A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201912408
Angew. Chem. 10.1002/ange.201912408

Link to VoR: http://dx.doi.org/10.1002/anie.201912408
http://dx.doi.org/10.1002/ange.201912408

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RESEARCH ARTICLE

Enantioselective Synthesis of Isoxazolines Enabled by Palladium-Catalyzed Carboetherification of Alkenyl Oximes

Lei Wang, Kenan Zhang, Yuzhuo Wang, Wenbo Li, Mingjie Chen, Junliang Zhang*

Abstract: Herein we reported a highly efficient Pd/Xiang-Phos catalyzed enantioselective carboetherification of alkenyl oximes with aryl or alkenyl halides, delivering various chiral 3,5-disubstituted and 3,5,5-trisubstituted isoxazolines in good yield with up to 97% *ee*. The sterically bulky and electron-rich (*S*, *R*s)-**NMe-X2** is responsible for the excellent reactivity and enantioselectivity. The salient features of this transformation include mild reaction conditions, general substrate scope, well functional group tolerance, good yields, high enantioselectivity, easy scale-up and application in late stage modification of bioactive compounds. The obtained products can be readily transformed into useful chiral 1, 3- aminoalcohols.

Introduction

Isoxazolines are key structural motifs in natural products, pharmaceutics, materials and agrochemicals (Figure 1). [1] They are also used as useful precursors to chiral acyclic building blocks such as *β*-hydroxy ketones, and *γ*-aminoalcohols in organic synthesis. [2] Therefore, the development of new methods for their efficient synthesis has kept attracting much attention, for examples, Loh's group firstly reported Pd-catalyzed allylic oxime cyclization for the dioxygenation of an alkene.[3a] Later, the groups of Han[4a] and others reported the radical difunctionalization route to promote cyclization of β, γ-unsaturated oximes to synthesize isoxazolines. [4] Very recently, Shi's group reported a gold redox catalysis strategy for cyclization/arylation of allylic oximes to afford the aryl-containing 3, 5-disubstituted isoxazolines.[4i]

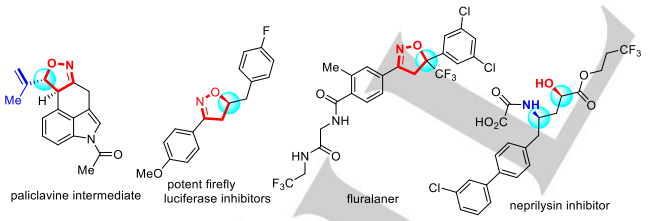

Figure 1. Chemical structures of biological active isooxazoline and 1,3-aminoalcohol.

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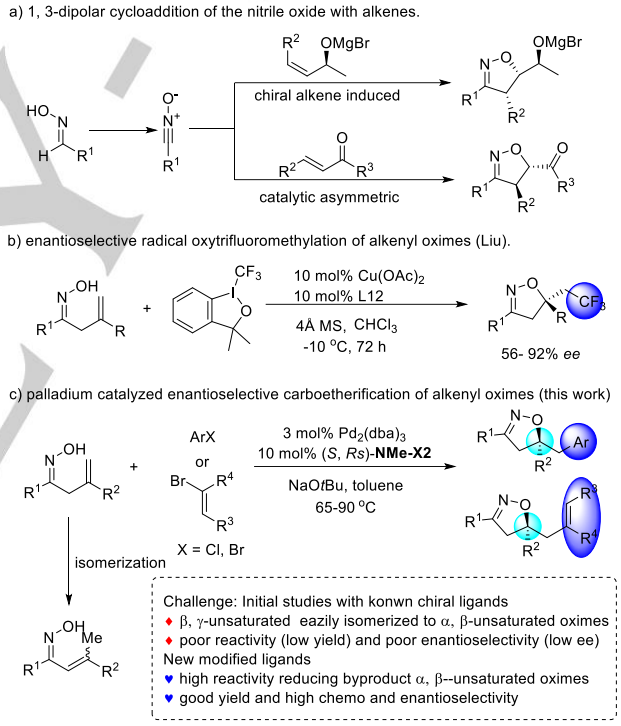
Despite significant progress in the racemic synthesis, the development of asymmetric versions still poses considerable challenges and only a few strategies have been explored so far. In general, the classic method for synthesis of enantioenriched isoxazolines are 1, 3-dipolar cycloaddition via chiral auxiliary strategy or Lewis acid asymmetric catalysis (Scheme 1a).[5-8] In 2018, Liu[9a] and co-workers demonstrated an elegant enantioselective radical oxytrifluoromethylation of alkenyl oximes enabled by the use of copper/cinchona alkaloid-based sulfonamide, leading to an *α*-tertiary stereocenter with CF_3-containing isoxazolines (Scheme 1b).



Scheme 1. Enantioselective synthesis of isoxazolines.

