Carbene Complexes

Three/Four/Five-Component Diastereoselective Cyclization of Fischer Carbene Complexes, Lithium Enolates, and Allylmagnesium Bromide**

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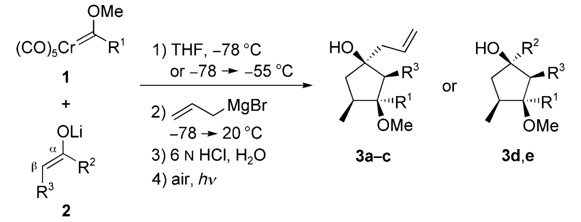
The 1,2-addition reaction of metal enolates to Group 6 Fischer alkoxy carbene complexes produces anionic (1-alkoxy-3-oxoalkyl)pentacarbonylmetalate species, which evolve further to give different organic products, depending on the reaction conditions and the structural features of the reaction partners.[1] Aryl methoxy carbene complexes react with lithium or potassium enolates of ketones[2] and with lithium enolates of α-haloesters[3] to provide open-chain products after hydrolysis with acid. Alkenyl methoxy carbene complexes also undergo nucleophilic attack at the carbene carbon atom when they are treated with methyl ketone lithium enolates, leading to acyclic unsaturated ketones[2] when the reaction mixture is quenched at low temperature and to five-[4] or seven-membered[4a] carbocycles when the reaction is allowed to reach room temperature. These diastereoselective cyclizations involve intramolecular addition of lithium allylmetalate intermediates, generated in situ, to either the carbonyl group or the β carbon atom of an alkenyl ketone. However, to date no examples have been reported of the nucleophilic addition of metal enolates to the carbene carbon atom of either alkynyl or alkyl carbene complexes.

On the other hand, 1-alkoxyalkyl pentacarbonylmetalate species, generated by reduction of alkoxy carbene complexes with *N*-methyl-1,4-dihydropyridine[5] or samarium diiodide/methanol[6], underwent insertion of CO to give α-alkoxyacyl tetracarbonylmetalate intermediates.[7] These acyl chromate or tungstate complexes undergo intermolecular 1,4-addition to electron-deficient olefins,[5,6] intramolecular insertion of an alkene or alkyne,[5] or intramolecular cyclopropanation of a carbon–carbon double bond.[5]

Herein we describe a novel selective synthesis of highly substituted cyclopentanols and 1,4-cyclohexanediols by a three-, four-, or five-component sequential coupling reaction[8] of a Fischer carbene complex, a ketone or ester lithium enolate, and allylmagnesium bromide.

The successive reaction of chromium carbene complexes **1** with β-substituted lithium enolates **2** and then with allylmagnesium bromide under the reaction conditions summarized in Table 1 led, after hydrolysis with acid and decoordination of the metal center, to 1,2,3,3,4-pentasubstituted cyclopentanols **3**, which were obtained in each case as a single diastereoisomer. 1-Allylcyclopentanols **3a-c** were formed when ester lithium enolate **2a**[9] was used in a process that involves four reacting components and the formation of four new C−C bonds (Table 1, entries 1–3). Other 1-substituted cyclopentanols **3d,e** were isolated from the reactions with ketone lithium enolates **2b,c**[10] and represent the coupling of three reacting components with the formation of three new C−C bonds (Table 1, entries 4 and 5). This sequential one-pot synthesis of cyclopentanols proceeded successfully with aryl and heteroaryl carbene complexes **1a,d** and **1b**, respectively, and even with alkyl carbene complex **1c**, which contains an acidic hydrogen atom at the tertiary center α to the carbene carbon atom.

Table 1: 1,2,3,3,4-Pentasubstituted cyclopentanols **3** prepared by one-pot three- or four-component coupling of carbene complexes **1**, lithium enolates **2**, and allylmagnesium bromide.



Entry	1	R^1	2	R^2	R^3	Method[a]	3	Yield [%][b]
1	**a**	2-naphthyl	**a**	MeO	Me	A	**a**	79
2	**b**	2-furyl	**a**	MeO	Me	A	**b**	73
3	**c**	$(CH_2)_4CH$[c]	**a**	MeO	Me	A	**c**	87
4	**d**	Ph	**b**	Et	Me	B	**d**	80
5	**a**	2-naphthyl	**c**	$(CH_2)_4$		B	**e**	78

[a] Reaction conditions: Method A: **2a** (1.2 equiv), −78 °C, 15 min; $CH_2{=}CHCH_2MgBr$ (2.5 equiv), −78 °C, 30 min; then 20 °C, 20 min. Method B: **2b,c** (1.2 equiv), −78 → −55 °C, 45 min; $CH_2{=}CHCH_2MgBr$ (1.5 equiv), −78 °C, 30 min; then 20 °C, 20 min. [b] Yield of isolated product based on the corresponding carbene complex **1**. [c] Cyclopentyl.

