Unexpected Rearrangement in the Heck Cyclization of Positional Isomers of Chiral 2,3-Disubstituted Perhydro-1,3-benzoxazines

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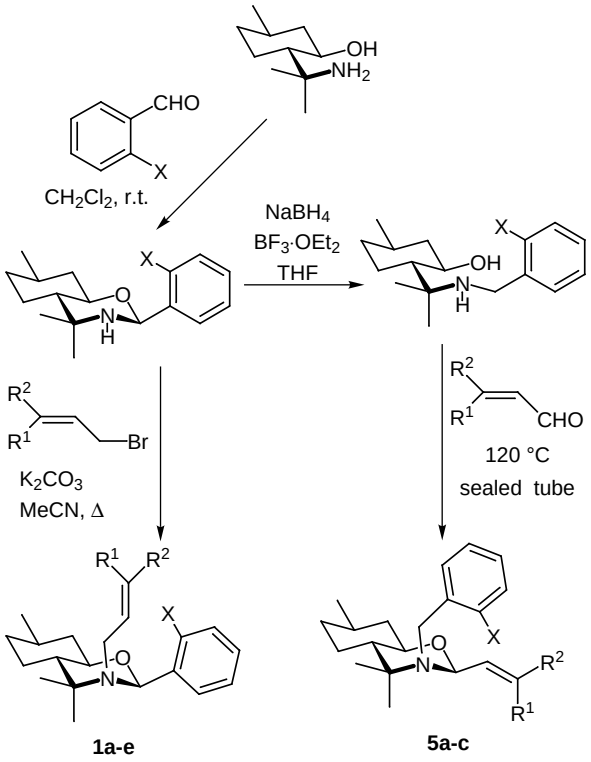
Abstract: The intramolecular Heck cyclization on 2,3-disubstituted perhydro-1,3-benzoxazines, derived from (–)-8-amino menthol, easily proceeds at reflux of acetonitrile or DMF. The behavior of positional isomers was quite different. Reaction of 2-aryl-3-allyl perhydro-1,3-benzoxazines occurred as expected giving exclusively 6-*exo* cyclization products. On the contrary, regioisomeric 3-(iodobenzyl)-2-vinyl derivatives gave the normal cyclization compounds and rearranged 1,2-dihydroisoquinoline nucleus.

Key words: cyclizations, Heck reaction, palladium, rearrangements

Intramolecular diastereoselective Heck reaction has been widely used in the construction of carbo- and heterocycles,[1] including isoquinoline derivatives.[2] Two main strategies have been used to control the stereochemistry of the reaction: the use of chiral phosphines as ligands,[3] or by using chiral auxiliaries such as ethers[4] or amino ethers.[5] In this way, we have recently reported that chiral perhydro-1,3-benzoxazines, derived from (–)-8-aminomenthol, are excellent chiral auxiliaries for the synthesis of enantiopure tetrahydro isoquinolines[6] and related substances by anionic cyclizations,[7] and we envisaged a tetrahydroisoquinoline nucleus could be formed by intramolecular Heck reaction of conveniently substituted perhydro-1,3-benzoxazines. However, we describe herein that the reaction follows a different way on positional isomers **1** and **5**. Whereas 2-aryl-3-allyl substituted perhydro-1,3-benzoxazines **1a**–**e** give a mixture of normal cyclization compounds **2**–**4**, the isomeric 2-allyl-3-aryl substituted derivatives **5a**–**c** led to the normal cyclization products, and the enamine derivatives **9a**–**c**, resulting from an unusual rearrangement process.

The chiral perhydro-1,3-benzoxazines **1a**–**e** for the Heck reaction were synthesized in two steps, with excellent yields, by condensation of (–)-8-aminomenthol with *o*-iodobenzaldehyde (for **1a**–**c**) or salicylaldehyde triflate[8] (for **1d**–**e**), followed by N-alkylation with the corresponding allyl bromide in the presence of potassium carbonate.[9] In turn, compounds **5a**–**c** were prepared, in three steps, by reaction of (–)-8-aminomenthol with *o*-iodobenzaldehyde followed by reduction with diborane, and condensation of the resulting *N*-(*o*-iodobenzyl)amino menthol with the corresponding α,β-unsaturated aldehyde[7] (Scheme 1).



