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Reaction Mechanisms

Silver(I)-Catalyzed Addition of Phenols to Alkyne Cobalt Cluster Stabilized Carbocations

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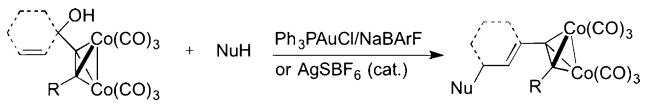
Abstract: A smooth catalytic method to use phenols as the nucleophilic partner in the Nicholas reaction has been developed. The method uses either Ag^{I} or Au^{I} catalysts with $AgClO_4$ or $AgBF_4$ as the most efficient catalysts tested. Neither additional additives nor cocatalysts were required and the formation of the corresponding phenol adducts occurred in excellent yields. The process has the single limitation of the inability of less nucleophilic phenols (4-nitrophenol) to generate the corresponding adducts. Additionally, the reaction is highly diastereoselective. DFT calculations allow a catalytic cycle to be proposed that involves trimetallic intermediates; the rate-determining step of the reaction is hydroxy-group elimination in a cobalt–silver trimetallic intermediate.

Introduction

The Nicholas reaction, namely, the reaction of a cation adjacent to an alkyne–$Co_2(CO)_6$ cluster with nucleophiles, is among the most powerful and widely used synthetic reaction based on an stoichiometric transition-metal complex.[1] The main shortcoming of this otherwise versatile reaction is the necessity of using an acid to generate the carbocation from the corresponding propargylic alcohol–$Co_2(CO)_6$ complex.[2] Different strategies have been developed to circumvent this limiting factor.[3] Recently, we reported the possibility of using gold(I) and silver(I), in particular, as catalysts for the Nicholas reaction.[4] The catalyzed reaction proceeds smoothly at room temperature in good to excellent yield and the use of the catalyst minimizes the formation of byproducts. Oxygen (alcohols) and carbon (allyl silanes, aromatic, and heteroaromatic) nucleophiles were compatible with the catalytic process (Scheme 1).



NuH = ROH (R ≠ Ar), ArH, HetArH

Scheme 1. The catalytic Nicholas reaction.

However, the "classical" Nicholas reaction is not suitable for phenols due to the poor nucleophilicity of such systems and the incompatibility of using more nucleophilic phenolate anions under the conditions required to generate the cation adjacent to the alkyne–$Co_2(CO)_6$ cluster. Our catalytic reaction would offer the opportunity to close this gap in the synthetic applications of this reaction. Moreover, we have segregated the catalyzed reaction mechanistically from the classical process. In the only example in which a phenol has been productively used in a Nicholas reaction, the reaction proceeded by C-arylation in a Friedel–Crafts-type reaction, instead of an O-alkylation.[5] Herein, we report the development of a general catalytic Ag^{I} approach to the addition of phenols to different propargylic–$Co_2(CO)_6$ clusters, together with a preliminary DFT study of the mechanism of these processes. Moreover, it is demonstrated that gold(I) is also an efficient catalyst in these processes.

Results and Discussion

The viability of the catalytic reaction between a metal-cluster-stabilized cation and a phenol was tested in the reaction of the propargylic alcohol–$Co_2(CO)_6$ complex **1a** and 4-methoxyphenol as a nucleophile (Scheme 2). The reaction was initially

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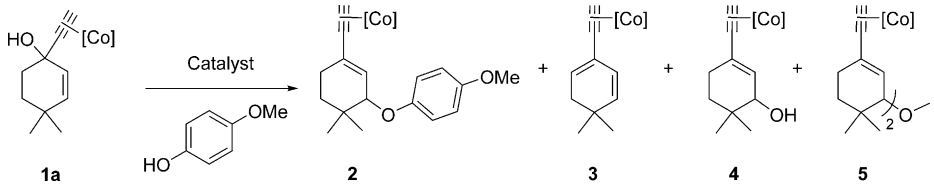
Supporting information for this article and ORCIDs for some of the authors are available on the WWW under http://dx.doi.org/10.1002/chem.201600288. The Supporting Information contains experimental details for compounds **5**; TMS-propargyl alcohol precursors of **7a**, **12a**, **13a**, **20A**, and **20B**; a complete collection of NMR spectra; and coordinates of the DFT-calculated structures.



Scheme 2. Initial tests of the catalytic Nicholas reaction with phenolic nucleophiles.

tested under the reaction conditions developed by us to add non-phenol nucleophiles to cobalt-stabilized carbocations. When $AgSbF_6$ was used as the catalyst (5%), compound **2** was isolated in 54% yield together with compound **3** derived from an elimination reaction (3%), alcohol **4** (3%), and ether **5** (< 3%). It is remarkable that no C-alkylation products are observed at the phenolic aromatic ring.

Once we demonstrated that the Ag^I catalyst formed the O-alkylation product in good yields, we tested several Ag^I salts. The most relevant results obtained in the optimization tests are compiled in Table 1.

Table 1. Results for catalyst optimization in the Nicholas reaction.

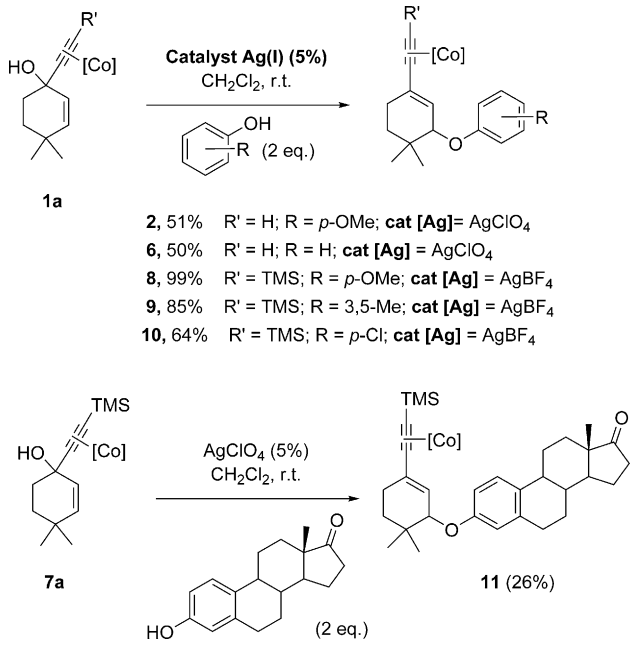
Entry	Catalyst ([mol%])	Phenol [equiv]	Ratio[a] 2	3	4	5
1	$AgSbF_6$ (10)	1	1	0.3	0.4	0.4
2	$AgBF_4$ (5)	1	1	–	0.4	0.3
3	$AgClO_4$ (5)	1	1	0.1	0.2	0.2
4	$AgClO_4$ (5)	2	1[b]	–	–	–
5	$AgSbF_6$, $AgClO_4$	–	–	detected in variable proportions		

[a] Determined by the integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures. [b] Compound **2** was isolated in 51% yield.