The analogous consecutive treatment of carbene complexes **1** with β-unsubstituted lithium enolates **4** and allylmagnesium bromide resulted in the diastereoselective formation of 1,3,3,5-tetrasubstituted cyclohexane-1,4-diols **5** (Table 2). The reaction proceeded similarly to that with β-substituted enolates (Table 1): The experiments with ester lithium enolate **4a** afforded 1-allylcyclohexane-1,4-diols **5a-c** in which five reacting components have been joined together with the formation of five new C−C bonds (Table 2, entries 1–3). On the other hand, the reactions with ketone lithium enolates **4b,c** provided 1-substituted cyclohexane-1,4-diols **5d-f** by the assembly of four reacting components with the creation of four new C−C bonds (Table 2, entries 4–6). Aryl

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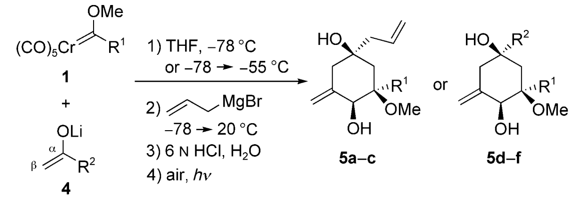
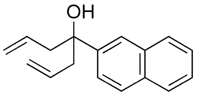
Table 2: 1,3,3,5-Tetrasubstituted cyclohexane-1,4-diols **5** prepared by one-pot four- or five-component coupling of carbene complexes **1**, lithium enolates **4**, and allylmagnesium bromide.



Entry	1	R^1	4	R^2	Method[a]	5	Yield [%][b]
1	a	2-naphthyl	a	EtO	A	a	79
2	e	3-furyl	a	EtO	A	b	81
3	f	*t*BuC≡C	a	EtO	A	c	83
4	d	Ph	b	Me	B	d	82
5	c	$(CH_2)_4CH$[c]	b	Me	B	e	87
6	a	2-naphthyl	c	Ph	B	f	91

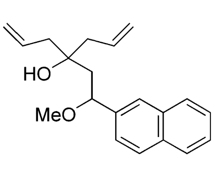
[a] Reaction conditions: Method A: **4a** (1.2 equiv), −78 °C, 15 min; $CH_2=CHCH_2MgBr$ (2.5 equiv), −78 °C, 30 min; then 20 °C, 20 min. Method B: **4b,c** (1.2 equiv), −78 → −55 °C, 45 min; $CH_2=CHCH_2MgBr$ (1.5 equiv), −78 °C, 30 min; then 20 °C, 20 min. [b] Yield of isolated product based on the corresponding carbene complex **1**. [c] Cyclopentyl.

(**1a,d**), heteroaryl (**1e**), alkyl (**1c**), and also alkynyl (**1f**) carbene complexes can be used as starting materials for the construction of cyclohexane-1,4-diols **5**.



6 16%

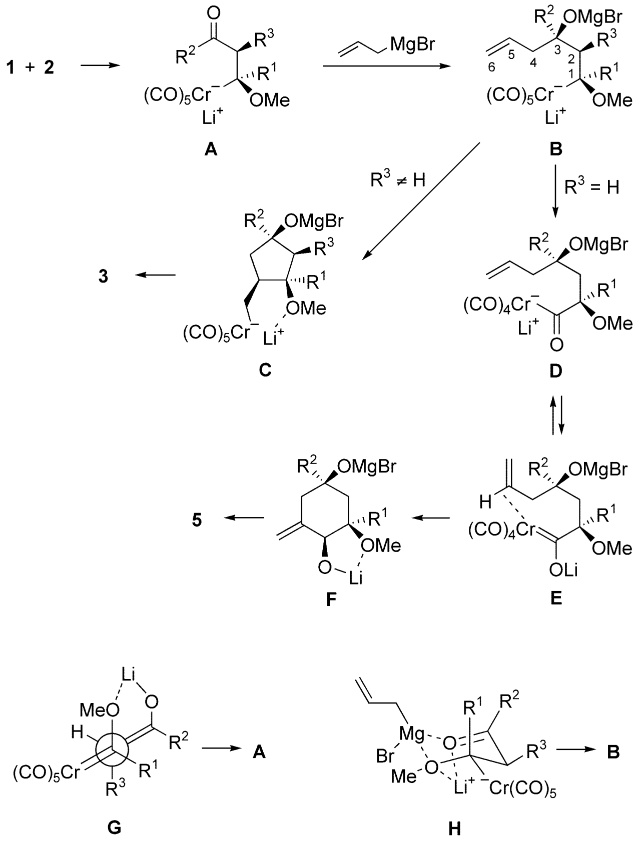
The addition of ester lithium enolates **2a** and **4a** to the carbene carbon atom of carbene complexes **1** occurred smoothly at −78 °C, but in the case of ketone lithium enolates **2b,c** and **4b,c** it was necessary to raise the temperature of the reaction to −55 °C to drive the addition reaction to completion. Indeed, a mixture of product **5f** (61 %) and tertiary alcohol **6** (16 %) was isolated in the experiment in which the temperature of the reaction step of **1a** with the lithium enolate of acetophenone, **4c**, was maintained at −78 °C for 45 min (instead of 45 min between −78 and −55 °C; see Table 2, entry 6). Compounds **5** and **6** were easily separated by column chromatography. The formation of alcohol **6**, whose structure does not contain the enolate framework, can be explained by direct addition of allylmagnesium bromide to the carbene carbon of starting carbene complex **1a**, which remains in the reaction mixture as a result of an incomplete addition of ketone enolate **4c** at −78 °C. Furthermore, a shorter reaction time in the second reaction step led also to a mixture of two products, of which the major is a non-annulated derivative. Thus, treatment of the reaction mixture obtained by addition of enolate **4a** to carbene complex **1a** with allylmagnesium bromide at −78 °C for only 5 min (instead of 30 min; see Table 2, entry 1) and then at room temperature for 20 min, furnished cyclohexanediol **5a** (32 %) along with tertiary alcohol **7** (45 %), which does incorporate the enolate framework in its structure. These two compounds **5a** and **7** were, likewise, separable by column chromatography.



