et_4NBH_4 in the reaction of dihydronaphthalene (Table II, entry 8). In all the reactions in this table (except for acenaphthylene and 1-cyclopropyl-1-phenylethylene) the major compounds that were present in the reaction mixture after the specified reaction period were the aryl-conjugated ketoxime and the substrate olefin. In the case of acenaphthylene, a small amount of side product accompanied the substrate and oxime on TLC. In the reaction of cyclopropylphenylethylene, the substrate disappeared and two unidentified compounds were formed (a total of 73 mg of the products starting with 124 mg of the substrate). NMR spectra of these compounds showed that the cyclopropyl ring was still present in both of the products. No products of side reactions such as hydrogenation of the styrene derivatives to those of ethylbenzene or hydrodimerization to 2,3-diphenylbutadienes, nor lower molecular weight compounds formed from the products or substrates were generally found by TLC or GC analyses. Ethyl cinnamate and 2,3-benzofuran were completely unreactive under the experimental conditions examined. The low reactivity of the latter compound might be ascribed to its aromaticity. However, the reason for the low reactivity of ethyl cinnamate is not clear at present. The substrate was recovered after the reaction. Similar results were also obtained with methyl cinnamate. However, a phenyl-substituted butadiene, 1-phenyl-1,3-butadiene, gave the oxime of methyl 2-phenylvinyl ketone, regioselectively, in a high yield. This regioselectivity of the reaction of 1,3-diene is found also in cobalt-catalyzed oxygenation under related reaction conditions.[5] In relation to this regioselectivity, Johnson and others reported on an S_H2 reaction of an allylcobalt complex.[8] If the reaction of alkyl nitrite proceeds through the radical mechanism, the regioselective product of 1-phenyl-1,3-butadiene could be explained by a related rearrangement.

A change in the reaction medium from benzene to more polar solvents such as *N*,*N*-dimethylformamide or 2-propanol resulted in the slow conversion of the substrate to oxime (Table III). A related tendency was found also in the reaction of alkylcobalt complex, $PhCH(CH_3)Co(DH)_2py$, with ethyl nitrite.[9] With the use of isopentyl nitrite instead of ethyl nitrite, the yield of oxime was low even at elevated temperatures (Table I, entry 10, and Table III, entry 11). This observation suggests that the steric bulkiness of alkyl nitrite influences the reactivity of ni-

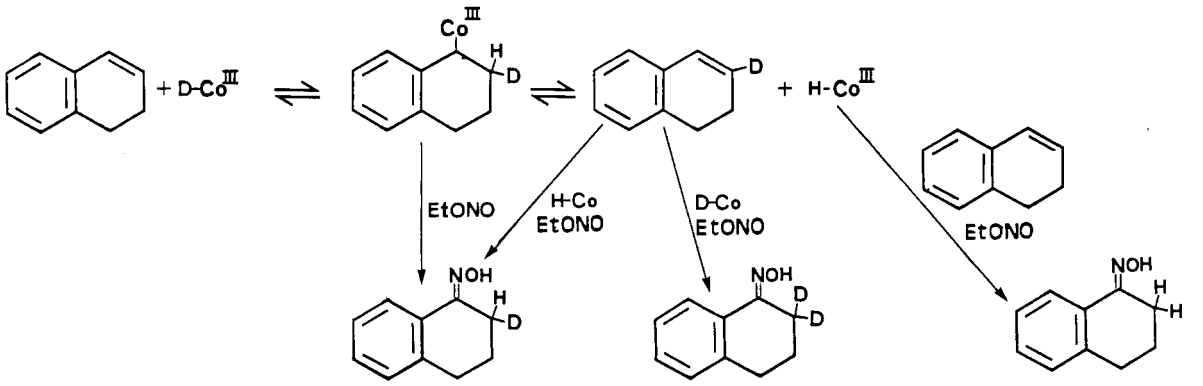
(5) Okamoto, T.; Oka, S. *J. Org. Chem.* **1984**, *49*, 1589.
(6) Okamoto, T.; Oka, S. *J. Chem. Soc., Chem. Commun.* **1984**, 289. Okamoto, T.; Kobayashi, K.; Oka, S.; Tanimoto, S. *J. Org. Chem.* **1987**, *52*, 5089.
(7) For the substituted ethylenes of low reactivity, the rate of reaction of hydrocobalt complex with the substrate is slow, keeping the steady-state concentration of hydrocobalt complex relatively high. This complex, in turn, can react with oxime slowly. Even with substrates that give a good yield of oxime in the catalytic reaction, prolonged stirring of the reaction mixture after through consumption of the substrate resulted in lowering of the product yield.
(8) Johnson, M. D. *Acc. Chem. Res.* **1983**, *16*, 343. Funabiki, T.; Gupta, B. D.; Johnson, M. D. *J. Chem. Soc., Chem. Commun.* **1977**, 653. Gupta, B. D.; Funabiki, T.; Johnson, M. D. *J. Am. Chem. Soc.* **1976**, *98*, 6697.
(9) Okamoto, T.; Kobayashi, K.; Oka, S.; Tanimoto, S., manuscript in preparation.

