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First intermolecular Pauson–Khand reaction of 7-azanorbornenes. Control of the regioselectivity by the effect of the substituents attached to the olefinic partner

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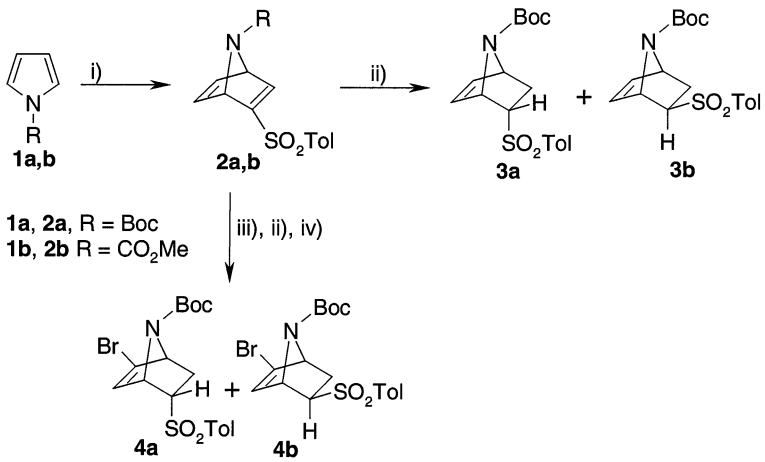
Abstract—High regioselectivity in the intermolecular Pauson–Khand reaction of 7-azanorborn-5-enes has been found by using 5-bromo-2-*endo*-tosyl derivatives as the olefinic partner.

Among the different types of cycloannulation reactions for the assembly of cyclopentenones, the Pauson–Khand reaction, a formal [2+2+1] cycloaddition between an alkyne, an alkene and CO promoted by $Co_2(CO)_8$, has progressively become one of the most versatile approaches.[1] In this context, the Pauson–Khand reaction of bicylic alkenes has deserved special consideration, as the stereochemical information contained in the bicycles is conserved throughout the process, allowing for the synthesis of annulated cyclopentenones with total control of the relative stereochemistry of the chains attached at positions C-4 and C-5.[2] However, regiochemical issues arise when the starting bicycles are not symmetrically substituted with respect to the alkene moiety. In these cases, two regioisomeric cyclopentenones can be expected from the intermolecular Pauson–Khand reaction. Control of the regioselectivity is crucial in the development of synthetically useful intermolecular reactions of this type.

Studies carried out on bicyclo[2.2.1]heptenes,[3–5] bicyclo[3.2.0]heptenes,[5] 8-oxabicyclo[3.2.1]octenes,[6,7] 7-oxabicyclo[2.2.1]heptenes,[8] bicyclo[3.3.0]octenes[9] and 2,3-diaza bicyclo[2.2.1]heptenes[4] have shown that the regiochemical outcome of the reaction is substrate-dependent, and mainly stems from steric interactions between the alkene and the alkyne–$Co_2(CO)_6$ moiety at two different levels: (i) the coordination step; (ii) the



Scheme 1. *Reagents and conditions*: (i) HC≡C-SO_2Tol; (ii) $NaBH_4$, MeOH, 0°C, 15 min; (iii) PhSeBr, $CHCl_3$, rt, 6 h; (iv) H_2O_2/NaOH, THF, 0°C–rt, 18 h.

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insertion step. On the other hand, the regiochemistry of intramolecular Pauson–Khand reactions can also be modified by complexation effects. Thus, the attachment of heteroatoms in the alkene moiety, in particular sulfur, has proven to be of great use.[10] No such effect has been observed in the intermolecular version with bicyclic alkenes.[4–8] However, heteroatoms (halogen and OR) directly bonded to the alkene carbons have been shown to control the regioselectivity of cyclopentenone formation in a concomitant cycloaddition–reduction sequence.[8,11]

