Synthetic Methods

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Synthesis and Application of β-Substituted Pauson–Khand Adducts: Trifluoromethyl as a Removable Steering Group**

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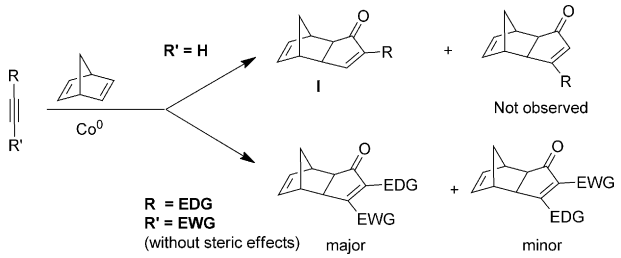
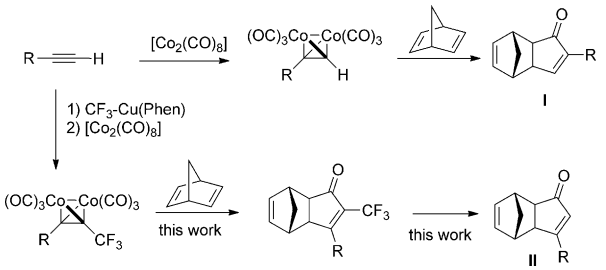
The Pauson–Khand reaction (PKR) is a well-established methodology for the construction of cyclic and polycyclic structures containing five-membered rings.[1,2] Since its discovery in 1973 this reaction has been widely used in organic synthesis. The intramolecular PKR has been extensively applied to build polycyclic compounds. In this case, both the stereo- and regioselectivity are controlled by the substrate. The intermolecular version of the reaction has been less exploited because of its smaller range of reactive alkenes,[3] although it has the advantage that in many cases the stereochemistry can be controlled by the presence of either chiral auxiliaries[4] (bound to the alkyne or the alkene) or chiral ligands[5] (bound to the intermediate cobalt complex). However, one of the difficulties encountered with the intermolecular PKR is the control of the regiochemical outcome.[6–10] While this control is achieved when dealing with terminal alkynes (in this case only the α-substituted cyclopentenone **I** is formed[8]), with internal nonsymmetric alkynes the regiochemistry of the PK adducts depends on a combination of steric and electronic effects, which are difficult to predict (Scheme 1).[7–10] In the absence of steric effects, electron-donating groups (EDGs) show preference for the α-position, whereas electron-withdrawing groups (EWGs) tend to displace to the β-position.[9] However, recent studies have shown that the electronic effects are much less significant than previously described and can, therefore, be overcome by the steric effects.[10]

In previous studies of the intermolecular PKR of nonsymmetric fluorinated alkynes we observed that the electron-withdrawing effect of the fluorinated substituents had little impact on the regioselectivity.[11] Unexpectedly, these fragments ended up in the α-position of the PK adduct. To ascertain whether this was a purely steric effect, herein we studied the regioselectivity of the PKR of a family of trifluoromethylacetylenes. In all cases the regioselectivity was complete, being the PK adduct with the trifluoromethyl in α-position the only one observed. The subsequent study of the reactivity of these adducts allowed us to find an efficient procedure to remove the trifluoromethyl group. Therefore we uncovered a new procedure, outlined in Scheme 2, to prepare the previously unknown β-substituted PK adducts **II**. Here we describe the first synthesis of the regioisomeric PK adducts of terminal alkynes **II** and their practical application to the formal synthesis of α-cuparenone.



Scheme 1. General trends of the regioselectivity of intermolecular PKR.



Scheme 2. Standard intermolecular PKR for internal alkynes affording adducts **I** and the sequence for the synthesis of the regioisomers **II** described here. The trifluoromethylation Cu reagent CF_3-Cu(Phen) was prepared as described in the Experimental Section.

