DOI: 10.1002/adsc.201100711

Synthesis of Olefin-Oxazoline Ligands (OlefOx) by Rhodium(III)-Catalyzed Oxidative Olefination

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Received: September 14, 2011; Revised: November 10, 2011; Published online: February 23, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201100711.

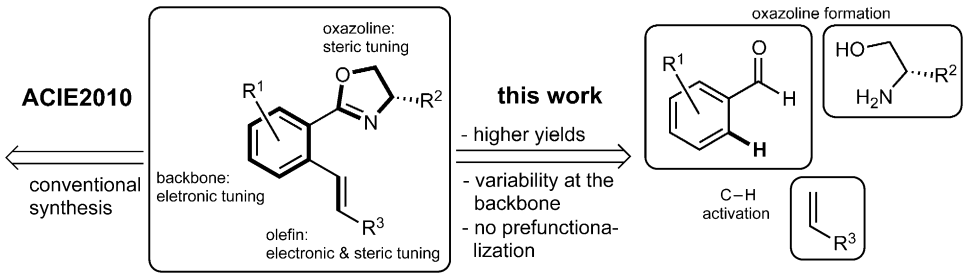
Abstract: The rhodium(III)-catalyzed oxidative olefination of 2-aryloxazolines is described and has been employed for the synthesis of olefin-oxazoline ligands (OlefOx). The highly modular synthesis starting from readily available 2-aryloxazolines can be performed under an atmosphere of air as the terminal oxidant with catalytic amounts of copper(II)-acetate.

Keywords: C–H activation; olefination; olefins; oxazolines; rhodium

Following the recent success of chiral diene ligands,[1] a range of chiral bidentate C_1 symmetrical olefin ligands[2] has been applied successfully to asymmetric catalysis.[3] The oxazoline moiety is a more common and privileged[4] motif in ligands for asymmetric catalysis,[5] with bisoxazolines[6] (BOX) and phosphine-oxazolines[7] (PHOX) being the most prominent examples.[8] In 2010 the bidentate olefin-oxazoline ligands (OlefOx) were introduced and applied successfully in the rhodium-catalyzed 1,4 conjugate addition.[9] The unique electronic and structural behavior of the η^2-binding olefin, the privileged η^1-binding oxazoline fragment taken together with the variability of both entities provides a versatile ligand system for asymmetric catalysis.

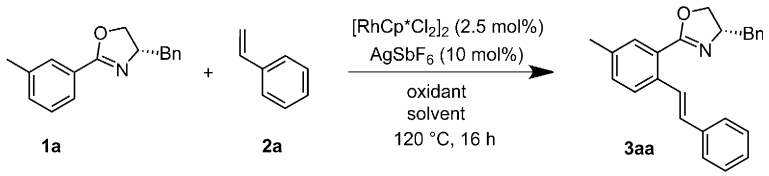
The disadvantages in the previously reported synthesis of OlefOx ligands are the low yields for a range of substrates and, more importantly, the lack of variation of substituents in the backbone of the ligand, which could provide further electronic tuning of the olefin. Therefore it was our aim to explore a new pathway that overcomes these problems.

The oxidative Heck reaction, as pioneered by Fujiwara and Moritani,[10] has become an increasingly important transformation in organic chemistry for C–C coupling,[11] as it obviates prior functionalization steps and minimizes waste formation. The palladium,[12] rhodium[13] and ruthenium[14] catalyzed reactions have been recently investigated intensively. A method that does not require prefunctionalization and that allows the substitution of the backbone would represent a great improvement. The direct oxidative olefination, using the oxazoline moiety as a directing group[15] would therefore be highly desirable. Herein we report a novel, highly modular synthesis of OlefOx ligands by oxidative olefination of readily available 2-aryloxazolines (Scheme 1).[16]



Scheme 1. Retrosynthethic analysis of OlefOx formation.

Table 1. Optimization of reaction conditions.[a]



