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Regioselectivity in Intermolecular Pauson-Khand Reactions of Dissymmetric Fluorinated Alkynes

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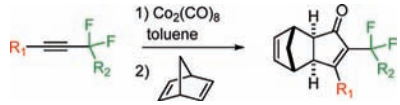
ABSTRACT



Stoichiometric and catalytic intermolecular Pauson−Khand reactions (PKRs) of dissymmetric fluorinated alkynes were performed, affording regioselectively α-fluorinated cyclopentenones. Ethyl 4,4,4-trifluorobutynoate was an excellent substrate; its reaction with norbornadiene gave the corresponding PKR adduct in good yield and complete regioselectivity. Conjugate addition of nitroalkanes or cyanide to this adduct is stereospecific and entails concomitant loss of a trifluoromethyl group. This reaction can be exploited to prepare cyclopentenones featuring quaternary centers.

The Pauson−Khand reaction (PKR) has become one of the preeminent transformations for synthesizing cyclic and polycyclic targets with five-membered rings,[1,2] as it enables rapid access to valuable functionalized intermediates for diverse chemistries. Furthermore, the recent development of catalytic[3] and enantioselective[4] methodologies for intermolecular PKRs has facilitated preparation of enantiomerically enriched cyclopentenones.[2,5] Whereas the intermolecular reaction of terminal alkynes to give α-substituted cyclopentenones[6] is always regioselective, the less frequently used internal alkynes can afford two regioisomers. Although the PKR can sometimes be highly regioselective,[5a] the regiochemistry is influenced by steric and electronic effects and

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(1) (a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Chem. Commun.* **1971**, 36. (b) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977.

(2) For recent reviews on the Pauson−Khand reaction, see: (a) Lee, H. W.; Kwong, F. Y. *Eur. J. Org. Chem.* **2010**, 789. (b) Park, J. H.; Chang, K. M.; Chung, Y. K. *Coord. Chem. Rev.* **2009**, *253*, 2461. (c) Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022. (d) Park, K. H.; Chung, Y. K. *Synlett* **2005**, 545. (e) Boñaga, L V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795.

(3) (a) Cabot, R.; Lledo, A.; Reves, M.; Riera, A.; Verdaguer, X. *Organometallics* **2007**, *26*, 1134. (b) Lledo, A.; Sola, J.; Verdaguer, X.; Riera, A.; Maestro, M. A. *Adv. Synth. Catal.* **2007**, *349*, 2121.

(4) (a) Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A.; Maestro, M. A.; Mahia, J. *J. Am. Chem. Soc.* **2000**, *122*, 10242. (b) Verdaguer, X.; Pericàs, M. A.; Riera, A.; Maestro, M. A.; Mahia, J. *Organometallics* **2003**, *22*, 1868. (c) Verdaguer, X.; Lledó, A.; López-Mosquera, C.; Maestro, M. A.; Pericàs, M.; Riera, A. *J. Org. Chem.* **2004**, *69*, 8053. (d) Sola, J.; Riera, A.; Verdaguer, X.; Maestro, M. A. *J. Am. Chem. Soc.* **2005**, *127*, 13629. (e) Solà, J.; Revés, M.; Riera, A.; Verdaguer, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 5020. (f) Revés, M.; Achard, T.; Solà, J.; Riera, A.; Verdaguer, X. *J. Org. Chem.* **2008**, *73*, 7080. (g) Ji, Y.; Riera, A.; Verdaguer, X. *Org. Lett.* **2009**, *11*, 4346.

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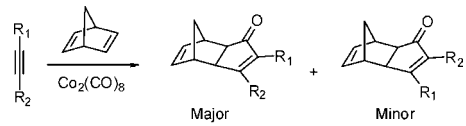
may be difficult to predict.[7] In general, the bulkiest substituent on the alkyne tends to end up α to the carbonyl group. Among sterically similar substituents on the alkyne, the more strongly electron-withdrawing group tends to end up at the β position[6d] (Scheme 1).

Scheme 1. Regioselectivity of the Pauson−Khand Reaction[a]



[a] EWG: electron-withdrawing group. EDG: electron-donating group.

