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Investigation of a Stereoselective Co-Mediated Rearrangement Reaction

David R. Carbery,[†] Serge Reignier,[†] Neil D. Miller,[‡] Harry Adams,[†] and Joseph P. A. Harrity*,[†]

Department of Chemistry, University of Sheffield, Brook Hill, Sheffield S3 7HF, U.K., and Department of Medicinal Chemistry, Neurology CEDD, GlaxoSmithKline Research and Development, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY, U.K.

j.harrity@sheffield.ac.uk

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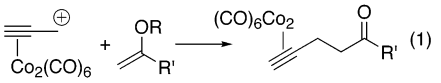
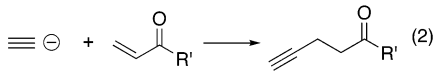
A stereocontrolled approach to α-alkyl β-alkynyl cyclohexanones is reported through a Lewis acid mediated rearrangement reaction of enol ethers bearing an Co-alkyne moiety. The reaction proceeds with high levels of stereoselectivity in the presence of Ti- and B-Lewis acids to provide a range of α,β-disubstituted cyclohexanones in high yield although the products are prone to epimerization at the α-position in the presence of the B-promoter system. The potential for an enantioselective variant of this process is outlined, and a rationale for the observed stereochemical trends and detailed structural analyses of the ketone products are described.

Introduction

The stabilization of propargylic cations by a dicobalt hexacarbonyl cluster was reported by Nicholas and Pettit 30 years ago and has since provided one of the richest areas of research in transition-metal organometallic chemistry.[1] These intermediates have found widespread synthetic utility due to their participation in a variety of nucleophilic addition reactions. Recent studies on the nature of the so-called Nicholas carbocations by Mayr and co-workers have shown that they are particularly suited to reactions with π-nucleophiles.[2] In this context, the addition of enolates and enol ethers to Nicholas carbocations provides β-alkynyl ketones and esters (eq 1). This process is complimentary to conjugate addition strategies shown in eq 2 since these same intermediates are not generally readily accessed due to the low propensity for alkyne transfer from alkynylcuprate reagents.[3,4]





A drawback to the Co-mediated approach outlined in eq 1 is that the propargyl cation surrogate (usually a propargyl ether) and enolate moieties must be prepared independently and in a linear fashion. Furthermore, problems associated with regiochemical control during enolate formation can result in product mixtures.[5] To address these issues, we have recently been investigating a Lewis acid mediated rearrangement reaction[6] as an effective means of generating cyclic β-alkynyl ketones.[7] As outlined in Scheme 1, we envisaged that Lewis acid mediated rupture of **1** would provide the Nicholas carbocationic intermediate **2** *complete with regiodefined enolate moiety*. We were particularly intrigued by the potential for stereocontrol during the ring-closing reaction and anticipated that the stereochemistry of the enol ether in **1** might be manifested in the newly formed α-stereogenic center in **3**. We wish to report herein the results of our studies toward the employment of the rearrangement process in the stereoselective preparation of α-functionalized β-alkynyl cyclohexanones.

[†] University of Sheffield.

[‡] GlaxoSmithKline Research and Development.

(1) (a) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207. (b) Caffyn, A. J. M.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Hegedus, L. S., Eds.; Pergamon: Oxford, 1995; Vol. 12, p 685. (c) Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809. (d) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133.

(2) Kuhn, O.; Rau, D.; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 900.

(3) (a) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210. (b) Posner, G. H.; Chapdelaine, M. J.; Lentz, C. M. *J. Org. Chem.* **1979**, *44*, 3661.

(4) For examples of successful conjugate addition reactions of alkynes to cyclic enones, see: (a) Hansen, R. T.; Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1978**, *100*, 2244. (b) Schwartz, J.; Carr, D. B.; Hansen, R. T.; Dayrit, F. M. *J. Org. Chem.* **1980**, *45*, 3053. (c) Maruoka, K.; Shimada, I.; Imoto, H.; Yamamoto, H. *Synlett* **1994**, 519. (d) Kim, S.; Park, J. H.; Jon, S. Y. *Bull. Korean Chem. Soc.* **1995**, *16*, 783. (e) Kim, S.; Park, J. H. *Synlett* **1995**, 163. (f) Eriksson, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182.

(5) (a) Tyrrell, E.; Heshmati, P.; Sarrazin, L. *Synlett* **1993**, 769. (b) Magnus, P.; Carter, P.; Elliot, J.; Lewis, R.; Harling, J.; Pitterna, T.; Bauta, W. E.; Fortt, S. *J. Am. Chem. Soc.* **1992**, *114*, 2544.

(6) For a related rearrangement reaction which uses oxonium ion stabilization, see: (a) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Lim, J. J. *Org. Lett.* **1999**, *1*, 909. (b) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Beauchamp, T. J. *Org. Lett.* **1999**, *1*, 913. (c) For a related O to C rearrangement see: Buffet, M. F.; Dixon, D. J.; Edwards, G. L.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1815. (d) Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720. (e) Sollogoub, M.; Mallet, J.-M.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 362.

(7) For a preliminary report of this work, see: Carbery, D. R.; Reignier, S.; Myatt, J. W.; Miller, N. D.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2584.

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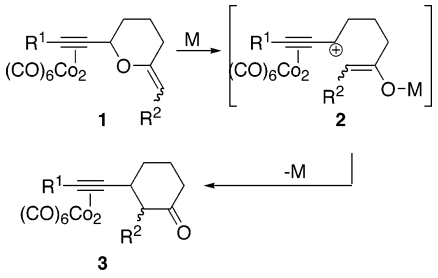
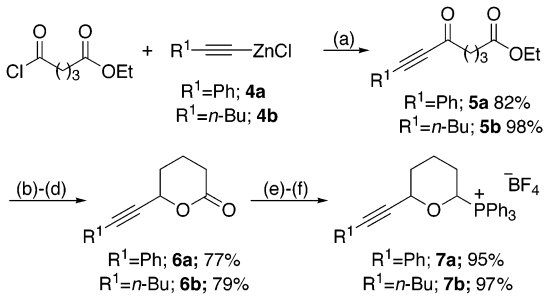
SCHEME 1



SCHEME 2[a]



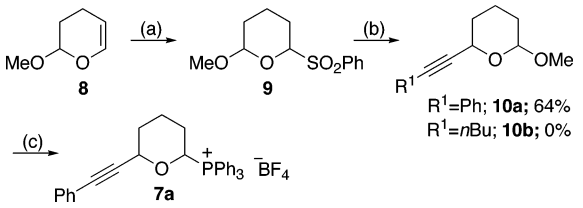
[a] Key: (a) −78 to 0 °C, THF, 1 h; (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 25 °C, 1 h; (c) KOH, *t*-BuOH−H_2O (1:1), 0.5 h; (d) DCC, DMAP, CH_2Cl_2, 25 °C, 2 h; (e) (i) DIBAL-H, TMSCl, −78 °C, THF, 1 h; (ii) K_2CO_3, MeOH. (f) $PPh_3 \cdot HBF_4$, CH_3CN, 4 Å MS, 82 °C, 2 h.

Results

1. Synthesis of Alkyne-Substituted Enol Ethers. Inspection of the literature suggested that the simplest and most general method for the preparation of substrate enol ethers would be the Wittig coupling protocol developed by Ley and co-workers.[8] Accordingly, we investigated two routes to the requisite pyranyl triphenylphosphonium salts. Our first approach was concerned with the preparation of alkyne-substituted δ-lactones which is outlined in Scheme 2. Addition of an alkynylzinc reagent **4a/b** to commercially available ethyl glutaryl chloride provided keto esters **5a/b**. Luche reduction, saponification, and DCC-mediated lactonization provided compounds **6a/b** which were transformed to the phosphonium salts **7a/b** upon reduction with DIBAL-H and treatment with triphenylphosphonium tetrafluoroborate.