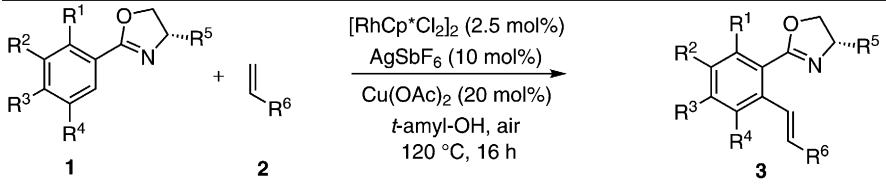
Entry	Oxidant (equiv.)	Solvent	Yield of **3aa** [%][b]
1	$Cu(OAc)_2$ (2.1)	*t*-amyl-OH	40
2[c]	$Cu(OAc)_2$ (2.1)	*t*-amyl-OH	29
3[d]	$Cu(OAc)_2$ (2.1)	*t*-amyl-OH	29
4	$Cu(OAc)_2$ (2.1)	DMF	34
5	AgOAc (2.1)	*t*-amyl-OH	18
6[e]	**$Cu(OAc)_2$ (0.2)**	***t*-amyl-OH**	**55**
7[e,f]	$Cu(OAc)_2$ (0.2)	*t*-amyl-OH	55
8[g]	$Cu(OAc)_2$ (0.2)	*t*-amyl-OH	54
9[e,h]	$Cu(OAc)_2$ (0.2)	*t*-amyl-OH	37
10[g,i]	$Cu(OAc)_2$ (0.2)	*t*-amyl-OH	<5
11[g]	$Cu(OAc)_2$ (0.2)	1,4-dioxane	50
12[e]	$Cu(OAc)_2$ (0.2)	DMF	37
13[e]	$Cu(OAc)_2$ (0.1)	*t*-amyl-OH	47
14[g]	$Cu(OAc)_2$ (0.1)	*t*-amyl-OH	46

[a] *Reaction conditions:* **1a** (0.50 mmol), **2a** (0.75 mmol), 2.5 mL solvent.
[b] Isolated yields.
[c] 5 mol% $[RhCp^*Cl_2]_2$, 20 mol% $AgSbF_6$.
[d] 140 °C instead of 120 °C.
[e] Reaction was run under air.
[f] AgOTf instead of $AgSbF_6$.
[g] Reaction was run under oxygen.
[h] 42 h reaction time.
[i] 2.2 equiv. of Na_2CO_3 as additive.

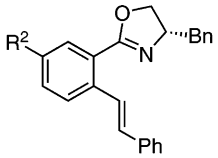
As model substrates for our reactions, we chose oxazoline **1a** and styrene (**2a**) and started the optimization (Table 1) with typical conditions from our previous work.[13d] With stoichiometric amounts of $Cu(OAc)_2$ the yield was 40% (Table 1, entry 1). However, surprisingly the best result was obtained with an only substoichiometric amounts of $Cu(OAc)_2$ using air as the terminal oxidant (Table 1, entry 6). In prospect of a possible upscaling of the reaction the reduced Cu(I) waste formation is very desirable. Even though the isolated yield was only modest with 55%, it still represents a major improvement compared to our previous synthesis.

With the optimized conditions in hand we continued our study with a variety of different substituents on the OlefOx backbone (Table 2). Electron-poor substituents (**1b**), electron-neutral (**1a**) as well as electron-rich ones (**1f**) were tolerated to give the desired products (**3ba**, **3aa**, **3fa**). For halogenated oxazolines (**1c**, **1d**) the isolated yield was only about 26–29% (**3ca**, **3da**) and in these reactions we were able to reisolate large amounts of starting material. This could indicate the possibility of catalyst-poisoning during the reaction. For regioselective mono-olefination, it was crucial to have a minimum of steric demands in the *meta*-positions (e.g., Me, CF_3). The use of a smaller group, like methoxy, led to an inseperable mixture of both possible mono-olefinated and di-olefinated products. The steric demand of the methoxy group in the *meta*-position is too low to block the neighboring positions, as can be seen by applying 2,5-dimethoxyoxazolines (**1f**, **1j**) to the reaction, providing the desired olefinated products (**3fa**, **3ja**). The scope of the backbone could further be expanded from phenyl to naphthyl systems (**1g**). The next variation was the use of different substituents at the 4-position of the oxazoline. When switching to L-valinol-derived oxazolines (**1h**–**1j**), the isolated yields increased (*cf.* **3aa** and **3ha**, **3ba** and **3ia**) and to L-phenylglycinol the yield decreased (*cf.* **3aa** and **3ka**). To further demonstrate the high modularity of the synthesis, a range of different olefins was used. With acrylates (**2b**) the best yields could be achieved (**3ab**, **3ib**), whereas the use of 2-vinylnapththalene (**2f**) decreased the isolated yield by a large amount. Finally, the use of different substituted styrenes (**2c**, **2d**, **2e**) generally led to a decrease in isolated yields (**3ic**, **3id**, **3ie**).

