Multicomponent Reactions

DOI: 10.1002/ange.201004413

Enantioselective Synthesis of 4-Hydroxy-2-cyclohexenones through a Multicomponent Cyclization**

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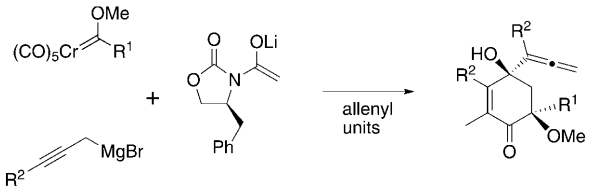
Multicomponent reactions (MCRs) that combine three or more substrates and produce several bonds and stereocenters in a single operation have recently emerged as a powerful strategy for the rapid construction of complex molecular architectures.[1] Fischer carbene complexes (FCCs) containing Group 6 transition metals have been recognized as very effective reagents to promote a wide range of multicomponent coupling reactions.[2] In this context, our research group has successfully described the diastereoselective synthesis of either pentasubstituted cyclopentanols or tetrasubstituted 1,4-cyclohexanediols by a multicomponent sequential reaction of a Fischer alkoxycarbene complex, a ketone or ester lithium enolate, and allylmagnesium bromide.[3] To explore new multicomponent synthetic strategies with substrates containing an alkyne/allene unsaturation and to prepare the corresponding derivatives as enantiomerically pure compounds, we turned our attention to *N*-acyloxazolidinones. The 1,3-oxazolidin-2-one system, which was first employed as a chiral auxiliary by Evans, has been successfully and widely applied in asymmetric synthesis.[4] The enolates of chiral nonracemic *N*-acyl-1,3-oxazolidin-2-ones have been mainly used in asymmetric alkylation and aldol addition reactions.[4,5]

Herein, we report a novel diastereoselective multicomponent cyclization that combines an alkoxycarbene complex of chromium, an imide lithium enolate, and an initially prepared propargylic organomagnesium reagent. Incorporation of the Grignard reagent as an allenyl unit occurred with subsequent insertion of a carbonyl ligand to produce 4-allenyl-4-hydroxy-2-cyclohexenones with high asymmetric induction (Scheme 1).

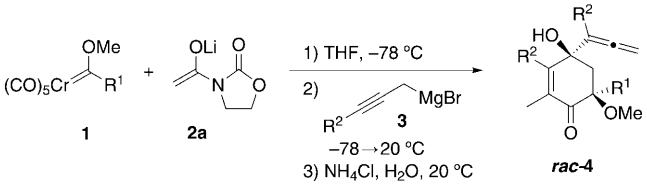


Scheme 1. Five-component synthesis of novel 4-allenyl-4-hydroxy-2-cyclohexenones by sequential coupling of three starting materials.

The feasibility of the envisaged coupling reaction was initially explored using the lithium enolate of 3-acetyloxazolidin-2-one **2a** (prepared with lithium diisopropylamide (LDA) in THF at −78 °C) and propargylic organomagnesium reagents **3a–d** (R^2 = Me, Et, Bu, Ph) generated from the corresponding propargylic bromide and Mg (0.3 mol% $HgCl_2$, Et_2O, 0 °C). Thus, the successive reaction of a chromium methoxycarbene complex **1** with imide lithium enolate **2a**, and then with a 3-substituted propargylmagnesium bromide (**3a–d**), performed under the reaction conditions summarized in Table 1, led, after hydrolysis and decoordination of the metal species by exposure to air and light, to the corresponding 2,3,4,4,6,6-hexasubstituted 2-cyclohexenone ***rac*-4** as a single diastereoisomer. In these reactions, mainly aryl (Table 1, entries 1–6 and 10–12) and heteroaryl carbene complexes (Table 1, entries 7, 8, and 13) in addition to an alkylcarbene derivative (Table 1, entry 9) were employed.