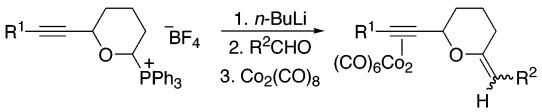
While this route was fairly efficient and provided large quantities of **7a/b**, we sought a more expedient approach to these compounds and subsequently developed an alternative and shorter route as shown in Scheme 3.[9] Treatment of commercially available pyran **8** with phenylsulfinic acid provided **9**, which was treated with the appropriate alkynylzinc reagent to incorporate the alkyne moiety. Unfortunately, while this transformation was quite straightforward with the phenylacetylene-derived organozinc reagent, this technique could not be carried out successfully when applied in an analogous way to 1-hexyne. Nonetheless, treatment of pyranyl ether **10a** with triphenylphosphonium tetrafluoroborate furnished the phosphonium salt **7a** in good yield.

SCHEME 3[a]



[a] Key: (a) $PhSO_2H$, CH_2Cl_2, 25 °C, 2 h; 78%; (b) RC≡CZnBr, THF; (c) $PPh_3 \cdot HBF_4$, CH_3CN, 4 Å MS, 82 °C, 2 h; 85%.

TABLE 1. Synthesis of Enol Ether Complexes



Entry	R^1	R^2	*E/Z*	Yield
1	*n*-Bu	Ph	1:1[a]	**11;** 78%
2	Ph	Ph	1.2:1[a]	**12;** 68%
3	*n*-Bu	*i*-Pr	7:1[b]	**13;** 61%
4	Ph	*i*-Pr	8:1[b]	**14;** 62%
5	*n*-Bu	*t*-Bu	100:0	**15;** 26%
6	Ph	*t*-Bu	100:0	**16;** 67%
7	Ph		4:1[b]	**17;** 61%
8	Ph	Et	3:1[b]	**18;** 46%
9	Ph	Me	3:1[b]	**19;** 68%

[a] *E*/*Z* isomers were separable by column chromatography. [b] *E*/*Z* isomers were inseparable and were used in subsequent reactions as a mixture.

Having developed a flexible method for the preparation of the phosphonium salts, we set about preparing a series of enol ether substrates. Generation of the phosphonium ylide by treatment with *n*-butyllithium at −78 °C followed by addition of the appropriate aldehyde gave the desired enol ethers in good yield and in various ratios of *E*/*Z* isomers after complexation with dicobalt octacarbonyl.[10] The flexibility of this method allowed us to prepare enol ether substrates bearing alkyl groups having a range of steric sizes as shown in entries 1−9 in Table 1. The *E*/*Z* isomers of phenyl-substituted enol ethers **11** and **12** could be separated chromatographically, but all other mixtures were found to be inseparable.

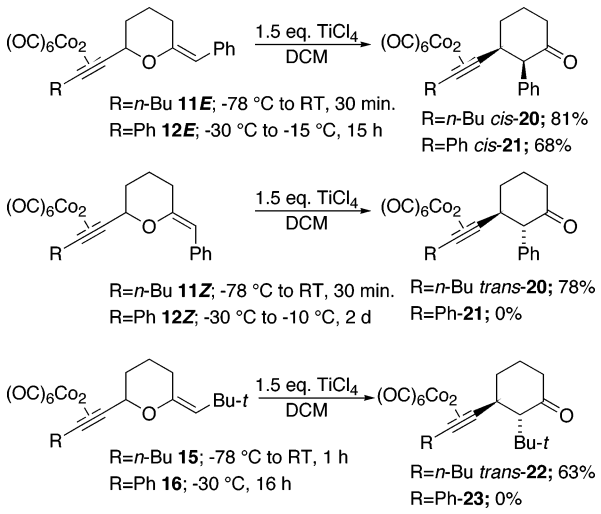
2. Enol Ether Rearrangement Reactions. We next turned our attention to the key rearrangement reactions. For simplicity, we first examined the rearrangement of isomerically pure enol ethers with a view to uncovering the stereochemical course of the rearrangement process; the results are outlined in Scheme 4. Treatment of (*E*)-phenyl-substituted enol ethers **11*E*** and **12*E*** with $TiCl_4$ resulted in a smooth rearrangement reaction to provide the cis-disubstituted cyclohexanones **20** and **21** in high yield. Notably, the rearrangement of **12*E*** proceeded much more slowly than that of **11*E***, and careful temperature control was required to minimize reaction times while preventing excessive elimination to the enyne (particularly problematic at temperatures > −20 °C). We envisage that the observed difference in rates of ring closure is

(8) Ley, S. V.; Lygo, B.; Organ, H. M.; Wonnacott, A. *Tetrahedron* **1985**, *41*, 3825.

(9) Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293.

(10) The configuration of *E*/*Z* isomers was assessed by NOESY studies or by inspection of the ^{13}C NMR chemical shifts of the carbon β to the ether oxygen: Barillier, D.; Strobel, M. P.; Morin, L.; Paquer, D. *Tetrahedron* **1983**, *39*, 767.

SCHEME 4

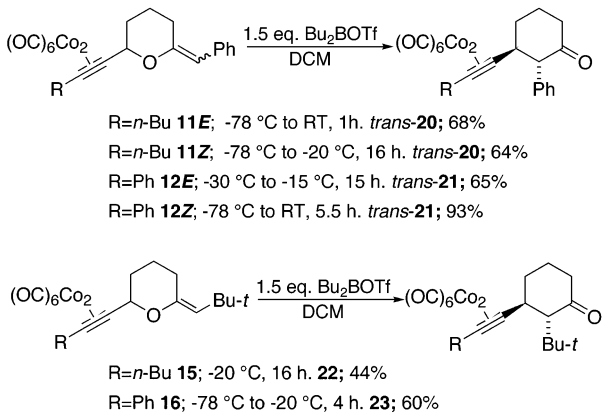


due to the relative steric size of the Ph substituent on the alkyne when compared to that of *n*-Bu. Indeed, the observation that bulky alkyne substituents can effect the rate of nucleophile addition to Nicholas carbocations has been previously reported by Schreiber and co-workers.[11] We next examined the rearrangement reaction of *Z*-phenyl-substituted enol ethers **11*Z*** and **12*Z***. Treatment of **11*Z*** with $TiCl_4$ provided the corresponding trans-cyclic ketone **20** in good yield; however, we were disappointed to find that phenylacetylene-derived enol ether **12*Z*** did not provide ketone products but gave a mixture of compounds resulting from hydration and elimination of the carbocationic intermediate. The stereochemistry of the product ketones **20** and **21** was assigned on the basis of the ^{1}H NMR coupling constants observed at the benzylic position (trans isomer: H_{Bn} d, J = 11.6 Hz; cis isomer: H_{Bn} d, J = 5.2 Hz) and were consistent with those reported for related compounds.[12] Indeed, the stereochemistry of *trans*-**20** was later confirmed by X-ray crystallography.[13]

Superficially, a similar outcome was observed in the rearrangement of enol ethers bearing the bulky *t*-Bu group. Specifically, rearrangement of **15** proceeded in moderate yield to provide the ketone **22** as a single isomer which was later assigned as trans (vide infra); in contrast, **16** did not produce cyclohexanone product in the presence of $TiCl_4$ under a range of conditions (Scheme 4).

In an effort to improve the scope of the rearrangement reaction with respect to substrates bearing a phenylacetylene moiety (i.e., **12*Z*** and **16**), we undertook a brief study of a range of alternative Lewis acids. Our initial findings suggested that Bu_2BOTf was a promising alternative to $TiCl_4$ and we reexamined the rearrangement of substrates **11**, **12**, **15** and **16** with this reagent, the results are outlined in Scheme 5. We were pleased to find

SCHEME 5



that the change in Lewis acid promoter allowed all enol ether substrates to undergo a smooth transformation to the appropriate ketones. Additionally, all substrates provided the corresponding trans-substituted diastereomeric ketones only. The formation of trans products in all cases suggested to us that the ketones were prone to epimerization under the reaction conditions, and this was further supported by the following experiments: (1) Quenching the B-mediated rearrangement of substrate **12*E*** at −30 °C after only 1 h provided a 1.4:1 mixture of *cis*/*trans*-ketones **21**, in 52% combined yield. (2) Subjection of *cis*-**21** to Bu_2BOTf (DCM, −78 to −20 °C, 16 h) resulted in complete isomerization to *trans*-**21** (86% isolated yield). Unfortunately, the unavailability of *cis*-**22/23** meant that we could not carry out a similar control reaction in the *t*-Bu-substituted series; notably, however, the relative configuration of compounds *trans*-**22/23** did not change on exposure to Bu_2BOTf.