With regard to the significance of chiral isoxazolines, the development of asymmetric methods for their synthesis is still highly desirable. Recently, our group developed a series of chiral sulfinamidephosphine (**Sadphos**) ligands, so called **Ming-Phos**, **Xu-Phos**, and **Xiang-phos**.[11] Inspired by their good performance in asymmetric transition-metal catalysis as well as Chen[3b] and Mosher's[3c] elegant work on the palladium-catalyzed alkenyl oximes carboetherification[10] reactions for the synthesis of racemic isoxaolines, we became very interested in whether the asymmetric version of palladium-catalyzed reaction could be realized by the employment of our developed **Sadphos** ligand. However, this hypothesis will face considerable challenges: (1) How to minimize the isomerization of *β*, *γ*-unsaturated oximes to

10.1002/anie.201912408

α, *β*-unsaturated oximes.[3b, 12] (2) How to efficiently control both chemoselectivity and enantioselectivity. Herein, we describe an efficient palladium/**Xiang-Phos** catalyzed enantioselective alkenyl oximes carboetherification with both aryl halides (Br, Cl) and alkenyl bromides, delivering chiral 3, 5-disubstituted and 3,5,5-trisubstituted isoxazolines in good yields with up to 98% *ee* (Scheme 1c).

Results and Discution

Optimization of Reaction Conditions. In our initial study, *β*, *γ*-unsaturated ketoxime **1a** and 4-bromotoluene **2a** were selected as the model substrates. A series of commercially available chiral ligands were first investigated (Figure 2). Unfortunately, N, P-ligands **L1-L2** provided **3a** in poor yield with low enantioselectivity. When bisphosphine ligands such as Josiphos (**L3-L4**), (*S*)-MeO-DTBM-Biphep (**L5**), (*R*)-BINAP (**L7**), (*R*, *R*)-DIPAMP (**L8**) as well as (*R*)-QuinoxP® (**L9**) were further examined, the desired product **3a** was also obtained in low yield with up to 48% *ee*. Moreover, Binol-derived phosphoramidite(**L10**) was found to be inefficient either in this reaction. In these reactions, the low yield was attributed to the isomerization reaction of the *β, γ*-unsaturated oximes to *α, β*-unsaturated oximes.

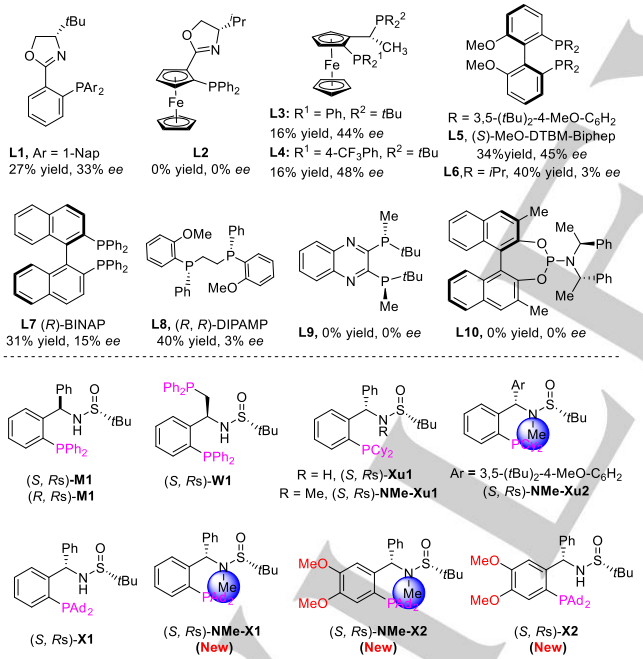
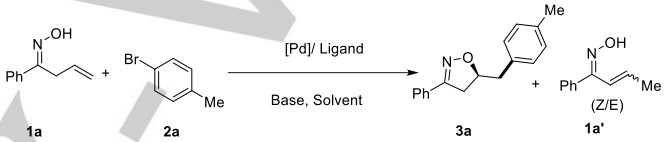


Figure 2. Screened chiral ligands in this work.

We next turned our attention to our developed **Sadphos** ligands. Unfortunately, **Ming-Phos** (*R*, *Rs*)-**M1**, (*S*, *Rs*)-**M1**, **Wei-Phos** (*S*, *Rs*)-**W1** and **Xiang-Phos** (*S*, *Rs*)-**X1** as well as **Xu-Phos** (*S*, *Rs*)-**Xu1** could not deliver the desired product **3a** at all and byproduct *α*, *β*-unsaturated oxime **1a'** was ontained in good yield (Table 1, entries 1-5). In contrast, 72 % yield of **3a** was obtained albeit with only 3% *ee* with the use of (*S*, *Rs*)-**NMe-Xu1** as the ligand, indicating the NH moiety of **Xu-Phos** might inhibit the carboetherification (Table 1, entry 6 vs entry 5). When (*S*, *Rs*)-**NMe-Xu2** with a bulk aryl group was used, the ee was slightly improved from 3% to 28% (Table 1, entry 7). Gratifyingly, with the use of more bulky *N*-methyl **Xiang-Phos** (*S*, *Rs*)-**NMe-X1** as ligand**, 3a** was isolated in 50% yield with 89% *ee* (Table 1, entry 8). Further lowering the reaction temperature resulted in lower yield and the more byproduct **1a'** was detected (Table 1, entry 9). To address this issue, we proposed that increasing the oxidative addition rate of the arylbromide with PdLn via increasing the electron-richness of ligand might favor the subsequent carboetherification reaction and thus improved the reaction yield. The (*S*, *Rs*)-**NMe-X2** bearing two electron-donating methoxy groups on the aryl backbone was then prepared and subjected to the reaction. To our delight, the yield was indeed significantly improved to 82% with the enantioselectivity increasing to 96% *ee* (Table 1, entry 10).