The use of silver(I) catalysts led to the formation of up to four different isolable reaction products (Table 1). Compound **2** was the desired product, whereas compounds **3**–**5** were the products derived from elimination of the alcohol (**3**), the rearranged alcohol (**4**), and the product (**5**) derived from the reaction of $Co_2(CO)_6$–**1a** with rearranged alcohol **4**, respectively. As seen from the results in Table 1, the use of either $AgSbF_6$ or $AgBF_4$ produced desired product **2** together with variable amounts of compounds **3**–**5** (Table 1, entries 1 and 2). The use of $AgClO_4$ and a 1:1 ratio of Co complex/4-methoxyphenol produced cleaner reaction mixtures, but products **3**, **4**, and **5** could still be detected. By increasing the Co complex/4-methoxyphenol molar ratio to 1:2, compound **2** was obtained as a single reaction product. It should be noted that, in the absence of nucleophile, the reaction of **1a** with $AgSbF_6$ or $AgClO_4$ produced mixtures of compounds **3**–**5**, the relative proportions of which were dependent on the catalysts (Table 1, entry 5). Furthermore, the use of Ph_3PAuCl (5%)/NaBArF (7%) led to Nicholas product **2** together with **4**. Due to badly resolved ^1H NMR spectra, the ratio of **2**/**4** could not be determined, and the mixture was purified by column chromatography to allow for the isolation of **2** in a respectable yield of 76%.

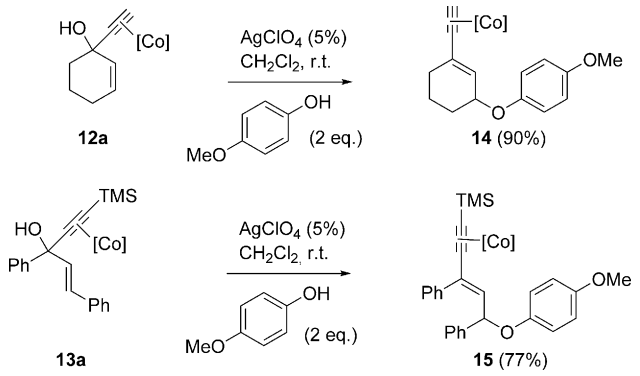
Finally, we tested the reaction of complex **1a** under standard conditions for the Nicholas reaction. Thus, complex **1a** was treated with 4-methoxyphenol at −20 °C in the presence of $BF_3{\cdot}Et_2O$ (1.3 equiv). A 1:0.7 mixture of compounds **2** and **4** was recovered in very low yield (≤15%). Clearly, the advantages of using silver(I) or gold(I) in these reactions is demonstrated. Due to the lower cost of silver catalysts than gold catalysts, we continued this study by using silver(I) derivatives.

Once the suitability of the Ag^I-catalyzed addition of phenols to propargylic alcohol–Co_2CO_6 complexes was demonstrated, the versatility of the process with different phenols was considered. Thus, complex **1a** was reacted with phenol and 4-methoxyphenol in the presence of 5 mol% of $AgClO_4$ in CH_2Cl_2 and in a 1:2 molar ratio of Co complex/phenol, forming the corresponding adducts **6** and **2** in 50 and 51% yield, respectively. Complex **7a**, which lacked a terminal alkyne hydrogen, also reacted smoothly with 4-methoxyphenol, 3,5-dimethylphenol, 4-chlorophenol, and estrone, in the presence of a 5 mol% of $AgBF_4$, leading to the corresponding adducts **8**, **9**, **10**, and **11**, respectively, in good to excellent yields. In the case of estrone ($AgClO_4$ 5 mol%), adduct **11** was obtained in low yield due to extensive decomposition of the product during purification (Scheme 3).



Scheme 3. The scope of the catalytic Nicholas reaction. TMS = trimethylsilyl.

Complex **12a**, which lacked both Me groups at the cyclohexene ring, and the open-chain complex **13a** also reacted smoothly with 4-methoxyphenol in the presence of $AgClO_4$ (5 mol%), leading to the corresponding adducts **14** and **15**, respectively, in excellent yields (Scheme 4).



Scheme 4. Expanding the scope of the catalytic Nicholas reaction.

The catalytic addition of phenols to monoterpene derivatives (more prone to rearrangements) was next tested. (*R*)-(−)-Carvone-derived complex **16a** reacted with 4-methoxyphenol and 3,5-dimethylphenol to yield the corresponding adducts **17** and **18** in good yields (Scheme 5). The reaction was highly selective in the case of **17** and yielded a mixture (92:8) of stereoisomers, and was completely selective for **18**. Again, the reaction of **16a** with estrone yielded the hybrid compound **19**, although in low yield, due to extensive decomposition during purification.[6]

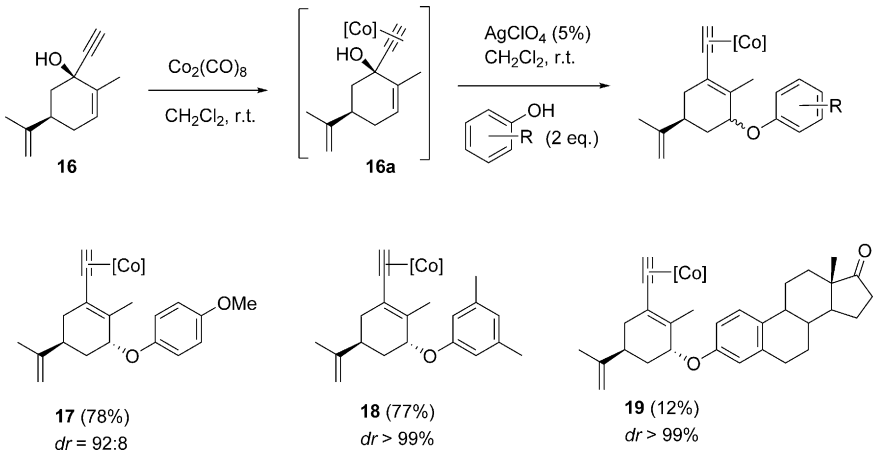
An analogous reaction of the corresponding (1*R*)-(−)-myrtenal derivative **20A**[7] with $Co_2(CO)_8$ and 4-methoxyphenol formed adduct **21a** (Scheme 6).[8]

The reaction of this complex derived from **20A** deserves further discussion. The addition of lithium acetylide to (1*R*)-(−)-myrtenal produces two diastereomeric alcohols, **20A** and **20B**, which were separated by chromatography. Each separated alcohol was complexed to form Co derivatives and reacted with 4-methoxyphenol by using $AgClO_4$ as the catalyst under standard conditions. Compound **20A** was much more reactive (4 h) than **20B** (48 h). Complex **21b** was unstable and was reacted with TMANO to eliminate the Co moiety, forming **22** in essentially quantitative yield.[8] Notably, both reactions were completely diastereoselective. The reasons behind the different reactivities of both diastereomeric alcohols **20** can be traced to the director effect of the alcohol during the first stages of the catalytic cycle and is discussed below.