Table III. Effect of Various Reaction Conditions for the Nitrosation of Styrene[a]

catalyst[b]	solvent	reductant[b]	nitrite[b]	reaction time, h	yield,[c] %
(0)	benzene	Et_4NBH_4 (1.0)	EtONO (2.5)	25	no reaction
(0.1)	benzene	Et_4NBH_4 (1.0)	EtONO (4.5)	20	87
(0.1)	benzene	Et_4NBH_4 (1.5)	EtONO (2.5)	20	92
(0.1)	benzene	Et_4NBH_4 (1.0)	EtONO (2.5)	25	84
(0.2)	benzene	Et_4NBH_4 (1.0)	EtONO (1.3)	24	64[d]
(0.2)	benzene	Et_4NBH_4 (1.0)	EtONO (1.3)	24	67
(0.2)	benzene	Et_4NBH_4 (1.0)	EtONO (2.5)	18	82
(0.2)	benzene	Et_4NBH_4 (1.0)	EtONO (2.5)	28	93
(0.1)	DMF	Et_4NBH_4 (1.0)	EtONO (2.5)	25	26
(0.1)	2-propanol	Et_4NBH_4 (1.0)	EtONO (2.5)	26	65
(0.1)	2-propanol	Et_4NBH_4 (1.0)	EtONO (2.5)	50	71
(0.1)	2-propanol/DME (1/1)	Et_4NBH_4 (1.0)	EtONO (2.5)	25	61
(0.1)	2-propanol/DME (1/1)	Et_4NBH_4 (1.0)	EtONO (2.5)	50	74
(0.1)	2-propanol/DME (1/1)	Et_4NBH_4 (1.0)	isopentylONO (3.0)	25	42

[a] Reaction conditions: by the catalysis of $ClCo(DH)_2py$ under Ar at room temperature. [b] Values in the parentheses indicate equivalents per substrate. [c] Yields were determined by gas chromatography. [d] Under irradiation of a 500-W tungsten lamp at 70 V.

Scheme I



trosation. Then a reaction mechanism involving the generation of free NO under the reaction conditions would be less plausible. This assumption is supported by the finding that the catalytic reaction is influenced little by the irradiation of the reaction mixture with tungsten lamp, except for the formation of a small amount of more polar compounds, which is probably due to further reduction of the product. There was no significant change in the catalyst under irradiation. If the reaction proceeds through the formation of NO, it should be accelerated by irradiation due to the light-induced dissociation of alkyl nitrite.[10] The effects of some other reaction conditions are also included in Table III.

