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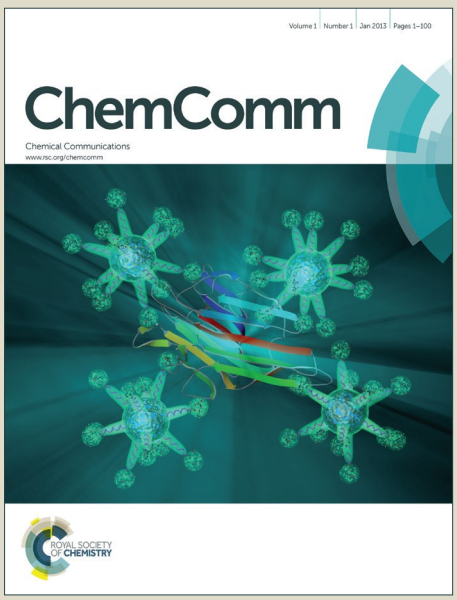

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Pauson-Khand reaction using alkynylboronic esters: solving a long-standing regioselectivity issue

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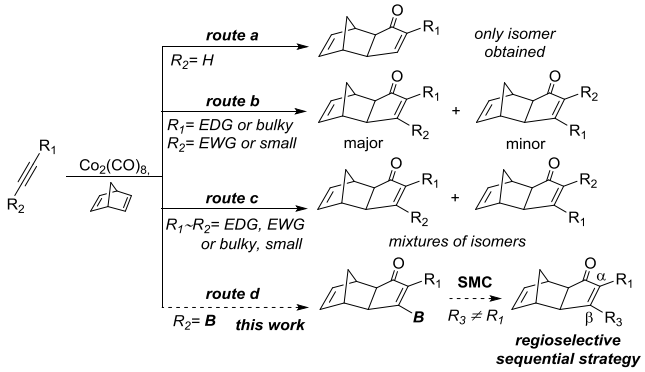
The first intermolecular Pauson-Khand reaction conducted with internal alkynylboronic esters, allows the installation of the boronic ester moiety in β-position of the cyclopentenone with total regio- and stereoselectivity.

Introduction

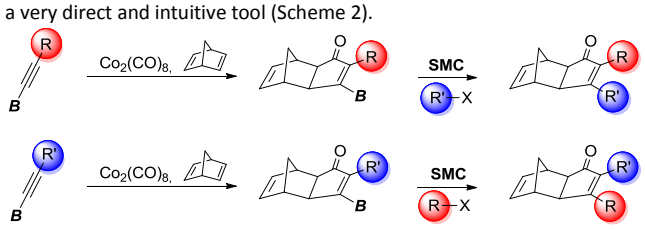
Since its first report by Khand and Pauson in the early seventies,[1] the Pauson-Khand reaction (PKR) has proven to be a very powerful tool to build cyclopentenone cores. The reaction consists of a [2+2+1] cycloaddition involving an alkyne, an alkene and carbon monoxide allowing the assembly of architecturally complex molecules from very simple starting materials.[2] The intermolecular version has to face challenging issues namely the regioselective addition of alkenes and alkynes. Towards this end, terminal alkynes have been successfully employed yielding the α-substituted adduct in a regioselective manner (Scheme 1, route a). However, internal nonsymmetric alkynes can potentially provide both regioisomers.[3] Interestingly, when sterically or electronically biased internal alkynes are used, the largest or the most electrondonating group (EDG) is, mainly (but not exclusively) placed in α-position of the resulting adduct (Scheme 1, route b). However, when non-biased alkynes are used mixtures of α/β-substituted adducts are observed (Scheme 1, route c).[4] This fact has been supported by recent computational studies where the lack of electronic or steric differentiation along the triple bond does not allow, in some cases, a clear distinction in the regioselective outcome of the reaction.[5] Bearing these limitations in mind, we envisioned the possibility of using boron chemistry to solve the lack of selectivity in PKR reaction for internal alkynes, complementing the current approaches to prepare α,β-diarylcyclopentenones, namely the Nazarov reaction,[6] Ni- and Pd-catalysed annulations[7] or Au-catalyzed [4+1] cyclizations.[8]

Our proposal is based on a two-step strategy and its usefulness lies in the use of internal alkynylboronic esters which take advantage of the polarization along the triple bond falling into a specific case of biased internal alkynes (Scheme 1, route d). Internal alkynylboronic esters are versatile synthons that have been successfully used in a vast array of reactions such as standard Suzuki-Miyaura cross-couplings[9] or cycloaddition reactions,[10] but its use in the PKR is surprisingly unprecedented in the literature.