Table 1. Optimization of reaction conditions.[a]



Entry	Ligand	Pd sources	Base	Yield[b] (*Ee*[c])(%) of 3a/1a'
1	(*R*, *Rs*)-**M1**	$Pd_2(dba)_3$	NaO*t*Bu	0 (-)/85
2	(*S*, *Rs*)-**M1**	$Pd_2(dba)_3$	NaO*t*Bu	0 (-)/73
3	(*S*, *Rs*)-**W1**	$Pd_2(dba)_3$	NaO*t*Bu	0 (-)/75
4	(*S*, *Rs*)-**X1**	$Pd_2(dba)_3$	NaO*t*Bu	0 (-)/77
5	(*S*, *Rs*)-**Xu1**	$Pd_2(dba)_3$	NaO*t*Bu	0 (-)/78
6	(*S*, *Rs*)-**NMe-Xu1**	$Pd_2(dba)_3$	NaO*t*Bu	72 (3)
7	(S, *Rs*)-**NMe-Xu2**	$Pd_2(dba)_3$	NaO*t*Bu	70 (28)
8	(*S*, *Rs*)- **NMe-X1**	$Pd_2(dba)_3$	NaO*t*Bu	50 (89)
9[d]	(*S*, *Rs*)-**NMe-X1**	$Pd_2(dba)_3$	NaO*t*Bu	38 (88)
10[d]	(*S*, *Rs*)-**NMe-X2**	$Pd_2(dba)_3$	NaO*t*Bu	82(96)
11[d]	(*S*, *Rs*)-**X2**	$Pd_2(dba)_3$	NaO*t*Bu	trace(-)/60
12[d]	(*S*, *Rs*)-**NMe-X2**	$PdCl_2$	NaO*t*Bu	16 (92)
13[d,e]	(*S*, *Rs*)-**NMe-X2**	$Pd(OAc)_2$	NaO*t*Bu	23(94)
14[d]	(*S*, *Rs*)-**NMe-X2**	$[Pd(allyl)Cl]_2$	NaO*t*Bu	68 (96)
15[d,e]	(*S*, *Rs*)-**NMe-X2**	$PdCl_2(CH_3CN)_2$	NaO*t*Bu	44 (55)
16[d]	(*S*, *Rs*)-**NMe-X2**	$Pd_2(dba)_3$	K_2CO_3	44 (88)
17[d]	(*S*, *Rs*)-**NMe-X2**	$Pd_2(dba)_3$	Cs_2CO_3	55 (92)
18[d]	(*S*, *Rs*)-**NMe-X2**	$Pd_2(dba)_3$	Na_2CO_3	0(-)/80
19[d,f]	(*S*, *Rs*)-**NMe-X2**	$Pd_2(dba)_3$	NaO*t*Bu	33 (94)
20[d,g]	(*S*, *Rs*)-**NMe-X2**	$Pd_2(dba)_3$	NaO*t*Bu	47 (94)
21[d,h]	(*S*, *Rs*)-**NMe-X2**	$Pd_2(dba)_3$	NaO*t*Bu	42 (90)

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), NaO*t*Bu (1.5 equiv), 3 mol% $Pd_2(dba)_3$, and 10 mol% ligand in 2.0 mL toluene, 100 °C under Ar for 12 h. [b] Isolated yield. [c] *Ee* was determined by HPLC analysis [d] 70 °C , 12 h. [e] 5 mol % palladium catalysts. [f] THF, [g] 1,4-dioxane and [h] DCE were used respectively as solvent.

For comparison, the use of (*S*, *Rs*)-**X2** with NH moiety only give trace amount of the product **3a** (Table 1, entry 11). Other palladium sources such as $PdCl_2$, $Pd(OAc)_2$, $Pd(CH_3CN)_2Cl_2$ and