The effects of catalysts are summarized in Table IV. In contrast to the reaction with NO, $Co^{II}(DH)_2(H_2O)_2$ was as effective as the corresponding Co^{III} complex as a catalyst for nitrosation. This finding contrasts with the related NO reaction, in which inhibition by NO was observed when $Co^{II}(DH)_2(H_2O)_2$ was used as the catalyst. The catalytic activity of Co^{II} complex was recovered by the addition of pyridine to the reaction mixture, which prevented the coordination of NO on the catalyst.[6] In both the catalytic reactions in the presence of Co^{II} complex and the stoichiometric reaction of RCo^{III} complex, a stable NO complex, $(NO)Co(DH)_2py$ precipitated during the NO reaction, a phenomenon that was not observed in the alkyl nitrite reaction. Different observations in the catalysis of this Co^{II} complex is additional evidence against the involvement of NO during the reaction of alkyl nitrite. Little difference in the yields of the reactions catalyzed by Co^{II}(salpro) and Co^{II}(salpro)(py) would indicate that the effects of the axial ligand in this catalytic reaction are small.

Table IV. Effect of Catalysts in the Nitrosation of Styrene with EtONO[a]

catalyst (equiv to styrene)	yield, %
$ClCo(DH)_2Py$ (0.05)	78
(0.10)	94
$Co(DH)_2(H_2O)_2$ (0.10)	95
Co(salpro)py (0.10)	19
Co(salpro) (0.10)	20
Co(TPP) (0.05)	0
Co(phthalocyanine) (0.06)	0

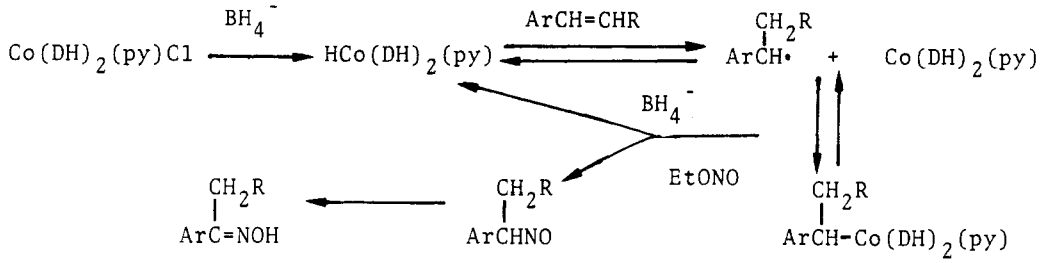
[a] Reaction conditions were the same as in Table I. Reaction time, 25 h. Yields were determined by gas chromatography. Ethylbenzene and 2,3-diphenylbutane were not detected.

Thus, the reaction discussed yields conjugated oximes regioselectively in high yields from ring-substituted styrenes, phenylbutadiene, and some cyclic aryl-conjugated olefins. The reaction mechanisms involving NO^+ or NO are less plausible, as described above. In the related cobalt-catalyzed reactions of O_2 and NO with the aryl-conjugated ethylenes, we proposed a nonchain free-radical reaction mechanism together with evidence for the intermediate formation of alkylcobalt complexes. In this context, it is notable that alkyl nitrite was known as an inhibitor of the free-radical polymerization, and that a free-radical substitution reaction of alkyl nitrite was reported at elevated temperatures.[11] By the similar procedures as in our previous work, an alkylcobalt complex was also confirmed to be involved in this catalytic process, affording the corresponding oxime by subsequent reaction with alkyl nitrite at room temperature: When the reaction of 1,2-dihydronaphthalene was carried out with $NaBD_4$ as

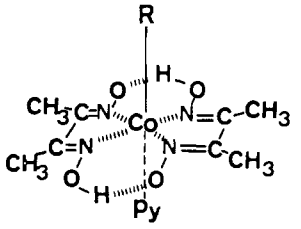
(10) Barton, D. H. R. *Pure Appl. Chem.* **1968**, *16*, 1.

(11) Kharasch, M. S.; Metzer, T. H.; Nudenberg, W. *J. Org. Chem.* **1957**, *22*, 37.