The relatively routine stereochemical assignments of α-Ph-substituted ketones by ^{1}H NMR spectroscopy was not successful in the case of α-*t*-Bu analogues; however, ketone **23** proved to be crystalline and was therefore submitted for X-ray crystallographic analysis. While the X-ray structure allowed us to unambiguously assign the trans stereochemistry, it also proved to uncover a remarkable and unexpected conformation. As outlined in Figure 1, ketone **23** was found to adopt a chair conformation with both the Co-cluster and the *t*-Bu moieties disposed in axial positions, presumably to avoid costly gauche interactions that would be encountered in the alternative chair conformation where both units were in equatorial positions. The chair conformation was found to be slightly distorted with the C(16)−C(17) bond approximately 8° out of plane with the C(19)−C(20) bond.[14] Indeed, this conformation accounted for the very small $J_{H\alpha-H\beta}$ coupling constant observed in the ^{1}H NMR spectrum (H_α at C-2 appears as a slightly broadened singlet at 2.45 ppm). Notably, a similar splitting pattern in **22** was noted and suggested the same configuration and a similar conformation in this compound.

We believe that the observed configuration and conformational bias is a consequence of the preference for large alkyl groups in 2-substituted cyclohexanones to adopt an axial orientation (2-alkyl effect)[15] and the aforementioned unfavorable gauche interactions encoun-

(11) For a detailed discussion of the dynamic behaviour of Nicholas carbocations as well as their reactivity and stability, see: Schreiber, S. L.; Klimas, M. T.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749.

(12) (a) Rettig, M.; Sigrist, A.; Rétey, J. *Helv. Chim. Acta* **2000**, *83*, 2246. (b) Hatzigrigoriou, E.; Wartski, L.; Seyden-Penne, J.; Toromanoff, E. *Tetrahedron* **1985**, *41*, 5045.

(13) Crystallographic data for *trans*-**20** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 194399. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

(14) Taken as an average of the two smaller bisecting angles.

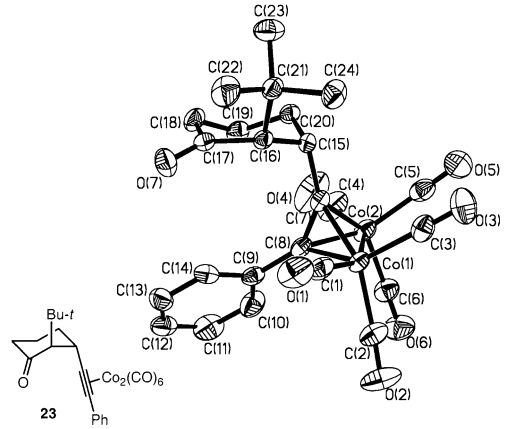


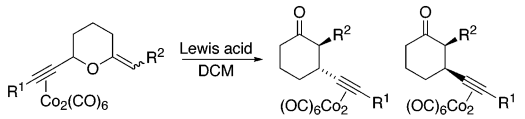
FIGURE 1. ORTEP diagram of ketone **23**. Thermal ellipsoids are drawn at the 50% probability level. Selected bond distances (Å) and angles (deg): Co(1)−Co(2) 2.459(6), Co(1)−C(7) 1.986(3), Co(2)−C(7) 1.982(3), Co(1)−C(8) 1.993(3), Co(2)−C(8) 1.957(3), C(7)−C(8) 1.337(4); C(15)−C(16)−C(17) 113.8(2), C(16)−C(17)−C(18) 120.0(3), C(7)−C(15)−C(16)−C(21) 140.9(3). For clarity, only one of the two enantiomeric structures in the asymmetric unit is shown.

tered in the diequatorial conformation. Additionally and importantly, to the best of our knowledge this X-ray cystal structure represents the first crystallographic evidence for an axial α-*t*-Bu cyclohexanone and demonstrates that these species can exist in a chair rather than a boat or twist boat conformation.[15a,b,e,16,17]

These preliminary experiments suggested that high levels of diastereocontrol could be obtained in the rearrangement reaction; however, the stereoselectivity of this transformation appeared to vary with Lewis acid promoter and substrate. In an effort to further probe this issue, we turned our attention to the rearrangement of the remaining substrates which were employed directly as *E*/*Z*-isomer mixtures; the results are outlined in Table 2.

We first examined the Ti-mediated rearrangement of *i*-Pr-substituted enol ether derived from 1-hexyne **13** which was employed as a 7:1 *E*/*Z* mixture. Efficient conversion of **13** to a 5:1 trans/cis mixture of ketones **24** (stereochemical assignments described later) was observed that matched closely the expected product ratio for a stereoselective rearrangement whereby *E*-enol ether → *trans*-ketone and *Z*-enol ether → *cis*-ketone (Table 2, entry 1). Indeed, the fact that starting material and product isomer ratios were not identical was to be expected in a reaction that did not provide quantitative conversion to ketone given that individual enol ether isomers will not necessarily rearrange to the appropriate ketone in precisely the same yield. Rearrangement of the related phenylacetylene derived substrate **14** was very inefficient, and only *trans*-**25** could be isolated from the reaction mixture, albeit in low yield (Table 2, entry 2). Finally, Et- and Me-substituted enol ethers **18** and **19**

TABLE 2. Enol Ether Rearrangement Reactions



Entry	Substrate	R^1	R^2	*E*/*Z*	Lewis acid	Conditions	Yield (*trans*:*cis*)
1	**13**	*n*Bu	*i*Pr	7:1	$TiCl_4$	-78 °C to 25 °C, 30 min.	**24**; 70% (5:1)
2	**14**	Ph	*i*Pr	8:1	$TiCl_4$	-30 °C, 16 h	**25**; 29% (100:0)
3	**18**	Ph	Et	3:1	$TiCl_4$	-30 °C, 16 h	**26**; 56% (1:3)
4	**19**	Ph	Me	3:1	$TiCl_4$	-30 °C to -20 °C, 13 h	**27**; 70% (1:5)
5	**13**	*n*Bu	*i*Pr	7:1	Bu_2BOTf	-78 °C to -20 °C, 2 h	**24**; 56% (100:0)
6	**14**	Ph	*i*Pr	8:1	Bu_2BOTf	-78 °C to -20 °C, 2 h	**25**; 71% (100:0)
7	**17**	Ph		4:1	Bu_2BOTf	-78 °C, 30 min.	**28**; 47% (0:100)
8	**18**	Ph	Et	3:1	Bu_2BOTf	-78 °C to -20 °C, 4 h	**26**; 52% (1:3)
9	**19**	Ph	Me	3:1	Bu_2BOTf	-78 °C to -35 °C, 90 min.	**27**; 65% (1:3)

underwent rearrangement in moderate to good yield to provide ketone products **26** and **27**, respectively (Table 2, entries 3 and 4). In these cases, the predominance of *E*-enol ether starting materials was reflected in the generation of cis diastereomers as the major products in each case.

The action of Bu_2BOTf on all substrates in Table 2 (entries 5−9) provided the same major isomer to that observed in Ti-mediated rearrangement reactions. Nonetheless, as observed in the case of phenyl-substituted enol ethers, the ketones were prone to epimerization at higher reaction temperatures or over long reaction times. For example, methyl-substituted enol ether **19** provided ketone **27** as a 3:1 cis/trans mixture in 65% yield by conducting the reaction at −78 °C over 45 min. followed by −35 °C over 45 min (Table 2, entry 9). In contrast, when the reaction was conducted at −20 °C over 16 h only the trans isomer was isolated in 47% yield.

The stereochemical assignments of compounds **24**−**28** varied in complexity. Whereas α-Me-substituted ketone **27** was readily assigned by inspection of the coupling constants at the β-H, the remaining complexes had more complex spectra which made such routine assignments more difficult. Once again, however, we were pleased to find that suitable crystals of compounds **25** and **28**[18] could be grown and we were therefore in a position to employ X-ray analysis to assign their relative configurations.

