Tandem annulations: a one operation construction of bicyclo[3.3.0]octan-1-ol and bicyclo[3.2.1]octan-1-ol skeletons by a three-component coupling reaction of alk-4-enyl iodides with CO and alkenes in the presence of zinc

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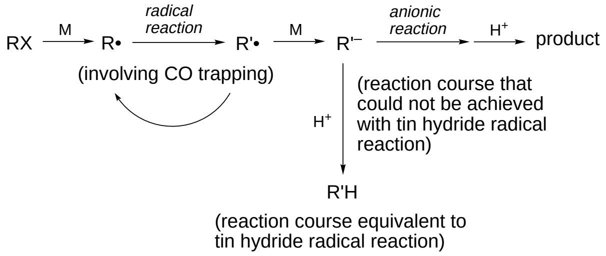
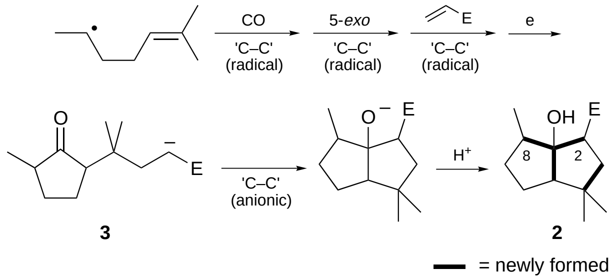
Under a one-electron reduction system composed of zinc and an aprotic solvent, alk-4-enyl iodides react with CO and alkenes to give bicyclo[3.3.0]octan-1-ols and bicyclo[3.2.1]octan-1-ols *via* radical/anionic dual annulations.

Tin radical mediated C1 chemistry has the potential to play an increasingly important role in the synthesis of a variety of carbonyl compounds.[1] In a previous paper, we have shown that a one-electron reduction system composed of zinc and a protic solvent can replace some of the useful transformations developed for tin hydride mediated radical carbonylation reactions.[2] An attractive feature of metal mediated one-electron reduction chemistry is its applicability to the design of unique tandem reaction systems, in which two different species, radicals and anions, can be subtly combined in synthetically useful reactions (Scheme 1).[3] Recent reports provide a useful reminder of the effectiveness and importance of this concept.[4] Here we report a three-component coupling reaction of alk-4-enyl iodides, CO and alkenes in the presence of zinc that delivers bicyclo[3.3.0]octanols[5] and bicyclo[3.2.1]octanols, providing the first demonstration that radical carbonylation can be successfully sequenced by consecutive radical/anionic reactions.

In radical carbonylation using a reductive metal/protic solvent system, after an acyl radical cyclization and addition to a C–C double bond, the newly formed radical is reduced to an anion, which is subsequently protonated.[2] In aprotic solvents, however, the anionic species could conceivably undergo nucleophilic addition to the newly formed internal carbonyl group rather than undergoing protonation.[6] To test this hypothesis, we conducted the reaction of 6-iodo-2-methylhept-2-ene **1** with zinc under CO pressures in aprotic solvents to determine if a bicyclic compound is produced *via* a pathway outlined in Scheme 2. After several experiments, we found that when the usual zinc powder[7] was used in THF or MeCN solvent, the desired reaction took place. In a stainless steel autoclave, a THF solution of **1** (476 mg, 2 mmol, 0.1 M), acrylonitrile (53 mg, 1 mmol) and zinc (197 mg, 3 mmol) was sitrred under CO pressure (60 atm) at 60 °C. After 10 h, the anticipated 2-cyano-4,4,8-trimethylbicyclo[3.3.0]octan-1-ol **2** (137 mg, 71% yield, 60 : 40) was obtained after isolation by flash chromatography on silica gel (Table 1, entry 1). Only two of the four possible diastereoisomers were produced, as judged by both ^{1}H and ^{13}C NMR spectroscopy. A separation of the diastereoisomers was performed by careful chromatography on silica gel, and the absolute structures were confirmed to be *exo* at the CN group and either *endo* or *exo* at the Me group by NOE experiments.§ The major isomer was identified as 8-*exo*-Me, and the minor as 8-*endo*-Me. The consecutive radical/anionic reactions shown in Scheme 2 account for the formation of **2**: (i) an alkyl radical, formed by a one-electron reduction of the starting iodide, adds to CO; (ii) the resulting acyl radical cyclizes in the 5-*exo* mode to give a tertiary alkyl radical; (iii) this radical adds to acrylonitrile; (iv) the resulting α-cyano radical is reduced to an α-cyano anion **3**; (v) anion **3** adds to an internal carbonyl group, (vi) protonation during the work-up leads to bicyclo[3.3.0]octan-1-ol **2**. The observed diastereoselectivities with respect to the *exo*-orientation of the CN group may be rationalized on the basis of steric effects in the anionic cyclization step: the transition state giving the *endo*-CN product is disfavoured, due to steric repulsion between the CN group and the cyclopentanone ring (Fig. 1).[8]



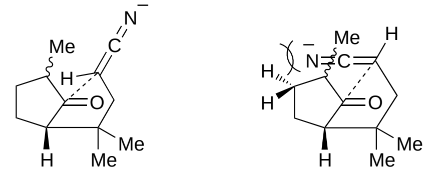
Scheme 1



Scheme 2

Similarly, carbonylation of **1** in the presence of methyl acrylate and zinc gave the corresponding bicyclo[3.3.0]octanol **4** in 50% yield (entry 2). Again, only two of the four possible diastereoisomers were produced. With diethyl fumarate, a mixture of four isomers of bicyclo[3.3.0]octanol **5** was obtained in 52% yield (entry 3).