Scheme II



the reductant, the recovered substrate at a conversion of 66% showed a 26% incorporation of deuterium. The deuterium distribution in the product oximes, which were isolated in a total yield of 65% was determined to be 12.8% nondeuteriated, 82.4% monodeuteriated, and 5.0% dideuteriated adducts by GC–MS. The results coincide with those observed in the oxygenation, supporting the state of equilibrium between the alkylcobalt complex and the substrate (Scheme I).[12] Support of the succeeding reaction of organocobalt with alkyl nitrite is presented by using the control reaction of the independently prepared bis(dimethylglyoximato)(1-phenyl-1-ethyl)cobalt complex (**1a**) with ethyl nitrite. When **1a** and the nitrite was

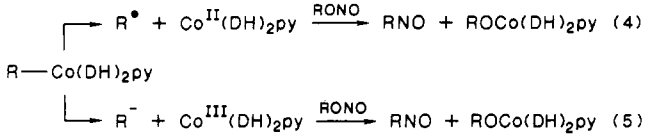


1a: R = $C_6H_5CHCH_3$

b: R = $C_6H_5C{=}CH_2$

stirred at room temperature, acetophenone oxime was formed in a yield of 45.9% on the basis of used **1a**, accompanied a 45.5% yield of styrene in accordance with the known chemistry of alkylcobalt complexes.[13] In the presence of an amount of Et_4NBH_4 equivalent to the complex, styrene was consumed, giving acetophenone oxime as the sole product in a yield of 75% based on the amount of **1a** used. It is notable that tetrahydroborate ion is required only in the formation step of alkylcobalt complex from styrene and cobalt catalyst but it is not necessary in the nitrosation step. In an attempt to catalyze the reaction with phenylacetylene, acetophenone oxime was formed with a low yield (5%) and a α-alkenylcobalt complex (**1b**) was isolated with a yield of 29% after purification. This finding is further support for the reaction mechanism through the intermediate formation of an organocobalt complex. Since a carbon–cobalt bond in the α-alkenylcobalt complex is stronger than that of a α-alkylcobalt complex,[13] further reaction of the alkenylcobalt complex with alkyl nitrite can be estimated to be slow. A small yield of oxime as the product might be formed after the reduction of the carbon–carbon double bond of **1b** into **1a**.

The reaction mechanism is thus proposed is Scheme II. Although the retarding effect of polar solvents suggests a nonpolar rate-determining step such as the homolysis of the cobalt–carbon bond as shown in eq 4, the polar heterolytic reaction mechanism (eq 5) is not completely eliminated.



Experimental Section

NMR spectra, GC–MS spectra, and gas chromatograms were recorded with a Hitachi R-24B, a Hewlett-Packard 5992B, and a Shimadu GC-4CM instrument, respectively. NMR spectra were measured in $CDCl_3$ unless otherwise noted and chemical shifts are listed in ppm with reference to TMS.

$ClCo^{III}(DH)_2py$,[14] $Co^{II}(DH)_2(H_2O)_2$,[14] Co^{II}(salpro),[15] and (1-phenylethyl)$Co(DH)_2py$[16] were prepared according to the literature methods. Co^{II}(TPP) and Co^{II}(phthalocyanine) were commerical products (Aldrich Chemical Co. and Wako Pure Chemical Industries, Ltd., respectively). Ethyl nitrite was a commercial 15 (w/w) solution in ethanol (Tokyo Kasei Chemical Ind. Co.). Solvents were distilled under Ar before use.

Derivatives of styrene were prepared by the Wittig reaction. A typical procedure is described below for 1-phenyl-1,3-butadiene: in a flask fitted with a dropping funnel and a reflux condenser was placed methyltriphenylphosphonium bromide (10.7 g, 30 mmol). The air in the flask was replaced by Ar, and dry deaerated tetrahydrofuran (100 mL) was added to the flask. *n*-Butyllithium (19.2 mL of a 1.56 M solution in hexane, 30 mmol) was added dropwise to the suspension in 15 min, and the mixture was stirred for 1.5 h at room temperature. Cinnamaldehyde (3.8 ml, 30 mmol) was then added to it, and the resulting mixture was stirred for 1 h at room temperature. After the solution was stirred for 5 h further at 65 °C, it was allowed to cool to room temperature. The subsequent addition of diethyl ether (25 mL) and hexane (25 mL) gave a precipitate, which was removed by filtration. The filtrate was purified through a short silica gel column, and the product diene was isolated by distillation in the presence of a small amount of hydroquinone. Yield 2.62 g, 67%.