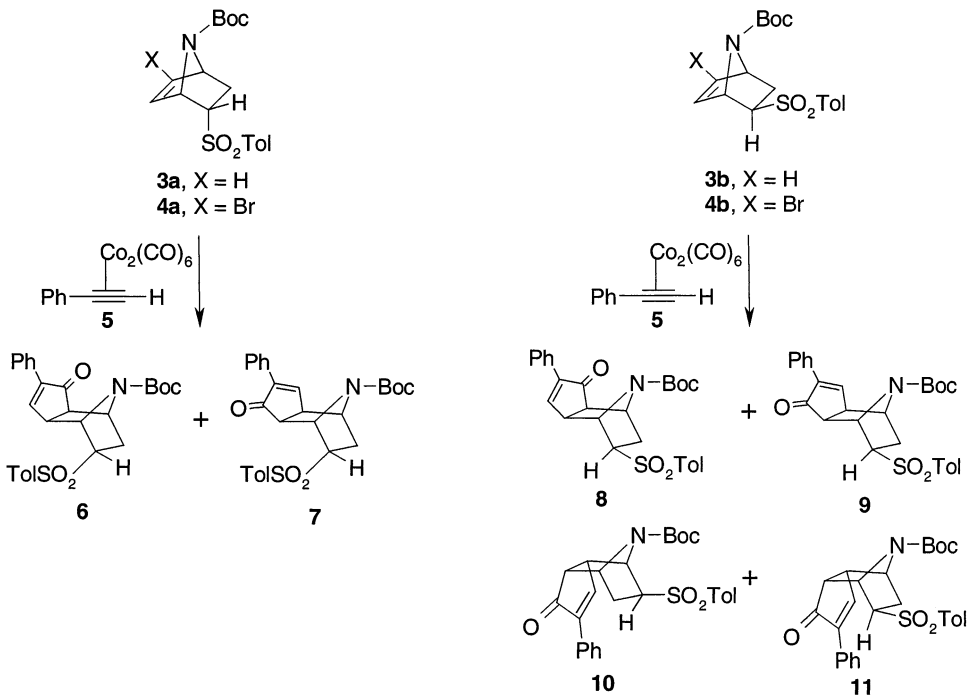
7-Azabicyclo[2.2.1]heptenes, which are easily prepared from the cycloaddition of pyrroles with electron-deficient alkynes,[12] have been widely used as starting materials for the preparation of bioactive molecules.[13] Taking into account the synthetic potential of these bicycles together with the above given considerations, we have chosen these substrates in order to explore the regioselectivity of their intermolecular Pauson–Khand reaction, in what constitutes, as far as we know, the first report of this process on 7-azanorbornene derivatives.

Cycloaddition of pyrroles **1** with *p*-(tolyl)ethynylsulfone (Scheme 1) afforded the 7-azanorbornadienes **2a**,**b**.[12] Selective reduction of the double bond conjugated with the sulfone moiety gave the 7-azanorborn-5-enes **3a** and **3b** as a 75:25 mixture, which was separated by chromatography. On the other hand, regioselective bromophenylselenation of **2a** followed by reduction of the conjugated double bond and oxidative elimination of the phenylselenyl group allowed for the synthesis of the bromoderivatives **4a** and **4b** as a 25:75 mixture (70% yield), which was separated by chromatography. Attempted bromophenylselenation of compounds **3a** or **3b** followed by oxidative elimination of the phenylselenyl group originated decomposition of the starting materials.

Careful reaction conditions must be chosen in handling compounds **2**–**4** in order to avoid the retro-Diels–Alder reaction. The *N*-methylmorpholine *N*-oxide promoted Pauson–Khand reaction of 7-azanorbornadienes **2a**,**b** with complex **5** was carried out at rt under two different conditions: (A) in CH_2Cl_2 solution; and (B) in CH_2Cl_2 solution in the presence of 4 Å molecular sieves and using a reaction vessel which had been previously washed with NaOH and dried. However, retrocycloaddition to the starting pyrroles **1a**,**b** was the only reaction observed.