We chose *p*-methoxyphenylacetylene **1a** as a model substrate to explore our synthetic proposal, since the electron-donating nature of the *p*-methoxyphenyl group and its medium size should favor to end up at the α-position. The trifluoromethylated alkyne was synthesized from **1a** by following the procedure described by F.-L. Qing and coworkers.[12] This alkyne was difficult to purify, because of its volatility and highly lipophilic character. These features

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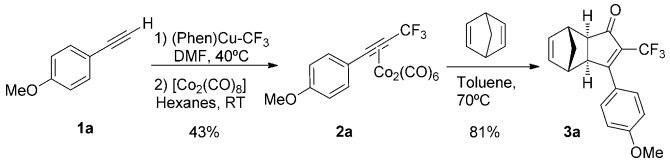
hindered the chromatographic separation of the desired product from the homocoupling byproducts. To overcome these problems, we proceeded to treat the crude reaction mixture of the alkyne in hexanes with $[Co_2(CO)_8]$. The resulting dicobalt hexacarbonyl complex **2a** was purified by chromatography without further problems (Scheme 3). The pure complex **2a** was subjected to the thermal PKR (toluene, 70 °C) with norbornadiene. Both ^1H and ^{19}F NMR spectra of

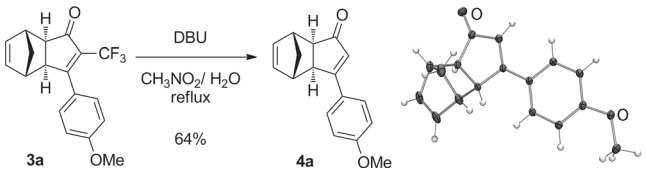


Scheme 3. Synthesis and PKR of trifluoromethyl acetylene **2a**.

the reaction crude showed only one PK adduct, which was isolated in 81 % yield.[13] The NMR spectra led us to assign the product to the α-trifluoromethylated PK adduct **3a**. The regiochemical outcome, which was the opposite of the standard selectivity on the basis of electronic criteria, led us to propose that the electronic effect of the trifluoromethyl substituent is much weaker than expected, so the reaction outcome is determined by steric effects.

To check the scope of our approach, we tested a series of terminal alkynes **1b–k** (Table 1). The substitution pattern included aliphatic, olefinic, and aromatic groups with a large range of substituents with distinct electronic properties. The trifluoromethyl group was introduced to these alkynes by following Qing's procedure[12] with minor modifications (see the Supporting Information). The reaction crude products of the trifluoromethylated alkynes were complexed with $[Co_2(CO)_8]$ and purified by silica gel chromatography to afford complexes **2b–k** in good to excellent yield. The corresponding PKR of these complexes with norbornadiene proceeded smoothly by heating the toluene solution at 70 °C. In all cases, a single regioisomer was obtained in good to excellent yield.

We next tackled the removal of the trifluoromethyl group. After some experimentation we found that treatment of PK adduct **3a** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in nitromethane with a small amount of water afforded enone **4a** in good yield (Scheme 4). Although the yield was not quantitative, the reaction was clean, and cyclopentenone **4a** was easily purified. Crystals suitable for X-ray diffraction were obtained from dichloromethane/hexanes. The structure

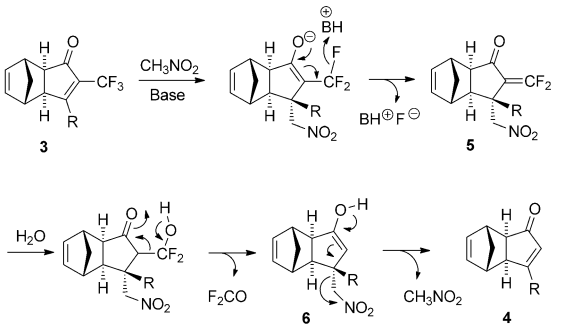


Scheme 4. Removal of the CF_3 group from the PKR adduct **3a** and ORTEP drawing of cyclopentenone **4a** with the thermal ellipsoids set at 50% probability.

of **3a** could be thus determined[14] (Scheme 4), and consequently the regiochemistry of the previous PKR was confirmed.

