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Enantioselectivity in the synthesis of 3,5-disubstituted Δ^2-isoxazolines

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ABSTRACT

The *R*-isomer of ISO-1, a 3,5-disubstituted Δ^2-isoxazoline, has been implicated as a potential therapeutic agent for the treatment of Type 1 Diabetes via the antagonism of macrophage migration inhibitory factor (MIF). Δ^2-Isoxazolines can be prepared by the palladium(II)-mediated cyclization of substituted β,γ-unsaturated oximes. While this reaction results in racemic mixtures, we have developed a stereoselective variant of this method based on the incorporation of an enantiomeric palladium complex in the reaction mixture. The use of chiral bisoxazoline ligands in the palladium(II)-mediated ring closure reaction has been shown to enhance the enantiomeric excess due to chirality at C5 of the Δ^2-isoxazoline.

ISO-1, a 3,5-disubstituted Δ^2-isoxazoline (Fig. 1), has been shown to antagonize the human macrophage migration inhibitory factor (MIF).[1] MIF is a homopolymeric trimer with tautomerization activity similar in nature to the bacterial enzymes 5-carboxymethyl-2-hydroxymuconate isomerase and 4-oxalocrotonate tautomerase.[2] MIF has also been linked to the onset and progression of Type 1 Diabetes; antagonism of MIF by ISO-1 has been shown to limit and/or prevent the progression of diabetes in transgenic mice.[3] Studies of ISO-1 and the active site of MIF as surmised by X-ray crystallography indicate that the *R*-stereoisomer of ISO-1 should exist as the eutomer and exhibit the maximum antagonistic effect.[4] However, the variety of substituted Δ^2-isoxazolines examined in these studies was relatively limited.

Δ^2-Isoxazolines used in previous studies were prepared via the 1,3-dipolar cycloaddition of an aryl nitrile oxide and an unsaturated ester.[5] Yields in this reaction can be quite good, but the scope is limited in the functionality present in the reaction. Furthermore, the regiochemistry of the cycloaddition is dictated by substitution patterns on the two reactants. In most cases, the expected 3,5-disubstituted Δ^2-isoxazolines can be obtained.

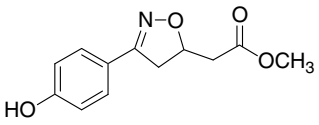
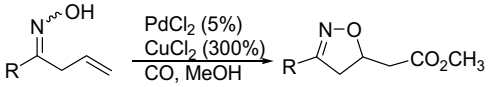


Figure 1. ISO-1 antagonizes macrophage migration inhibitory factor.

In our laboratory, we have explored the regiochemically controlled formation of 3,5-disubstituted Δ^2-isoxazolines via the intramolecular nucleometalation/methoxycarbonylation of a β,γ-unsaturated oxime (Scheme 1).[6] Similar intramolecular palladium(II) catalyzed reactions exist in the literature for a wide variety of unsaturated nucleophiles.[7] In our hands, for example, the palladium(II)-mediated catalyzed ring closure of 1-(*p*-hydroxyphenyl)-3-buten-1-one oxime gives rise to ISO-1 in acceptable yield. Synthesis of the β,γ-unsaturated oximes used in that study involved the Grignard addition of allylmagnesium bromide to a commercially available aldehyde, oxidation of the resulting alcohol, and treatment with hydroxylamine to provide the expected oxime as a mixture of syn and anti isomers.[6]

Given that the palladium(II)-mediated cyclization of a β,γ-unsaturated oxime can be a regiochemically controlled route to 3,5-disubstituted Δ^2-isoxazolines, we envisioned a stereoselective palladium(II)-mediated reaction to preferentially form the eutomeric ISO-1 analogs. In recent literature, Trost illustrated the use of bulky chiral ligands to control stereochemistry.[8] He demonstrated that steric bulk, when oriented in a particular direction pseudo-orthogonal to the plane of the ligand–metal bonds, dramatically improved the enantioselectivity in a [3+2] cycloaddition.

Based on computational analysis within our lab (Spartan, semi-empirical AM1), a set of requirements were proposed for the ligands in the palladium(II)-mediated cyclization of β,γ-unsaturated oximes (Scheme 1). According to this analysis and in order to



Scheme 1. Palladium(II)-mediated ring closure.