By a similar procedure, other substrates were prepared as follows: *p*-methoxystyrene (yield 82%), *m*-nitrostyrene (yield 34%), *o*-chlorostyrene (yield 70%), *o*-methylstyrene (yield 50%), *o*-bromostyrene (yield 79%), 1-cyclopropyl-1-phenylethylene (yield 85%), *o*-allyoxystyrene (yield 75%; bp 79.5–81.0 °C (6 mmHg); ^1H NMR δ 4.45–4.53 (m, 2 H), 5.16–6.23, (m, 5 H), 6.75–7.51 (m, 5 H); ^{13}C NMR δ 69.09 (t), 112.33 (d), 114.31 (t), 117.18 (t), 120.87 (d), 126.48 (d), 127.07 (s), 128.71 (d), 131.69 (d), 133.39 (d), 155.73 (s)).

A typical procedure for the catalytic reaction of aryl-conjugated ethylenes with alkyl nitrite is shown for the reaction of styrene: a flask containing $ClCo^{III}(DH)_2py$ (35 mg, 0.087 mmol) and Et_4NBH_4 (189 mg, 0.87 × 1.5 mmol) was deaerated, and dry

(12) A reviewer pointed out the formation hydrogenation product when alkylcobalt complex is formed. However, this complex is not highly reactive with BH_4^- in our hands. The main route of hydrogenation seems to be the reaction of alkylcobalt complex with hydrocobalt complex. It can be estimated that, in the presence of an excess amount of olefin compared with the catalyst, the concentration of hydrocobalt complex is too low to put the hydrogenation process in competition with nitrosation.

(13) Halpern, J. *Acc. Chem. Res.* **1982**, *15*, 238.

(14) Schrauzer, G. N. *Inorg. Synth.* **1968**, *11*, 61.

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deaerated benzene (3 mL) was added to the flask under Ar. To the green suspension thus prepared was added ethyl nitrite (1.4 mL of 15% solution, 0.87 × 2.5 mmol). The mixture became a brown homogeneous solution. Subsequently, the substrate (0.87 mmol) was added by syringe, and the solution was stirred for 25 h at room temperature. After the addition of water (10 mL) to the reaction mixture, the product was extracted with ether (2 × 10 mL). The ethyl layer was dried with Na_2SO_4 and concentrated. Acetophenone oxime was isolated in a 94% yield (110 mg) after purification by column chromatography (Wakogel C-200, and eluted with 20% ethyl acetate/hexane, R_f 0.29). By a similar procedure, various oximes were prepared as listed in Table I and II. Spectral data are presented below: *o*-(allyloxy)acetophenone oxime, ^{1}H NMR δ 2.26 (s, 3 H), 4.52–4.60 (m, 2 H), 5.18–5.47 (m, 2 H), 5.86–6.23 (m, 1 H), 6.84–7.40 (m, 4 H), 9.2 (br s, 1 H); ^{13}C NMR δ 15.39 (q), 69.33 (t), 112.73 (d), 117.42 (t), 120.93 (d), 127.48 (s), 129.58 (d), 130.11 (d), 133.21 (d), 156.61 (s), 157.08 (s); 3-oxo-3-phenyl-1-propanol oxime, ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 3.07 (t, J = 6.8 Hz, 2 H), 3.82 (br t, J = 6.8 Hz, 2 H), 7.22–7.74 (m, 5 H), 10.75 (s, 1 H); mass (M^+) 165; 3-methoxypropiophenone oxime, ^{1}H NMR δ 3.13 (t, J = 6.0 Hz, 2 H), 3.34 (s, 3 H), 3.65 (t, J = 6.0 Hz, 2 H), 7.30–7.75 (m, 5 H).

