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Diastereoselective Formation of Tertiary Stereocenters *via* Mizoroki-Heck Reaction

Ane R. Azcargorta,[1] Esther Lete,[1] and Nuria Sotomayor[1]*

[1] Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco / Euskal Herriko Unibertsitatea UPV/EHU. Apdo. 644. 48080 Bilbao, Spain. http://www.ehu.es/oms

* Author to whom correspondence should be addressed; E-Mail: nuria.sotomayor@ehu.eus; Tel.: +34 946015389; Fax: +34 946012748.

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Abstract: The diastereoselective Mizoroki-Heck reaction of *N*-benzylpyrrolidines that incorporate a protected allylic alcohol moiety allows the synthesis of enantiomerically pure pyrrolo[1,2-*b*]isoquinolines, generating a tertiary stereocenter. The best results were obtained with the use of bulky phosphanes, as P(*o*-Tol)$_3$. When a good leaving group, such as pivaloyl is used as a protecting group, the *trans*-10-vinyl substituted pyrroloisoquinoline (10S,10aS)-**2a** is obtained as the major diastereoisomer in moderate yield. On the other hand, when the allylic alcohol is protected as a silyl ether, the protected alcohol is retained, obtaining an enol ether, whichafter deprotection and reduction leads to the *trans*-10-hydroxymethyl substituted pyrrolisoquinoline (10*S*,10a*S*)-**5,** in enantiomerically pure form, with complete diastereoselectivity.

Keywords: Palladium; diastereoselective Heck reaction; alkaloids; pyrrolo[1,2-*b*]isoquinolines

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1. Introduction

The Mizoroki-Heck reaction (M-H), has found wide application in the preparation of complex organic molecules, from simple substrates including heterocycles.[1] Particularly, the enantioselective intramolecular M-H reaction has emerged as an excellent tool for the construction of polycyclic frameworks.[2]

In connection with our interest our interest in palladium catalyzed reactions[3] we recently showed that quaternary stereocenters can be

generated using chiral phosphane ligands as (*R*)-BINAP, through a cascade polyene cyclization.[4]

The pyrrolo[1,2-*b*]isoquinoline core is also the characteristic structural unit present in numerous biologically active compounds, as the phenanthroindolizidine alkaloids.[5] In this context, we have shown that the 6-*exo* carbolithiation of 2-alkenylpyrrolidines takes place with complete diastereoselectivity, allowing the synthesis of enantiomerically pure hexahydropyrrolo[1,2-*b*]isoquinolines in high yields.[6] On the other hand, the Mizoroki-Heck reaction of this type of pyrrolidines leads to enantiomerically pure 10-alkyidene substituted hexahydropyrrolo[1,2-*b*]isoquinolines7 Therefore, we decided to investigate further the scope of Mizoroki-Heck intramolecular reaction towards the stereo controlled synthesis of pyrrolo[1,2-*b*]isoquinolines, generating a tertiary stereocenter, using a diastereoselective approach.

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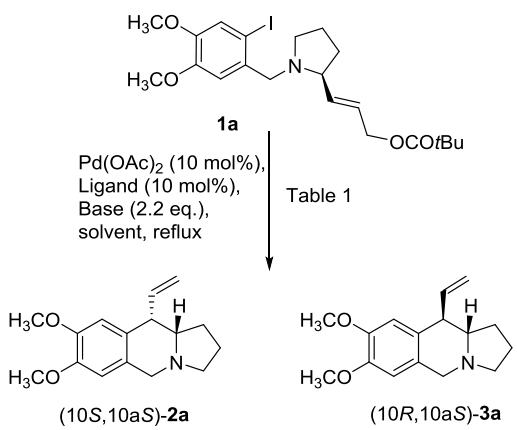
2. Results and Discussion

To start studying the generation of a tertiary centre, we selected as substrate an enantiomerically pure *N*-benzylpyrrolidine that incorporates a protected allylic alcohol, as pivalate **1a**, which was prepared in enantiomerically pure form from commercially available *N*-Boc L-prolinal. (Scheme 1).



Scheme 1.