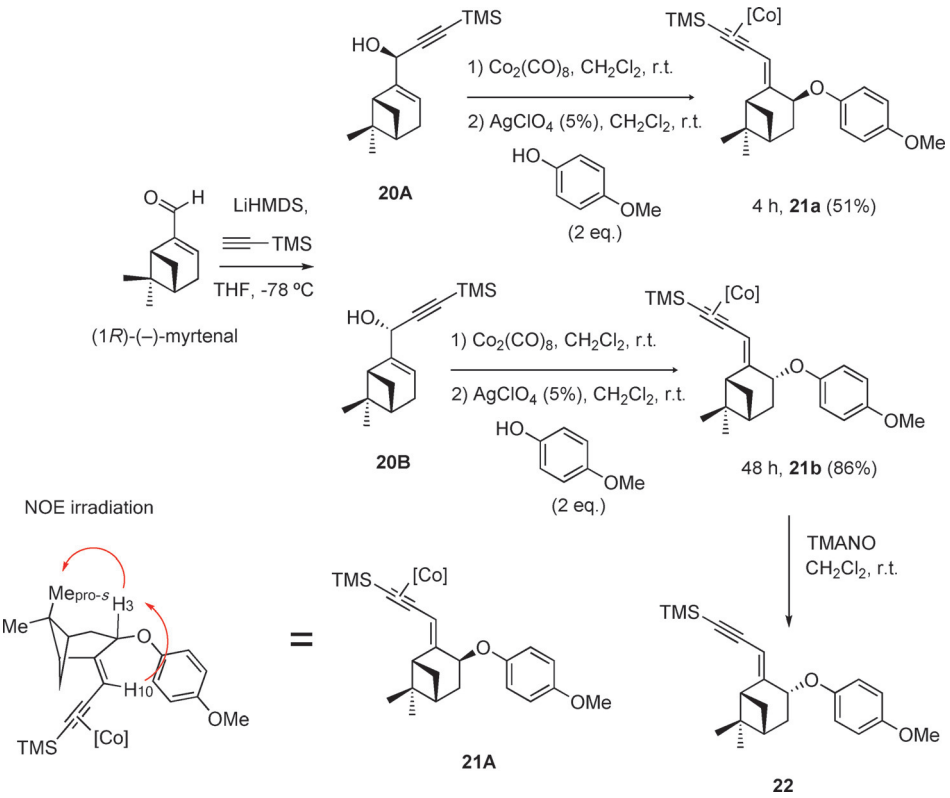
Finally, the reactions of aromatic Co complex **23a** with different phenols were addressed. Complex **23a** lacks an enyne system in its structure; hence it should broaden the scope of this catalytic processes. In this regard, the reactions of complex **23a** with phenol, 4-methoxyphenol, and 4-chlorophenol formed adducts **24**–**26**, respectively, in excellent yields, although in these cases it was necessary to increase the amount of phenol to a molar ratio of 3:1 relative to the Co complex. In addition, $AgBF_4$ gave cleaner crude reaction mixtures than $AgClO_4$. Analogously, the reaction of complex **27a**, with the TMS group, and 4-methoxyphenol formed adduct **28** in 77% yield (Scheme 7). Interestingly, complex **29a** was unreactive under all tested conditions (this behavior has been previously observed in our studies).[4]

To complete this study, a double-catalyzed Nicholas reaction was effected in complex **30a** derived from diol **30** (obtained by addition of trimethylsilylethynyllithium to terephthalaldehyde). Under typical catalysis with $AgBF_4$ (5 mol%), the double addition product **31** was obtained in nearly quantitative (94%) yield as a mixture of inseparable isomers (Scheme 8).

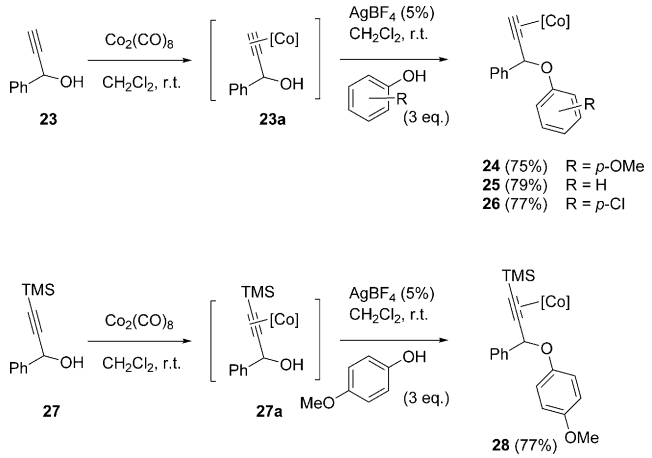
To obtain some mechanistic clues and to ascertain the catalytic role of silver(I), we carried out additional experiments. Thus, the reaction of complex **1a** and 4-methoxyphenol (1:3 molar ratio) with $NaBF_4$ or $NaClO_4$ (5 mol%), under identical conditions to those used above, lead to the quantitative recovery of the starting material; this excludes the possibility of the counterion (BF_4^- or ClO_4^-) having some role in the promotion of the reaction.



Scheme 5. The use of terpene derivatives in the catalytic Nicholas reaction.



Scheme 6. Diastereoselective process for the catalytic Nicholas reaction. LiHMDS = lithium hexamethyldisilazide, TMANO = trimethylamine *N*-oxide.

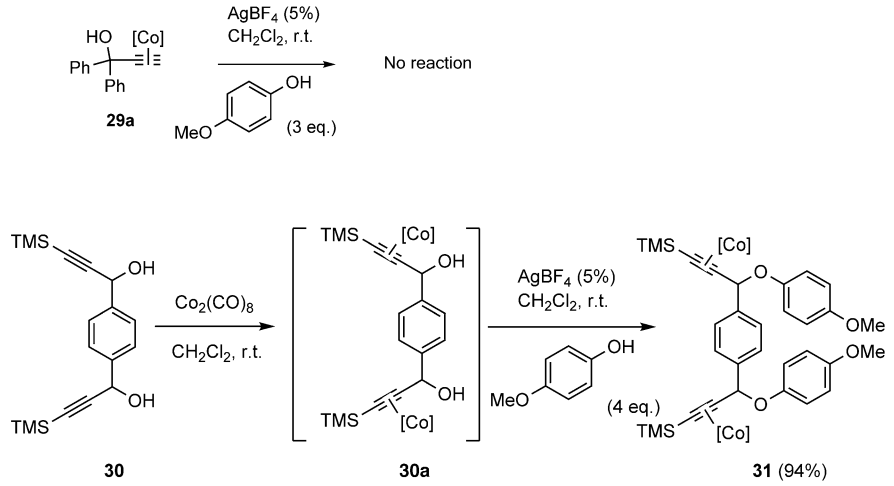


Scheme 7. The use of aromatic propargylic complexes in the catalytic Nicholas reaction.