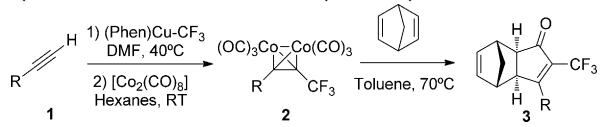
The remaining PK adducts were treated under the same conditions yielding products **4b–k** in satisfactory yields (Table 2) except for adduct **3j**. In this case, although the final product was detected by NMR spectroscopy, it could not be purified from the reaction by-products.

Although the mechanism of this novel reaction is unknown, we hypothesized that the removal of the CF_3 group could take place after a Michael addition of nitromethane, which would afterwards be removed. Adduct **3c** was selected to perform experiments to shed light on the mechanism. As expected, treatment of **3c** with DBU/nitromethane/H_2O afforded cyclopentenone **4c** in good yield. The essential role of nitromethane was readily confirmed, since the reaction did not take place in toluene or in dioxane. In a mixture of toluene/nitromethane, the reaction occurred at a lower rate and yield. Small amounts of water also play an essential role in the reaction. Its complete removal by using dry nitromethane led to a dramatic decrease of the conversion, which did not reach completion even after 18 h. Addition of 5 equivalents of water to dry nitromethane gave the same reaction yield as using nitromethane directly without purification. Other nucleophiles such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or cyanide in acetonitrile (without nitromethane) were successful only in the latter case, but with a lower conversion or yield. The base was substituted by tetrabutylammonium fluoride (TBAF) and the same dependence of nitrometane/water was observed (a summary of these experiments is shown in the Supporting Information). These experiments are consistent with the observation that the loss of fluoride occurred after the Michael addition of nitromethane to the enone. Since a loss of fluoride in α-trifluoromethyl ketones had been reported by Mikami and Itoh,[15] and also took place in a related compound reported by our group,[11] we propose a plausible mechanism for this reaction (Scheme 5). After conjugate addition of nitromethane, elimination of fluoride would give a difluoroenone **5**, which, after conjugate addition of water followed by a retro-aldol reaction would afford an intermediate enol **6**. Retro-Michael reaction of nitromethane on this substrate would yield the observed product **4**. None of the proposed intermediates (**5, 6**) were detectable by NMR

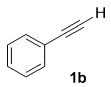
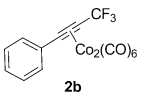
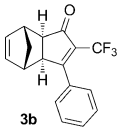
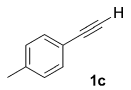
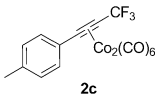
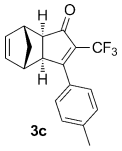
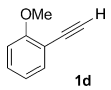
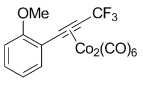
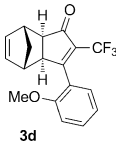
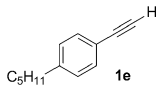
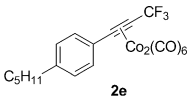
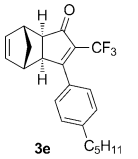
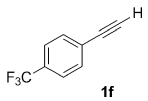
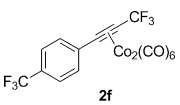
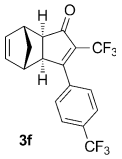
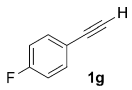
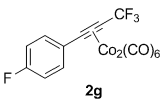
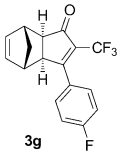
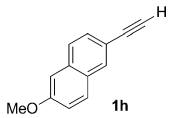
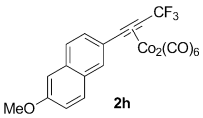
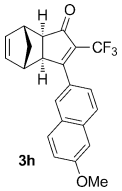
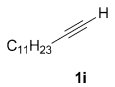
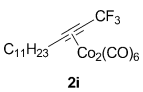
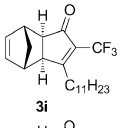
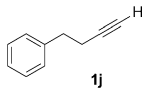
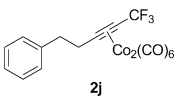
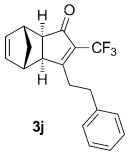
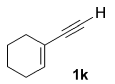
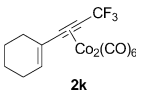
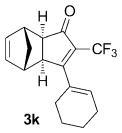


Scheme 5. Postulated mechanism for the CF_3 elimination.

