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Diastereoselective Pauson–Khand reactions on aromatic substrates

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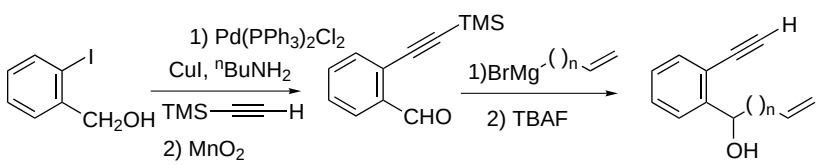
Abstract—The synthesis of several natural products' frameworks is carried out by means of a diastereoselective intramolecular Pauson–Khand reaction promoted by molecular sieves. Diastereoselectivity is achieved only if a coordinating group is present at a convenient distance from the alkene moiety. Naphthalenes can be obtained directly under refluxing toluene conditions.

The use of the Pauson–Khand reaction as key step for obtaining natural products' skeletons is becoming one of the most useful applications of this cocyclization.[1,2] Several new ways of promotion have allowed an increase in the scope of this reaction, traditionally limited to a few aliphatic systems.[3] In particular, we have recently introduced zeolites as new promoters for Pauson–Khand reactions.[4] Following our ongoing program to extend the intramolecular Pauson–Khand reaction to aromatic substrates, we have already reported the use of aryl propargyl ethers[5] and enynoindoles[6] as new substrates for this cocyclization. Nevertheless, several natural products have tricyclic aromatic hydrocarbon structures and, thus, we herein apply our methodology to the synthesis of indenes and tetralines. We have found an interesting influence of coordinating groups in the diastereoselectivity of this process.

The starting materials were readily obtained from 2-iodobenzyl alcohol **1**, following Scheme 1. Shonogashira coupling,[7] followed by MnO_2 oxidation and reaction with an appropriate Grignard reagent, gave alcohols **3a** and **4a**. These alcohols were submitted to the Pauson–Khand reaction and were also converted into the other starting materials. Thus, protection of the hydroxyl with different groups gave compounds **3b–d** and **4b,c**. Phthalimido derivatives **3e** and **4d** were also obtained by Mitsunobu reactions.

The Pauson–Khand reactions were carried out in all cases under two different experimental conditions: combining trimethylamine *N*-oxide (TMANO) with molecular sieves in toluene at room temperature (method A) and only with molecular sieves as promoters in refluxing toluene (method B).[8] The results are summarized in Table 1.

All reactions gave good yields under both experimental conditions except for substrates containing phthalimido groups, which decomposed in refluxing toluene, and, in the case of substrate **3e**, did not react at room temperature. All the mixtures of diastereoisomers were sepa-



Scheme 1.

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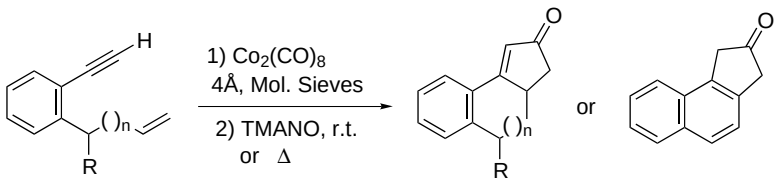
Table 1. Synthesis of indenes **5** and tetralines **6**