Formation of compounds ***rac*-4** reveals the successful addition of imide enolate **2a** to the carbene complex **1**, which

Table 1: Diastereoselective synthesis of 4-hydroxy-2-cyclohexenones ***rac*-4**.[a]



Entry	**1**	R^1	**3**	R^2	***rac*-4**	Yield [%][b]
1	**1a**	Ph	**3a**	Me	***rac*-4a**	80
2	**1b**	2-naphthyl	**3a**	Me	***rac*-4b**	54
3	**1c**	*p*-$MeOC_6H_4$	**3a**	Me	***rac*-4c**	69
4	**1d**	*p*-$TBSOC_6H_4$	**3a**	Me	***rac*-4d**	71
5	**1e**	*p*-ClC_6H_4	**3a**	Me	***rac*-4e**	75
6	**1f**	*p*-BrC_6H_4	**3a**	Me	***rac*-4f**	52
7	**1g**	5-TMS-2-furyl	**3a**	Me	***rac*-4g**	70
8	**1h**	5-TMS-2-thienyl	**3a**	Me	***rac*-4h**	61
9	**1i**	cyclopentyl	**3a**	Me	***rac*-4i**	65
10	**1a**	Ph	**3b**	Et	***rac*-4j**	71
11	**1j**	*p*-$CF_3C_6H_4$	**3b**	Et	***rac*-4k**	57
12	**1c**	*p*-$MeOC_6H_4$	**3c**	Bu	***rac*-4l**	63
13	**1g**	5-TMS-2-furyl	**3d**	Ph	***rac*-4m**	55

[a] Reaction conditions: 1) **2a** (1.2 equiv), −78 °C, 15 min; 2) **3** (2.6 equiv), −78 °C, 30 min; then −55 °C, 12 h; then −55→20 °C, 8 h. [b] Yield of isolated product based on carbene complex **1**. TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran, TMS = trimethylsilyl.

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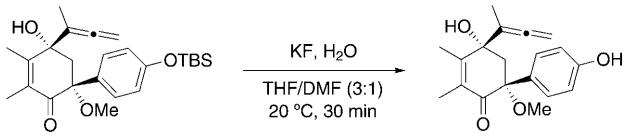
[**] Financial support of this work by the MEC of Spain (grant no. CTQ2007-61048/BQU) and the Principado de Asturias (project no. IB08-088) is gratefully acknowledged. M.G.S. and R.D.C. thank the MEC of Spain for a FPU predoctoral fellowship.

Supporting information for this article, including experimental details, is available on the WWW under http://dx.doi.org/10.1002/anie.201004413.

occurs at low temperature and is an almost instantaneous reaction. The formation of these compounds also indicates the selective incorporation of the organomagnesium reagent as an allenyl unit.[6,7] The structure of these novel derivatives ***rac*-4** combines five reacting components in a sequential diastereoselective coupling process where the carbene ligand, the enolate framework, one of the two allenyl groups, and a carbonyl ligand have come together to form the highly substituted cyclohexene core (formal $[2_E+2_A+1_C+1_{CO}]$ cyclization).[8,9]

Subsequently, analogous experiments were conducted with lithium enolate **2b**, prepared from (*S*)-3-acetyl-4-benzyl-2-oxazolidinone and LDA (THF, −78 °C), and the results are summarized in Table 2. The reactions with different aryl/heteroarylcarbene complexes **1** and different propargylic organomagnesium bromides **3a–d** afforded the corresponding 2-cyclohexenones **4**, which contain two quaternary stereocenters at the α and γ positions and that were uniformly generated either as highly enantioenriched or enantiomerically pure compounds.[10] The chemical yield of compound **4l** could be slightly improved using the corresponding organocerium reagent prepared by treatment of Grignard reagent **3c** with $CeCl_3$ (Table 2, entry 11).[11] Furthermore, the reactions performed under the experimental conditions indicated in Table 2 with carbene complexes **1a**,**d**, lithium enolate **2c** derived from (*R*)-3-acetyl-4-benzyl-2-oxazolidinone, and 2-butynylmagnesium bromide (**3a**) gave access to the enantiomers of compounds **4a**,**d** (***ent*-4a**,**d**; see structures following Table 2) which were also formed with excellent enantioselectivities.