In the reaction of phenylacetylene (phenylacetylene, 1.27 mmol; $ClCo^{III}(DH)_2py$, 0.25 mmol; Et_4NBH_4, 1.30 mmol; EtONO (15% solution), 1.4 mL; benzene 3 mL for 47 h at room temperature), acetophenone oxime was formed in a 4.7% yield by GC analysis. An orange complex crystallized out during the workup. The complex was washed successively with ether, water, and ether (the complex was slightly soluble in ether), dried in vacuo, and identified as bis(dimethylglyoximato)(1-phenyl-1-ethenyl)-pyridinecobalt(III),[17] (**1b**) (34 mg, 29% yield on the basis of the amount of cobalt complex used).

The deuterium incorporation study was carried out by using 1,2-dihydronaphthalene as the substrate (0.845 mmol) and $NaBD_4$ as the reductant (2 × 0.845 mmol) for 36 h at room temperature. After the usual workup, 37 mg of the substrate was recovered (34% yield) and 89 mg (65% yield on a used substrate basis) of oxime was isolated. The deuterium content of the recovered dihydronaphthalene was estimated by the integral ratio of NMR spectra, and the ratio of the products having d_0, d_1, and d_2 atom(s) was determined by mass spectroscopy.

The reaction of **1a** (95 mg, 0.20 mmol) with EtONO (0.5 mL, ca. 0.8 mmol) was examined by stirring the mixture for 5 h in benzene (3 mL) under Ar at room temperature. The reaction products were identified by gas chromatography in the presence of diphenyl ether as the internal standard to be acetophenone oxime (45.9% yield) and styrene (45.5% yield). In the presence of an amount of Et_4NBH_4 equivalent to the complex, acetophenone oxime was the sole product in a yield of 75.0%. No ethylbenzene was formed.

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A 5C + 5C Bicycloaromatization Reaction via an Aldol Condensation Cascade: A Regioselective Synthesis of Functionalized Naphthalenes from Acyclic Precursors

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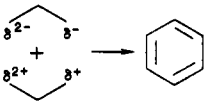
A regioselective synthesis of naphthalene derivatives **51** was developed by the reaction of 1,3,5-tris(trimethylsiloxy)-1-methoxyhexa-1,3,5-triene (**2**) with the 1,3,5-tris-electrophiles **50** and trimethylsilyl triflate. Three carbon–carbon bonds are formed in this aldol condensation cascade, where the regiochemistry is controlled by the different reactivities at the sites of the acyclic precursors.

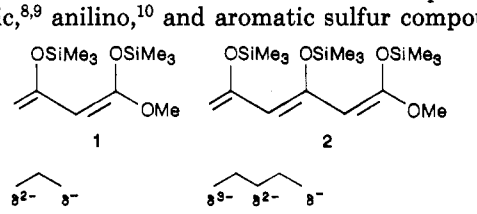
Introduction. A major challenge in organic synthesis today is to devise reactions that can form several carbon–carbon bonds in one operation leading to the construction of polycyclic structures with proper regio- and stereochemical control.

It is recognized that one of the important pathways in nature to assemble polycyclic compounds is the aldol-type reaction of β-polyketide precursors.[1-5] In the laboratory, the controlled aldol condensation of these precursors inspired by biogenetic considerations has been extensively studied by Harris. This has been applied in an elegant fashion to a biomimetic synthesis of 6-methylpretetramide.[6] However, the success of this approach is still somewhat limited due to the difficulty in controlling the direction of the condensation.

Recently, a cycloaromatization reaction was developed in our laboratories for the synthesis of methyl salicylates (eq 1).[7,8] It involves the condensation of 1,3-bis(trimethylsiloxy)-1-methoxybuta-1,3-diene (**1**), the dianion equivalent of methyl acetoacetate, with various 1,3-dielectrophiles under $TiCl_4$ promotion. The regiochemistry of the reaction is controlled by the differing reactivities at the sites of the nucleophilic and electrophilic components. The reaction has been further developed to give phenolic,[8,9] anilino,[10] and aromatic sulfur compounds.[11]



(1)



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