n=0, **3**
n=1, **4**

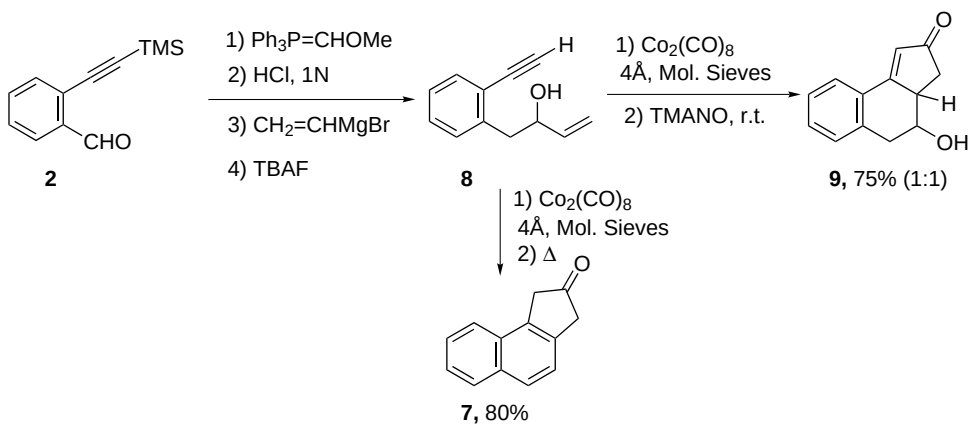
n=0, **5**
n=1, **6**

7

Entry	Substrate	R	Method	Product	*Trans*/*cis*[a]	Yield (%)
1	**3a**	OH	A	**5a**	1:1	60[b]
			B	Dec.[c]	–	–
2	**3b**	OTBS	A	**5b**	2:1	80[b]
			B	**5b**	4:1	82[b]
3	**3c**	OTBDPS	A	**5c**	2:1	52[b]
			B	**5c**	4:1	50[b]
4	**3d**	OAc	A	**5d**	1:1	87[b]
			B	**5d**	1:1	57[b]
5	**3e**	Phth	A	N.R.	–	–
			B	Dec.[c]	–	–
6	**4a**	OH	A	**6a**	>19:1	77[d,e]
			B	**7**	–	75[d]
7	**4b**	OTBS	A	**6b**	1:1	64[b]
			B	**6b**	2:1	64[b]
8	**4c**	OAc	A	**6c**	>19:1	75[d,e]
			B	**6c**+**7**	>19:1	53[d,e]+15[d]
9	**4d**	Phth	A	**6d**	>19:1	86[d,e]
			B	N.R.	–	–

[a] The *trans*/*cis* ratio was calculated by integration of well-resolved signals in the ^{1}H NMR spectra of crude reaction mixtures. The major isomer was identified by NOE experiments.
[b] Pure mixture of isomers.
[c] Total decomposition of starting material was observed.
[d] Pure material with correct spectroscopic data (^{1}H, ^{13}C NMR, IR).
[e] Only the *trans* isomer was detected by NMR

rated by column chromatography and the compounds characterized. The relative stereochemistry of the stereogenic carbons was assigned by NOE experiments and were found to be *trans* for all the major products. Compound **4a** gave different products depending on the reaction conditions. Thus, the hydroxy tetraline **6a** was obtained at room temperature, while in refluxing toluene, dehydration and isomerization lead to naphthalene **7** in good yields.[9] Stereoselectivity of the process deserves a mention. None of the reactions, in which five-membered rings were formed, gave important diastereoselectivities, the *trans*/*cis* ratio being slightly better when raising the reaction temperature. On the contrary, compounds **4**, where the inducing stereogenic center is further away, gave surprising results. When reacting compound **4a**, we only observed one product in the NMR spectrum of the crude material. This was also the case with compounds **4c** and **4d**, but not with



2

8

9, 75% (1:1)

7, 80%

Scheme 2.

the TBS-protected compound **4b**, which reacted with low diastereoselectivity. We can explain these results by assuming that the electron pairs of the oxygen present in all the substituents coordinate with the cobalt in a similar fashion to that for the directed Pauson–Khand reaction described by Kraft.[10] This coordination may neither occur in the case of compound **4b**, due to the bulky substituent, nor in compounds **3**, due to the proximity of the coordinating group to the double bond that avoids complexation. We are currently investigating the structure of the cobalt complexes of these starting materials and extending this methodology to substrates bearing other coordinating groups.

In an attempt to verify that the distance of the coordinating group to the double bond is crucial to achieve diastereoselectivity, we prepared compound **8** following the method of Scheme 2 and submitted it to the experimental conditions described before. The results showed no diastereoselectivity at room temperature, and the formation of the naphthalene **7** under refluxing conditions. Again, the hydroxy group seems to be too close to the alkene to allow coordination to the cobalt.

In conclusion, indenes, tetralines and a naphthalene can be prepared by diastereoselective Pauson–Khand reaction of aromatic enynes. The reactions are achieved if appropriate coordinating groups are situated at a suitable distance from the alkene moiety.

Acknowledgements

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8. For experimental conditions, see Ref. 5.
9. Spectroscopic data for **6a** and **7**. **Compound 6a**: Yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.79 (td, 1H, $J_1=13.7$ Hz, $J_2=3.3$ Hz), 2.16 (dd, 1H, $J_1=18.1$ Hz, $J_2=3.3$ Hz), 2.38–2.44 (m, 1H), 2.73 (dd, 1H, $J_1=18.1$ Hz, $J_2=6.6$ Hz), 3.17 (bs, 1H), 3.52–3.58 (m, 1H), 4.92–4.93 (m, 1H), 6.36 (d, 1H, $J=2.2$ Hz), 7.36–7.40 (m, 1H), 7.44–7.46 (m, 2H), 7.64 (d, 1H, $J=7.7$ Hz); ^{13}C NMR ($CDCl_3$) δ 208.5, 174.9, 139.1, 131.6, 130.5, 129.1, 128.5, 126.6, 124.0, 66.9, 41.9, 37.1, 33.7; IR (neat) ν 3390, 2910, 1690, 1665, 1595 cm^{-1}. **Compound 7**: Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 2H), 2.58 (s, 2H), 7.28 (d, 1H, $J=8.2$ Hz), 7.39 (t, 1H, $J=6.6$ Hz), 7.47 (dt, 1H, $J_1=6.6$ Hz, $J_2=1.1$ Hz), 7.60 (d, 1H, $J=8.8$ Hz), 7.78 (d, 1H, $J=7.7$ Hz), 8.01 (d, 1H, $J=8.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 205.2, 133.0, 132.7, 132.2, 131.1, 128.9, 128.3, 125.7, 125.6, 124.4, 123.6, 20.7, 14.4; IR (neat) ν 3050, 2920, 1690, 1600 cm^{-1}.
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