Discussion

Ti-Promoted Rearrangement Reaction. The Ti-promoted rearrangement reactions of enol ethers bearing small to moderately sized alkyl groups (Me, Et, Ph) follow a consistent pattern whereby *E*-enol ether is converted to cis-disubstituted ketone and the *Z*-enol ether is converted to the corresponding trans diastereomer (substrates **11** and **12** in Scheme 4 and entries 3 and 4 in

(15) (a) Allinger, N. L.; Blatter, H. M. *J. Am. Chem. Soc.* **1961**, *83*, 994. (b) Rickborn, B. *J. Am. Chem. Soc.* **1962**, *84*, 2414. (c) Cotterill, W. D.; Robinson, M. J. T. *Tetrahedron* **1964**, *20*, 765. (d) Cotterill, W. D.; Robinson, M. J. T. *Tetrahedron* **1964**, *20*, 777. (e) Nishio, M.; Hirota, M. *Tetrahedron* **1989**, *45*, 7201. (e) For a general discussion, see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 731−737.

(16) Djerassi, C.; Hart, P. A.; Warawa, E. J. *J. Am. Chem. Soc.* **1964**, *86*, 78.

(17) This conformation of **23** is reminiscent of *all-trans*-1,2,3,4,5,6-hexaisopropylcyclohexane in which all groups are located in the axial position to minimise repulsive steric interactions in the all-equatorial conformation. See: (a) Goren, Z.; Biali, S. E. *J. Am. Chem. Soc.* **1990**, *112*, 893. (b) Golan, O.; Goren, Z.; Biali, S. E. *J. Am. Chem. Soc.* **1990**, *112*, 9300.

(18) The stereochemical assignment of related complex **24** was reported previously;[7] furthermore, the ^1H NMR chemical shift values and coupling constants measured for this compound match closely those observed for **25**. Crystallographic data for *trans*-**25** and *cis*-**28** are included in the Supporting Information.

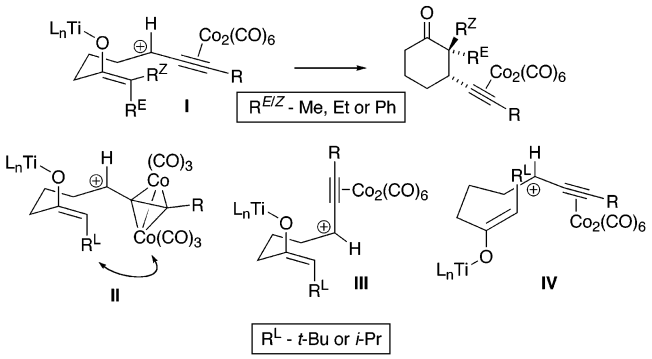


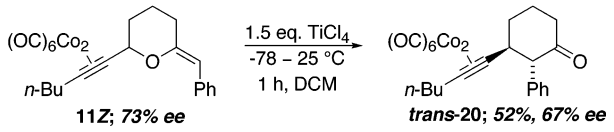
FIGURE 2.

Table 2). In contrast, sterically larger *t*-Bu-substituted enol ether **15** (Scheme 4) and *i*-Pr-substituted enol ether **13** (entry 1, Table 2) show an opposite trend whereby *E*-enol ether is transformed to *trans*-ketone. We chose to exclude substrate **14** (entry 2, Table 2) from our analysis because of the poor efficiency of the rearrangement reaction in this case (29% yield). We believe that these observations suggest that the Ti-promoted reactions of enol ethers bearing Me, Et, and Ph substituents proceeds through a chair transition state **I** as depicted in Figure 2. In the case of the *t*-Bu- and *i*-Pr-substituted substrates, the different stereochemical outcome suggests a different transition state. Indeed, in these cases it is feasible that a similar chair transition state would engender greater unfavorable steric interactions between the Co-cluster and these larger groups (**II**, Figure 2). Indeed, 180° rotation of the propargylic carbon would alleviate this steric clash and alternative chair transtion state **III** may operate in this case. The observation that the *t*-Bu and Co-cluster moieties can be orientated in diaxial positions in a chair conformation (Figure 1) suggests that this mode of ring closure is not unreasonable. Finally, a transition state which orientates the Co-cluster in a pseudoequatorial position can be envisaged via boatlike transition state **IV**.

B-Promoted Rearrangement Reaction. The question of stereoselectivity in the B-mediated rearrangement reactions is somewhat clouded by the tendency for the cis-substituted ketones to undergo isomerization to the trans isomers under the reaction conditions. Isomerization can be slowed by maintaining low reaction temperatures; however, this is usually at the expense of reaction efficiency. This was particularly evident in the but-1-enyl-substituted enol ether **17** rearrangement (entry 7, Table 2) which must be carried out at −78 °C over a short reaction time because of its tendency to undergo Lewis acid mediated Prins cyclization reactions.[19] Nonetheless, the fact that similar stereochemical trends to the Ti-mediated reaction can be observed at lower temperatures suggests that the reaction proceeds in a manner analogous to that mediated by $TiCl_4$ before epimerization processes take over.

Enantioselective Rearrangement Reaction. Having investigated conditions that would allow the generation of α-alkyl *β*-alkynyl ketones with high levels of diastereocontrol, we have recently begun studies toward the generation of these compounds with control of absolute stereochemistry. In particular, we were intrigued by the potential for the rearrangement reaction to maintain stereochemical integrity at the propargylic stereogenic center. Indeed, Muehldorf and co-workers have demonstrated that intramolecular Co-promoted Friedel−Crafts reactions can take place at an enantioenriched propargylic center with minimal racemization.[20] Accordingly, we prepared enantioenriched enol ether complex **11*Z*** by employing a slightly modified version of the routes outlined in Scheme 2 and Table 1 (vide supra). Our preliminary studies suggest that an enantioselective rearrangement is viable. As outlined in Scheme 6, we were pleased to find that the Ti-mediated rearrangement of **11*Z*** provided *trans*-**20** in good yield with typically high levels of diastereocontrol, but more importantly, with minor levels of racemization at the propargylic center.[21] The scope of this highly stereoselective process is currently under investigation in our laboratories; nonetheless, this observation demonstrates the potential of the Co-mediated rearrangement strategy for the regio- and stereodefined introduction of functionality into cyclic ketone products.

SCHEME 6



11*Z*; *73% ee* **trans-20; *52%, 67% ee***

Conclusions

We have developed a stereocontrolled approach to α-alkyl *β*-alkynyl cyclohexanones through a Co-mediated rearrangement reaction of enol ethers. The employment of $TiCl_4$ Lewis acid promoter allows the rearrangement reaction to proceed stereoselectively where the product stereochemistry is dictated by the geometry of starting enol ether double bond. Those substrates that have proved problematic in the Ti-mediated reaction can be transformed to ketone products through the utilization of Bu_2BOTf. While the B-mediated rearrangement reaction appears to show similar stereochemical trends at lower temperature, the ketone products are prone to epimerization during reaction to the thermodynamically more stable trans diastereomers. Finally, preliminary results show the potential of this strategy for the introduction of funtionality at the α- and *β*-positions with absolute control of stereochemistry.

Additionally, this methodology has also uncovered some notable and unambiguous conformational data through X-ray crystallographic analysis. Of particular interest is the α-*t*-Bu cyclohexanone **23** which shows an axial *t*-Bu moiety in a cyclohexanone chair conformation.

(19) These substrates undergo rearrangement and Prins cyclisation even at low temperature in the presence of $TiCl_4$: Carbery, D. R.; Miller, N. D.; Harrity, J. P. A. *Chem. Commun.* **2002**, 1546.

(20) Muehldorf, A. V.; Guzman-Perez, A.; Kluge, A. F. *Tetrahedron Lett.* **1994**, *35*, 8755.

(21) Enantioselective reduction of ketone **5b** (Scheme 2) to the propargylic alcohol was carried out using the method of Midland and co-workers: Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. The enantiomeric purity of the starting complex **11*Z*** could not be determined directly but was measured at the lactone precursor (**6b**, Scheme 2). The absolute configurations of **11*Z*** and ***trans*-20** have not been determined.

The extension of these studies to other cyclic ketones of different ring sizes and with greater substitution is currently underway and will be reported in due course.