Scheme 1 Regioselective scenarios of alkynes in intermolecular PKR.

Herein, we describe, the first PKR using internal alkynylboronic esters, with an exclusive formation of a single *exo* stereoisomer and the β-regioisomer. Subsequently, the B-substituted cyclopentenones are subjected to a Suzuki-Miyaura cross-coupling (SMC) allowing the overall sequential installation of α and β substitutions. This strategy allows access to both regioisomers by simply reversing the order of introduction of the substituents converting it in a very direct and intuitive tool (Scheme 2).



Scheme 2. Selection of the regioisomer by a sequential strategy.

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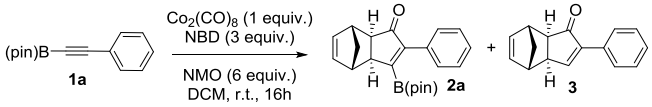
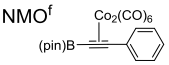
Results and discussions

We initiated our study by optimizing the PKR using 4,4,5,5-tetramethyl-2-(phenylethynyl)-1,3,2-dioxaborolane (**1a**) as a model substrate (Table 1). We found that the optimal reaction conditions were the combination of $Co_2(CO)_8$ (1 equiv.), norbornadiene (NBD, 3 equiv.), 4-methylmorpholine *N*-oxide (NMO, 6 equiv.) in dichloromethane (0.03 M) at room temperature yielding the corresponding adduct **2a** in 75% isolated yield (Table 1, entry 1). Along with the desired product **2a**, the protodeborylated side-product **3** was obtained in 9% yield. However, when thermal conditions were used, in toluene, the yield of adduct **2a** dropped to 38% together with 12% yield of side-product **3** (Table 1, entry 2), probably due to decomposition of intermediate species during the reaction. Attempts to stabilize the cobalt complex with PPh_3 had a detrimental impact on the yield lowering it to 20% of **2a** (entry 3). Furthermore, changing from dichloromethane to acetone resulted in the major formation of the side-product **3** (entry 4). Lower temperatures or slow addition of NMO did not provide any benefit to the reaction outcome (entries 5 and 6). Side-product **3** is presumably formed during the complexation step of alkyne **2a** with cobalt carbonyl complex. In order to shed light on the origin of **3**, we synthesized the hexacarbonylic complex **4**[11] to test it in the PKR. Adduct **2a** was obtained in comparable yields to the one of the optimized conditions (compare entry 1 with 7). It is plausible to think that **1a** forms two hexacarbonylic complexes, namely complex **4** and the corresponding standard hexacarbonylic complex bearing the terminal (deborylated)phenylacetylene, in which both undergo PKR forming **2a** and **3**, respectively. Experiments based on the decomposition of **2a** by treatment with silica-gel or activated charcoal did not provide any traces of **3**.

Table 1 Intermolecular PKR of **1a**.[a]