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greatly influence the approach of the oxime nucleophile to only one face of the alkene, the ligand must be chiral and bidentate. Moreover, the groups on the chiral ligand should exhibit sufficient bulk and be oriented in the same pseudo-orthogonal direction as explored by Trost. Finally, in our analysis, groups that extended well past the binding site for palladium(II) were predicted to exhibit the greatest stereoselectivity in the cyclization reaction.

Introduction of a chiral ligand into the reaction illustrated in Scheme 1 does provide stereochemical control of the reaction.[9] To explore the scope of the reaction, a wide variety of ligands were employed, including oxazolines (OX), bisoxazolines (BOX), and substituted phosphines. The use of these ligands coordinates well with the requirements for the introduction of enantioselectivity in this reaction. Moreover, the bulkiness of the substituents and the orientation of that bulk were studied. Reaction conditions and results for stereoselectivity (% ee) are reported for each ligand used in this study (Scheme 2 and Table 1).

The phosphines (Table 1, entries 4 and 12–14) did not appear to be optimal ligands as evidenced by both reaction yield and % ee. Those ligands that contained at least one oxazoline ring worked moderately well to support enantioselectivity in this reaction. Within that series, an increase in the steric bulk and changing the ligand from monodentate (OX) to bidentate (BOX), caused an increase in the enantiomeric excess. The use of a tridentate ligand, see Table 1, entry 11, did provide enantioselectivity in the reaction; however, the orientation of the isopropyl groups in ligand **L11** is directed away from the palladium(II) binding side. Such orientation agrees with the prediction that enantioselection would be reduced dramatically. Similarly, as the orientation of the groups was directed toward the binding site of the palladium, the enantiomeric excess increased. Dramatically, when both steric bulk was increased and the orientation of the groups toward the metal binding site was maximized, the enantiomeric excess significantly increased. In order to explore the dual implementation of bulkiness and orientation in chiral ligands, a systematic study of the enantiomeric excess generated from the use of BOX ligands was undertaken.

For example, in the OX series, increase in steric bulk resulted in an increase in enantiomeric excess (entry 2 vs 1). In the BOX series, orientation of steric bulk away from the metal center (entry 5) resulted in moderate enantiomeric excess. Direction of that steric bulk toward the pseudo-orthogonal position (entries 6 and 7) at first did not seem to increase enantiomeric excess. However, as the size of the steric bulk increased from *t*-butyl to phenyl to benzyl (entries 7–9), the enantiomeric excess increased dramatically. For instance, ligand **L7** provided 15% ee, **L8** showed 34% ee, and **L9** gave 57% ee. We predict that as steric bulk increases further, as would be the case in 2-naphthyl or 2-anthracenyl substituted BOX ligands, the % ee should dramatically increase.

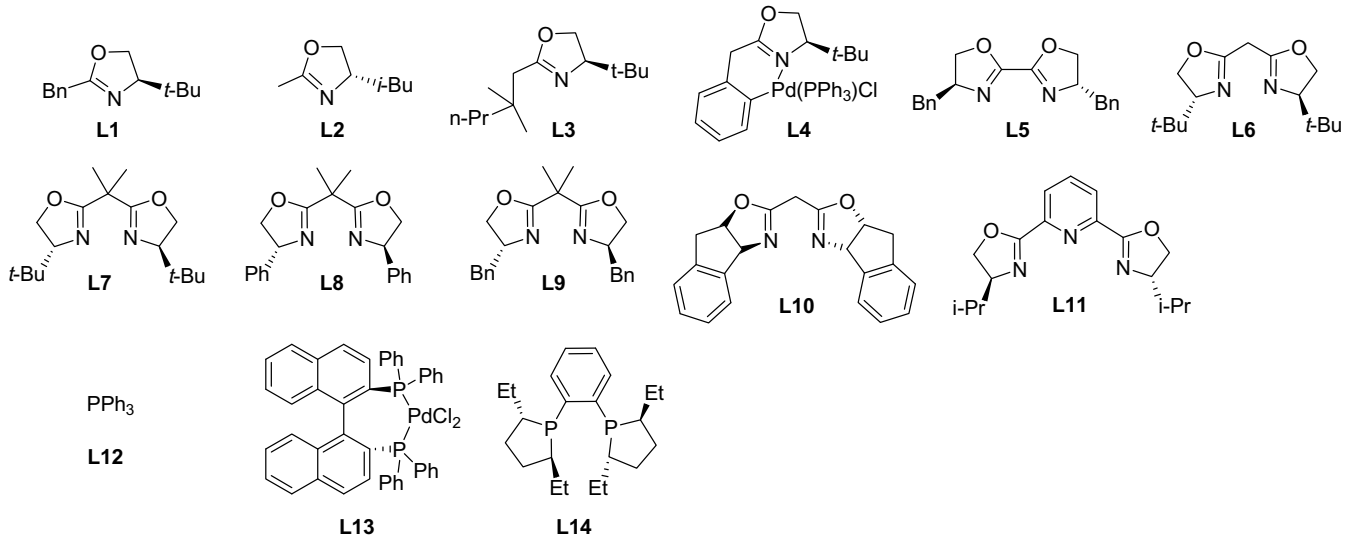
Table 1
Reaction outcomes for the use of ligands from Scheme 2 in the reaction noted in Scheme 1, where R = *p*-CH_3Ph