Experimental Section

General Methods. IR spectra were recorded on a FT spectrometer, ν_{max} in cm^{-1}. NMR spectra were recorded on a 250 or 400 MHz spectrometer; chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$: δ 7.27 ppm for ^1H, $CDCl_3$: δ 77.0 ppm for ^{13}C, with complete proton decoupling). Enantiomer ratios were determined by chiral HPLC with a CHIRACEL OD (25 cm × 0.46 cm) chiral column. HRMS were recorded in Electrospray mode (TOF ES) or by using FAB, EI, or CI techniques. Melting points are uncorrected. Preparative routes to phosphonium salts **7a**,**b** and analytical data for compounds **11**, **13**, **20**, and **24** have been reported elsewhere.[7]

All reactions were conducted in flame-dried glassware under an inert atmosphere of dry nitrogen. All reagents were used as received from commercial suppliers unless otherwise stated. Tetrahydrofuran and diethyl ether were distilled from sodium metal/benzophenone ketal. Petroleum ether (40−60 °C) was distilled from molecular sieves. Dichloromethane and toluene were distilled from calcium hydride. *N*,*N*-Diisopropylamine was distilled from potassium hydroxide.

(*E*)/(*Z*)-Dicobalthexacarbonyl-2-benzylidene-6-phenylethynyltetrahydropyran 12. Phosphonium salt **7a** (641 mg, 1.20 mmol, 1.0 equiv) was dissolved in THF (8 mL) and cooled to −78 °C. *n*-Butyllithium (2.5 M in hexanes) (530 μL, 1.32 mmol, 1.1 equiv) was added dropwise generating a deep red solution that was stirred for a further 5 min prior to addition of neat benzaldehyde (150 μL, 1.48 mmol, 1.2 equiv). The reaction was stirred for a further 2 h at −78 °C, warmed to room temperature, and poured into water. The product was extracted twice with ether (2 × 15 mL); the organic extracts were washed with water (2 × 15 mL) and brine (15 mL), dried over magnesium sulfate, and filtered through a pad of Celite; and the solvent was removed in vacuo. The crude mixture was dissolved in 1 mL of ether and treated with petroleum ether (20 mL) before cooling to −78 °C and decanting the organic extracts from the formed precipitates through a pad of Celite. Solvent was removed in vacuo and the crude enol ether dissolved in DCM (5 mL) before being added via cannula to octacarbonyldicobalt (380 mg, 1.11 mmol, 1.1 equiv) in DCM (5 mL) at room temperature. The mixture was stirred for 1 h at room temperature before filtering through a pad of Celite and removal of solvent in vacuo. The crude enol ether complex was further purified on silica gel (petrol/ether/Et_3N 100:2:1). Enol ether complex **12** was recovered as separable *E*- and *Z*-isomers (*E*-isomer 248 mg, 0.44 mmol, 37%; *Z*-isomer 210 mg, 0.37 mmol, 31%).

(*Z*)-**12**: mp = 102.4−104.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.79−1.99 (2H, m), 2.00−2.09 (1H, m), 2.18−2.25 (1H, m), 2.40−2.46 (2H, m), 5.18 (1H, dd, J = 10.8, 2.5 Hz), 5.52 (1H, s), 7.07−7.20 (3H, m), 7.31−7.35 (3H, m), 7.50−7.59 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 30.6, 33.7, 78.8, 90.8, 96.4, 108.1, 125.6, 127.8, 127.9, 128.4, 128.9, 129.6, 135.7, 137.6, 154.0, 199.3(b); FTIR (CH_2Cl_2/cm^{-1}) ν_{max} 3057 (m), 3025 (m), 2951 (s), 2867 (s), 2091 (s), 2054 (s), 2030 (s), 1975 (m), 1660 (m), 1614 (m); HRMS calcd for $C_{26}H_{19}Co_2O_7$ (MH^+) 560.9795, found 560.9771.

(*E*)-**12**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.70−1.94 (2H, m), 1.95−2.04 (1H, m), 2.17−2.25 (1H, m), 2.30−2.41 (1H, m), 2.88−2.96 (1H, m), 5.02 (1H, dd, J = 10.7, 2.5 Hz), 6.21 (1H, d, J = 1.5 Hz), 7.16−7.42 (6H, m), 7.62−7.66 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 24.9, 33.1, 79.5, 90.2, 96.8, 110.2, 125.8, 127.8, 128.2, 128.8, 128.8 129.8, 136.4, 137.8, 155.4, 199.4 (b); FTIR (film/cm^{-1}) ν_{max} 3078 (s), 3060 (s), 3024 (s), 2091 (s), 2051 (s), 2001 (s), 1975 (s), 1658 (s), 1615 (s), 1600 (s); HRMS calcd for $C_{26}H_{19}Co_2O_7$ (MH^+) 560.9795, found 560.9774.

(*E*)/(*Z*)-Dicobalthexacarbonyl-2-isobutylene-6-phenylethynyltetrahydropyran 14. The general procedure for the preparation of cyclic enol ethers was followed using phosphonium salt **7a** (839 mg, 1.57 mmol, 1.0 equiv), *n*-butyllithium (2.5 M in hexanes, 0.69 mL, 1.73 mmol, 1.1 equiv), isobutyraldehyde (156 μL, 1.73 mmol, 1.1 equiv), and tetrahydrofuran (30 mL). The general procedure for the preparation of the cobalt complexes was followed using crude enol ether and octacarbonyldicobalt (590 mg, 1.72 mmol, 1.1 equiv) in petroleum ether (40−60 °C) (10 mL). Enol ether complex **14** was recovered (509 mg, 62%) as a deep red oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, J = 6.7 Hz, *Z*-isomer), 0.97 (3H, d, J = 6.7 Hz, *Z*-isomer), 0.98 (3H, d, J = 6.7 Hz, *E*-isomer), 1.01 (3H, d, J = 6.7 Hz, *E*-isomer), 1.64−2.16 (11H, m, *E*/*Z*-isomers), 2.42 (dh, 1H, J = 9.6, 6.7 Hz, *E*-isomer), 2.52−2.59 (1H, m, *E*-isomer), 2.88 (1H, dhept, J = 8.8, 6.7 Hz, *Z*-isomer), 4.44 (1H, dd, J = 8.8, 1.2, *Z*-isomer), 4.75−4.82 (2H, m, *E*/*Z*-isomers), 4.91 (1H, dd, J = 9.5, 1.6 Hz, *E*-isomer), 7.28−7.37 (6H, m, *E*/*Z*-isomers), 7.60−7.64 (4H, m, *E*/*Z*-isomers); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*E*-isomer) 23.5, 23.6, 24.2, 24.4, 25.7, 33.7, 79.7, 90.2, 97.4, 116.7, 127.7, 128.7, 129.9, 137.9, 151.2, 199.4 (b). (*Z*-isomer) 23.8, 23.9, 24.0, 29.5, 30.9, 33.9, 79.1, 90.2, 97.4, 117.0, 127.7, 128.7, 129.7, 137.9, 150.4, 199.5 (b); FTIR (film/cm^{-1}) ν_{max} 3077 (w), 2960 (w), 2868 (w), 2092 (s), 2052 (s), 1679 (w), 1616 (w); HRMS calcd for $C_{23}H_{21}Co_2O_7$ (MH^+) 526.9951, found 526.9933.