Table 1: Synthesis and PKR of trifluoromethylated alkynes **2b–k**.



1 **2** **3**

Entry	Alkyne	Complex **2**	Yield **2** [%]	PK adduct **3**	Yield **3** [%]
1	 **1b**	 **2b**	55	 **3b**	77
2	 **1c**	 **2c**	91	 **3c**	95
3	 **1d**	 **2d**	70	 **3d**	74
4	 **1e**	 **2e**	69	 **3e**	99
5	 **1f**	 **2f**	44	 **3f**	70
6	 **1g**	 **2g**	62	 **3g**	81
7	 **1h**	 **2h**	70	 **3h**	80
8	 **1i**	 **2i**	87	 **3i**	79
9	 **1j**	 **2j**	60	 **3j**	77
10	 **1k**	 **2k**	70	 **3k**	70

spectroscopy. Attempts to trap enol **6** with an electrophile were unsuccessful.

To demonstrate the synthetic potential of these newly available compounds, a formal synthesis of α-cuparenone was envisaged. α-Cuparenone is a bicyclic sesquiterpene that belongs to the cuparene family. It was isolated from *Thuja orientalis*, an evergreen coniferous tree endemic to Asia, by Dev and Chetty in 1964.[16] Its synthesis has been tackled using various approaches.[17] The final steps of several of them involve the alkylation and reduction of the key intermediate **7.**[18] We set about to obtain this intermediate by a retro-Diels–Alder reaction of **8**, which in turn would be prepared by methyl conjugate addition on the corresponding regioisomeric PK adduct **4c** (Scheme 6).

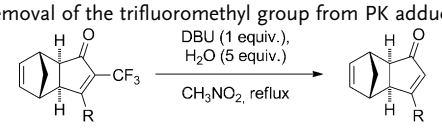
The methyl conjugate addition to enone **4c** required some experimentation. Lithium dimethylcuprate afforded only the 1,2-addition product.[19] The conjugate addition of dialkyl zinc species catalyzed by nickel(II)[20] to **4c** was also fruitless. Finally, the nickel-catalyzed addition of trimethylaluminium[21] yielded the desired 1,4-addition product **8** as a single diastereomer in a satisfactory 67% yield (Scheme 7). The final step, the retro-Diels–Alder reaction, was carried out under microwave conditions and yielded key intermediate **7** in high yield and purity. The spectroscopic data coincided with those reported.[18c]

In conclusion, under thermal conditions, the PKR of norbornadiene with internal trifluoromethyl alkynes provided the PK adducts with complete regioselectivity in good to excellent yields. A wide variety (11 examples) of internal trifluoromethyl alkynes including aromatic, aliphatic, and olefinic substituents was tested, affording in all cases the regioisomer bearing the CF_3 group attached to the α-position. Treatment of these PK adducts with DBU in nitromethane/water resulted in the loss of the CF_3 group, thereby providing the β-substituted cyclopentenones that correspond to the regioisomers of the normal PKR of terminal alkynes. The unprecedented reaction for removal of the trifluoromethyl group proved to be general (10 examples), and a reasonable mechanism has been proposed. The overall process constitutes the first example of a PKR with terminal alkynes with inverse regiochemistry. This methodology was successfully applied to the formal synthesis of α-cuparenone.