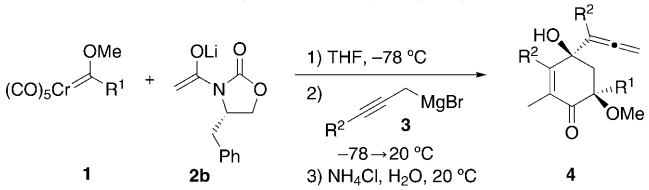
The structure and relative stereochemistry of products **4** were ascertained by 1D and 2D NMR spectroscopic experiments[12] (the latter studies were carried out with compounds **4c**,**f**,**h**) and further confirmed by single-crystal X-ray analysis of ***ent*-5d**, which allowed us to establish the absolute configuration of the stereogenic carbon atoms (see the Supporting Information).[13] Compound ***ent*-5d** was obtained after removal of the *tert*-butyldimethylsilyl (TBS) protective group of **ent-4d** by treatment with potassium fluoride (saturated aqueous solution) in THF/DMF (3:1) at room temperature (Scheme 2). The reaction occurred without diminishing the *ee* value. A similar procedure allowed the conversion of **4d** into phenol derivative **5d** (80%, 99% *ee*). The enantiomeric purity of compounds **5d** and ***ent*-5d** was checked by HPLC analysis on a chiral stationary phase using a Chiralcel OD-H column.



***ent*-4d** 99% *ee* **ent-5d** 75%, 99% *ee*

Scheme 2. Removal of the TBS group. DMF = *N*,*N*-dimethylformamide.

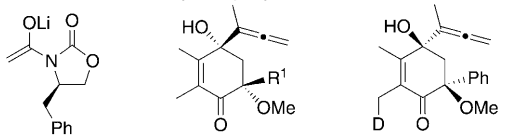
Table 2: Enantioselective synthesis of 4-hydroxy-2-cyclohexenones **4**.[a]



1 **2b** **4**

Entry	**1**	R^1	**3**	R^2	**4**	Yield [%][b]	*ee* [%][c]
1	**1a**	Ph	**3a**	Me	**4a**	84	99
2	**1b**	2-naphthyl	**3a**	Me	**4b**	51	99
3	**1c**	*p*-$MeOC_6H_4$	**3a**	Me	**4c**	70	98
4	**1d**	*p*-$TBSOC_6H_4$	**3a**	Me	**4d**	79	99
5	**1e**	*p*-ClC_6H_4	**3a**	Me	**4e**	69	97
6	**1f**	*p*-BrC_6H_4	**3a**	Me	**4f**	53	99
7	**1g**	5-TMS-2-furyl	**3a**	Me	**4g**	72	99
8	**1h**	5-TMS-2-thienyl	**3a**	Me	**4h**	53	98
9	**1a**	Ph	**3b**	Et	**4j**	80	99
10	**1j**	*p*-$CF_3C_6H_4$	**3b**	Et	**4k**	61	99
11	**1c**	*p*-$MeOC_6H_4$	**3c**	Bu	**4l**	56 (70)[d]	99
12	**1g**	5-TMS-2-furyl	**3d**	Ph	**4m**	50	99