1/5	a	b	c	d	e
R^1	H	H	Me	H	Me
R^2	H	Me	Me	Me	Me
X	I	I	I	OTf	OTf

Scheme 1 Synthesis of starting compounds from (–)-8-aminomenthol

The intramolecular Heck reaction was performed under Jeffery conditions,[10] and the first attempt was tested on compound **1c** by refluxing for 8 h a 0.2 M solution in DMF with $Pd(OAc)_2$[11] (5%), Ph_3P (15%), TBAB (1 equiv) and KOAc (4 equiv). In these conditions, we obtained a complex reaction mixture where it was possible to isolate cyclization compounds **2c** (48%), **3c** (12%) and 8-(benzoylamino) menthol (14%) (entry 3 in Table). The same reaction mixtures were obtained in reactions where triphenylphosphine was changed by triphenylarsine, or the palladium acetate was substituted by $Pd_2(dba)_3$. The addition of silver acetate did not modify the chemical yields nor the stereoselectivity of the reaction.

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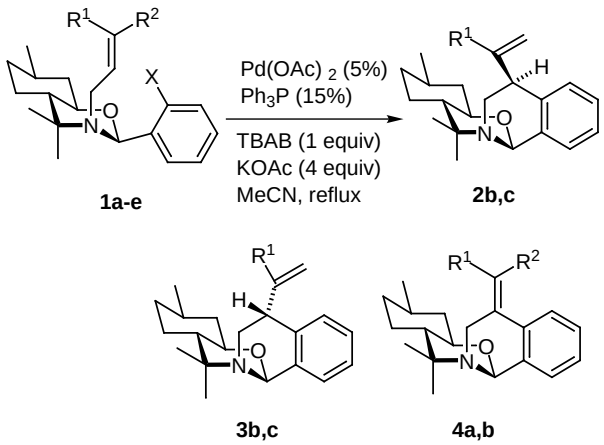
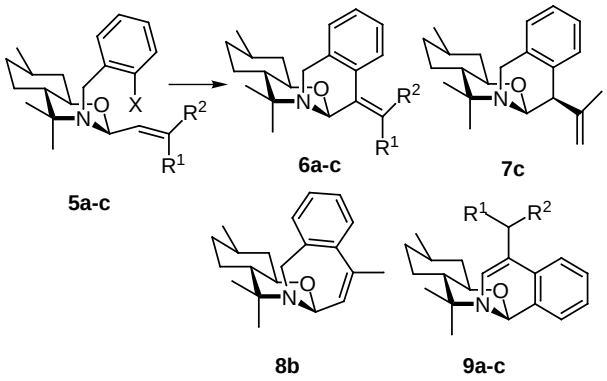
On the contrary, substantial increase in the chemical yield, de and cleaner reaction mixtures were observed when the reactions were carried out in acetonitrile as solvent. The intramolecular Heck reaction for compounds **1a**,**b**,**d**,**e** was then performed under the above experimental conditions by using acetonitrile as solvent, and the results are summarized in Scheme 2 and Table (entries 1–6).



Scheme 2 Heck cyclization of compounds **1a**–**e**.

It is noteworthy that the cyclizations occurred regiospecifically in a 6-*exo* mode for all the compounds and as expected, unsubstituted perhydro-1,3-benzoxazine **1a** led to a single methylene derivative **4a**. On the contrary, compound **1b**, with a methyl group at the external olefinic carbon, yielded a mixture (6:1) of the most stable ethylidene derivative **4b** and the unconjugated 4-substituted derivative **2b** as a single diastereomer with configuration *S* at the newly created stereocenter. The change of iodine in **1b** to a triflate group in **1d** diminished both the stereoselection and the regioselectivity in the final step of the catalytic cycle. Cyclization of **1d** gave an equimolar mixture of conjugated cyclization compound **4b** and unconjugated epimeric **2b** and **3b**. Interestingly, iodide **1c** cyclized to a mixture (4:1) of epimers **2c** and **3c**, but the triflate **1e** led, in lower yield, to a mixture (2:1) of the same compounds and 8-(benzoylamino) menthol, resulting from the degradation of the starting compound.

The behavior of positional isomers **5a**–**c** was different from that shown by **1a**–**e**. As a general trend, the intramolecular Heck reaction on **5a**–**c** occurred much more quickly than for **1a**–**e**, and the reactions were completed after heating in the same experimental conditions for only 1 h (Scheme 3 and Table, entries 7–14). In addition, compound **5b**, derived from *trans*-crotonaldehyde, gave 6-*exo*-cyclization compound **6b** (69%), a small quantity of 7-*endo*-cyclization product **8b** (8%) and, quite surprisingly, enamine **9b** (23%) (entry 10). **5c** lead to a mixture (5:1) of 6-*exo*-cyclization isomers **6c** and **7c**, and the enamine **9c** (16%) (entry 13), and 2-vinyl substituted perhydro-1,3-benzoxazine **5a** afforded an equimolar mixture of 6-*exo*-cyclization compound **6a** and rearranged enamine **9a** after heating for 2 h (entry 7).



Scheme 3 Heck cyclization of compounds **5a**–**c**.