Entry	Ligand	Solvent[a]	Reaction time (h)	Yield[b] (%)	% ee[c]
1	**L1**	CH_3OH	2[d]	71	41
2	**L2**	CH_3OH/CH_2Cl_2	7	83	4
3	**L3**	CH_3OH/CH_2Cl_2	6	77	8
4	**L4**	CH_3OH	6	0	na
5	**L5**	CH_3OH/CH_2Cl_2	7	83	43
6	**L6**	CH_3OH/CH_2Cl_2	7	84	19
7	**L7**	CH_3OH/CH_2Cl_2	6	73	15
8	**L8**	CH_3OH/CH_2Cl_2	6	67	34
9	**L9**	CH_3OH/CH_2Cl_2	6	86	57
10	**L10**	CH_3OH/CH_2Cl_2	6	91	2
11	**L11**	CH_3OH/CH_2Cl_2	7	77	16
12	**L12**	CH_3OH/CH_2Cl_2	6	0	na
13	**L13**	CH_3OH	6	0	na
14	**L14**	CH_3OH/CH_2Cl_2	6	36	6

[a] Solvent used in reaction as pure methanol, or as a 4:1 mixture with dichloromethane according to the general procedure.
[b] Percent yield as determined by ^{1}H NMR.
[c] Percent enantiomeric excess as determined by comparison to the pure enantiomer isolated by chiral chromatography (Whelk-O1).
[d] Reaction progress was followed by TLC and was generally completed after 2–3 h. Doubling the reaction time did not affect the yield or % ee of the product.

Current efforts to explore the enantioselectivity in the synthesis of 3,5-disubstituted Δ^2-isoxazolines are being concentrated on the synthesis of 2-naphthyl and 2-anthracenyl substituted BOX ligands. Improved enantioselectivity in this reaction may also be achieved by pre-forming the palladium(II)-ligand complex via treatment of the BOX ligand with $Pd(OAc)_2$ prior to its introduction to the unsaturated oxime.

In summary, it has been demonstrated that the palladium(II)-mediated cyclization of β,γ-unsaturated oximes provides a convenient route to 3,5-disubstituted Δ^2-isoxazolines in good yield. The regiochemistry of this reaction can be completely controlled.



Scheme 2. Ligands used in the present study.

In addition, research has shown that this ring closure can be stereoselective without loss of yield upon addition of OX or BOX ligands. Results illustrate that BOX ligands work the best, and increases in steric bulk, with respect to both size and orientation, improve the stereoselectivity of the reaction.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tetlet.2008.04.125.

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9. General procedure: To a 25 mL flask containing a stirbar, were added $PdCl_2$ (5 mol %) and $CuCl_2$ (300 mol %), and an atmosphere of CO (balloon) applied. Methanol (3 mL, anhyd) was added and the mixture was stirred for 5 min. The appropriate ligand (5 mol %) was dissolved in CH_2Cl_2 (1 mL) or CH_3OH (1 mL) and added by syringe. The solution was allowed to stir for 10 min before addition of 1-(*p*-toluyl)-3-buten-1-one (1.20 mmol) was added as a solution in methanol (1 mL). The reaction mixture was stirred at room temperature for 6 h. The reaction mixture was then extracted into ethyl acetate (75 mL) and washed with water (50 mL), sodium bicarbonate (5%, 50 mL × 2), water (50 mL × 2), and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated to give the crude product. ^1H NMR spectra were obtained and radial chromatography (silica, hexane–ethyl acetate gradient) was used to isolate the isoxazoline for determination of optical purity.