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Development of a Co-Mediated Rearrangement Reaction**

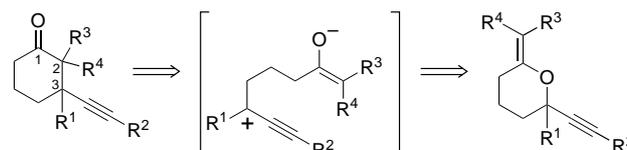
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Dedicated to Professor Peter L. Pauson

The conjugate addition of organocuprates to enones represents an important fundamental approach to the elaboration of carbonyl-containing compounds through a C–C

bond-forming reaction.^[1] This process is extremely versatile for alkyl, alkenyl, and aryl group incorporation, however, the inclusion of an alkynyl unit in this fashion is much more limited.^[2] Nonetheless, the conjugate addition of alkynyl alanes does take place in the presence of a Ni catalyst.^[3] Additionally, the use of Lewis acids such as aluminum tris(2,6-diphenylphenoxide) (ATPH),^[4] silyl triflates,^[5] and iodotrimethylsilane^[6] can promote the conjugate addition of alkynyl metal compounds to cyclic enones, although the employment of β -substituted substrates generally prevents addition completely or leads to very poor product yields.

We envisaged a strategically different approach to these compounds (Scheme 1), whereby disconnection of the C2–C3 bond in the cyclic ketone would generate an enolate bearing a



Scheme 1. Retrosynthetic analysis of the formation of cyclic ketones through an enol ether rearrangement.

distal propargylic carbocation. We further surmised that this intermediate might be generated from a cyclic enol ether. To aid scission of the propargylic C–O bond of the enol ether, we examined the effect of the hexacarbonyldicobalt unit on the alkyne because of its ability to stabilize positive charge at the α -position strongly.^[7] Notably, related intramolecular additions of enolates to cobalt-stabilized carbocations have been reported, however, these studies required the propargyl ether and enolate moieties to be prepared independently and in a linear fashion. Furthermore, problems associated with regiochemical enolate formation can result in poor cyclization regioselectivity.^[8] We anticipated that the proposed rearrangement technique would overcome some of these problems whilst providing a direct method for the preparation of α -substituted products from appropriately armed enol ether substrates. We report herein our initial findings on the scope of the rearrangement process for the synthesis of β -alkynyl substituted cyclic ketones.

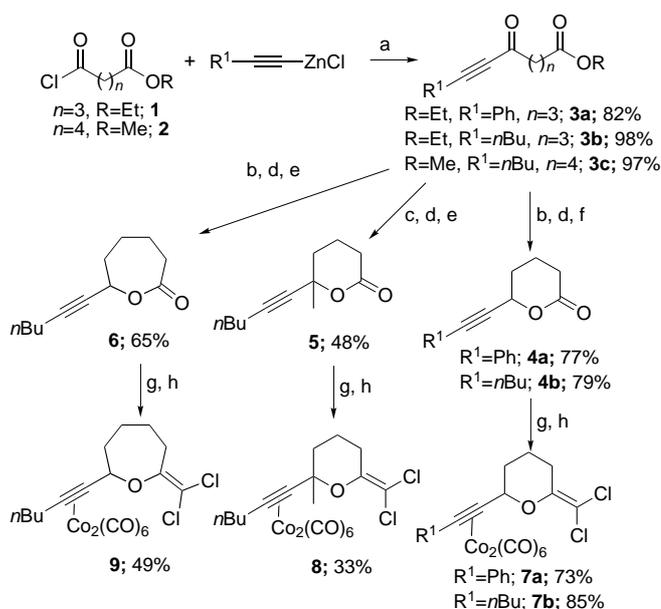
We embarked on this study by examining the rearrangement of readily available and easily handled *gem* dichloro substituted enol ethers. These compounds were prepared from the corresponding lactones following the method of Lakhri and Chapleur (Scheme 2).^[9] Addition of an alkynyl zinc reagent to commercially available **1** provided keto esters **3a** and **3b**; the homologous compound **3c** was prepared in a similar manner from **2**. Substituted δ -lactones **4a,b** were generated by a Luche reduction and saponification before ring closure. The quaternary substituted analogue **5** was prepared by an analogous procedure but with alkylation of **3b** using MeLi/TiCl₄^[10] in the initial step. ϵ -Lactone **6** was prepared from keto ester **3c** by a similar route. With the key intermediates lactones **4–6** in hand, we prepared the corresponding enol ethers in one step using PPh₃/CCl₄.^[9] Finally, exposure of the enol ethers to octacarbonyldicobalt at room

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.