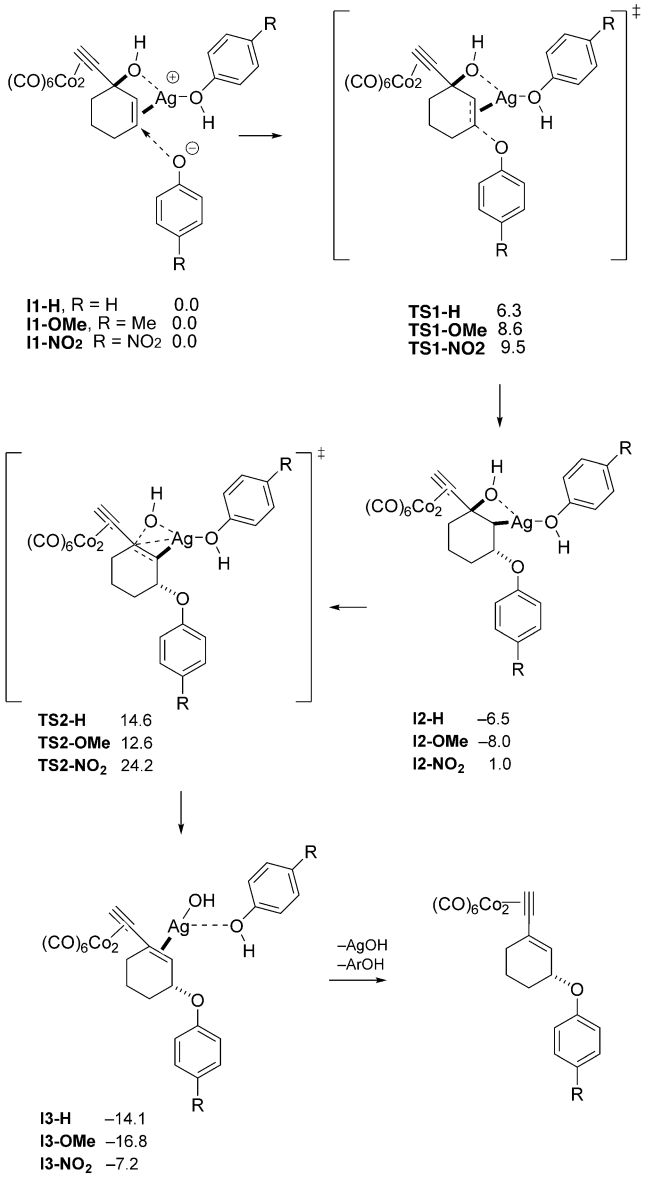
More acidic 4-nitrophenol (and subsequently less nucleophilic) was unreactive under standard conditions, as well as the phenolate salts derived from reactive phenols. The results obtained in these cases indicated that silver phenolate was not the catalytic species, but inhibited the reaction by quenching the active silver species.

To gain some insight into the mechanism, we studied this catalytic reaction by computational means (see the Computational details section). All calculations were performed at the DFT level by using the M06 functional,[9] which accounted for dispersion interactions and delivered good accuracy for transition-metal chemistry.[10] All reported energies correspond with Gibbs energies (in kcal mol^{-1}) in dichloromethane as a solvent. The reaction begins with the coordination of 4-methoxyphenol–Ag^{I} to form the **I1-OMe** intermediate (Scheme 9) on the same face as the alcohol (coordination is according to the experimental data described above directed by the alcohol). Intermediate **I1-OMe** has a trimetallic structure with the silver atom coordinated to the double bond, the alcohol (loosely), and the phenol. 4-Methoxyphenol was unreactive towards **I1-OMe**, whereas anion 4-MeO$C_6H_4O^-$ (formed by the reaction of the phenol with AgOH species generated in the reaction media, see below) smoothly added to C3 via **TS1-OMe** ($\Delta G^{\ddagger}$ = 8.6 kcal mol^{-1}) to form a second intermediate, **I2-OMe**, located 8.0 kcal mol^{-1} below **I1-OMe**. Intermediate **I2-OMe** evolves to the reaction product **I3-OMe** via **TS2-OMe** ($\Delta G^{\ddagger}$ = 20.6 kcal mol^{-1}). Finally, intermediate **I3-OMe** extruded AgOH to form the isolated product and catalyst (AgOH additionally acted as a base to deprotonate a new phenol molecule to form the reagent 4-methoxyphenol-Ag^{I}; Figure 1 and Scheme 9).

To support this proposal, analogous reaction pathways were calculated for phenol (reactive) and 4-nitrophenol (unreactive). The principal difference between the three reagents was found in the second step of the reaction (the addition of the phenolate to **I1** depended little on the nature of the phenol). The process involving **TS2-H** ($\Delta G^{\ddagger}$ = 21.1 kcal mol^{-1}) is similar to that reported for **TS2-OMe** ($\Delta G^{\ddagger}$ = 20.6 kcal mol^{-1}). Interestingly, the breakage of **I2-NO$_2$** via **TS-NO$_2$** ($\Delta G^{\ddagger}$ = 24.2 kcal mol^{-1}) is now higher in energy than previously observed,[11] which is congruent with the lower affinity of 4-nitrophenol for silver,



Scheme 8. The double catalytic Nicholas reaction.



Scheme 9. Calculated reaction pathway.

and therefore, a lower ability to stabilize the emerging positive charge in **TS2-NO$_2$**. This may justify the inertness of 4-nitrophenol in these reactions, probably coupled to the fact that the increased acidity may poison the silver catalysts.

Conclusion

For the first time, a smooth catalytic method to use phenols as the nucleophilic partner in the Nicholas reaction has been developed. The method was general and several silver(I) and gold(I) catalysts can be employed. Among them, the most efficient were either $AgClO_4$ or $AgBF_4$. Additional additives or co-catalysts were not required to obtain good to excellent yields. Both enyne and arylalkyne derivatives were suitable for these transformations. The only shortcoming of this process was the inability of the less nucleophilic phenols (4-nitrophenol) to generate the corresponding adducts. Moreover, by working with chiral substrates, very high selectivity of the reaction was demonstrated. The stereochemistry of the addition of the phenol was directed by the configuration of the alcohol.

DFT calculations gave a preliminary overview of the catalytic cycle, which involved trimetallic intermediates and explained the relative reactivities of different phenols that were directly related to the phenolate substituent.

Experimental Section

General

All reactions were carried out under an argon atmosphere. All solvents used herein were purified by distillation and were freshly distilled immediately before use. CH_2Cl_2 was purified by using a Pure Solv PS-MD-5 system. $BF_3{\cdot}Et_2O$ was distilled prior to use. Flame-dried glassware was used for moisture-sensitive reactions. Silica gel (Merck: 230–400 mesh) was used as the stationary phase for the purification of crude reaction mixtures by flash column chromatography. Identification of products was made by TLC (Kieselgel 60F-254). NMR spectra were recorded at 25 °C in $CDCl_3$ on a Bruker Avance 300 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are given in ppm relative to $CDCl_3$ (^{1}H, $\delta =$

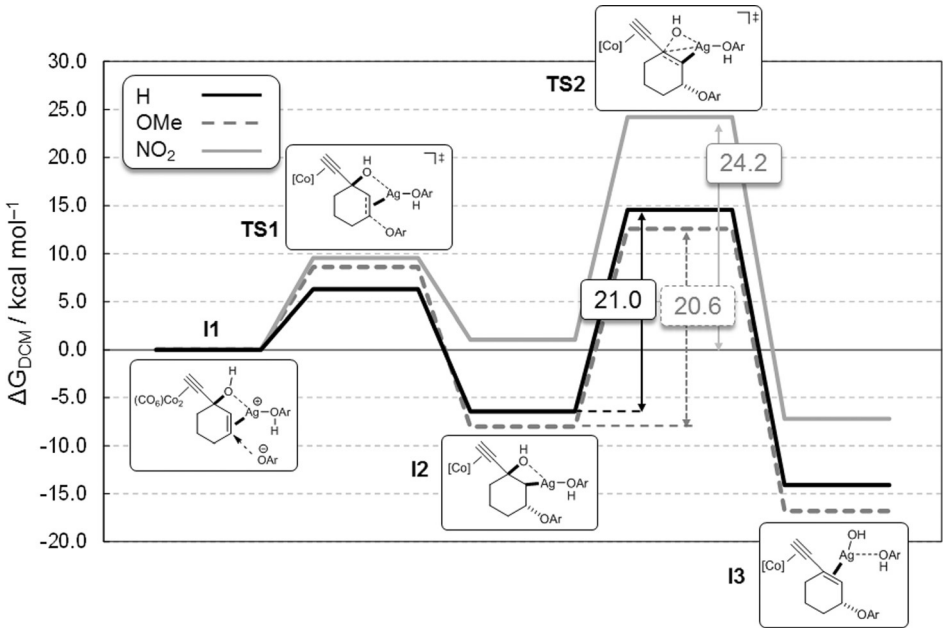


Figure 1. Calculated reaction pathway.