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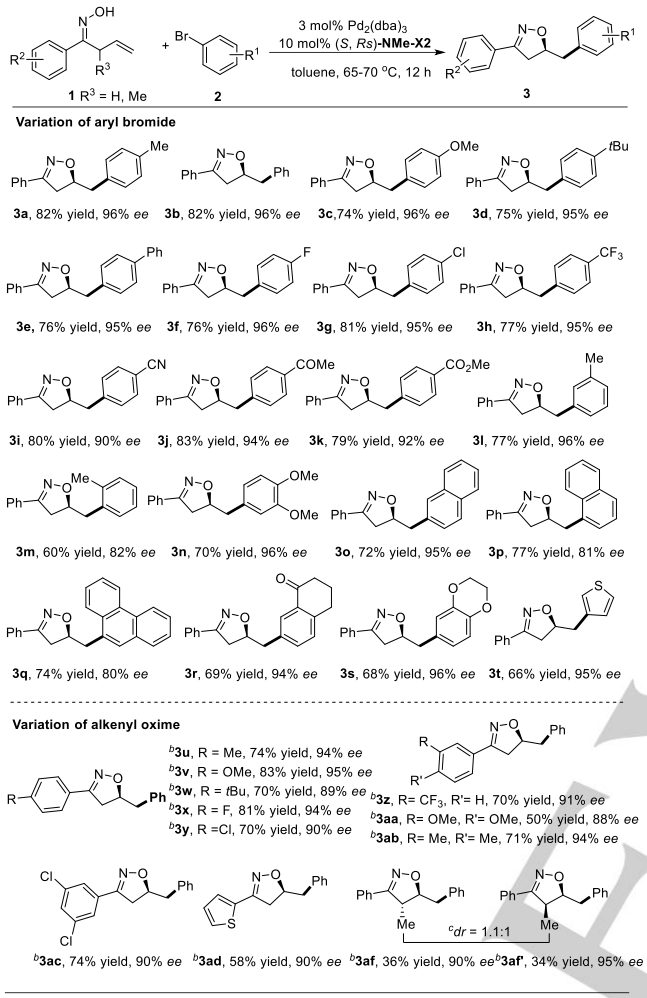
allylpalladium(II) chloride gave **3a** in lower yield.(Table 1, entries 12-15). Further base and solvent screening didn't give better result (Table 1, entries 16-21).



Scheme 2. Substrate scope of aryl bromides. [a] Unless otherwise noted, all reactions were carried out with 0.2 mmol of **1a**, 0.4 mmol of **2**, NaO*t*Bu (1.5 equiv), 3 mol% $Pd_2(dba)_3$ and 10 mol% ligand in 2.0 mL of toluene, 65 °C under Ar for 12 h. [b] 70 °C under Ar for 12 h. [c] The *dr* was determined by NMR analysis.

Enantioselective Synthesis of 3,5-disubstituted Isoxazolines. With the optimal reaction conditions in hand, we then explored the scope of aryl bromides with alkenyl oxime **1a** (Scheme 2). Both electron-donating and electron-withdrawing group at the para-position of aryl bromides are compatible, delivering 3, 5-disubstituted isoxazolines **3a**-**3k** in good yields with 90-96% *ee*. The absolute configuration of **3g** was confirmed by X-ray crystallography. Besides, aryl bromides bearing substitution at *meta*- and *ortho*-substituent(s) were also applicable to give the desired **3l**-**3n** in moderate yields with up to 96% *ee*. Moreover, polycyclic aryl and heteroaryl bromides could be employed to afford **3o-3t** in moderate yields with good enantioselectivity. Inspired by the above results, we then turned to explore the reaction scope via variation of the alkenyl oximes. Various *para*- and *meta*-substituents on the aromatic ring of the oximes were well tolerant, delivering **3u-3z** in 70-83% yields with 89-95% *ee*. A range of the alkenyl oximes, including those disubstituted phenyl ring, naphthyl ring and heteroaryl also reacted smoothly to furnish **3aa**-**3ad** in moderate to good yields with 88-94% *ee*.

Enantioselective Synthesis of 3, 5, 5-trisubstituted Isoxazolines. We next examined the reaction scope of aryl bromides with *gem*-disubstituted alkenes **1** (Scheme 3). Electron-neutral, -donating and -withdrawing substituents were generally compatible, durnishing 3, 5, 5-trisubstituted isoxazolines **4a-4m** bearing α-tertiary stereocenter in 71-97% yields with up to 97% ee. Moreover, a range of heteroaryl bromides, in particular, pyridinyl, thiophenyl, furanyl, indolyl, quinolinyl containing substrates were successful to produce **4q**-**4w** in moderate to good yields with up to 96% *ee*. To demonstrate potential applications, late-stage modification of various natural products, biologically active molecules and pharmaceuticals were conducted. The clofibrate derivative **4x** could be obtained in 77% yield with 96% *ee***.** The late stage modification of racemic 4-bromo-phenylalanine delivered **4y** in 95% yield with 95% ee and a 1.2:1 *dr*. Particularly, Menthol, carbohydrate, derived chiral isoxazolines **4z**-**4aa** were afforded in good yields and moderate to high diastereoselectivities.

Given that greater abundance of aryl chlorides and less price, the development of conditions that allow use of aryl chlorides in this reaction is important. Gratifyingly, various aryl chlorides including electron rich, electron-neutral and electron-poor were also applicable to this transformation, the corresponding isoxazolines were obtained in 40-78% yields with 83−96% *ee* (Scheme 3). Notably, the poorer yield is some cases was caused by the more double bond isomerisation of substrate. Moreover, both 2-chloronaphthalene and 6-chlorinequinoline could be employed to form **4m**, **4ac** and **4ad** in 71−81% yields with 89-91% ee. A range of alkenyl oximes with electron-rich and electron-deficient functional groups at the aryl and heteroaryl were well tolerated, giving **4ag–4al** in 65–95% yields with 92–95% *ee*. In addition, products **4am-4an** could be also obtained with excellent enantioselectivities albeit in relatively lower yields. Moverover, compounds **4ap-4aq** were isolated in excellent yields high enantioselectivities. Notably, an aryl-substituted alkene could also be employed in this reaction to give **4ar** in 87% yield with 62% *ee*, further modification of the ligand is necessary.