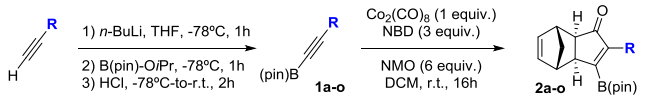


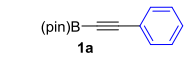
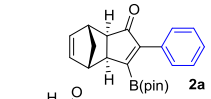
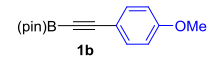
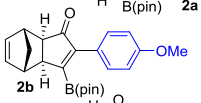
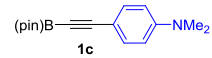
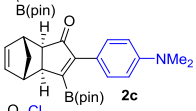
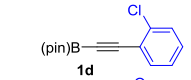
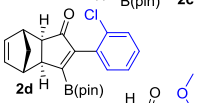
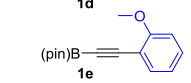
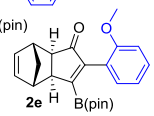
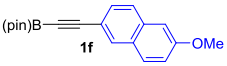
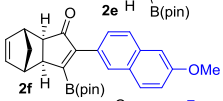
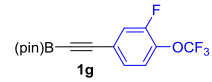
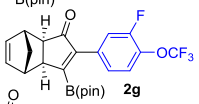
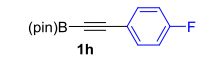
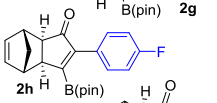
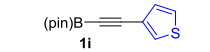
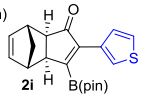
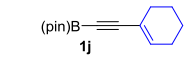
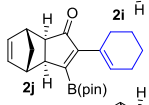
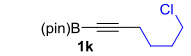
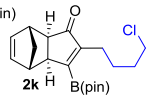
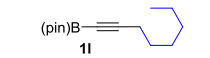
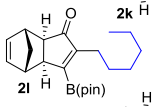
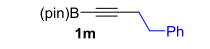
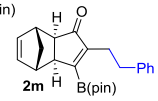
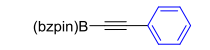
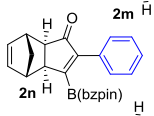
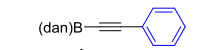
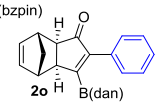
Entry	Change from optimized conditions	2a (%)[b]	3 (%)
1	none	89 (75)[c]	9
2[d]	using thermal conditions	38	12
3[d]	using thermal conditions[e] with 1 equiv. PPh_3	20	13
4	with acetone instead of DCM	23	37
5	0ºC instead of r.t.	70	15
6	with slow addition of NMO[f]	75	20
7	using complex **4**[g] 	82 (75)[c]	6

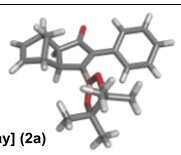
[a]**1a** (0.6 mmol), $Co_2(CO)_8$ (1 equiv.), NBD (3 equiv.), NMO (6 equiv.) in DCM (0.03 M) at r.t. during 16h. [b]NMR yield using 1,1,2,2-tetrachloroethane as internal standard. [c]Isolated yield. [d]Thermal conditions: **1a**, $Co_2(CO)_8$ (1 equiv.), NBD (3 equiv.) in toluene (0.1 M) at 70 ºC. [e]At 100 ºC. [f] *Via* syringe pump. [g]**4** (0.2 mmol), NBD (3 equiv.), NMO (6 equiv.) in DCM (0.03 M) at r.t.

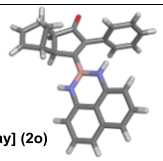
We next turned our attention to study the preparative scope of this reaction (Table 2). Towards this end, we succeeded to convert a wide range of terminal alkynes into their corresponding alkynylboronic pinacol esters (**1a-1o**), using the methodology developed by Brown and Srebnik.[2] The fifteen internal alkynes reacted with norbornadiene, in the presence of $Co_2(CO)_8$ and NMO, to give a unique single exo-stereoisomer and β-regioisomer of the α,β-substituted cyclopentenones (Table 2).

Table 2 Synthesis of alkynylboronic esters and their application into the PKR.[a,b]



Entry	Alkynes **1**	Yield **1** (%)	PK adduct **2**	Yield **2** (%)
1	 **1a**	72	 **2a**	75
2	 **1b**	64	 **2b**	53
3	 **1c**	61	 **2c**	60
4	 **1d**	67	 **2d**	66
5	 **1e**	67	 **2e**	68
6	 **1f**	72	 **2f**	65
7	 **1g**	75	 **2g**	55
8	 **1h**	81	 **2h**	65
9	 **1i**	69	 **2i**	71
10	 **1j**	78	 **2j**	59
11	 **1k**	69	 **2k**	64
12	 **1l**	64	 **2l**	72
13	 **1m**	89	 **2m**	68
14[c,d]	 **1n**	64	 **2n**	61
15[c,e]	 **1o**	53	 **2o**	81