7.27 ppm and ^{13}C, $\delta = 77.0$ ppm). IR spectra were recorded on a MIR (8000–400 cm^{-1}) spectrometer as solid films by slow evaporation of the solvent by using the attenuated total reflectance (ATR) technique. MS spectra (HRMS) were acquired on a QTOF 6520: HP-1200 (Agilent Technologies) mass spectrometer.

Compounds **1a**,[4] **3**,[4] **4**,[4] **16**,[4] **23**,[4] and **30**[12] were prepared by following previously described methods.

General procedure for the Nicholas reaction

$Co_2(CO)_8$ (1.2 equiv) was added to a solution of the corresponding propargylic alcohol (1.0 equiv) in dry CH_2Cl_2 (0.1 M) under an argon atmosphere. The mixture was stirred at room temperature overnight. The crude reaction was filtered through a short pad of Celite and concentrated in vacuo, and the obtained dicobalt hexacarbonyl complex was used without further purification. $AgBF_4$ or $AgClO_4$ (5 mol%) and the corresponding phenol (2.0 or 3.0 equiv) were added under argon atmosphere at room temperature to a solution of the propargylic–$Co_2(CO)_6$ complex (1.0 equiv) in dry CH_2Cl_2 (0.03 M),. The reaction mixture was stirred until no starting material was observed by TLC analysis. The crude reaction mixture was filtered through Celite and concentrated in vacuo. Flash column chromatography on SiO_2 of the residue gave pure products. Optional workup and purification implied washing the crude reaction mixture with 5% NaOH and extraction with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford pure reaction products.

Complex 2

Following the general procedure, from alkyne–cobalt complex **1a** (52.0 mg, 0.12 mmol), 4-methoxyphenol (30.0 mg, 0.24 mmol), and $AgClO_4$ (1.3 mg, 6.1 μmol), and after SiO_2 chromatography (hexane/EtOAc 50:1), pure **2** was obtained (33.0 mg, 51%). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.87$ (d, $J = 9.2$ Hz, 2H), 6.82 (d, $J = 9.2$ Hz, 2H), 6.17 (s, 1H), 6.15 (s, 1H), 4.28 (s, 1H), 3.77 (s, 3H), 2.44–2.34 (m, 1H), 2.33–2.24 (m, 1H), 1.75 (dt, $J = 13.6$, 5.3 Hz, 1H), 1.62 (ddd, $J = 13.6$, 8.6, 6.4 Hz, 1H), 1.05 ppm (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 199.7$, 154.2, 153.0, 136.7, 128.6, 117.7, 114.8, 91.8, 82.0, 72.9, 55.8, 34.3, 34.0, 28.7, 27.1, 21.1 ppm; IR (ATR): $\tilde{\nu} = 2093$, 2054, 2025, 1504, 1223, 1100, 1034, 824, 800 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{23}H_{20}Co_2NaO_8$ $[M+Na]^+$: 564.9714; found: 564.9729.

Complex 6

Following the general procedure, from alkyne–cobalt complex **1a** (51.0 mg, 0.12 mmol), phenol (22.0 mg, 0.23 mmol), and $AgClO_4$ (1.2 mg, 5.8 μmol), and after SiO_2 chromatography (hexane/EtOAc 50:1), pure **6** was obtained (30.0 mg, 50%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$ (d, $J = 8.4$ Hz, 2H), 6.94 (t, $J = 8.4$ Hz, 3H), 6.17 (s, 2H), 4.42 (d, $J = 2.2$ Hz, 1H), 2.55–2.18 (m, 2H), 1.77 (ddd, $J = 13.6$, 5.8, 4.6 Hz, 1H), 1.65 (ddd, $J = 13.6$, 8.7, 6.4 Hz, 1H), 1.05 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 199.6$, 158.9, 136.9, 129.7, 128.2, 120.9, 116.2, 80.65, 72.9, 34.4, 34.0, 28.7, 27.1, 20.9 ppm; IR (ATR): $\tilde{\nu} = 2959$, 2925, 1594, 1263, 1153, 1055, 860, 843, 801, 748, 703 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{22}H_{18}Co_2NaO_7$ $[M+Na]^+$: 534.9614; found: 534.9697.

Complex 8

Following the general procedure, from alkyne–cobalt complex **7a** (52.0 mg, 0.10 mmol), 4-methoxyphenol (24.8 mg, 0.20 mmol), and $AgBF_4$ (1.0 mg, 5.1 μmol), and after SiO_2 chromatography (hexane/EtOAc 60:1), pure **8** was obtained (67.7 mg, 99%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.85$ (m, 4H), 6.14 (s, 1H), 4.28 (s, 1H), 3.77 (s, 3H), 2.47–2.24 (m, 2H), 1.83–1.56 (m, 2H), 1.07 (s, 3H), 1.05 (s, 3H), 0.27 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 200.5$, 154.3, 152.8, 137.2, 128.4, 118.2, 114.8, 82.2, 79.9, 55.9, 38.1, 34.4, 33.9, 28.9, 27.1, 21.0, 0.8 ppm; IR (ATR): $\tilde{\nu} = 2962$, 2088, 2050, 2022, 1672, 1506, 1249, 1226, 1035, 841 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{26}H_{28}Co_2NaO_8Si$ $[M+Na]^+$: 637.0117; found: 637.0120.

Complex 9

Following the general procedure, from alkyne–cobalt complex **7a** (52.0 mg, 0.12 mmol), 3,5-dimethylphenol (23.0 mg, 0.19 mmol),

and $AgClO_4$ (1.0 mg, 4.7 μmol) and after washing with 5% NaOH and extraction with CH_2Cl_2, pure **9** was obtained (48.9 mg, 85%). Due to the instability of complex **9**, characterization was accomplished for the demetalated analogue **9l**.

Complex 10

Following the general procedure, from alkyne–cobalt complex **7a** (52.0 mg, 0.12 mmol), 4-chlorophenol (26.7 mg, 0.21 mmol), and $AgClO_4$ (1.0 mg, 5.2 μmol), and after SiO_2 chromatography (hexane/EtOAc 50:1), pure **10** was obtained (41.6 mg, 64%). Due to the instability of complex **10**, characterization was accomplished for the demetalated analogue **10l**.