Enantioselective Synthesis of Isoxazolines with the Use of Alkenyl Bromides. Olefin groups are one of the simplest and most useful functional transformations in organic synthesis. Inspired by the above good results, expanding this reaction from aryl halides to alkenyl bromides is desirable (Scheme 4). We firstly examined the partners with *β*, *γ*-unsaturated oxime **1a** and 2-bromopropene. To our surprises, the desired product **6a** was afforded in 65% yield and 94% *ee*. Various aromatic ring of the oximes bearing electron-donating and electron-withdrawing groups, such as 4-methoxy, 4-methyl, 4-tert-butyl, 4-fluoro, 4-chloro, 3, 4-dimethyl and 3, 5-dichloro were well tolerated, and the desired alkenyl isozolines **6b-6h** were isolated in moderate to good yields with excellent enantioselectivities (90-96% *ee*). Notably, halogens

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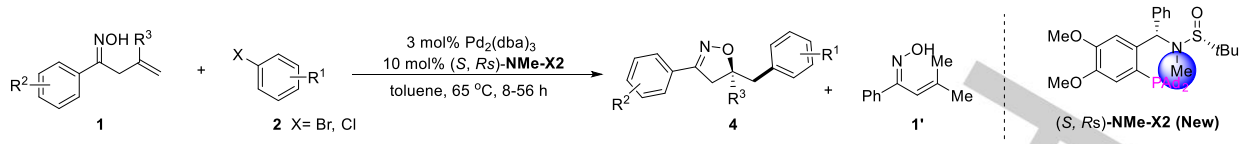
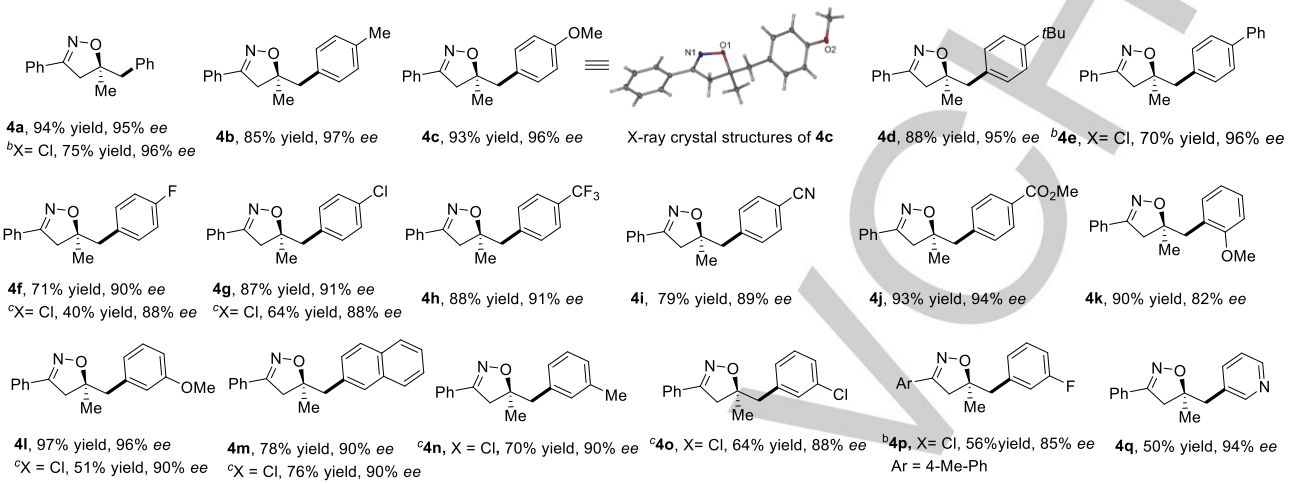