(*E*)-Dicobalthexacarbonyl-2-(2,2-dimethylpropylidene)-6-hex-1-ynyltetrahydropyran 15. The general procedure for the preparation of cyclic enol ethers was followed using phosphonium salt **7b** (841 mg, 1.64 mmol, 1.0 equiv), *n*-butyllithium (2.5 M in hexanes, 0.72 mL, 1.80 mmol, 1.1 equiv), trimethylacetaldehyde (200 μL, 1.80 mmol, 1.0 equiv), and tetrahydrofuran (25 mL). The general procedure for the preparation of the cobalt complexes was followed using crude enol ether and octacarbonyldicobalt (671 mg, 1.97 mmol, 1.2 equiv) in petroleum ether (40−60 °C) (20 mL). Enol ether complex **15** was recovered (219 mg, 26%) as a deep red oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.3 Hz), 1.10 (9H, s), 1.47 (2H, sx, J = 7.4 Hz), 1.57−1.73 (4H, m), 1.86−1.95 (1H, m), 1.96−2.01 (1H, m), 2.07 (1H, dddd, J = 13.9, 12.3, 4.9, 1.5 Hz), 2.65 (1H, ddd, J = 13.9, 3.6, 2.4 Hz), 2.79−2.85 (2H, m), 4.57 (1H, dd, J = 10.4, 2.5 Hz), 5.11 (1H, d, J = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.7, 23.4, 26.1, 29.7, 31.6, 33.5, 33.6, 33.9, 80.1, 97.5, 98.9, 120.4, 152.4, 200.1 (b); FTIR (film/cm^{-1}) ν_{max} 2962 (s), 2875 (s), 2086 (s), 2044 (s), 1700 (s), 1615 (m), 1468 (s); HRMS calcd for $C_{22}H_{27}Co_2O_7$ (MH^+) 521.0421, found 521.0412.

(*E*)-Dicobalthexacarbonyl-2-(2,2-dimethylpropylidene)-6-phenylethynyltetrahydropyran 16. The general procedure for the preparation of cyclic enol ethers was followed using phosphonium salt **7a** (695 mg, 1.30 mmol, 1.0 equiv), *n*-butyllithium (2.5M in hexanes, 0.57 mL, 1.42 mmol, 1.1 equiv), trimethylacetaldehyde (158 μL, 1.42 mmol, 1.0 equiv), and tetrahydrofuran (30 mL). The general procedure for the preparation of the cobalt complexes was followed using crude enol ether and octacarbonyldicobalt (490 mg, 1.42 mmol, 1.0 equiv) in petroleum ether (40−60 °C) (10 mL). Enol ether complex **16** was recovered (387 mg, 55%) as a deep red oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (9H, s), 1.66−1.83 (2H, m), 1.91−2.01 (1H, m), 2.04−2.17 (2H, m), 2.68−2.75 (1H, m), 4.79 (1H, dd, J = 2.3, 10.6 Hz), 5.19 (1H, d, J = 1.5 Hz), 7.27−7.37 (3H, m), 7.59−7.64 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 26.2, 29.8, 31.7, 33.8, 80.2, 90.2, 97.4, 120.7, 127.7, 128.7, 129.9, 137.9, 152.6, 199.5 (br); FTIR (film/cm^{-1}) ν_{max} 3078 (w), 2960 (w), 2866 (w), 2091 (s), 2052 (s), 1669 (w); HRMS calcd for $C_{24}H_{23}Co_2O_7$ (MH^+) 541.0108, found 541.0089.

(*E*)/(*Z*)-Dicobalthexacarbonyl-2-pent-4-enylidene-6-phenylethynyltetrahydropyran 17. The general procedure for the preparation of cyclic enol ethers was followed using phosphonium salt **7a** (673 mg, 1.26 mmol, 1.0 equiv), *n*-butyllithium (2.5 M in hexanes, 0.56 mL, 1.39 mmol, 1.1 equiv), 4-pentenal (150 μL, 1.52 mmol, 1.2 equiv), and tetra-

hydrofuran (10 mL). The general procedure for the preparation of the cobalt complexes was followed using crude enol ether and octacarbonyldicobalt (430 mg, 1.26 mmol, 1.0 equiv) in DCM (5 mL). Enol ether complex **17** was recovered (414 mg, 0.77 mmol, 61%) as a deep red oil and as an inseparable 4:1 mixture of *E*/*Z* isomers: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.64−2.39 (18H, m, *E*/*Z*-isomers), 2.52−2.69 (2H, m, *E*/*Z*-isomers), 4.64 (1H, t, J = 6.9 Hz, *Z*-isomer), 4.78−5.25 (7H, m, *E*/*Z*-isomers), 5.74−6.00 (2H, m, *E*/*Z*-isomers), 7.29−7.48 (6H, m, *E*/*Z*-isomers), 7.58−7.52 (4H, m, *E*/*Z*-isomers); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (*E*-isomer) 23.3, 24.1, 25.5, 33.6, 34.5, 79.7, 90.2, 97.3, 108.0, 114.7, 127.8, 128.8, 129.9, 137.9, 138.4, 153.1, 199.4 (b); (*Z*-isomer) 23.7, 23.8, 29.5, 33.9, 34.1, 79.1, 90.2, 97.3, 108.3, 114.3, 127.6, 128.8, 129.7, 137.9, 138.7, 152.4, 199.4 (b); FTIR (film/cm^{-1}) ν_{max} 3079 (m), 3063 (m), 2945 (m), 2936 (m), 2922 (m), 2865 (m), 2852 (m), 2093 (s), 2058 (s), 2019 (s), 1975 (m), 1681 (m), 1679 (m), 1642 (w), 1613 (w); HRMS calcd for $C_{24}H_{21}Co_2O_7$ (MH^+) 538.9951, found 538.9934.

(*E*)/(*Z*)-Dicobalthexacarbonyl-2-propylidene-6-phenylethynyltetrahydropyran 18. The general procedure for the preparation of cyclic enol ethers was followed using phosphonium salt **7a** (566 mg, 1.06 mmol, 1.0 equiv), *n*-butyllithium (2.5 M in hexanes, 0.51 mL, 1.28 mmol, 1.2 equiv), propionaldehyde (120 μL, 1.65 mmol, 1.6 equiv), and tetrahydrofuran (5 mL). The general procedure for the preparation of the cobalt complexes was followed using crude enol ether and octacarbonyldicobalt (360 mg, 1.05 mmol, 1.0 equiv) in DCM (5 mL). Enol ether complex **18** (251 mg, 0.49 mmol, 46%) was recovered as a deep red oil and as an inseparable 3:1 mixture of *E*/*Z* isomers: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.5 Hz, *Z*-isomer), 1.02 (3H, t, J = 7.5 Hz, *E*-isomer), 1.67−2.34 (15H, m, *E*/*Z*-isomers), 2.52−2.66 (1H, m, *E*-isomer), 4.63 (1H, t, J = 7.2 Hz, *Z*-isomer), 4.79−4.91 (2H, m, *E*/*Z*-isomers), 5.10 (1H, td, J = 7.7, 1.4 Hz, *E*-isomer), 7.28−7.42 (6H, m, *E*/*Z*-isomers), 7.56−7.69 (4H, m, *E*/*Z*-isomers); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (*E*-isomer) 15.1, 19.3, 23.4, 24.0, 33.7, 79.7, 90.1, 97.4, 110.7, 127.7, 128.8, 129.9, 137.9, 152.3, 199.5 (b); (*Z*-isomer) 14.8, 17.7, 23.9, 29.5, 33.9, 79.1, 90.1, 97.4, 118.9, 127.7, 128.8, 129.8, 137.9, 151.7, 199.5 (b); FTIR (film/cm^{-1}) ν_{max} 2963 (m), 2870 (m), 2092 (s), 2052 (s), 2021 (s), 1680 (m), 1616 (m); HRMS calcd for $C_{22}H_{19}Co_2O_7$ (MH^+) 512.9795, found 512.9778.