Fluorinated substrates are very rarely used in PKRs. Indeed, only a few examples of intramolecular PKR of fluorinated enynes have been described.[8,9] Moreover, to the best of our knowledge, there are no reports on intermolecular PKR of fluorinated substrates. Considering the importance of fluorinated compounds,[10] we sought to explore intermolecular PKRs of fluorinated alkynes and investigate how these strongly electron-withdrawing groups affect regioselectivity.

We chose several terminal or internal alkynes (**1**−**4**) containing fluorine atoms at the propargylic position (Figure 1).

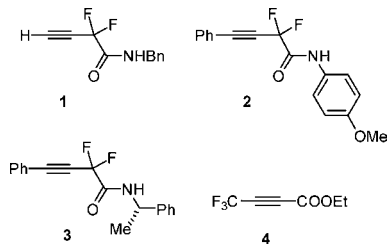
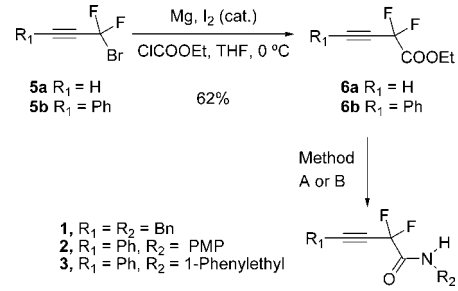


Figure 1. Four α-fluorinated alkynes studied.

The amides **1**−**3** were easily prepared from the readily available bromodifluoroacetylenes **5**.[11] The Grignard derivative of the corresponding acetylenes were treated in Barbier-type conditions with ethyl chloroformate to give the esters **6**. Amination using sodium hydride in THF or $AlMe_3$ in CH_2Cl_2 provided amides **1**−**3** in good yields (69−85%) (Scheme 2).[11] Ethyl 4,4,4-trifluorobutynoate (**4**), although commercially available, was prepared from trifluoroacetic anhydride by the highly convenient Hamper's procedure.[12]

Scheme 2. Preparation of the Fluorinated Alkynes **1**−**3**[a]



[a] Method A: $NaH/R_2NH_2/THF/-50$ °C/1−3 h. Method B: $AlMe_3/R_2NH_2/CH_2Cl_2/0$ °C/2−4 h (ref 11).

Stoichiometric PKRs of the terminal alkyne **1** and of the internal alkynes **2** and **3** were first studied. The alkynes were treated with dicobalt octacarbonyl in toluene at room temperature to cleanly form the corresponding hexacarbonyl cobalt complexes (monitored by TLC). Once the complexes had been formed, norbornadiene (10 equiv) was added, and the solution was heated at 70 °C until the starting cobalt complexes disappeared by TLC. The adducts **7**−**9** (derived from **1**−**3**, respectively) were obtained in moderate yields with complete regioselectivity (**7** and **8**, as racemates; and **9**, as a 1:1 mixture of diastereoisomers) (Table 1). Most surprisingly, in all cases, the fluorinated moiety was located at the α-position of the enone. Contrary to our expectations, the bulky phenyl group was β to the carbonyl and the EWG α. The regiochemistry of adducts **7**−**9** was unambiguously established by NMR on the basis of the coupling between the carbon and fluorine atoms. Furthermore, the calculated chemical shifts of the olefinic carbons fit particularly well with the recorded values. Lastly, these results were confirmed by X-ray crystallography of compound **8** (Figure 2).

The stoichiometric PKR of ethyl 4,4,4-trifluorobutynoate (**4**)[12] under the standard conditions afforded the cyclopentenone **10** in excellent yield (Table 1). Purification of the intermediate cobalt hexacarbonyl complex (**11**) did not improve the yield. The structure of the major isomer was carefully analyzed by NMR: again, the trifluoromethyl group was found to be at the α position of the enone. For the sake of comparison, ethyl

(5) (a) Vazquez-Romero, A.; Cardenas, L.; Blasi, E.; Verdaguer, X.; Riera, A. *Org. Lett.* **2009**, *11*, 3104. (b) Vazquez-Romero, A.; Rodriguez, J.; Lledo, A.; Verdaguer, X.; Riera, A. *Org. Lett.* **2008**, *10*, 4509. (c) Iqbal, M.; Duffy, P.; Evans, P.; Cloughley, G.; Allan, B.; Lledo, A.; Verdaguer, X.; Riera, A. *Org. Biomol. Chem* **2008**, *6*, 4649. (d) Iqbal, M.; Evans, P.; Lledo, A.; Verdaguer, X.; Pericas, M. A.; Riera, A.; Loeffler, C.; Sinha, A. K.; Mueller, M. J. *ChemBioChem* **2005**, *6*, 276.