4a, 94% yield, 95% *ee*
[b]X= Cl, 75% yield, 96% *ee*

4b, 85% yield, 97% *ee*

4c, 93% yield, 96% *ee*

X-ray crystal structures of **4c**

4d, 88% yield, 95% *ee*

[b]**4e**, X= Cl, 70% yield, 96% *ee*

4f, 71% yield, 90% *ee*
[c]X= Cl, 40% yield, 88% *ee*

4g, 87% yield, 91% *ee*
[c]X= Cl, 64% yield, 88% *ee*

4h, 88% yield, 91% *ee*

4i, 79% yield, 89% *ee*

4j, 93% yield, 94% *ee*

4k, 90% yield, 82% *ee*

4l, 97% yield, 96% *ee*
[c]X = Cl, 51% yield, 90% *ee*

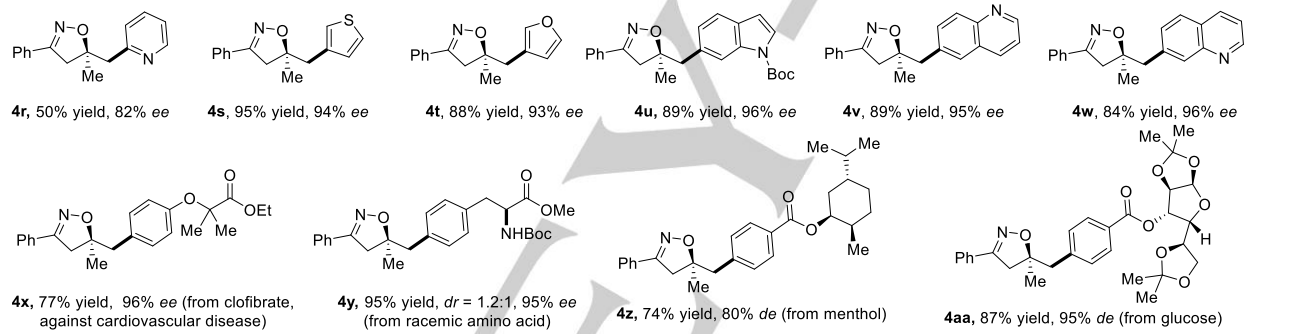
4m, 78% yield, 90% *ee*
[c]X = Cl, 76% yield, 90% *ee*

[c]**4n**, X = Cl, 70% yield, 90% *ee*

[c]**4o**, X= Cl, 64% yield, 88% *ee*

[b]**4p**, X= Cl, 56%yield, 85% *ee*
Ar = 4-Me-Ph

4q, 50% yield, 94% *ee*



4r, 50% yield, 82% *ee*

4s, 95% yield, 94% *ee*

4t, 88% yield, 93% *ee*

4u, 89% yield, 96% *ee*

4v, 89% yield, 95% *ee*

4w, 84% yield, 96% *ee*

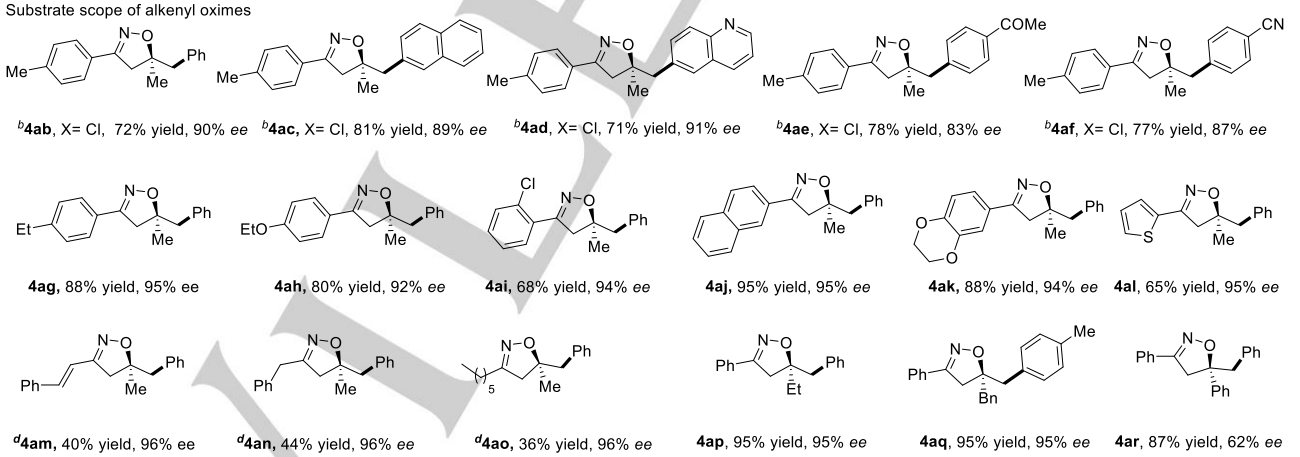
4x, 77% yield, 96% *ee* (from clofibrate, against cardiovascular disease)

4y, 95% yield, *dr* = 1.2:1, 95% *ee* (from racemic amino acid)

4z, 74% yield, 80% *de* (from menthol)

4aa, 87% yield, 95% *de* (from glucose)