Experimental Section

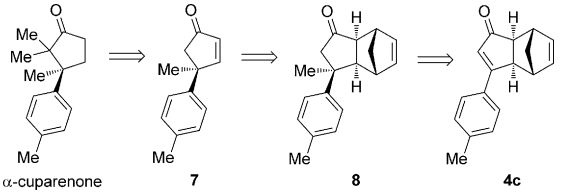
General preparation of cobalt complexes **2**: To a Schlenk flask, Ag_2CO_3 (1 mmol, 2 equiv), phenantroline (1 mmol, 2 equiv), CuCl (1 mmol, 2 equiv), *t*BuOK (1 mmol, 2 equiv), and anhydrous DMF (10 mL) were added under nitrogen. The red-brown solution was stirred at room temperature for 30 min. Trifluoromethyltrimethylsilane ($TMSCF_3$; 2.5 mmol, 5 equiv) was added, and the reaction heated one hour at 40 °C. A solution of the terminal alkyne

Table 2: Removal of the trifluoromethyl group from PK adducts **3**.

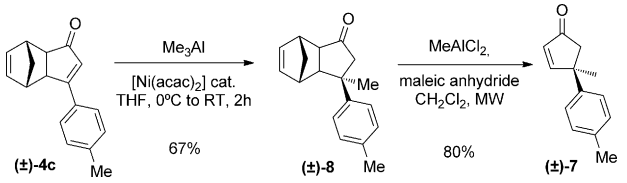


3 **4**

Entry	PK adduct	R	Product	Yield [%]
1	**3b**	phenyl	**4b**	55
2	**3c**	tolyl	**4c**	64
3	**3d**	2-methoxyphenyl	**4d**	51
4	**3e**	4-pentylphenyl	**4e**	68
5	**3f**	4-(trifluoromethyl)phenyl	**4f**	57
6	**3g**	4-fluorophenyl	**4g**	59
7	**3h**	6-methoxynaphtalene-2-yl	**4h**	58
8	**3i**	undecyl	**4i**	61
9	**3j**	phenylethyl	**4j**	n.d.
10	**3k**	cyclohex-1-en-1-yl	**4k**	40



Scheme 6. Retrosynthetic analysis of α-cuparenone.



Scheme 7. Synthesis of key intermediate **7**. MW = microwave, acac = acetylacetonate.

1 (0.5 mmol, 1 equiv) in DMF (3 mL) was slowly added to the mixture with a syringe pump (addition rate: 0.5 mL h^{-1}). The reaction was stirred overnight and quenched by addition of water and hexanes. While stirring vigorously in open air, a solution of NH_3/NH_4Cl (1:3) was added. After 30 min stirring, the phases were separated, and the organic layer was washed with water, dried ($MgSO_4$), and filtered. To the crude solution of the alkyne was added $[Co_2(CO)_8]$ (0.5 mmol, 1 equiv). The mixture was stirred under nitrogen at room temperature until the alkyne was completely consumed (monitored by TLC). The solution was evaporated and purified by chromatography (SiO_2/hexanes) affording cobalt complexes **2** as deep-red compounds.

General preparation of trifluoromethylcyclopentenones **3**: To a solution of cobalt complex **2** (0.21 mmol, 1 equiv) in anhydrous toluene (7 mL) was added norbornadiene (2.10 mmol, 10 equiv) under nitrogen. The mixture was stirred at 70 °C, and the reaction was monitored by TLC. When finished (approximately 24 h), the solvent was removed under reduced pressure and the crude purified by chromatography (SiO_2, hexanes/AcOEt) to afford trifluoromethylcyclopentenones **3.**

General preparation of cylopentenones **4**: To a solution of **3** (0.11 mmol, 1 equiv) in nitromethane (7 mL), water (0.01 mL, 0.55 mmol, 5 equiv) and DBU (0.11 mmol, 1 equiv) were added under nitrogen. The mixture was heated to reflux and the reaction monitored by TLC. When finished (approximately 1.5 h), the solvent was removed under vacuum and the crude was purified by chromatography (SiO_2/hexanes/AcOEt) to afford cyclopentenones **4**.

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