(*E*)/(*Z*)-Dicobalthexacarbonyl-2-ethylidene-6-phenylethynyltetrahydropyran 19. The general procedure for the preparation of cyclic enol ethers was followed using phosphonium salt **7a** (566 mg, 1.06 mmol, 1.0 equiv), *n*-butyllithium (2.5 M in hexanes, 0.45 mL, 1.12 mmol, 1.10 equiv), acetaldehyde (70 μL, 1.22 mmol, 1.2 equiv), and tetrahydrofuran (5 mL). The general procedure for the preparation of the cobalt complexes was followed using crude enol ether and octacarbonyldicobalt (380 mg, 1.11 mmol, 1.1 equiv) in DCM (5 mL). Enol ether complex **19** (346 mg, 0.69 mmol, 68%) was recovered as a deep red oil and as an inseparable 3:1 mixture of *E*/*Z* isomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (3H, dd, J = 6.6, 0.4 Hz, *E*-isomer), 1.63 (3H, dd, J = 6.6, 1.6 Hz, *Z*-isomer), 1.66−2.32 (11H, m, *E*/*Z*-isomers), 2.57−2.65 (1H, m, *E*-isomer), 4.63 (1H, q, J = 6.6 Hz, *Z*-isomer), 4.82, (1H, dd, J = 10.6, 2.3 Hz, *E*-isomer), 4.89 (1H, dd, J = 10.9, 2.3 Hz, *Z*-isomer), 5.12 (1H, qd, J = 7.1, 1.3 Hz, *E*-isomer), 7.29−7.40 (6H, m, *E*/*Z*-isomers), 7.56−7.65 (4H, m, *E*/*Z*-isomers); ^{13}C NMR (100 MHz, $CDCl_3$) δ (*E*-isomer) 11.1, 23.2, 23.6, 33.6, 79.6, 90.0, 97.3, 103.0, 127.7, 128.7, 129.9, 137.9, 153.1, 199.5 (b). (*Z*-isomer) 9.6, 23.8, 29.5, 33.9, 78.8, 90.0, 97.3, 102.7, 127.7, 128.7, 129.7, 137.9, 152.7, 199.5 (b); FTIR (film/cm^{-1}) ν_{max} 3059 (m), 2944 (m), 2923 (m), 2865 (m), 2092 (s), 2052 (s), 2030 (s), 1687 (m), 1614 (m); HRMS calcd for $C_{21}H_{16}Co_2O_7$ (M^+) 497.9560, found 497.9553.

Representative Experimental Procedure for Ti-Mediated Rearrangement Reactions. Preparation of *cis*-Dicobalthexacarbonyl-2-phenyl-3-phenylethynylcyclohexanone *cis*-21. Complex **12*E*** (60 mg, 0.107 mmol, 1.0 equiv) was dissolved in DCM (5 mL) and added to the reaction vessel via cannula before cooling to −30 °C. Titanium tetrachloride (18 μL, 0.160 mmol, 1.5 equiv) was added via syringe and the reaction mixture stirred for 14 h before warming to −15 °C and stirring for a further 1 h. The reaction was poured into water (15 mL), extracted with ether (15 mL), washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and filtered through a pad of Celite. Ketone complex *cis*-**21** (41 mg, 0.073 mmol, 68%) was isolated as a deep red oil after chromatography on silica gel (petrol/ether 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89−2.04 (1H, m), 2.27−2.37 (3H, m), 2.67 (1H, dddd, J = 13.4, 13.2, 13.2, 3.8 Hz), 2.80 (1H, ddd, J = 14.8, 14.2, 6.5 Hz), 3.82 (1H, ddd, J = 13.0, 5.3, 4.3 Hz), 4.11 (1H, d, J = 5.3 Hz), 7.10−7.40 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 29.8, 36.9, 47.2, 63.0, 93.7, 98.6, 127.5, 127.7, 128.8, 128.8, 128.9, 130.1, 135.3, 138.4, 199.2 (b), 209.1; FTIR (film/cm^{-1}) ν_{max} 3062 (m), 3030 (m), 2956 (m), 2870 (m), 2089 (s), 2052 (s), 1989 (s), 1969 (m), 1714 (s); HRMS calcd for $C_{26}H_{19}Co_2O_7$ (MH^+) 560.9795, found 560.9788.

Representative Experimental Procedure for B-Mediated Rearrangement Reactions. Preparation of *trans*-Dicobalthexacarbonyl-2-phenyl-3-phenylethynylcyclohexanone *trans*-21. Complex **12*E*** (40 mg, 0.07 mmol, 1.0 equiv) was dissolved in DCM (5 mL) and added to the reaction vessel via cannula before cooling to −30 °C. Dibutylboron trifluoromethanesulfonate (1 M in DCM, 100 μL, 1.06 mmol, 1.5 equiv) was added via syringe and the reaction stirred for 14 h before warming to −15 °C and stirring for a further 1 h. The reaction was poured into water (15 mL), extracted with ether (15 mL), washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and filtered through a pad of Celite. Ketone complex *trans*-**21** (26 mg, 0.046 mmol, 65%) was isolated as a deep red solid after chromatography on silica gel (petroleum ether/ether 5:1): mp = 95.0−96.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (1H, dddd, J = 13.0, 13.0, 10.9, 3.4 Hz), 1.91 (1H, ddddd, J = 12.7, 12.7, 12.7, 4.6, 3.1 Hz), 2.08−2.17 (1H, m), 2.31−2.40 (1H, m), 2.45 (1H, dddd, J = 14.2, 12.5, 6.2, 0.8 Hz), 2.57 (1H, ddddd, J = 14.1, 3.1, 3.0, 1.5, 1.5 Hz), 3.51 (1H, d, J = 11.1 Hz), 3.81 (1H, td, J = 11.1, 4.0 Hz), 6.99−7.19 (10H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 34.7, 41.2, 46.4, 64.1, 94.9, 102.0, 127.1, 127.4, 128.5, 128.5, 128.6, 129.6, 136.2, 138.5, 199.8 (b), 208.7; FTIR (CH_2Cl_2/cm^{-1}) ν_{max} 3064 (m), 3032 (m), 2950 (s), 2868 (s), 2089 (s), 2053 (s), 1988 (s), 1715 (s); HRMS calcd for $C_{26}H_{19}Co_2O_7$ (MH^+) 560.9795, found 560.9784.

***trans*-Dicobalthexacarbonyl-2-*tert*-butyl-3-(1-hexynyl)-cyclohexanone *trans*-22.** Following the representative procedure, complex **15** (120 mg, 0.23 mmol, 1.0 equiv) in DCM (10 mL) was treated with titanium tetrachloride (38 mL, 0.346, 1.5 equiv). Ketone complex *trans*-**22** (76 mg, 0.145 mmol, 63%) was isolated as a deep red oil after chromatography on silica gel (petroleum ehter/ether 5:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7.1 Hz), 1.06 (9H, s), 1.50 (2H, sx, J = 7.4 Hz), 1.56−1.65 (2H, m), 1.80 (1H, ddt, J = 13.3, 13.3, 4.2 Hz), 1.87−1.96 (1H, m), 2.00−2.10 (1H, m), 2.35 (1H, s, b), 2.38−2.47 (2H, m), 2.50−2.57 (1H, m), 2.64−2.79 (2H, m), 3.59−3.64 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 21.5, 21.6, 28.6, 29.9, 31.7, 33.1, 33.2, 41.1, 42.0, 65.4, 100.6, 103.0, 199.1 (br), 211.5; FTIR (film/cm^{-1}) ν_{max} 2961, 2875, 2086, 2044, 2016, 1699; HRMS calcd for $C_{22}H_{27}Co_2O_7$ (MH^+) 521.0421, found 521.0403.

***trans*-Dicobalthexacarbonyl-2-*tert*-butyl-3-phenylethynylcyclohexanone *trans*-23.** Following the representative procedure, complex **16** (75 mg, 0.139 mmol, 1.0 equiv) in DCM (10 mL) was treated with dibutylboron trifluoromethanesulfonate (1 M in DCM, 207 μL, 0.208 mmol, 1.5 equiv). Ketone complex *trans*-**23** (45 mg, 0.083 mmol, 60%) was isolated as a deep red solid after chromatography on silica gel (petroleum ether/ether 5:1): mp = 83.2−85.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s, *t*-Bu), 1.80−1.96 (3H, m), 2.29−2.43 (3H, m), 2.45 (1H, s), 3.76−3.80 (1H, m), 7.26−7.40 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 29.6, 30.7, 34.3, 41.9 (×2), 66.7, 94.2, 105.8, 127.5, 128.7, 129.2, 138.1, 199.4 (br), 212.2; FTIR

(CH_2Cl_2/cm^{-1}) ν_{max} 2961 (m), 2089 (s), 2050 (s), 2022 (s), 1699 (m); HRMS calcd for $C_{24}H_{23}O_7Co_2$ (MH^+) 541.0108. found 541.0109.