Substrate scope of alkenyl oximes



[b]**4ab**, X= Cl, 72% yield, 90% *ee*

[b]**4ac**, X= Cl, 81% yield, 89% *ee*

[b]**4ad**, X= Cl, 71% yield, 91% *ee*

[b]**4ae**, X= Cl, 78% yield, 83% *ee*

[b]**4af**, X= Cl, 77% yield, 87% *ee*

4ag, 88% yield, 95% ee

4ah, 80% yield, 92% *ee*

4ai, 68% yield, 94% *ee*

4aj, 95% yield, 95% *ee*

4ak, 88% yield, 94% *ee*

4al, 65% yield, 95% *ee*

[d]**4am**, 40% yield, 96% ee

[d]**4an**, 44% yield, 96% *ee*

[d]**4ao**, 36% yield, 96% *ee*

4ap, 95% yield, 95% *ee*

4aq, 95% yield, 95% *ee*

4ar, 87% yield, 62% *ee*

Scheme 3. Enantioselective synthesis of 3, 5, 5-trisubstituted isoxazolines. [a] Unless otherwise noted, all reactions were carried out with **1** (0.2 mmol), aryl bromide (0.4 mmol), NaO*t*Bu (1.5 equiv), 3 mol% $Pd_2(dba)_3$ and 10 mol% of ligand in 2.0 mL of toluene, 65 °C, Ar, 8 h. [b] 0.2 mmol of **1**, 0.6 mmol of aryl chloride, NaO*t*Bu (1.5 equiv), 3 mol% $Pd_2(dba)_3$ and 10 mol% ligand in 2.0 mL of toluene, 65 °C, Ar, 56 h. [c] 0.6 mmol of aryl chloride, 80 °C, Ar, 48 h. [d] 5 mol% allylpalladium(II) chloride dimer and 15 mol% of ligand in 2.0 mL of toluene, 70 °C , Ar, 40 h.

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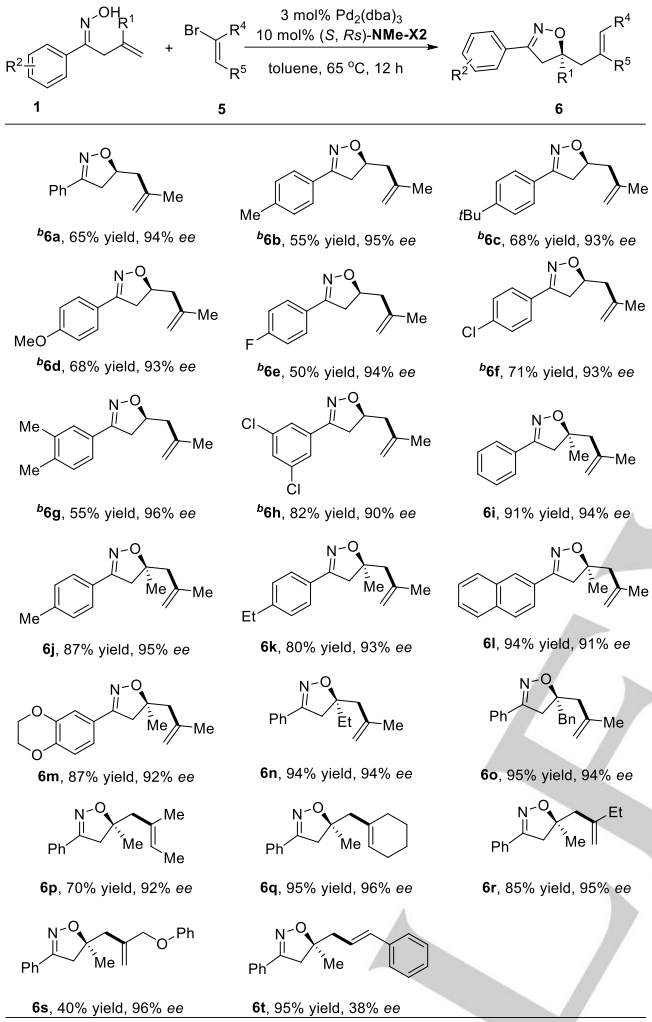
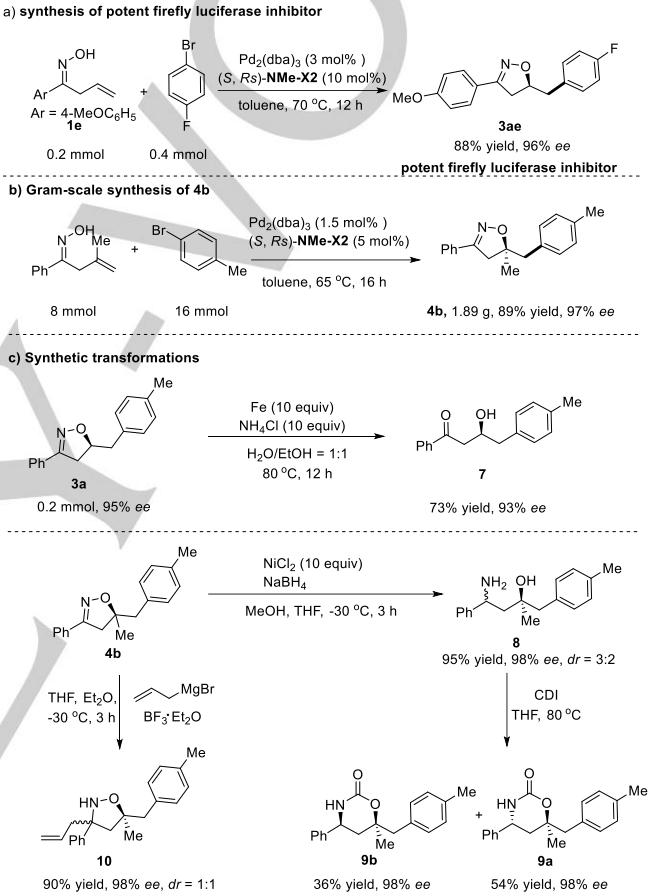
groups provide the handle for further functionalization. Moreover, gem-disubstituted alkenes oximes exhibit excellent activities, the corresponding *α*-tertiary stereocenter isoxazolines **6i-6o** were isolated in 80-95% yields and 91-95% *ee*. A variety of alkenyl bromides such as 2-bromo-2-butene, 1-bromocyclohexene and 2-bromo-1-butene furnished the products **6p-6s** in 40-95% yields with 92-96% *ee*. Notably, product **6t** was furnished in 95% yield with relatively low ee with the use of *β*-bromostyrene.