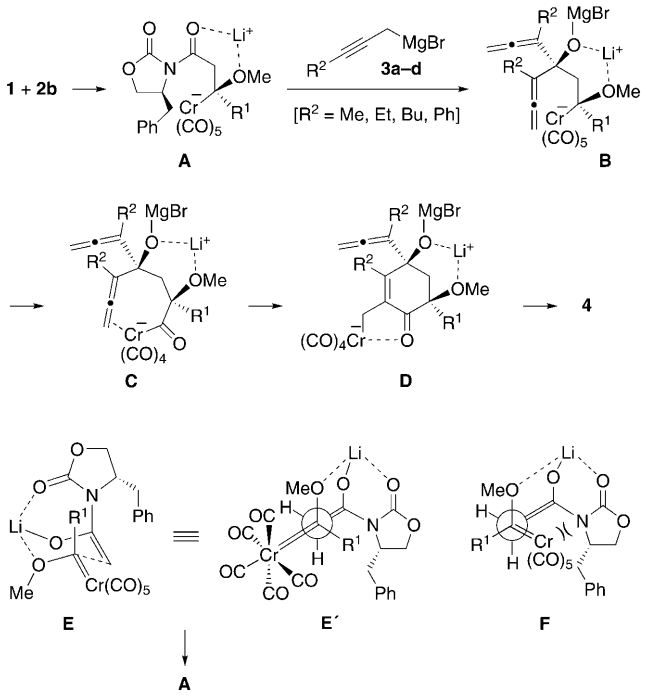
[a] Reaction conditions: 1) **2b** (1.2 equiv), −78 °C, 15 min; 2) **3** (2.6 equiv), −78 °C, 30 min; then −55 °C, 12 h; then −55→20 °C, 8 h. [b] Yield of isolated product based on carbene complex **1**. [c] Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase using a Chiralcel OD-H column, and was compared with the corresponding racemic mixture ***rac*-4**. [d] Yield when the reaction was carried out with the corresponding organocerium compound prepared from **3c** and $CeCl_3$ (1.2 equiv) in THF.



2c ***ent*-4a** 78%, 99% *ee* ***ent*-4d** 84%, 99% *ee* **4n** 79%, 44% D, 99% *ee*

The chemical characterization of a reaction intermediate was achieved by using a deuterium source. To this effect, the reaction of carbene complex **1a** with enolate **2b** and organomagnesium **3a** was quenched at −30 °C with an excess amount of deuterated hydrochloric acid (1 M DCl in Et_2O), thereby affording compound **4n** that contains a deuterium atom bonded to the α-Me group but with only 44% deuterium incorporation (see structure following Table 2).[14]

A plausible mechanistic pathway to explain the formation of compounds **4** is outlined in Scheme 3 and consecutively involves: 1) initial addition of the imide lithium enolate **2** (**2b** in the Scheme) to the carbene carbon atom of complex **1** leads to lithium alkylpentacarbonylchromate intermediate **A**; 2) subsequent double addition of the organomagnesium derivative **3a–d** to the exocyclic carbonyl group of the *N*-acyl-2-oxazolidinone moiety which entails an unprecedented removal of this chiral auxiliary group,[15] proceeds regioselectively incorporating two allenyl units and provides adduct **B**; 3) insertion of CO into the $C(sp^3)$–Cr σ bond of adduct **B** affords allenyl substituted lithium acyltetracarbonylchromate complex **C**; 4) a final intramolecular carbometalation reaction of the terminal C=C bond of one of the allene groups produces allylchromate intermediate **D.** The origin of this regioselective insertion of the allene fragment into the C(O)–Cr σ bond with selective formation of the C(O)–C bond at the

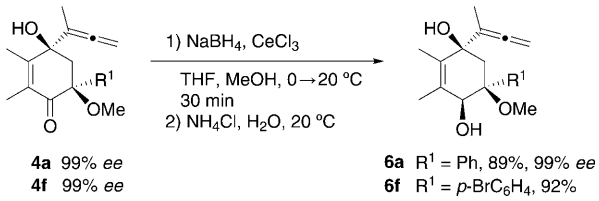


Scheme 3. Mechanistic pathway for the formation of 4-hydroxy-2-cyclohexenones **4**.

central allene carbon would be the generation of the most stable σ-allylic/π-allylic chromate complex **D**.[16] This intermediate, which has a concurrent homoenolate nature, is susceptible to further elaboration. Thus, at −30 °C intermediate **D** (R^1 = Ph, R^2 = Me) is trapped with DCl as described above. Chelation of the lithium atom to both sp^3-hybridized oxygen atoms of the chain as shown in intermediate **C** may control the selective new insertion into the C(O)−Cr bond of the adequately positioned allenyl unit.[3c] The final protonation of complex **D** leads to 4-hydroxy-2-cyclohexenone **4**.

