



Exploring the enantioselective Heck-Matsuda reaction with electron-rich endocyclic olefins – 2,3-dihydrofuran asymmetric arylation

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INTRODUCTION

The Heck reaction is a powerful tool for C-C bond formation, being widely used in the modern organic synthesis. The Heck-Matsuda reaction (HM), which employs arenediazonium salts as arylating agents, is gaining increasing prominence, requiring milder reaction conditions and simpler experimental procedures.¹ Recently, our research group reported the first example of the enantioselective HM reaction employing chiral bis-oxazoline ligands.² We present herein studies aiming at the enantioselective arylation of 2,3-DHF, a cyclic activated olefin.

RESULTS AND DISCUSSION

The arylation of 2,3-DHF (**1**) with diazonium salt **2** was chosen as a model reaction. The reaction conditions previously developed in our group led to a mixture of diastereomeric acetals **3**, derived from addition of methanol to the isomerized Heck adduct, in 50% yield and 48% e.e. (Entry 1, Table 1).

Table 1. Arylation of 2,3-DHF with arenediazonium salt **2**.

Entry	1 : 2	Base (equiv.)	[] (mol.L ⁻¹)	Yield (%)	e.e. (%)
1	1:2	DTBMP (1)	[0,15]	50	48
2	1:2	ZnCO ₃ (1)	[0,15]	40	0
3	1:2	ZnCO ₃ (0,5)	[0,15]	37	36
4	1:2	CaCO ₃ (0,5)	[0,15]	17	0
5	1:2	2,6-lut (1)	[0,15]	15	43
6	1:2	Proton Sponge (1)	[0,15]	23	17
7	10:1	DTBMP (1)	[0,15]	71	45
8	10:1	DTBMP (1)	[0,07]	89	43
9	10:1	DTBMP (1)	[0,30]	77	41
10 ^a	10:1	DTBMP (1)	[0,15]	83	51
11 ^{a,b}	10:1	DTBMP (1)	[0,15]	84	48

a) Reaction at 0 °C. b) 4-OMe-(C₆H₄)-N₂PF₆ was employed.

We evaluated other bases (Entries 2-6), excess of olefin (Entry 7); concentration (Entries 7-9), temperature (Entry 10) and counteranion nature (Entry 11).

With this briefly “optimized” conditions in hands, we evaluated a series of chiral *N,N* ligands. The results are shown in Figure 1.

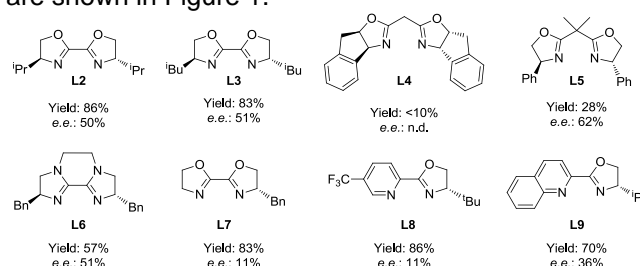
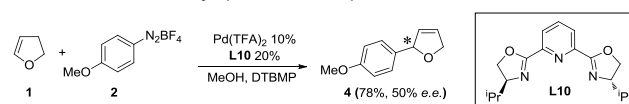


Figure 1. Other chiral *N,N*-ligands evaluated in this work.

Other similar ligands led to very similar results, while the use of methylene bridged **L4** led to a much decreased reactivity. The best enantioselectivity was achieved with **L5** (difficult to reproduce). C-2 symmetry seems to be an important ligand feature, since ligands **L7-L9** led to decreased enantioselectivities.

Interestingly, when an analogous PyBox ligands was used, the primary Heck adduct was obtained as the major product, with a comparable level of enantioselectivity (Scheme 1).



Scheme 1. Arylation of 2,3-DHF using a PyBox ligand.

CONCLUSION

This work demonstrates the potential of an enantioselective HM arylation of 2,3-DHF, despite the moderate enantioselectivities so far achieved. The product outcome can also be controlled by the proper choice of ligands, leading to the primary or isomerized methoxylated Heck adducts. Further optimization studies are ongoing.

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