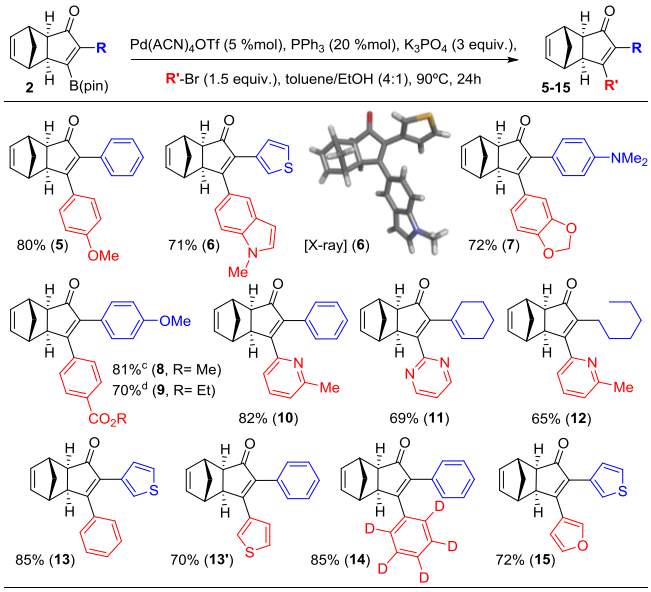
[a]As for Table 1, entry 1. [b]Isolated yields. [c]See Supporting Information for detailed synthetic procedure. [d]bzpin: benzopinacol. [e]dan: 1,8-diaminonaphthalene

As shown in table 2, the substitution pattern includes aromatic groups with a vast array of substituents with different electronic properties (entries 1-8), heteroaryl group (entry 9), olefinic (entry

10) or aliphatic groups (entries 11 and 13). However, when hindered alkynes such as *tert*-butylalkynylboronic pinacol ester or trimethylsilylalkynylboronic pinacol ester were used, the PKR failed to yield the corresponding adduct. Alkynes bearing Bbzpin (bzpin: benzopinacol) or Bdan (dan: 1,8-diaminonaphthalene) moieties were also tolerated (entries 14 and 15). In all cases, the resulting adducts were obtained with total stereo- and regioselectivity since none of the other possible isomers were detected by analytical means.[13] Suitable crystals of **2a** and **2o** for X-ray diffraction analysis were successfully obtained for the first time from pentane and the selectivity of the pinacolboryl moiety in β position of cyclopentenones could be unequivocally confirmed (Table 2, bottom). It confirms that the total regioselectivity observed is overweighed by electronic effects over the steric ones since adducts **2a** and **2o**, both bearing different steric requirements, exclusively placed the boryl moiety in β position. Overall, we believe that the results presented in Table 2 not only demonstrate a high reactivity and functional group compatibility, but also the potential of alkynylboronic esters in stereo- and regioselective PKR, comparable to the [2+2+1] cycloaddition from biased nonsymmetric internal alkynes,[14] and the two-step protocol to form β-substituted cyclopentenones using the trifluoromethyl group as a removable steering group.[15a,b]

In order to demonstrate the usefulness of the β-boryl α-substituted cyclopentenones, we next turned our attention to their application towards the SMC, in line with our tunable synthetic strategy (Scheme 2) as a reliable and straightforward methodology.[16] The reaction conditions were optimized using adduct **2a** as model substrate and 4-methoxyphenyl bromide as reagent, to furnish the desired α,β-disubstituted cyclopentenone **5** in 80% isolated yield (Table 3), in the presence of $Pd(ACN)_4OTf$ (5% mol), PPh_3 (20% mol), K_3PO_4 (3 equiv.) in a mixture of toluene/ethanol (4:1) at 90 ºC during 24 hours. Our protocol was optimal for the assembly of several compounds regardless of their electronic properties or substitution pattern, providing the selective α,β-disubstituted cyclopentenones (**5-15**) with moderate to high isolated yields ranging 65-85% (Table 3). More interestingly, our methodology enabled the regioselective construction of challenging substrates that cannot be accessed through a standard PKR, for instances: (1) compounds **6**, **7** and **10-12** were synthesized installing the most hindered substituent in β position, (2) compounds **5** and **7-9**, bearing electronically or sterically non-differentiable substituents in both positions were successfully obtained, (3) isomers that are usually not accessible when carrying out standard PKR such in the case of compound **12**, holding an alkyl group in the α position. It should be highlighted that a number of heterocycles could be easily made. Crystals of **6** were successfully analysed by X-ray diffraction confirming the regioselectivity of the overall strategy claimed here.[17] However, the strength of this methodology lies in the possibility of preparing specific regioisomers bearing negligible distinction in the substitution between α and β positions which would yield no selectivity through a standard PKR. Thus, compounds **14** and **15**, containing minimal differentiation between both positions such as phenyl *versus* d_5-phenyl or 3-thionyl *versus* 3-furyl, could be successfully prepared.