Complex 11

Following the general procedure, from alkyne–cobalt complex **7a** (61.0 mg, 0.12 mmol), estrone (64.8 mg, 0.24 mmol), and $AgClO_4$ (1.2 mg, 6.0 μmol), and after SiO_2 chromatography (hexane/EtOAc 50:1), pure **11** was obtained (24.0 mg, 26%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, J = 8.6 Hz, 1H), 6.78–6.70 (m, 1H), 6.70–6.60 (m, 1H), 6.21–6.11 (m, 1H), 4.37 (s, 1H), 2.94–2.80 (m, 2H), 2.51 (dd, J = 18.3, 8.3 Hz, 1H), 2.44–1.91 (m, 8H), 1.81–1.41 (m, 8H), 1.04 (s, 6H), 0.91 (s, 3H), 0.28 (s, 6H), 0.16 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 221.2, 200.2, 156.9, 137.9, 137.3, 132.4, 128.5, 126.5, 116.7, 116.3, 81.0, 50.6, 48.2, 44.2, 38.5, 36.0, 34.5, 33.9, 31.7, 29.8, 28.9, 27.1, 26.7, 26.0, 21.7, 20.8, 14.0, 0.8 ppm; IR (ATR): $\tilde{\nu}$ = 2926, 2086, 2047, 2018, 1740, 1605, 1496, 1263, 1250, 841, 733, 701 cm^{-1}; HRMS (ESI): m/z calcd for $C_{37}H_{42}ClCo_2O_8Si$ $[M+Cl]^-$: 795.1001; found: 795.1009.

Complex 14

Following the general procedure, from alkyne–cobalt complex **12a** (54.0 mg, 0.13 mmol), 4-methoxyphenol (32.0 mg, 0.26 mmol), and $AgClO_4$ (1.4 mg, 6.6 μmol), and after washing with 5% NaOH and extraction with CH_2Cl_2, pure **14** was obtained (60.5 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (d, J = 9.1 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 6.25 (s, 1H), 6.20 (s, 1H), 4.71 (s, 1H), 3.77 (s, 3H), 2.45–2.20 (m, 2H), 2.06–1.91 (m, 2H), 1.91–1.68 ppm (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 199.8, 154.3, 151.8, 138.9, 128.5, 118.1, 114.8, 73.4, 55.8, 31.2, 29.9, 28.3 ppm; IR (ATR): $\tilde{\nu}$ = 2932, 2093, 2053, 2022, 1506, 1225, 1105, 1040, 824 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{16}Co_2NaO_8$ $[M+Na]^+$: 536.9401; found: 536.9397.

Complex 15

Following the general procedure, from alkyne–cobalt complex **13a** (52.0 mg, 0.09 mmol), 4-methoxyphenol (21.8 mg, 0.18 mmol), and $AgClO_4$ (0.9 mg, 4.5 μmol), **15** was obtained after several purifications by chromatography (42 mg, 77%). Due to instability of this product, only characteristic NMR signals are given. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74–7.63 (m, 1H), 7.62–7.53 (m, 2H), 7.39–7.28 (m, 11H), 6.97–6.83 (m, 3H), 6.82–6.65 (m, 4H), 6.41 (d, J = 9.3 Hz, 1H), 5.33 (d, J = 9.5 Hz, 1H), 3.75 (s, 3H), 0.16 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.8, 155.0, 142.1, 140.5, 133.9, 128.7, 128.6, 128.5, 128.1, 126.8, 120.0, 114.5, 80.2, 55.8, 0.6 ppm.

Complex 17

Following the general procedure, from alkyne–cobalt complex **16a** (76.0 mg, 0.16 mmol), 4-methoxyphenol (40.0 mg, 0.32 mmol), and $AgClO_4$ (1.6 mg, 8.0 μmol), and after SiO_2 chromatography (hexane/EtOAc 60:1), pure **17** was obtained (71.4 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.92 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.35 (s, 1H), 4.77 (d, J = 11.1 Hz, 2H), 4.55 (s, 1H), 3.78 (s, 3H), 2.69–2.46 (m, 2H), 2.28–2.07 (m, 2H), 2.00 (s, 3H), 1.78 (s, 3H), 1.53 ppm (td, J = 13.4, J = 3.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 199.9, 154.5, 152.7, 148.5, 132.8, 131.1, 118.4, 114.9, 109.4, 88.5, 78.3, 74.8, 55.9, 38.0, 36.4, 32.1, 21.3, 19.7 ppm; IR (ATR): $\tilde{\nu}$ = 2962, 2091, 2051, 2019, 1504, 1259, 1211, 1090, 1031, 796, 750, 702 cm^{-1}; HRMS (ESI): m/z calcd for $C_{25}H_{22}Co_2NaO_8$ $[M+Na]^+$: 590.9871; found: 590.9848.

Complex 18

Following the general procedure, from alkyne–cobalt complex **16a** (67.0 mg, 0.14 mmol), 3,5-dimethylphenol (34.0 mg, 0.28 mmol), and $AgClO_4$ (1.5 mg, 7.2 μmol), and after washing with 5% NaOH and extraction with CH_2Cl_2, pure **18** was obtained (61.1 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.69–6.51 (m, 3H), 6.34 (s, 1H), 4.76 (d, J = 10.6 Hz, 2H), 4.68 (brs, 1H), 2.64–2.48 (m, 2H), 2.29 (s, 6H), 2.26–2.14 (m, 2H), 1.96 (s, 3H), 1.77 (s, 3H), 1.59 ppm (td, J = 13.7, 4.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.8, 158.7, 148.5, 139.5, 132.8, 131.0, 123.0, 114.1, 109.4, 74.8, 72.3, 37.8, 36.5, 32.3, 21.6, 21.3, 19.6 ppm; HRMS (ESI): m/z calcd for $C_{26}H_{24}Co_2NaO_7$ $[M+Na]^+$: 589.0084; found: 589.0062.

Complex 19

Following the general procedure, from alkyne–cobalt complex **16a** (83.0 mg, 0.18 mmol), estrone (97.0 mg, 0.36 mmol), and $AgClO_4$ (1.8 mg, 9.0 μmol), and after SiO_2 chromatography (hexane/EtOAc 40:1 to 20:1), pure **19** was obtained (15.0 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, J = 8.6 Hz, 1H), 6.78 (dd, J = 8.6, 2.6 Hz, 1H), 6.72 (d, J = 2.6 Hz, 1H), 6.34 (s, 1H), 4.76 (d, J = 15.5 Hz, 2H), 4.67 (s, 1H), 2.99–2.79 (m, 2H), 2.62–2.53 (m, 1H), 2.53–2.43 (m, 1H), 2.46–2.31 (m, 2H), 2.31–2.01 (m, 6H), 1.95 (s, 3H), 1.77 (s, 3H), 1.68–1.43 (m, 8H), 0.91 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 221.1, 200.0, 156.7, 148.5, 138.1, 132.7, 131.1, 126.6, 116.5, 113.7, 109.4, 88.5, 74.8, 50.5, 48.2, 44.2, 38.5, 38.0, 36.5, 36.0, 32.2, 31.7, 29.8, 26.7, 26.0, 21.7, 21.3, 19.6, 14.0 ppm; IR (ATR): $\tilde{\nu}$ = 2927, 2858, 2091, 2053, 2025, 1738, 1604, 1573, 1496, 1453, 1279, 1244, 1099, 1053, 1036, 1008 cm^{-1}; HRMS (ESI): m/z calcd for $C_{36}H_{36}ClCo_2O_8$ $[M+Cl]^-$: 749.0768; found: 749.0834.