We demonstrated cases where the initial acyl radical cyclization takes place in the 5-*exo* mode. An extension of the present strategy, which uses a system that favours 6-*endo*

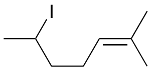
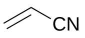
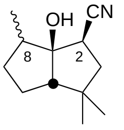
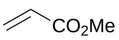
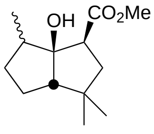
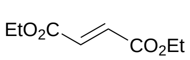
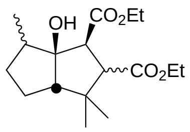
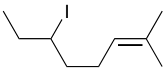
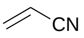
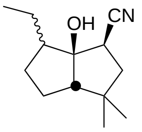
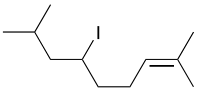
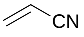
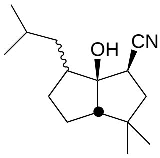
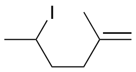
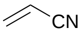
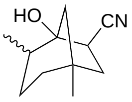
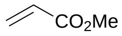
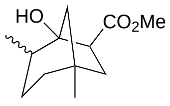


favoured TS
(leading to *exo*-CN isomer)

disfavoured TS
(leading to *endo*-CN isomer)

Fig. 1

Table 1 Synthesis of bicyclic octanols[a]

Entry	Alk-4-enyl iodide	Alkene	Product (% yield,[b] *exo*/*endo* ratio[c])
1	 **1**		 **2** (71, 60:40)
2	**1**		 **4** (50, 52:48)
3	**1**		 **5** (52, 32:31:20:17)[d]
4	 **6**		 **7** (63, 61:39)
5	 **8**		 **9** (64, 59:41)
6	 **10**		 **11** (51, 57:43)
7	**10**		 **12** (43, 50:50)

[a] Conditions: alk-4-enyl iodide (2 mmol), alkene (1 mmol), Zn (3 mmol), CO (60 atm), THF (10–20 ml), 60 °C, 10–22 h. [b] Isolated yields (based on the alkene used) by column chromatography for the *endo*/*exo* mixture. [c] Determined by ^{1}H NMR spectroscopy (except for entry 3: GC). [d] Stereochemistry was not determined.

cyclization[9] rather than 5-*exo* cyclization to the construction of bicyclo[3.2.1]octanol skeletons was also successful. Thus, we examined 5-iodo-2-methylhex-1-ene **10**, a substrate having a methyl group at an internal position on the alkene. As expected, the reaction of **10** with CO and acrylonitrile in the presence of zinc led to bicyclo[3.2.1]octanol **11** in 51% isolated yield (entry 6). Similarly, reaction with methyl acrylate yielded the corresponding bicyclo[3.2.1]octanol **12** in 43% yield (entry 7).

This study demonstrates that radical carbonylation can be successfully combined with a sequential radical/anionic reaction system,[10] which is of great synthetic potential. The reaction reported here provides a convenient route to bicyclo[3.3.0]octanols and bicyclo[3.2.1]octanols from easily accessible starting compounds, such as alk-4-enyl iodides, CO and electron deficient alkenes. It is also noteworthy that the former reactions involve [4 + 1](radical)/[3 + 2](anionic) dual annulations, and the latter reactions involve [5 + 1](radical)/[3 + 2](anionic) dual annulations. We believe that the concepts outlined in this study have wide applicability for numerous synthetically useful processes.

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Footnotes and References

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§ Preparative HPLC (GPC columns, CHCl$_3$ as the eluent) is also available to separate the *endo*/*exo* isomers of **2**. Absolute structures were confirmed to be the *endo*/*exo* isomers at the 8-position by NOE experiments (8-*exo*-**2**: 5%, 2-H *vs.* 8-H-*endo*-**2**: 10% 2-H *vs.* 8-Me).

Selected data for 8-*exo*-**2**: colourless liquid, δ_H(CDCl$_3$, 600 MHz) 0.88 (s, 3 H), 1.11 (d, 3 H, J 6.63), 1.13 (s, 3 H), 1.13–1.18 (m, 1 H), 1.48 (ddt-like, 1 H, J *ca.* 6.6, 13.7, 2.0), 1.62–1.71 (m, 1 H), 1.83 (m, 1 H), 1.88 (dd, 1 H, J 6.19, 12.16), 1.95–2.03 (m, 1 H), 2.10–2.36 (m, 2 H) 2.62 (dd, 1 H, J 6.19, 12.83), 2.66 (br s, 1 H); δ_C (CDCl$_3$, 150 MHz) 13.30 (q), 23.02 (q), 25.53 (t), 31.06 (q), 34.37 (t), 34.59 (d), 40.39 (s), 44.87 (t), 45.00 (d), 61.39 (d), 93.27 (s), 120.06 (s).

Selected data for 8-*endo*-**2**: colourless liquid; δ_H(CDCl$_3$, 600 MHz) 0.89 (s, 3 H), 1.06 (d, 3 H, J 6.85), 1.15 (s, 3 H), 1.26–1.34 (m, 1 H), 1.53–1.61 (m, 1 H), 1.62–1.73 (m, 2 H), 1.85 (q, 1 H, J 5.72), 1.96 (dd, 1 H, J 6.60, 12.50), 2.11 (br s, 1 H), 2.14 (t-like, 1 H, J *ca.* 9.10 Hz), 2.20 (t-like, 1 H, J *ca.* 11.74), 2.71 (dd, 1 H, J 6.45, 11.15); δ_C (CDCl$_3$, 150 MHz) 12.53 (q), 24.00 (q), 24.12 (t), 30.16 (q), 35.72 (t), 38.95 (s), 39.17 (d), 45.50 (d), 46.75 (t), 63.55 (d), 91.14 (s), 120.06 (s).

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