Scheme 2. a) $-78^\circ\text{C}-0^\circ\text{C}$, THF, 1 h. b) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, MeOH, 25°C , 1 h. c) MeLi, TiCl_4 , Et_2O , $-78 \rightarrow -10^\circ\text{C}$. d) KOH, $t\text{BuOH}/\text{H}_2\text{O}$ (1:1), 0.5 h. e) 2-Chloro-1-methylpyridinium iodide, Et_3N , CH_2Cl_2 , 40°C , 2 h. f) DCC, DMAP, CH_2Cl_2 , 25°C , 2 h. g) PPh_3 , CCl_4 , 77°C . h) $[\text{Co}_2(\text{CO})_8]$, CH_2Cl_2 , 25°C . DCC = *N,N'*-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine.

temperature afforded complexes **7–9** as deep red solids/oils.^[11]

We initially screened a wide variety of Lewis acid promoters^[12] such as silyl triflates, Et_2AlCl , and SnCl_4 , but were disappointed to find that these produced complex reaction mixtures.^[13] In contrast, $\text{BF}_3 \cdot \text{OEt}_2$ and TiCl_4 were excellent promoters of the rearrangement process and furnished the α, α -dichloro ketone products in high yield (Table 1, entries 1 and 2). The rearrangement of 1-hexynyl substituted enol ether **7b** under our optimized conditions proceeded much more rapidly than that observed for **7a** (compare entries 1/2 with 3/4). This may reflect reduced steric congestion in **I** during C–C bond formation with $\text{R}^1 = n\text{Bu}$ in comparison to $\text{R}^1 = \text{Ph}$.^[14] Notably, this technique is applicable to the formation of quaternary substituted β -alkynyl cyclohexanones, for example, the dichloroenol ether **8** smoothly underwent rearrangement at 0°C in the presence of TiCl_4 to provide the corresponding ketone **12** in 84% yield (entry 5). We also found that the conversion of seven-membered cyclic enol ethers to the corresponding ketones is possible and indeed highly efficient in the one example studied (entry 6).^[15] Finally, ester-containing enol ether **10** was prepared from lactone **4b** by following the method of Shibasaki and co-workers^[16] and underwent rapid and clean rearrangement to the corresponding keto ester **14** in excellent yield.

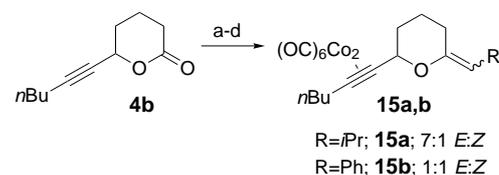
Having demonstrated the feasibility of the rearrangement process, we next turned our attention to examining alkyl substituted enol ethers which would provide a direct means of α -alkyl incorporation into the ketone products. Therefore,

Table 1. Rearrangement of ester and *gem* dichloro-substituted enol ethers.^[a]

Entry	Lewis acid	Enol ether	Product	Time	Yield [%]
1	$\text{BF}_3 \cdot \text{OEt}_2$			18 h	86
2	TiCl_4			9 h	83
3	$\text{BF}_3 \cdot \text{OEt}_2$			4 h	90
4	TiCl_4			10 min	97
5	TiCl_4			4 h	84
6	$\text{BF}_3 \cdot \text{OEt}_2$			3 h	98
7	TiCl_4			30 min	92 ^[b]

[a] All reactions were initiated at 0°C in CH_2Cl_2 with 1.5 equivalents of Lewis acid, allowed to warm to ambient temperature, and stirred until the starting material was completely consumed. [b] Complexation and rearrangement were carried out in one pot.