Complex 21a

Following the general procedure, from alkyne–cobalt complex **20A** (149.6 mg, 0.28 mmol), 4-methoxyphenol (69.5 mg, 0.56 mmol), and $AgClO_4$ (3.0 mg, 14.0 μmol), and after SiO_2 chromatography (hexane/EtOAc 80:1), pure **21a** was obtained (92 mg, 51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.84 (m, 4H), 6.20 (s, 1H), 4.78 (d, J = 7.6 Hz, 1H), 3.76 (s, 3H), 3.32 (t, J = 5.3 Hz, 1H), 2.59–2.32 (m, 2H; 4axial), 2.17 (dd, J = 14.7, 4.5 Hz, 1H), 2.07 (dd, J = 10.0, 4.5 Hz, 1H), 1.92 (d, J = 10.0 Hz, 1H), 1.38 (s, 3H), 0.74 (s, 3H), 0.32 ppm (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 200.3, 154.8, 151.9, 146.3, 125.4, 120.0, 114.8, 97.7, 80.3, 76.4, 55.8, 46.2, 41.9, 40.5, 33.2, 26.9, 25.9, 22.1, 1.2 ppm; IR (ATR): $\tilde{\nu}$ = 2934, 2084, 2046, 2017, 1505, 1248, 1222, 1039, 841 cm^{-1}; HRMS (ESI): m/z calcd for $C_{28}H_{30}Co_2NaO_8Si$ $[M+Na]^+$: 663.0266; found: 663.0286.

Complex 21b

Following the general procedure, from alkyne–cobalt complex **20B** (112.2 mg, 0.21 mmol), 4-methoxyphenol (52.0 mg, 0.42 mmol), and $AgClO_4$ (2.2 mg, 10.0 μmol), and after washing with 5% NaOH and extraction with CH_2Cl_2, pure **21b** was obtained (114.0 mg,

86%). Due to the instability of complex **21b**, characterization was accomplished for its demetalated analogue **22**.

Complex 24

Following the general procedure, from alkyne–cobalt complex **23a** (56.0 mg, 0.13 mmol), 4-methoxyphenol (50.0 mg, 0.4 mmol), and $AgBF_4$ (1.3 mg, 6.7 μmol), and after SiO_2 chromatography (hexane/EtOAc 30:1), pure **24** was obtained (55.0 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.38 (m, 2H), 7.38–7.27 (m, 3H), 6.85 (d, J = 8.9 Hz, 2H), 6.77 (d, J = 8.9 Hz, 2H), 6.15 (s, 1H), 6.01 (s, 1H), 3.73 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.2, 154.2, 151.8, 142.1, 128.8, 128.3, 125.8, 116.8, 114.7, 80.6, 72.1, 55.8 ppm; IR (ATR): $\tilde{\nu}$ = 2927, 2094, 2052, 2014, 1734, 1503, 1265, 1241, 1220, 1037, 822, 755, 700 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{14}ClCo_2O_8$ $[M+Cl]^-$: 558.9047; found: 558.9056.

Complex 25

Following the general procedure, from alkyne–cobalt complex **23a** (25.0 mg, 60.0 μmol), phenol (17.0 mg, 0.18 mmol), and $AgBF_4$ (0.6 mg, 3.0 μmol), and after washing with 5%NaOH and extraction with CH_2Cl_2, pure **25** was obtained (23.5 mg, 79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.40 (m, 2H), 7.39–7.29 (m, 3H), 7.25–7.18 (m, 2H), 6.98–6.87 (m, 3H), 6.26 (s, 1H), 6.03 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl3): δ = 199.5, 157.7, 141.9, 129.6, 128.9, 128.3, 125.8, 121.3, 115.8, 79.8, 72.0 ppm; IR (ATR): $\tilde{\nu}$ = 2922, 2852, 2096, 2056, 2026, 1738, 1598, 1492, 1262, 1220, 772 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{12}ClCo_2O_7$ $[M+Cl]^-$: 528.8941; found: 528.8967.

Complex 26

Following the general procedure, from alkyne–cobalt complex **23a** (26.0 mg, 60.0 μmol), 4-chlorophenol (23.0 mg, 0.18 mmol), and $AgBF_4$ (0.6 mg, 3.0 μmol), and after washing with 5% NaOH and extraction with CH_2Cl_2, pure **26** was obtained (24.5 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.30 (m, 5H), 7.17 (d, J = 7.4 Hz, 2H), 6.83 (d, J = 7.4 Hz, 2H), 6.20 (s, 1H), 6.02 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.1, 156.2, 141.4, 129.5, 129.0, 128.5, 126.2, 125.7, 117.1, 97.4, 80.4, 72.0 ppm; IR (ATR): $\tilde{\nu}$ = 2962, 2924, 2095, 2056, 2024, 1487, 1260, 1230, 1089, 1012, 796, 737, 700 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{11}Cl_2Co_2O_7$ $[M+Cl]^-$: 562.8551; found: 562.8566.

Complex 28

Following the general procedure, from alkyne–cobalt complex **27a** (66.0 mg, 0.13 mmol), 4-methoxyphenol (48.4 mg, 0.4 mmol), and $AgBF_4$ (1.3 mg, 6.7 μmol), and after SiO_2 chromatography (hexane/EtOAc 60:1), pure **28** was obtained (59.6 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.39 (m, 2H), 7.39–7.27 (m, 3H), 6.81 (d, J = 9.2 Hz, 2H), 6.74 (d, J = 9.2 Hz, 2H), 6.14 (s, 1H), 3.71 (s, 3H), 0.22 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.1, 154.1, 151.9, 141.9, 128.9, 128.5, 126.3, 116.6, 114.7, 81.2, 55.8, 0.8 ppm; IR (ATR): $\tilde{\nu}$ = 2957, 2089, 2049, 2018, 1505, 1248, 1221, 1038, 838, 758, 700 cm^{-1}; HRMS (ESI): m/z calcd for $C_{25}H_{22}ClCo_2O_8Si$ $[M+Cl]^-$: 630.9442; found: 630.9471.

Complex 31

Following the general procedure, from alkyne–cobalt complex **30a** (74.7 mg, 0.083 mmol), 4-methoxyphenol (41.2 mg, 0.33 mmol), and $AgBF_4$ (0.8 mg, 4.1 μmol) and after washing with 5% NaOH and extraction with CH_2Cl_2, pure **31** was obtained (87.5 mg, 94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (s, 1H), 7.42 (s, 1H), 6.66 (m, 4H), 6.08 (d, J = 5.7 Hz, 1H), 3.70 (s, 3H), 0.23–0.13 ppm (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.1, 154.2, 151.6, 142.2, 126.8, 116.9, 114.6, 113.0, 80.8, 55.9, 0.8 ppm; IR (ATR): $\tilde{\nu}$ = 2959, 2089, 2049, 2018, 1505, 1249, 1221, 1042, 837, 775 cm^{-1}; HRMS (ESI): m/z calcd for $C_{44}H_{38}ClCo_4O_{16}Si_2$ $[M+Cl]^-$: 1148.8720; found: 1148.872.