In fact, under classical Mizoroki-Heck conditions [$Pd(PPh_3)_4$ (10 mol%), $NaHCO_3$, Bu_4NCl, CH_3CN, reflux 48 h], pivalate elimination took place, generating a tertiary stereocenter. However, only a low yield (16%) of a diastereomeric mixture of pyrroloisoquinolines **2a** and **3a** was obtained, with moderate diastereoselectivity in favor of the *trans*-isomer **2a** (66:34 ratio). After some experimentation, we found that palladium acetate with a bulky phosphane, as tri-*ortho*-tolylphosphane (Scheme 1, Table 1) was required to obtain moderate to good yields of the diastereomeric mixture of pyrroloisoquinolines **2a** and **3a** (Table 1). The use of a mixture of CH_3CN/H_2O (10:1) as solvent resulted in reduced reaction times (72 h *vs* 5 h, entry 2 *vs* entry 1), obtaining a comparable yield with no loss of diastereoselectivity. Other phosphanes (entries 3-7) and bases (entry 8) were also used, but the diastereoselectivity was not improved. Both diastereomers could be separated and characterized. Their stereochemistry was established by NMR and confirmed by X-ray analysis (Figure 1)

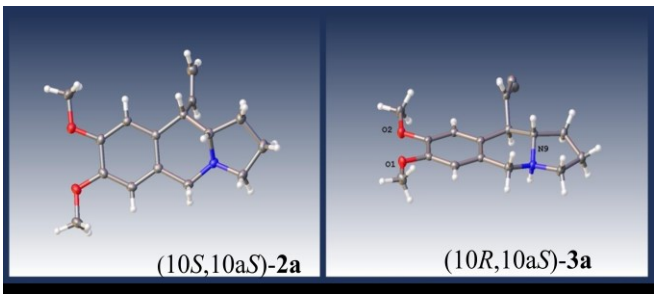
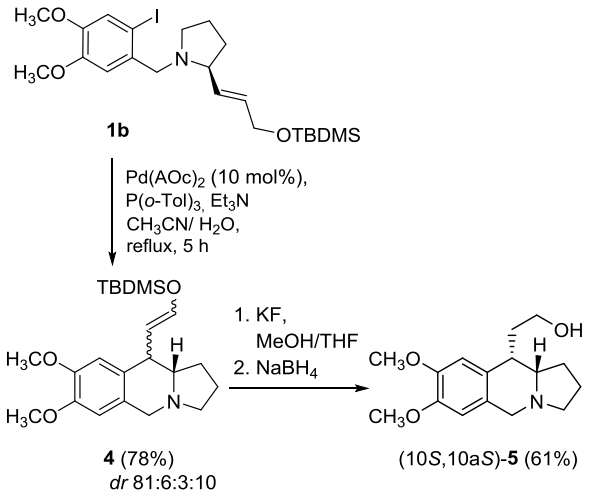


Figure 1. ORTEP plots of compounds **2a** and **3a**



Scheme 2.

Interestingly, when the allylic alcohol is protected with a TBDMS group (**1b**, Scheme 2), the protected alcohol is retained, generating a tertiary centre and obtaining an enol ether **4** in good yield, as a mixture of diastereomers with the *trans* major diastereomer as a *E*/*Z* mixture. The enol ether could be deprotected and the resulting aldehyde was reduced, to obtain alcohol **5** as a single diastereomer, enantiomerically pure.

Table 1. Pd(0)-catalyzed cyclization reactions of **1a**.

Entry	Ligand	Base	Solvent	Time (h)	Yield (%)	Ratio 2a/3a
1	P(*o*-Tol)$_3$	Et$_3$N	CH$_3$CN	72	51	83:17
2	P(*o*-Tol)$_3$	Et$_3$N	CH$_3$CN:H$_2$O	5	53	78:22
3	P*t*Bu$_3$	Et$_3$N	CH$_3$CN:H$_2$O	5	32	78:22
4	PCy$_3$	Et$_3$N	CH$_3$CN:H$_2$O	5	45	78:22
5	DavePhos	Et$_3$N	CH$_3$CN:H$_2$O	5	51	76:24
6	PPh$_3$	Et$_3$N	CH$_3$CN:H$_2$O	5	32	66:34
7	dppp	Et$_3$N	CH$_3$CN:H$_2$O	5	51	50:50
8	P(*o*-Tol)$_3$	BuNMe$_2$	CH$_3$CN:H$_2$O	5	35	72:28
9	P(*o*-Tol)$_3$[a]	Et$_3$N	CH$_3$CN:H$_2$O	22	46	79:21

[a] 5 mol% of Pd(AcO)$_2$ was used

4. Conclusions

Tertiary stereocenterss can be efficiently generated *via* Mizoroki-Heck reaction using protected allylic alcohol moieties. The β'-elimination can be controlled by selecting the protecting group (Piv or TBDMS). The best results in terms of yield and diastereoselectivity were obtained by using bulky phosphanes. Thus, *trans*-10-vinylpyrroloisoquinoline (10*S*,10a*S*)-**2a** and *trans*-10-hydroxymethylpyrroloisoquinoline (10*S*,10a*S*)-**5,** have been obtained in enantiomerically pure form.

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Conflicts of Interest

The authors declare no conflict of interest.

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