(6) (a) Schore, N. E. *Org. React.* **1991**, *40*, 1. (b) Krafft, M. E.; Romero, R. H.; Scott, I. L. *J. Org. Chem.* **1992**, *57*, 5277. (c) Arjona, O.; Csákÿ, A. G.; Murcia, M. C.; Plumet, J. *J. Org. Chem.* **1999**, *64*, 7338. (d) Robert, F.; Millet, A.; Gimbert, Y.; Konya, D.; Greene, A. E. *J. Am. Chem. Soc.* **2001**, *123*, 5396.

(7) De Bruin, T. J. M.; Michel, C.; Vekey, K.; Greene, A. E.; Gimbert, Y.; Milet, A. *J. Organomet. Chem.* **2006**, *691*, 4281.

(8) (a) Arimitsu, S.; Bottom, R. L.; Hammond, G. B. *J. Fluorine Chem.* **2008**, *129*, 1047. (b) Ferry, A.; Billard, T.; Langlois, B. R. *Synlett* **2005**, 1027. (c) Harthong, S.; Billard, T.; Langlois, B. R. *Synthesis* **2005**, 2253. (d) Ishizaki, M.; Suzuki, D.; Hoshino, O. *J. Fluorine Chem.* **2001**, *111*, 81.

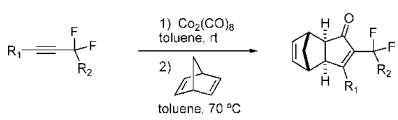
(9) (a) Nadano, R.; Ichikawa, J. *Chem. Lett.* **2007**, *36*, 22. (b) Nadano, R.; Fuchibe, K.; Ikeda, M.; Takahashi, H.; Ichikawa, J. *Chem. Asian J.* **2010**, *5*, 1875.

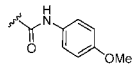
(10) *Modern fluoroorganic chemistry: synthesis, reactivity, applications*; Peer, K., Eds.; Wiley-VCH: Weinheim, 2004.

(11) (a) Fustero, S.; Fernández, B.; Bello, P.; del Pozo, C.; Arimitsu, S.; Hammond, G. B. *Org. Lett.* **2007**, *9*, 4251. and literature cited therein. (b) Arimitsu, S.; Fernández, B.; del Pozo, C.; Fustero, S.; Hammond, G. B. *J. Org. Chem.* **2008**, *73*, 2656. See also: (c) Fustero, S.; Bello, P.; Fernández, B.; del Pozo, C.; Hammond, G. B. *J. Org. Chem.* **2009**, *74*, 7690.

(12) (a) Hamper, B. C. *J. Org. Chem.* **1988**, *53*, 5558. (b) Hamper, B. C. *Org. Synth.* **1992**, *70*, 246.

Table 1. Intermolecular Pauson−Khand Reaction of the Fluorinated Alkynes **1**−**4**



Substrate	R_1	R_2	Prod.	yield
1	H	CONHBn	**7**	40%
2	Ph		**8**	48%
3	Ph		**9**	62%
4	COOEt	F	**10**	92%

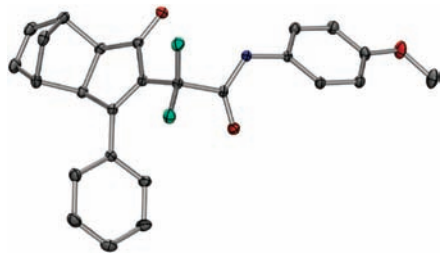


Figure 2. X-ray structure of compound **8**.

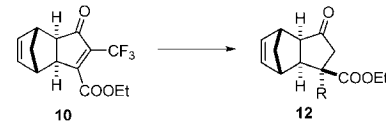
2-butynoate, the nonfluorinated analogue of **4**, was also tested. As described,[13] it gave regioisomer with the methyl group in the α position (analogous to **10**) in 91% yield.[6a,13] The fact that the same regioselectivity was observed for two electronically divergent compounds suggests that the strongly electron-withdrawing trifluoromethyl group slightly influences the regiochemistry of the reaction.