7 45%

The structure and relative stereochemistry of products **3** and **5**–**7** were ascertained by 1D and 2D NMR spectroscopy experiments. The latter were carried out with compounds **3a,d,e**, **5a,b**, and **7**.[11] Furthermore, X-ray single-crystal analysis of **5d** confirmed the structural assignment of cyclohexane-1,4-diols **5**.[12]

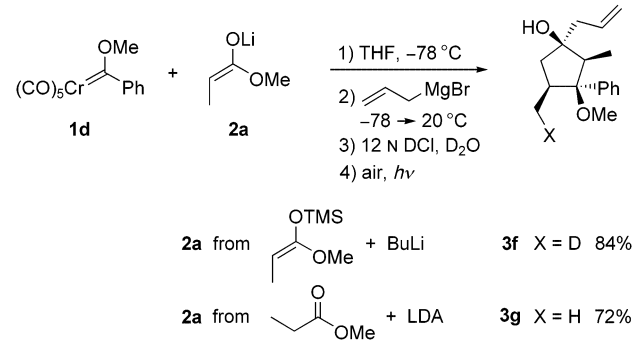
The ring skeleton of cyclopentanols **3** combine the carbene ligand, the enolate framework, and one or two allyl units, whereas that of cyclohexanediols **5** also incorporates a carbonyl ligand. Based on this information, a plausible mechanism to explain the formation of **3** and **5** is outlined in Scheme 1 and involves initial 1,2-addition of the appropriate lithium enolate **2** or **4** (= **2**, $R^3 = H$) to carbene complex **1**, which generates lithium 1-methoxy-3-oxoalkyl pentacarbonylchromate intermediate **A**. Subsequent addition of the organomagnesium reagent at low temperature to the corresponding ketone or ester functional group produces 5-hexenylchromate intermediate **B**, whose reactivity depends on the degree of substitution at C2. Complexes **B** with an organic group at C2 ($R^3 \neq H$) undergo an intramolecular carbometalation reaction to give cyclopentylmethylchromate derivatives **C**, which finally furnish cyclopentanols **3** upon protonation. On the other hand, tetrahedral intermediates **B** that do not have a substituent at C2 ($R^3 = H$) undergo migratory insertion of carbon monoxide to provide lithium acyl tetracarbonylchromate species **D**, which lead to 5-



Scheme 1. Proposed mechanism for the formation of compounds **3** and **5**.

methylenecyclohexane-1,4-diols **5**, presumably after intramolecular insertion of the carbene carbon atom into the secondary vinylic C–H bond, as indicated in intermediate **E**, and subsequent protonation of **F** (Scheme 1).[13,14,15] The observed diastereoselectivity in the first reaction step can be explained in terms of approach topology **G**, which is favored by coordination of the lithium center to the oxygen atom of the methoxy group. The diastereoisomer formed in the second reaction step can be rationalized by a chelation-controlled transition state in which the nucleophile (organomagnesium) adds to the less-hindered face (back face of model **H**) of the carbonyl group (Scheme 1).[16] Protonation of intermediate **B** before ring closing would account for the isolation of product **7**.

Evidence for the formation of intermediate **C** was provided by quenching the reaction with deuterium oxide and deuterated hydrochloric acid. However, the lithium enolate was derived from the corresponding silyl enol ether to avoid the presence of diisopropylamine, which at room temperature promotes protonation of the lithium alkyl chromate moiety. As shown in Scheme 2 the reaction of **1d** with **2a** (prepared from (*E*)-1-methoxy-1-trimethylsilyloxypropene[17] by treatment with BuLi) and allylmagnesium bromide afforded deuterated cyclopentanol **3f**, whereas the same experiment carried out with lithium enolate **2a** (generated from methyl propionate and LDA) produced undeuterated cyclopentanol **3g**.



Scheme 2. Formation of deuterated compound **3f** in the absence of *i*Pr$_2$NH.

In conclusion, a new synthetic sequence has been developed for the one-pot diastereoselective preparation from three simple precursors of singular cyclopentanols and cyclohexane-1,4-diols with up to four contiguous stereogenic centers. These formal [2+2+1] and [2+2+1+1] cyclization processes seem to involve intramolecular alkene insertion into an alkyl pentacarbonylchromate[18] and unprecedented lithioxycarbene complex insertion into a vinylic C–H bond, respectively.

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