On the other hand, when the 7-azanorbon-5-ene **3a**, with the tosyl group in *endo* position, was made to react with **5** under the aforementioned experimental conditions (Scheme 2), a mixture of the regioisomeric cyclopentenones **6** and **7** was isolated.[14,15] The formation of the diastereomeric *endo* cyclopentenones was not observed.

The results are given in Table 1. Better yields were observed following reaction conditions B, although the regiochemistry was low in both cases (entries 1 and 2). On the other hand, treatment of the 5-bromoderivative **4a** with complex **5** under reaction conditions A took place in a completely regioselective fashion (entry 3), whereas under reaction conditions B a drop in regioselectivity was observed, although the yield was better (entry 4). Insertion of the cobalt moiety away from the halogen was preferred, giving rise to the formation of **6** as a major product. It is also worth mentioning that, under reaction conditions B, partial reduction of **4a** to **3a** was noticed (15% **3a**).



Scheme 2. *Reagents and conditions*: Conditions A: CH_2Cl_2, NMO; Conditions B: CH_2Cl_2, 4 Å molecular sieves, NaOH, NMO.

Table 1. Reaction of 7-azanorbornenes **3** and **4** with the $Co_2(CO)_6$–alkyne complex **5**

No.	Reaction conditions[a]	**3**, **4**	Product ratio[b] (% yield)[c]
1	A	**3a**	**6**:**7** = 65:35 (45)
2	B	**3a**	**6**:**7** = 50:50 (85)
3	A	**4a**	**6**:**7** = 100:0 (60)
4	B	**4a**	**6**:**7** = 80:20 (80)
5	B	**3b**	**8**:**9** = 70:30 (10)
			10:**11** = 70:30 (10)
6	A	**4b**	**8**:**9** = 100:0 (50)
7	B	**4b**	**8**:**9** = 70:30 (40)
			10:**11** = 70:30 (5)

[a] Conditions A: CH_2Cl_2, NMO. Conditions B: CH_2Cl_2, 4 Å molecular sieves, NaOH, NMO.

[b] Determined by integration of the ^1H NMR spectra ($CDCl_3$, 300 MHz) of the crude reaction products.

[c] Isolated combined yields after chromatography.

When the 7-azanorbon-5-ene **3b**, with the tosyl group in *exo* position, was made to react with complex **5**, the corresponding cyclopentenones **8** and **9** were obtained in low yield, together with a 1:1 mixture of their *endo* diastereomers **10** and **11** (entry 5).[15,16] However, when the bromoderivative **4b** was used as the starting material, the diastereo- and regioselective formation of **8** was observed by using reaction conditions A (entry 6). When reaction conditions B were used instead, drop in regioselectivity, reduction of **4b** to **3b** (10% **3b**) and formation of the corresponding diastereomeric *endo* cyclopentenones were noticed (entry 7).

In summary, the diastereo- and regioselective intermolecular Pauson–Khand reaction of 7-azanorborn-5-enes has been described for the first time. The presence of bromine in the 5-position was required to ensure complete regioselectivity, and a tosyl substituent in 2-*endo* position was needed in order to avoid the formation of *endo* cyclopentenones. These findings may be extended to the control of the Pauson–Khand reaction in other bicyclic systems.

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14. All compounds described herein are racemic mixtures. Satisfactory analyses were found for all of them.
15. The structural assignment of compounds **6**, **8**, **10** and **7**, **9**, **11** was carried out on the basis of their ^1H NMR ($CDCl_3$, 300 MHz) spectra. Thus, a chemical shift difference of 0.7–1.2 ppm was observed between the H-2 and H-6 signals of compounds **6**, **8**, **10**, while this value was of 0–0.6 ppm for compounds **7**, **9**, **11**. Similar differences had been previously observed in the Pauson–Khand adducts of 2-substituted 7-oxanorbornenes and phenylacetylene. See Ref. 8.
16. Coupling of H-2 and H-6 of the *endo* adducts **10** and **11** with H-1 and H-7 was observed in their ^1H NMR ($CDCl_3$, 300 MHz) spectra. Coupling with H-1 and H-7 was not observed for H-2 and H-6 of the *exo* adducts **8** and **9**.