To confirm the surprising regiochemistry of adduct **10**, and to explore its synthetic potential, we attempted several conjugated additions of diverse nucleophiles to this compound beginning with lithium dialkylcuprates. Somewhat surprisingly, all attempts led to rapid decomposition of the products. A literature survey revealed that α-trifluoromethyl lithium enolates decompose easily by lithium fluoride elimination.[14] Seeking to avoid using lithium, we then tried conjugate addition of **10** to Grignard reagents, catalyzed by different sources of copper (CuI, CuCN, and CuBr), and to diethylzinc catalyzed by nickel(II). Unfortunately, these efforts also failed. Copper-catalyzed addition of trimethylaluminum gave the expected product as a mixture of diastereomers; however, the product was unstable and could not be fully characterized. However, heating enone **10** in nitromethane solution with a base (DBU or TBAF) gave a clean reaction (Table 2).

(13) Fonquerna, S.; Moyano, A.; Pericas, M. A.; Riera, A. *J. Am. Chem. Soc.* **1997**, *119*, 10225.

(14) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 4883.

Table 2. Conjugate Additions to the PKR Adduct **10**



reagent	base (equiv), temp (°C), time (h)	R		yield (%)
$MeNO_2$[a]	TBAF[b] (0.4), 80, 15	CH_2NO_2	**12a**	65
$MeNO_2$[a]	TBAF[b] (1), 90, 3	CH_2NO_2	**12a**	99
$MeNO_2$[a]	DBU (0.2), 80, 18	CH_2NO_2	**12a**	36
$MeNO_2$[a]	DBU (1)[c], 90, 1.5	CH_2NO_2	**12a**	56
$EtNO_2$[a]	TBAF[d] (0.4), 65, 1.5	$CH(CH_3)NO_2$	**12b**	57
KCN[e]	90, 1.5	CN	**12c**	50

[a] Used as a solvent. [b] Trihydrated salt. [c] Water (16 equiv) was added. [d] 1 M solution in THF. [e] In actonitrile as solvent.

The unexpected main product, **12a**, resulted from 1,4-addition of nitromethane with concomitant loss of the trifluoromethyl group. The structure of **12a** was confirmed by X-ray diffraction, enabling unambiguous assignment of the regiochemistry of the PKR adduct **10** (see Figure 3). The

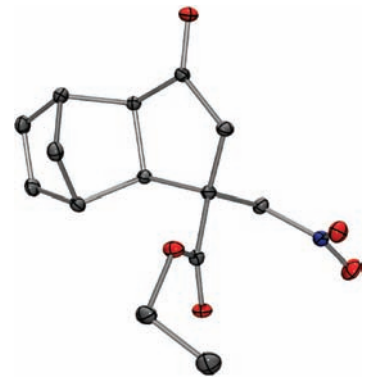
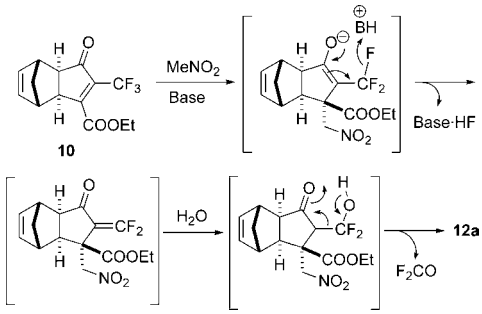


Figure 3. X-ray structure of compound **12a**.

same reaction (conjugate addition and loss of the trifluoromethyl group) also occurred when nitroethane or cyanide was used as nucleophile (see table 2). The yields improved when 1 equiv of base was used and, in the case of DBU, by addition of a small amount of water. The reaction was monitored by ^{19}F NMR, and a signal corresponding to HF-DBU was observed. A conceivable mechanism for the loss of the CF_3 group consistent with all these facts is shown in Scheme 3; after the conjugate addition, elimination of fluoride similar to the one proposed by Mikami[14] would give a difluoro enone. Conjugate addition of water (or nitromethane) to this enone followed by retro-aldol reaction (or retro-Michael) would afford the cyclopentanone **12a**.