The absolute sense of stereoinduction observed for this reaction is consistent with a chelated enolate approaching the carbene complex from the less hindered face as shown in six-membered chair-like transition state model **E** or in the Newman projection model **E′** (Scheme 3), which assumes an approximation of the reagents with an *anti* orientation of the donor and acceptor π systems and places the bulky substituent of the enolate away from the $(CO)_5Cr$ group to avoid steric interactions.[17] Notably, there is a high level of asymmetric induction observed in the addition of *N*-acetyloxazolidinone lithium enolates **2b**,**c** to the carbene carbon atom of FCCs **1** in comparison to the poor levels of enantioselection that these unsubstituted metal enolates (such as **2b**,**c**) exhibit in aldol condensation additions.[5a,18] This observed difference in diastereofacial selection may be a consequence of the larger size of the $(CO)_5Cr$ group compared with the oxygen atom of a carbonyl group. The bulkiest $(CO)_5Cr$ fragment would impose severe steric interactions with the oxazolidinone group as indicated in the approach topology **F** for addition to the opposite prochiral face of the carbene complex **1** (Scheme 3). This unfavorable steric interaction would be much lower with an oxygen atom at that position.[19]

The regioselective and diastereoselective reduction of the carbonyl group of compounds **4a**,**f** was readily accomplished under Luche conditions[20] ($NaBH_4$, anhydrous $CeCl_3$), thus affording *cis*-2-cyclohexene-1,4-diols **6a**,**f** as enantiomerically pure compounds (Scheme 4; the enantiomeric purity of **6a** was checked by HPLC analysis on a chiral stationary phase using a Chiralcel OD-H column). The configuration of compounds **6** was established from the 2D NOESY experiment on **6f**,[12] which revealed a *cis* relative disposition of the three oxygenated substituents (MeO and two OH groups). The relative configuration of the newly formed stereogenic center can be rationalized by assuming the formation of chelated intermediate **IV**[20] by coordinating the cerium ion to the oxygen atoms (the intramolecular hydrogen bond would favor the 1,3-diaxial orientation of the OH and MeO groups). In this conformation the delivery of the hydride occurred from the less hindered face of the ketone carbonyl group, thus producing the equatorial allylic alcohol (axial attack of hydride under Luche conditions is mainly observed in the reduction of substituted cyclohexenones).[20]



Scheme 4. Diastereoselective synthesis of *cis*-2-cyclohexene-1,4-diols **6**.

In summary, we have developed a novel cyclization reaction from three simple, readily available reacting materials: carbene complex, imide enolate, and propargylic→allenylic organomagnesium reagents. This process provides an efficient and diastereoselective access to densely functionalized 4-hydroxy-2-cyclohexenones that display unprecedented substitution patterns not readily accessible through other approaches. Both enantiomers of these products were prepared in a highly enantioenriched form using chiral *N*-acetyl-2-oxazolidinones in a strategy that involves the enantioselective generation of quaternary stereocenters. Further diastereoselective reduction of the carbonyl group of 4-hydroxy-2-cyclohexenones enlightens the potential synthetic application of these useful chiral building blocks.[21] This transition-metal-assisted multicomponent cyclization method proceeds through a pathway that entails new transformations: the addition of imide lithium enolates to Fischer carbene complexes is reported for the first time, the double organomagnesium addition to the exocyclic carbonyl group of *N*-acyl-2-oxazolidinones derivatives represents a new procedure for removal of this chiral auxiliary group, and the proposed intramolecular carbometalation of an allene with acyltetracarbonylchromate complexes is also an unprecedented process.

Received: July 19, 2010
Revised: September 17, 2010
Published online: November 10, 2010

Keywords: asymmetric synthesis · carbene ligands · carbocyclization · 2-cyclohexenones · multicomponent reactions

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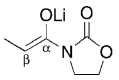
[8] Topological identification of the cyclization reaction used in a formal sense to describe the number of atoms provided by each fragment to the final cycloadduct (E = enolate anion, A = allenyl group, C = carbene ligand, CO = carbonyl ligand).