Table 3 Synthesis of α,β–disubstituted cyclopentenones through SMC.[a,b]



[a] **2** (0.14 mmol), $Pd(ACN)_4OTf$ (5% mol), PPh_3 (20% mol), K_3PO_4 (3 equiv.), R'-Br (1.5 equiv.) in toluene/EtOH (4:1) at 90 ºC during 24h. [b] Isolated yield. [c] With MeOH instead of EtOH. [d] From methyl 4-bromobenzoate.

In order to better illustrate the potential of this strategy, we selected a few examples from the literature which suffer of regioselectivity issues when synthesized through a standard PKR (Figure 1). Direct comparison with representative closely-related compounds, showed an substantial improvement in regioselectivity. Compounds **5** and **8** were obtained as single regioisomer while standard methodology afforded mixtures that are usually difficult to handle. Finally, cyclopentenones **13** and **13'** were independently obtained by simple reversal in the order of addition of the reagents, thus illustrating the ability to access both regioisomers.

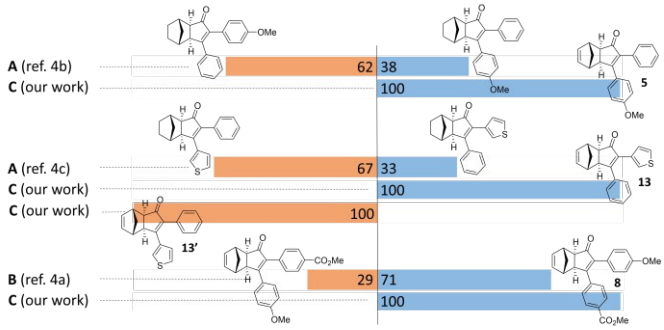
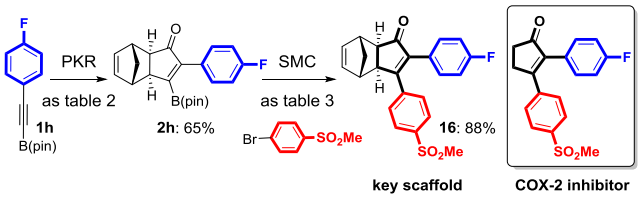


Figure 1 Regioselective outcome comparison of selected examples towards the application of our strategy. Reaction conditions: *Method A*: a) $Co_2(CO)_8$, DCE; b) norbornene, microwave, 90 ºC. *Method B*: a) $Co_2(CO)_8$, hexane; b) norbornadiene, 60 ºC. *Method C*: a) as for Table 2; b) as for Table 3.

We eventually focus our strategy to the synthesis of a known scaffold of cyclooxygenase-2 (COX-2)[18] (Scheme 3). COX-2 inhibitors are a type of non-steroidal anti-inflammatory drug that directly targets COX-2 enzymes which are responsible of inflammation and pain. We tackled its synthesis through our

sequential strategy starting from the alkynylboronic pinacol esters **1h**. PKR afforded exclusively the regioisomer **2h** (Table 2, entry 8) which was submitted to SMC reaction with 4-bromophenyl methyl sulfone, yielding **16** in 88% isolated yield as a key scaffold.



Scheme 3 Synthesis of a key scaffold **16**.

Conclusions

In summary, we have described an intermolecular Pauson-Khand reaction conducted with internal alkynylboronic esters installing the boronic ester moiety in β-position of the cyclopentenone with total regio- and stereoselectivity. More interestingly, the resulting adduct can be subsequently derivatised by Suzuki-Miyaura cross-coupling reaction allowing any combination of α,β-disubstituted cyclopentenones, solving a well-known and long-standing drawback about regioselective Pauson-Khand reactions. Overall, our approach also complements existing PKR protocols providing access to regioisomers that are not formed as the major isomers in standard PKR. Currently, the methodology is being exploited with other challenging substrates.

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