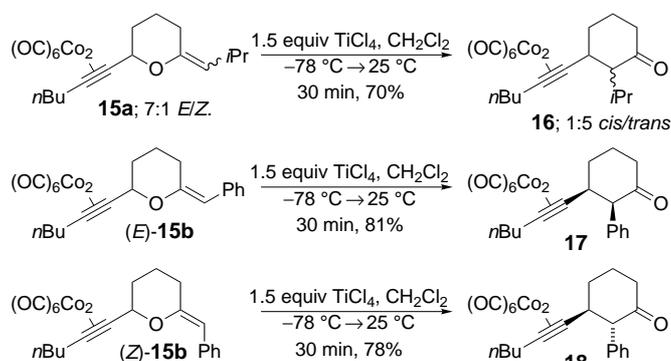
lactone **4b** was reduced to the corresponding lactol and subsequently treated with $\text{PPh}_3 \cdot \text{HBF}_4$, which provided the requisite phosphonium salt for elaboration to alkyl substituted enol ethers by the method of Ley et al.^[17] Generation of the phosphonium ylide by treatment with *n*-butyllithium at -85°C , followed by addition of isobutyraldehyde, gave enol ether **15a** as a 7:1 mixture of *E/Z* isomers on complexation with octacarbonyldicobalt. Additionally, the phenyl substituted enol ether complexes **15b** were readily generated as an equal mixture of *E/Z* isomers by an identical procedure (Scheme 3).



Scheme 3. a) 1) DIBAL-H, TMSCl, -78°C , THF, 1 h. 2) K_2CO_3 , MeOH, 84%. b) $\text{PPh}_3 \cdot \text{HBF}_4$, CH_3CN , 4 Å molecular sieves, 82°C , 2 h. c) *n*BuLi; RCHO, -85°C , THF, 1 h. d) $[\text{Co}_2(\text{CO})_8]$, hexanes, 2 h, 25°C . R = *i*Pr: **15a**, 61%; R = Ph: **15b**, 78% (over three steps from b). DIBAL-H = diisobutylaluminum hydride, TMS = trimethylsilyl.

Unfortunately, the *E/Z* isomers of **15a** were inseparable and accordingly were subjected to the rearrangement reaction as a mixture. Treatment of complexes (*E/Z*)-**15a** with TiCl_4 led to rapid and clean rearrangement to provide the corresponding α -substituted ketones **16** as a 5:1 mixture of

isomers (Scheme 4; major isomer tentatively assigned as *trans*) in high yield.^[18] In contrast to **15a**, the individual *E/Z* isomers of **15b** were readily separable by column chromatography, which allowed the rearrangement of each isomer to be studied individually. To our surprise, we found that the rearrangement of complexes **15b** proceeded stereospecifically such that (*E*)-**15b** provided the *cis*-substituted ketone **17**, whereas the *trans*-substituted ketone **18** was formed exclusively from (*Z*)-**15b**.^[19, 20]



Scheme 4. Transformation of enol complexes **15** to alkynyl ketones.

The origin of these different stereochemical outcomes is intriguing. At present, we are pursuing three possible rationales: 1) Rearrangement of complexes **15a** is mechanistically distinct from that of **15b**. 2) Enol ether isomerization (*E* ↔ *Z*) proceeds rapidly for **15a** (or the intermediate metal enolate) such that the relative ratios of *cis/trans*-**16** are determined by relative rates of rearrangement of each enol(ate) isomer. 3) Product **16** isomerizes under the reaction conditions.^[21]

In conclusion, we report a novel approach to β -alkynyl substituted cyclic ketones through a cobalt-mediated rearrangement reaction of cyclic enol ethers. This technique allows the direct and regiospecific α -incorporation of dichloro-, ester, aryl, and alkyl substituents which can be readily controlled by judicious choice of the enol ether substituent.