[9] Efforts to promote similar multicomponent cyclizations using β-substituted imide enolates proved to be unsuccessful. The experiments conducted with carbene complex **1a**, lithium enolate **I**, and 2-butynylmagnesium bromide (**3a**) afforded an open-chain coupling product. These results will be reported separately.



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[10] The reaction of cyclopentylcarbene complex **1i** with enolate **2b** and then with Grignard reagent **3a** previously treated with $CeCl_3$ (1.2 equiv) in THF, furnished product **4i** with very low chemical yield (10%) and low asymmetric induction (68% *ee*). In the absence of $CeCl_3$, formation of **4i** was not observed.

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[12] ^1H, ^{13}C, DEPT, HSQC, HMBC, COSY, and NOESY NMR spectra were measured.

[13] CCDC 783451 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] When quenching of the reaction with DCl (1M in Et_2O) was effected at 20 °C, incorporation of deuterium was not observed and **4a** (71%) was isolated, presumably as a result of the presence of diisopropylamine (see Ref. [3]).

[15] Recovery of the chiral auxiliary group can be achieved by flash column chromatography. For example, in the experiment of Table 2, entry 4, 76% of the chiral auxiliary group was recovered with this technique.

[16] By analogy, carbopalladation of allenes occurs highly regioselectively to form the π-allylpalladium intermediate; see for example: a) R. Grigg, A. Liu, D. Shaw, S. Suganthan, D. E. Woodall, G. Yoganathan, *Tetrahedron Lett.* **2000**, *41*, 7125 – 7128; b) S. Ma, Z. Gu, *J. Am. Chem. Soc.* **2005**, *127*, 6182 – 6183; c) Y. Abe, K. Kuramoto, M. Ehara, H. Nakatsuji, M. Suginome, M. Murakami, Y. Ito, *Organometallics* **2008**, *27*, 1736 – 1742.

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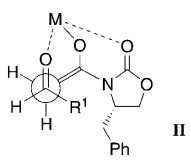
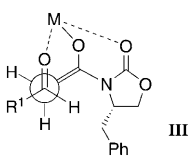
[19] Alternatively to this open transition state, a closed transition state as depicted in stereochemical models **II** and **III** has been more often proposed for aldol reactions with imide enolates (these two transition structures **II** and **III** will be of more similar energy); a) D. A. Evans, J. M Takacs, L. R. McGee, M. D. Ennis, D. J. Mathre, J. Bartroli, *Pure Appl. Chem.* **1981**, *53*, 1109 – 1127; b) D. A. Evans, C. W. Downey, J. T. Shaw, J. S. Tedrow, *Org. Lett.* **2002**, *4*, 1127—1130; see also: c) Y. Zhang, A. J. Phillips, T. Sammakia, *Org. Lett.* **2004**, *6*, 23 – 25; d) S. Shirokawa, M.



II



III

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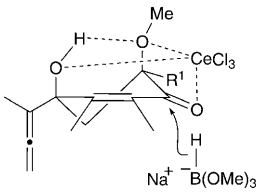
[21] In addition, compounds **4**–**6** contain a tertiary 2,3-allenol moiety. 2,3-Allenol derivatives are highly versatile synthetic intermediates that can be stereoselectively converted into numerous valuable compounds and, furthermore, these functionalized allenes are substructures found in some natural products: a) S. Ma, H. Hou, S. Zhao, G. Wang, *Synthesis* **2002**, 1643 – 1645; b) A. Fürstner, M. Méndez, *Angew. Chem.* **2003**, *115*, 5513 – 5515; *Angew. Chem. Int. Ed.* **2003**, *42*, 5355 – 5357; c) J. Li, W. Kong, C. Fu, S. Ma, *J. Org. Chem.* **2009**, *74*, 5104 – 5106; d) T. Miura, M. Shimada, P. de Mendoza, C. Deutsch, N. Krause, M. Murakami, *J. Org. Chem.* **2009**, *74*, 6050 – 6054; e) Z. Li, S. Z. Zard, *Org. Lett.* **2009**, *11*, 2868 – 2871.



IV