***trans*-Dicobalthexacarbonyl-2-isopropyl-3-phenylethynylcyclohexanone *trans*-25.** Following the representative procedure, complex **14** (65 mg, 0.124 mmol, 1.0 equiv) in DCM (8 mL) was treated with titanium tetrachloride (20 μL, 0.186 mmol, 1.5 equiv). Ketone complex *trans*-**25** (19 mg, 0.036 mmol, 29%) was isolated as a deep red solid after chromatography on silica gel (petroleum ether/ether 5:1): mp = 82.9−83.7 °C; ^{1}H NMR (400 MHz, C_6D_6) δ 0.80 (3H, d, J = 6.7 Hz), 0.95 (3H, d, J = 6.7 Hz), 1.26−1.42 (1H, m), 1.55−1.76 (3H, m), 1.85−2.07 (3H, m), 2.14 (1H, dd, J = 7.6, 5.0 Hz), 3.48 (1H, ddd, J = 10.6, 5.0, 5.0), 6.91−7.08 (3H, m), 7.43−7.51 (2H, m); ^{13}C NMR (100 MHz, C_6D_6) δ 19.3, 21.3, 22.8, 28.9, 31.0, 40.1, 43.7, 64.3, 94.7, 104.0, 128.9, 129.2, 131.9, 138.5, 199.9 (b), 209.6; FTIR (CH_2Cl_2/cm^{-1}) ν_{max} 2962 (m), 2089 (s), 2049 (s), 2028 (s), 1709 (s); HRMS calcd for $C_{23}H_{21}Co_2O_7$ (MH^+) 526.9951, found 526.9940.

***cis/trans*-Dicobalthexacarbonyl-2-ethyl-3-phenylethynylcyclohexanone.** Following the representative procedure, complex **18** (77 mg, 0.150 mmol, 1.0 equiv) in DCM (5 mL) was treated with titanium tetrachloride (25 μL, 0.225 mmol, 1.5 equiv). Ketone complexes *trans*-**26** (10 mg, 0.019 mmol, 13%) and *cis*-**26** (35 mg, 0.068 mmol, 43%) were isolated as deep red oils after chromatography on silica gel (petroleum ether/ether 5:1).

***trans*-26:** ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.75 (3H, t, J = 7.2 Hz), 1.37−1.74 (3H, m), 1.75−2.08 (2H, m), 2.10−2.64 (4H, m), 3.24 (1H, ddd, J = 10.2, 10.1, 4.0 Hz), 7.21−7.52 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 21.4, 25.5, 34.9, 42.0, 46.5, 60.1, 94.0, 104.1, 128.2, 129.2, 129.5, 138.5, 199.9 (b), 211.4; FTIR (film/cm^{-1}) ν_{max} 3078 (m), 2963 (m), 2866 (m), 2089 (s), 2056 (s), 1991 (s), 1971 (s), 1715 (s); HRMS calcd for $C_{22}H_{19}O_7Co_2$ (MH^+) 512.9795, found 512.9813.

***cis*-26:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (3H, t, J = 7.5 Hz), 1.68 (1H, ddd, J = 14.0, 12.3, 7.1 Hz), 1.86 (1H, dt, J = 13.7, 4.3 Hz), 1.91−2.05 (1H, m), 2.18−2.29 (2H, m), 2.09−2.18 (1H, m), 2.29−2.36 (1H, m), 2.33−2.41 (1H, m), 2.54−2.61 (1H, m), 3.48 (1H, dt, J = 11.8, 3.9 Hz), 7.32−7.45 (3H, m), 7.46−7.53 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 20.2, 26.1, 30.2, 37.7, 48.4, 60.0, 94.0, 99.9, 128.2, 129.3, 129.8, 138.2, 199.9 (b), 213.1; FTIR (film/cm^{-1}) ν_{max} 3074 (w), 3056 (w), 2965 (s), 2938 (s), 2874 (m), 20869s), 2052 (s), 2009 (s), 1970 (m), 1715 (s); HRMS calcd for $C_{22}H_{19}O_7Co_2$ (MH^+) 512.9795, found 512.9788.

***cis/trans*-Dicobalthexacarbonyl-2-methyl-3-phenylethynylcyclohexanone *trans*-27.** Following the representative procedure, complex **19** (85 mg, 0.171 mmol, 1.0 equiv) in DCM (5 mL) was treated with titanium tetrachloride (28 μL, 0.256 mmol, 1.5 equiv). Ketone complexes *trans*-**27** (9 mg, 0.018 mmol, 10%) and *cis*-**27** (50.7 mg, 0.103 mmol, 60%) were isolated as deep red oils after chromatography on silica gel (petrol/ether 5:1). ***trans*-27:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, d, J = 6.9 Hz), 1.88 (1H, tdd, J = 13.2, 4.4, 3.3 Hz), 2.0 (1H, tdd, J = 13.0, 11.5, 3.1 Hz), 2.21−2.38 (3H, m), 2.46 (1H, tdd, J = 13.5, 6.0, 0.9 Hz), 2.52−2.60 (1H, m), 3.12 (1H, td, J = 11.2, 3.6 Hz), 7.28−7.47 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 13.7, 25.1, 34.9, 41.3, 47.9, 53.0, 93.4, 103.9, 127.7, 128.8, 129.0, 138.1, 199.4 (b), 210.7; FTIR (film/cm^{-1}) ν_{max} 3078 (w), 2944 (m), 2869 (m), 2089 (s), 2051 (s), 2013 (s), 1715 (s); HRMS calcd for $C_{21}H_{17}Co_2O_7$ (MH^+) 498.9638, found 498.9652.

***cis*-27:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, d, J = 7.3 Hz), 1.78−1.92 (1H, m), 2.07−2.26 (3H, m), 2.35 (1H, dddd, J = 14.5, 3.2, 3.2, 1.4 Hz,), 2.63 (1H, ddd, J = 14.6, 13.1, 6.4 Hz), 2.83 (1H, qd, J = 7.2, 4.3 Hz), 3.49 (1H, dt, J = 11.2, 4.3 Hz), 7.26−7.40 (3H, m), 7.43−7.48 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 25.1, 29.3, 37.0, 47.2, 51.4, 93.6, 99.2, 127.7, 128.9, 129.3, 137.9, 199.5 (b), 213.1; FTIR (film/cm^{-1}) ν_{max} 3870 (m), 3855 (m), 2945 (s), 2867 (s), 2090 (s), 2053 (s), 2020 (s), 1988 (s), 1714 (s); HRMS calcd for $C_{21}H_{17}Co_2O_7$ (MH^+) 498.9638, found 498.9644.

***cis*-dicobalthexacarbonyl-2-(3-butenyl)-3-phenylethynylcyclohexanone *cis*-28.** Following the representative procedure, complex **17** (73 mg, 0.135 mmol, 1.0 equiv) in DCM (5 mL) was treated with dibutylboron trifluoromethanesulfonate (1 M in DCM, 205 μL, 0.202 mmol, 1.5 equiv). Ketone complex *cis*-**28** (34 mg, 0.063 mmol, 47%) was isolated as deep red solid after chromatography on silica gel (petroleum ether/ether 5:1): mp = 85.1−86.6 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.38−1.89 (6H, m,), 1.92−2.21 (2H, m), 2.27 (1H, dd, J = 14.5, 3.1 Hz), 2.50−2.83 (2H, m), 3.49 (1H, ddd, J = 10.9, 4.3, 4.1 Hz), 4.71 (1H, dd, J = 17.1, 1.1 Hz), 4.81 (1H, dd, J = 10.2, 0.8 Hz), 5.53 (1H, dddd, J = 16.8, 10.8, 6.1, 6.0 Hz), 7.30−7.51 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 25.8, 30.0, 30.5, 37.5, 47.6, 57.4, 93.9, 99.4, 114.9, 127.7, 128.9, 129.3, 136.9, 137.9, 199.5 (b), 212.6; FTIR (CH_2Cl_2/cm^{-1}) ν_{max} 3079 (m), 2947 (s), 2868 (m), 2088 (s), 2052 (s), 1990 (s), 1715 (s), 1642 (m), 1612 (w); HRMS calcd for $C_{24}H_{21}Co_2O_7$ (MH^+) 538.9951, found 538.9956.

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Supporting Information Available: ^{1}H, ^{13}C, and ^{1}H NOESY NMR spectra for select compounds and X-ray data for compounds **25** and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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