Experimental Section

Typical experimental procedure as exemplified by the rearrangement of complex **7b**: To a solution of **7b** (2.0 g, 3.75 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added TiCl_4 (616 μL , 10.0 mmol, 1.5 equiv) by syringe under nitrogen. The reaction mixture was stirred at 0 °C for 10 min and quenched by addition of saturated aqueous NaHCO_3 solution. The reaction mixture was poured into water, extracted with CH_2Cl_2 , dried with MgSO_4 , and the solvent removed in vacuo. Recrystallization of the crude complex afforded **11b** as a deep red solid (1.95 g, 97%), m.p. 77.1–78.3 °C; ^1H NMR (400 MHz, CDCl_3): δ = 0.99 (3H, t, J = 7.2 Hz), 1.46–1.56 (2H, m), 1.58–1.72 (2H, m), 1.75–1.86 (1H, m), 2.06–2.24 (3H, m), 2.64 (1H, dd, J = 9.0, 1.2 Hz), 2.91–3.04 (2H, m), 3.18 (1H, td, J = 14.4, 5.8 Hz), 3.63 ppm (1H, dd, J = 11.4, 3.7 Hz); ^{13}C NMR (100.6 MHz, CDCl_3): δ = 13.9, 22.7, 24.1, 32.7, 33.9, 34.5, 35.5, 57.0, 92.9 (2 × C), 101.2, 194.3, 199.8 ppm (br); $\tilde{\nu}$ = 2962 (s), 2936 (s), 2875 (s), 2092 (s), 2036 (s), 2022 (s), 1739 cm^{-1} (s); HR-MS calcd for $\text{C}_{18}\text{H}_{16}\text{O}_7\text{Cl}_2\text{Co}_2$: 531.8937, found: 531.8941.

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- E/Z* Enol ether assignments of **15a** and **15b** were made by comparison to ^1H NMR spectroscopic data reported in reference [16]. The configuration of isomers (*E*)/(*Z*)-**15a** could also be assigned on the basis of the chemical shifts of the ^{13}C NMR signal arising from the carbon atom β to the ether oxygen: D. Barillier, M. P. Strobel, L. Morin, D. Paquer, *Tetrahedron* **1983**, *39*, 767.
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Toromanoff, *Tetrahedron* **1985**, *41*, 5045. Spectral and analytical data for all new compounds can be found in the Supporting Information. CCDC-177450 (**7a**) and CCDC-177451 (**11a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

- [21] Subjection of individual isomers *cis*- and *trans*-**16** to 1.5 equiv TiCl_4 at $-78^\circ\text{C} \rightarrow 25^\circ\text{C}$ for 90 min resulted in only slight (ca. 5–10%) isomerization at the α center. Therefore, the lack of stereospecificity in **15a** \rightarrow **16** cannot be fully explained by rapid equilibration at the α -alkyl moiety of the product.

Rapid Phase Fluxionality as the Determining Factor in Activity and Selectivity of Highly Dispersed, Rh/Al₂O₃ in deNO_x Catalysis**

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Rhodium has for many years been a primary component in the make up of auto-exhaust catalysts because of its ability to catalyze the selective reduction of NO_x to N₂.^[1,2] A historical view of this type of system is of an active, but essentially static, phase comprising particulate metal; it is from this axiom that studies of metal single crystals^[2] have been accepted as models of macroscopic catalyst behavior. However, it has been established by IR^[3] and XAFS^[4] (X-ray absorption fine structure) spectroscopy that small rhodium particles (on alumina) undergo

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corrosive chemisorption to yield a mononuclear $\{\text{Rh}^{\text{I}}(\text{CO})_2\}$ species. In addition, the oxidation of Rh/Al₂O₃ under an atmosphere of air and oxygen has also been demonstrated by XAFS.^[5] Recently, using in situ, microreactor-based, energy-dispersive EXAFS (EDE)^[6] and mass spectrometry^[7] we have used the improved time resolution of these techniques to demonstrate that Rh on alumina is rapidly oxidized by NO.^[8] Herein we utilize these procedures to probe the correlation between metal structure and catalytic performance for the reduction of NO by H₂.