Table Intramolecular Heck Reaction of **1a**–**e** and **5a**–**c**

Entry	Compound	X	R^1	R^2	Solvent	Time (h)	Products (%)
1	**1a**	I	H	H	MeCN	8	**4a**(85)[a]
2	**1b**	I	H	Me	MeCN	7	**2b**(12) **4b**(72)[a]
3	**1c**	I	Me	Me	DMF	8	**2c**(48) **3c**(12)[a,b]
4	**1c**	I	Me	Me	MeCN	8	**2c**(64) **3c**(16)[a]
5	**1d**	OTf	H	Me	MeCN	7	**2b**(29) **3b**(29) **4b**(29)[a]
6	**1e**	OTf	Me	Me	MeCN	7	**2c**(40) **3c**(20)[a,c]
7	**5a**	I	H	H	MeCN	2	**6a**(50) **9a**(50)
8	**5a**	I	H	H	MeCN	8	**6a**(10) **9a**(90)
9	**5a**[d]	I	H	H	MeCN	1	**6a**(22) **9a**(78)
10	**5b**	I	H	Me	MeCN	1	**6b**(69) **8b**(8) **9b**(23)
11	**5b**	I	H	Me	DMF	1	**6b**(56) **8b**(12) **9b**(32)
12	**5b**[d]	I	H	Me	MeCN	1	**6b**(26) **8b**(10) **9b**(64)
13	**5c**	I	Me	Me	MeCN	1	**6c**(70) **7c**(14) **9c**(16)
14	**5c**[d]	I	Me	Me	MeCN	1	**6c**(57) **7c**(9) **9c**(34)

[a] Yields in parenthesis refer to pure and isolated compounds.
[b] 14% of 8-(*N*-benzoylamino) menthol was isolated.
[c] 25% of 8-(*N*-benzoylamino) menthol was isolated.
[d] Ph_3As, instead Ph_3P, was used as ligand.

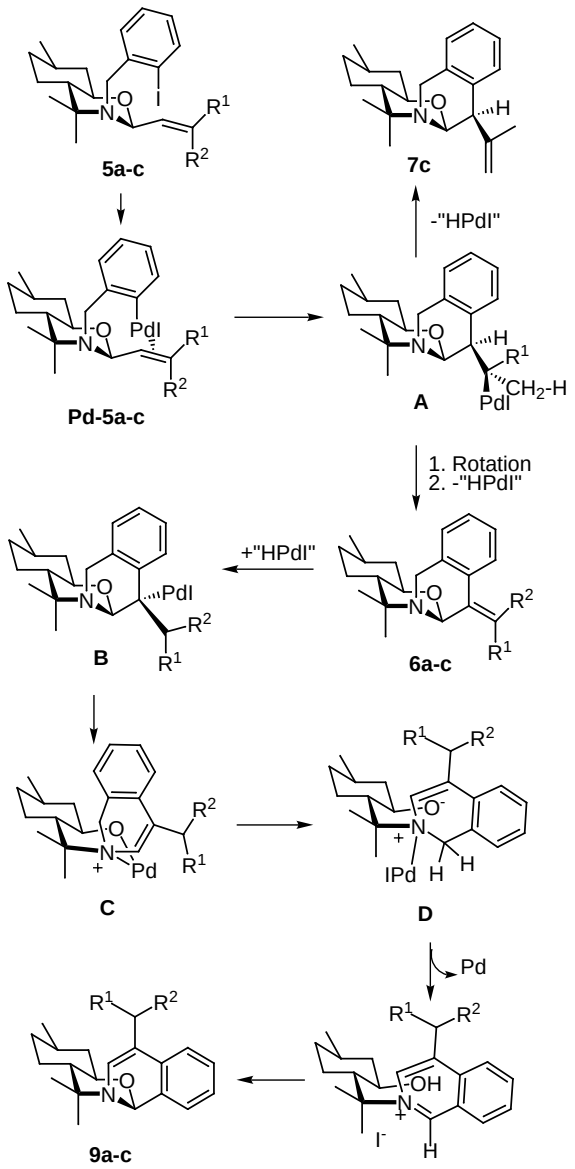
The remarkable formation of enamine derivatives **9** was very interesting, and some more experiments were necessary. In this way, we observed that the proportion of enamine increased when the reaction temperature was raised to reflux of DMF (compare entry 10 versus 11). In addition, when triphenylphosphine was changed to triphenylarsine as ligand in the reactions of **5a**–**c**, a high increase of the enamine proportion in the final reaction

mixtures was observed (compare entries 9, 12 and 14 versus 7, 11 and 13 respectively). Finally, the yield of enamine **9a** increased to 90% when the reaction of **5a** was refluxed in acetonitrile for 8 h[12] (compare entries 7 and 8), indicating that the formation of enamines **9** occurs from the normal cyclization products **6**. It is also interesting to note that enamines **9** were formed as single diastereomers as shown by NOE experiments.