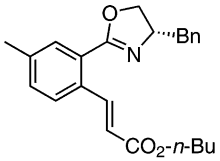
Table 2. Scope on the rhodium catalyzed olefination.[a]



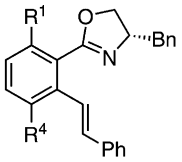
1 2 3



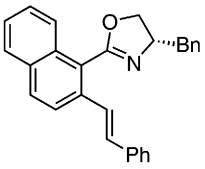
3aa, R^2 = Me, 55%[b]
3ba, R^2 = CF_3, 51%
3ca, R^2 = Cl, 26%
3da, R^2 = Br, 29%



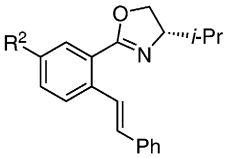
3ab, 57%



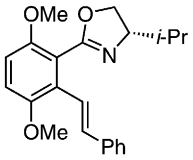
3ea, R^1 = Me, R^4 = H, 58%
3fa, R^1 = OMe, R^4 = OMe, 45%



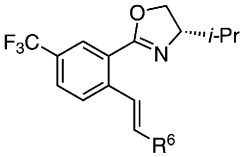
3ga, 46%



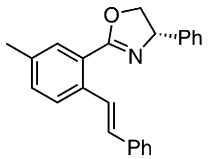
3ha, R^2 = Me, 63%
3ia, R^2 = CF_3, 71%



3ja, 53%



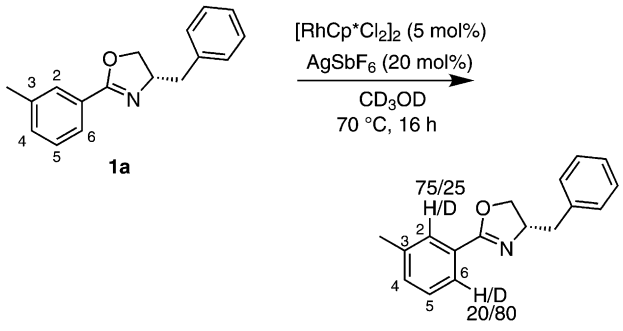
3ib, R^6 = CO_2-*n*-Bu, 76%
3ic, R^6 = 4-Cl-C_6H_4, 55%
3id, R^6 = 4-*t*-Bu-C_6H_4, 59%
3ie, R^6 = C_6F_5, 65%
3if, R^6 = 2-naphthyl, 37%



3ka, 39%

[a] *Reaction conditions:* **1** (1.0 mmol), **2** (1.5 mmol), 5 mL *t*-amyl-OH, isolated yields.
[b] Reaction was run on a 0.50 mmol scale.

To gain more insight into this transformation, a deuteration experiment was conducted. Treatment of **1a** with a catalytic amount of $[RhCp^*Cl_2]_2$ and $AgSbF_6$ in MeOH-d_4 at 70 °C for 16 h, resulted in 80% deuterium incorporation in the 6-position and 25% in the 2-position. This indicates that we have a reversible C–H bond activation step[17] and, more important, that only the *ortho*-positions can be functionalized under the reaction conditions. In addition the stereochemical integrity of the oxazoline moiety stays intact, as was shown by HPLC analysis of **1a** and *rac*-**1a**.



In conclusion, we have developed a new, efficient and highly modular synthetic pathway to a broad range of OlefOx ligands in modest to good yields. The employed C–H activation strategy significantly streamlines the synthesis. Furthermore, the successful use of air as the terminal oxidant is attractive. This new method allows the independent tuning of all three components, the oxazoline, the styrene and the backbone benzene ring. We expect our method to be useful for preparing new OlefOx ligands with interesting applications in asymmetric catalysis.

Experimental Section

General Procedure for the Olefination of 2-Aryloxazolines

In a flame-dried, screw-capped tube $[RhCp^*Cl_2]_2$ (0.025 mmol), $AgSbF_6$ (0.10 mmol), $Cu(OAc)_2$ (0.20 mmol), the 2-aryloxazoline **1** (1.0 mmol scale) in *t*-amyl alcohol (2.5 mL) and olefin **2** (1.5 equiv.) were united under argon. The tube was evacuated and vented with air two times, closed and then transferred to a pre-heated oil bath (120 °C) for 16 h. After cooling down to room temperature, NH_4OAc (approx. 1 mmol) was added and the mixture stirred for one more hour. Then the mixture was filtered through a short plug of silica with $EtOAc/CH_2Cl_2$, the solvent was removed under reduced pressure, subsequent purification by flash chromatography gave the desired product.

Acknowledgements

We thank Dr. Frederic W. Patureau, Dr. Björn T. Hahn and Nadine Kuhl for helpful discussions. Generous financial support by theDeutsche Forschungsgemeinschaft (SFB 858) is gratefully acknowledged.

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