Figure 1 shows the total NO conversion and N₂O (mass 44) production as a function of reaction temperature and feedstock composition. The net conversions and selectivity of the

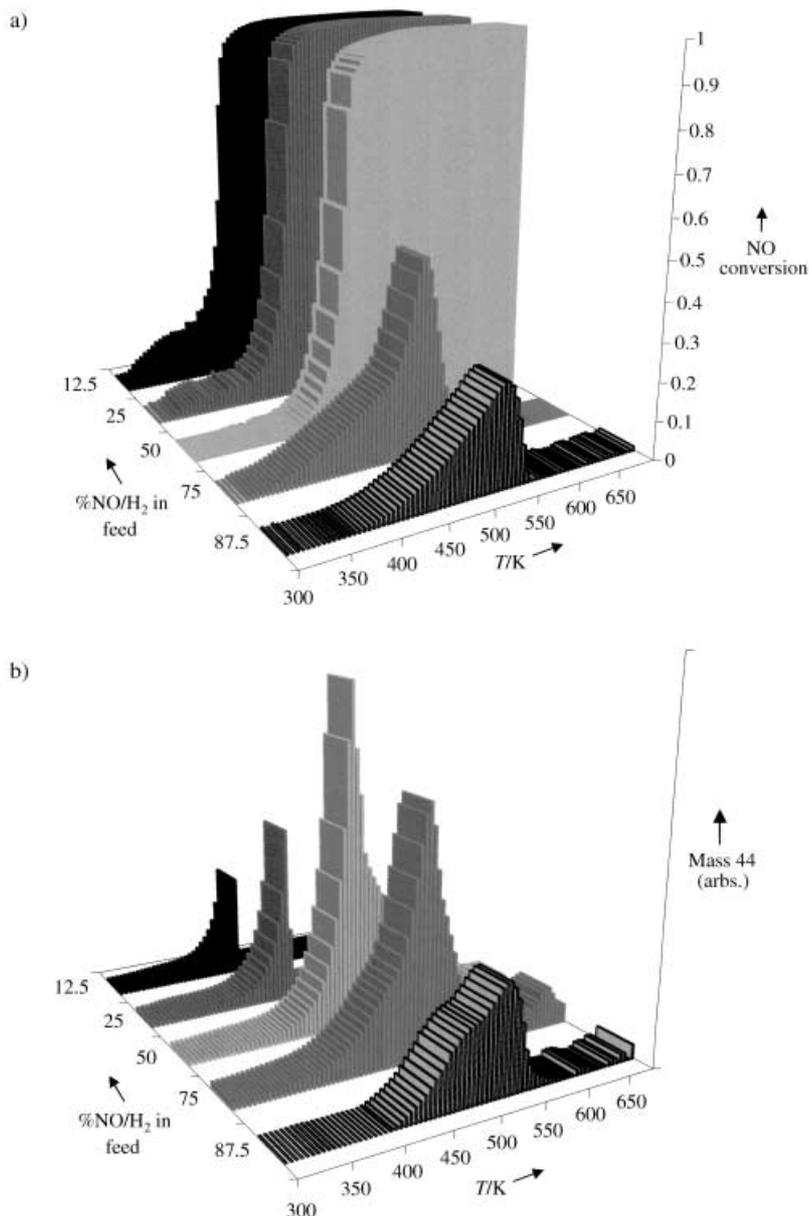


Figure 1. a) NO conversion as a function of reaction temperature and active feedstock composition in the reduction of NO/He by H₂/He over 5 wt % Rh/ γ -Al₂O₃ catalysts derived from $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$: catalyst charge: 20 mg; NO–H₂/He = 4/96; total gas flow = 10 mL min⁻¹, GHSV ca. $\sim 10^4$ h⁻¹. b) N₂O production (mass 44) as a function of reaction temperature and active feedstock composition in the reduction of NO by H₂ over 5 wt % Rh/ γ -Al₂O₃ catalysts derived from $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$: conditions as for Figure 1 a.