The formation of cyclization compounds **2**–**4** from 2-aryl-3-allyl substituted perhydrobenzoxazines **1** can be interpreted in agreement with the general way for the Heck reaction: oxidative addition of the aryl group, intramolecular carbopalladation of the double bond and *syn* reductive elimination.[13] The formation of regioisomers **2**, **3** or **4** depends upon the substitution pattern at the double bond and the sense of the final dehydropalladation step.[1] On the other hand, the stereoselective formation of **2c** versus **3c** in the reactions of **1c** or **1e** is a consequence of the predominance of the eclipsed coplanar conformation over the twisted one of the Pd-C and the double bonds in the transition state.[14] This is also valid for the formation of compounds **6a**–**c** from **5a**–**c** or **7c** from **5c**, while the small amount of the 7-membered derivative **8b** formed in the reactions of **5b** is a consequence of the competitive 7-*endo* cyclization process.[1d]

The formation of enamines is more interesting from a mechanistic point of view, and we propose a simplified transformation summarized in Scheme 4 on the basis of the following experimental facts: i) The increase of the reaction time favors the formation of **9** by decreasing the yield of the former cyclization compound **6**. ii) The substitution of Ph_3P to the poorer coordinating ligand Ph_3As also increases the proportion of enamines **9a**–**c**, probably due to the encouragement of the reversible β-hydride eliminations and additions.[15] The different behavior of the positional isomers **1** and **5** is not a consequence of their different structures but due to the special nature of the cyclization products **6** resulting from **5**, which are allylic N,O-acetals.

The cyclization process of **5a**–**c** starts with the formation of σ-palladium intermediates Pd-**5a**–**c** by oxidative addition of the aryl iodides to the Pd(0) complex followed by intramolecular carbopalladation to the palladium derivative **A**. Dehydropalladation with a hydrogen at the methyl group, only when $R^1 = R^2 = Me$, led to the final product **7c**, whereas *syn*-elimination with the hydrogen attached to the tertiary carbon yielded the allylic N,O-acetals **6a**–**c**. Readdition of a palladium hydride species to **6a**–**c** would lead to the intermediate **B**, which evolved to **C** after *syn*-dealkoxypalladation[16] because the better ability of the oxygen substituent as leaving group than that of the nitrogen substituent.[17] Evolution of **C** to the palladium-nitrogen[18] intermediate **D**, followed by *syn*-dehydropalladation would lead to the iminium intermediate[19] which cyclizes to the final enamines **9a**–**c**.



Scheme 4 Proposed pathway for the formation of Heck cyclization products **6**, **7**, and **9** from **5**.

In summary, we have shown that positional isomers of 2,3-disubstituted perhydro-1,3-benzoxazines, bearing an aryl group and a double bond as substituents, react in a different way under similar intramolecular Heck conditions. Cyclization compounds resulting from 2-vinyl-3-aryl substituted substrates suffer additional readdition of palladium hydride species, and *syn*-dealkoxypalladation with concomitant ring opening-ring closing to the rearranged enamines **9**.

Acknowledgement

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(12) *Heck Cyclization of Compound **5a**, Typical Procedure*: A stirred suspension of perhydro-1,3-benzoxazine **5a** (850 mg, 2 mmol), palladium acetate (17 mg, 0.1 mmol), potassium acetate (754 mg, 8 mmol), tetrabutylammonium bromide (650 mg, 2 mmol) and triphenylphosphine (80 mg, 0.3 mmol) in dry and deoxygenated acetonitrile (20 mL) was refluxed for 8 h. After being cooled to r.t., the solvent was evaporated, and the residue was partially dissolved in boiling hexane and filtered. The filtrate was evaporated giving **9a** (535 mg, 1.8 mmol, 90%) as an oily residue. ^{1}H NMR (δ): 0.85–1.18 (m, 2 H); 0.88 (d, *J* = 6.5 Hz, 3 H); 1.21–1.32 (m, 1 H); 1.39–1.53 (m, 2 H); 1.41 (s, 3 H); 1.43 (s, 3 H); 1.66–1.72 (m, 2 H); 1.82–1.86 (m, 1 H); 2.01 (s, 3 H); 3.74 (dt, *J* = 4.0 Hz, 10.4 Hz, 1 H); 6.16 (s, 1 H); 6.48 (s, 1 H); 7.14–7.17 (m, 2 H); 7.28–7.33 (m, 2 H). ^{13}C NMR (δ): 16.0; 19.9; 22.2; 25.4; 26.9; 31.3; 34.7; 41.1; 51.5; 57.4; 75.6; 82.4; 104.1; 120.5; 125.0; 126.4; 127.3; 127.9; 128.8; 132.0.

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