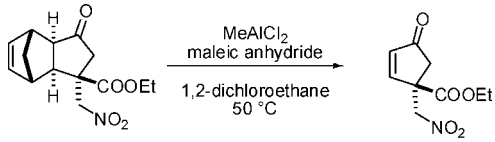
To explore the synthetic potential of this unexpected reaction in the preparation of cyclopentenones with a quaternary center in C4, compound **12a** was subjected to

Scheme 3. Proposed Mechanism for the Loss of CF_3 Group



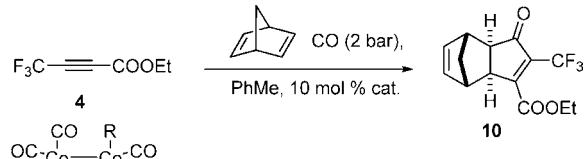
Grieco's retro-Diels−Alder conditions,[15] affording cyclopentenone **13a** in 60% yield (Scheme 4).

Scheme 4. Retro-Diels−Alder Reaction of Compound **12a**



Having explored the reactivity and the regioselectivity of the stoichiometric reaction, we turned our attention to the catalytic PKR of the alkyne **4** and norbornadiene. The reaction was done using 10 mol % of the cobalt−alkyne complex **11** formed in situ,and the reaction was run under CO (2 bar). In this case, cyclopentenone **10** was obtained in a moderate yield of 57%: the product was accompanied with substantial amounts of *endo* isomer, which had to be separated out by chromatography. To minimize the amount of the undesired *endo* isomer, another reaction was run using the less reactive triphenylphosphine dicobaltpentacarbonyl complex **14** as catalyst. This gave diastereomerically pure **10** in a noteworthy 73% yield (Scheme 5).

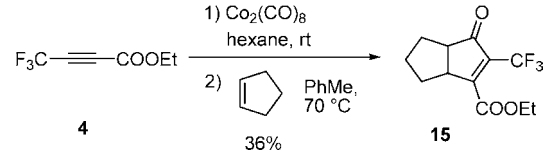
Scheme 5. Catalytic PKR of **4** with Norbornadiene



catalyst	temp (°C), *t* (h)	yield (%)
11	90, 18	57
14	70, 24	73

The reactivity of alkyne **4** was also tested with a less reactive olefin: cyclopentene. Reaction of the intermediate cobalt complex **11** with cyclopentene at 70 °C for 24 h gave the expected cyclopentenone **15** in 36% yield (Scheme 6).

Scheme 6. Stoichiometric PKR of **4** with Cyclopentene



Given the (well-known) poor reactivity of cyclopentene in PKRs,[6a] this yield is actually rather good.

In summary, PKRs of fluorinated alkynes under standard thermal conditions provided moderate to good yields of the desired cyclopentenones. Our most striking result was that the intermolecular version of the PKR is highly regioselective: in all the desired cyclopentenones formed, the fluorinated group was α to the enone. This is somewhat surprising, since for alkynes with sterically similar functional groups, the major regioisomer of the product usually has the EWG at the β position. Since the regioselectivity of the intermolecular PKR stems from a delicate balance between steric and electronic factors, our results indicate that the fluorine substituent's electronic effect is either much weaker than expected or is overridden by its steric hindrance. Therefore, a detailed theoretical study is clearly warranted to explain the regioselectivity of the PKR of fluorinated internal alkynes. We are planning to undertake such a study and will report on it in due course.

We also found that the PK adduct of ethyl 4,4,4-trifluorobutynoate and norbornadiene **10** can be prepared in good yield and with complete regioselectivity by either the stoichiometric or the catalytic version of this chemistry. Conjugate addition of nitroalkanes or cyanide to this adduct entails concomitant loss of the trifluoromethyl group. This reaction can be harnessed to prepare cyclopentenones having quaternary centers.

We are continuing to explore the vast synthetic potential of fluorinated alkynes as regioselective directors in intermolecular PKR in our laboratory.

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Supporting Information Available: Experimental procedures and characterization of compounds **7**−**15**; ^1H /^{13}C NMR spectra of compounds **7**−**10**, **12a**−**c**, **13a**, and **15**; X-ray crystallographic data of **8** and **12a** (CIF). This material is available free of charge via the Internet http://pubs.acs.org.

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(15) Grieco, P. A.; Abood, N. *J. Org. Chem.* **1989**, *54*, 6008.