Demetalation procedure

Up to 10.0 equivalents of TMANO were added at 0 °C in small portions in an open flask to a solution of the corresponding cobalt complex (1.0 equiv) in CH_2Cl_2 (0.02 M). The reaction mixture was stirred until no starting material was observed by TLC analysis (reaction mixture turned blue). The crude reaction was filtered through a mixture of Celite/SiO_2 (1:1) and concentrated in vacuo to obtain pure metal-free compounds **9l**, **10l**, and **22**.

Compound 9l

Following the general procedure, cobalt complex **9** (48.9 mg, 80.0 μmol) was treated with TMANO (18.0 mg, 0.24 mmol) in CH_2Cl_2 (5 mL). Pure compound **9l** was obtained as a yellow solid (22.2 mg 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.58 (s, 1H), 6.54 (s, 2H), 6.12 (s, 1H), 4.39 (s, 1H), 2.36–2.15 (m, 8H), 1.70–1.43 (m, 2H), 1.02 (s, 3H), 1.02 (s, 3H), 0.17 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.5, 139.4, 133.6, 123.3, 122.6, 113.5, 105.6, 93.5, 79.1, 34.0, 33.2, 29.8, 27.3, 27.3, 21.6, 20.8, 1.18 ppm; IR (ATR): $\tilde{\nu}$ = 2959, 2922, 2871, 2144, 1611, 1594, 1473, 1302, 1288, 1250, 1187, 1153, 860, 843, 760 cm^{-1}; HRMS (ESI): m/z calcd for $C_{21}H_{31}OSi$ $[M+H]^+$: 327.2139; found: 327.2123.

Compound 10l

Following the general procedure, cobalt complex **10** (41.6 mg, 67.0 μmol) was treated with TMANO (15.1 mg, 0.2 mmol) in CH_2Cl_2 (3.3 mL). Pure compound **10l** was obtained as a yellow solid (21.3 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.22 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 6.06 (s, 1H), 4.35 (q, J = 2.3 Hz, 1H), 2.30–2.13 (m, 2H), 1.67–1.46 (m, 2H), 1.02 (s, 3H), 1.01 (s, 3H), 0.17 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2, 132.5, 129.5, 125.7, 124.0, 117.2, 105.3, 94.0, 80.0, 33.8, 33.3, 29.8, 27.3, 27.1, 20.9, 1.2 ppm; IR (ATR): $\tilde{\nu}$ = 2959, 2926, 2871, 2144, 1594, 1489, 1238, 1025, 1006, 843, 760 cm^{-1}; HRMS (ESI): m/z calcd for $C_{19}H_{26}ClOSi$ $[M+H]^+$: 333.1363; found: 333.1367.

Compound 22

Following the general procedure, cobalt complex **21b** (114 mg, 0.18 mmol) was treated with TMANO (40.5 mg, 0.54 mmol) in CH_2Cl_2 (9.0 mL). Pure compound **22** was obtained as colorless oil (46.0 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.82 (s, 4H), 5.49 (s, 1H), 4.75 (d, J = 7.4 Hz, 1H), 3.77 (s, 3H), 3.22 (t, J = 5.4 Hz, 1H), 2.56 (dt, J = 6.4, 3.1 Hz, 1H), 2.30 (dd, J = 14.4, 7.5 Hz, 2H), 2.21–2.10 (m, 1H), 2.14–1.99 (m, 2H), 1.82 (d, J = 10.1 Hz, 1H), 1.36 (s, 3H), 0.74 (s, 3H), 0.17 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2, 154.3, 151.8, 118.0, 114.8, 108.7, 102.3, 99.3, 74.0, 55.9, 47.8, 41.9, 40.1, 32.7, 27.0, 26.3, 22.0, −0.4 ppm; IR (ATR): $\tilde{\nu}$ = 2952, 2915, 1630, 1505, 1249, 1223, 1104, 1039, 1009, 844, 760 cm^{-1}; HRMS (ESI): m/z calcd for $C_{22}H_{31}O_2Si$ $[M+H]^+$: 355.2088; found: 355.2085.

Computational details

All calculations were performed at the DFT level by using the M06 functional[9,10] with an ultrafine integration grid,[13] as implemented in Gaussian 09.[14] Cobalt and silver atoms were described by using the scalar relativistic Stuttgart–Dresden SDD pseudopotential[15] and its associated double-ζ basis set complemented with a set of f-polarization functions.[16] The 6-31G** basis set was used for the H, C, N, and O atoms.[17] All structures of reactants, intermediates, transition states, and products were fully optimized in dichloromethane ($\varepsilon = 8.93$) by using the SMD continuum model.[18] Transition states were identified by one imaginary frequency in the Hessian matrix. It was confirmed that transition states connected with the corresponding intermediates by means of application of the eigenvector corresponding to the imaginary frequency and subsequent optimization of the resulting structures. All energy values given in the text were Gibbs energies in dichloromethane at 298 K.

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[6] Assignment of the absolute stereochemistry of carbon C2 in compounds **17**, **18**, and **19** was established by NMR spectroscopy by using a similar method to that employed in our previous work.[4]

[7] The absolute configuration of the newly formed chiral centers of **20 A** and **20 B** was established by the reaction of **20 A** with both (*R*)- and (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride Mosher's acid chlorides, according to the procedure described by T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protoc.* **2007**, *2*, 2451. A comparison of the ^{1}H NMR spectroscopy data of the corresponding (*S*)- and (*R*)-esters unambiguously showed the *R* configuration for alcohol **20 A**, and subsequently, the *S* configuration for **20 B** (Scheme 6). These data were obtained as a reviewer suggestion during paper revision and fully supported the proposed reaction mechanism (Scheme 9) based on theoretical calculations.

[8] For an extensive study on the stereochemical outcome of the Nicholas reaction, see: a) E. Álvaro, M. C. de La Torre, M. A. Sierra, *Org. Lett.* **2003**, *5*, 2381; b) E. Álvaro, M. C. de La Torre, M. A. Sierra, *Chem. Eur. J.* **2006**, *12*, 6403. According to this procedure, selective irradiation under NOE conditions of the olefinic proton H-10 ($\delta = 6.23$ ppm) of compound **21 a** was performed. An intensity increase in the signal of H-3 confirmed the *E* stereochemistry of the double bond. Another NOE experiment to irradiate H-3 ($\delta = 4.81$ ppm) produced a NOE in the pro-*S* methyl group ($\delta = 0.75$ ppm), which confirmed the *syn* relationship between this methyl and H-3. In a similar manner, the stereochemistry of compounds **21 b** and **22** was also elucidated.

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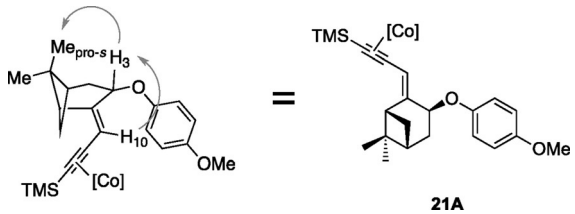

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