Scheme 4. Enantioselective synthesis of isoxazolines with alkenyl bromides. [a] Unless otherwise noted, all reactions were carried out with 0.2 mmol of **1**, 0.5 mmol of **5**, NaO*t*Bu (1.5 equiv), 3 mol% $Pd_2(dba)_3$ and 10 mol% ligand in 2.0 mL of toluene, 65 °C under Ar for 12 h. [b] 90 °C under Ar for 12 h.

Gram-scale Synthesis and Synthetic Applications. This Pd/**Xiang-Phos**-catalyzed asymmetric carboetherification could be applied to the enantioselective synthesis of the potent firefly luciferase inhibitor **3ae** and 88% yield with 96% *ee* were obtained (Scheme 5, a). The practicability of our method was demonstrated with the 8 mmol scale of reaction, the 1.89 g of **4b** was isolated in 89% yield without loss of the enantioselectivity (Scheme 5, b). To display the synthetic utility, several transformations of the isoxazolines have been carried out (Scheme 5, c). The enantioenriched isoxazolines can be transformed into the corresponding valuable chiral *β*-hydroxy ketones and 1, 3-aminoalcohols. For example, the simple reduction of **3a** smoothly generated the *β*-hydroxyketone **7** in 73% yield with 93% *ee*. Chiral isoxazole **4b** was selectively transformed to 1, 3-aminoalcohols **8** as a 3: 2 mixture of diastereomers in 95% yield with 98% *ee* by using the $NiCl_2/NaBH_4$ reduction system. The corresponding product **9** by further treatment with CDI, was isolated in 54% and 36% yields without diminishing the enantioselectivity. Furthermore, the addition of allylmagnesium bromide to **4b**, delivered **10** bearing two stereocenters with a 1:1 *dr*.



Scheme 5. Gram-scale synthesis and synthetic applications

Mechanistic Considerations for the Asymmetric Carboetherification. Based on by Wolfe's [13] studies as well as our own observation, the catalytic cycle and asymmetric induction model were proposed (Scheme 6). Oxidative addition of the aryl bromides to a (*S*, *R*s)-**NMe-X2** Pd(0) complex would provide Pd(II) complex **II**. With NaO*t*Bu as the base, ligand exchange between the bromide group and the substrate **1l** takes place to form the Pd complex **III**, which could undergo intramolecular insertion of the alkene into the Pd-O bond to afford Pd complex **IV**. Reductive elimination of complex Pd complex **IV** forms the product **4a** with concomitant regeneration of the Pd(0) catalyst. Remarkably, because of the slow oxidative addition of palladium to aryl chlorides, the side product **1l'** via the isomerization was

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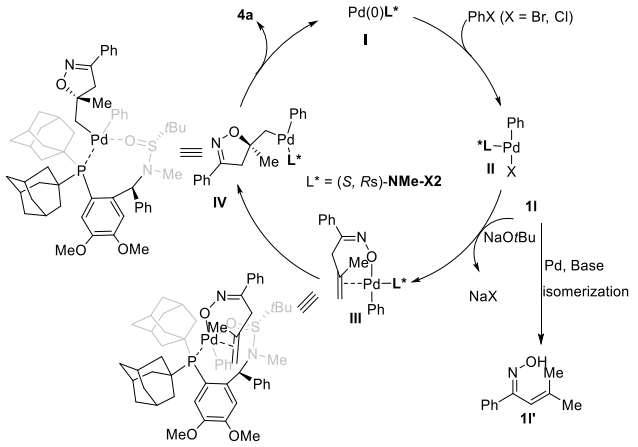
often detected and thus leading the lower yield of the desired carboalkoxylation product.



Scheme 6. Proposed catalytic cycle and asymmetric induction model.

Conclusion

In summary, we have successfully developed a new robust Pd/Xiang-Phos catalytic system for the asymmetric carboetherification of *β*, *γ*-unsaturated ketoximes with aryl halides and alkenyl bromides, which provide a rapid access to a series of chiral isoxazolines. The new chiral monophosphorus ligand (*S*, *R*s)-**NMe-X2** was responsible for the excellent reactivity and enantioselectivity of these transformations. The salient features of this reaction including mild reaction conditions, general substrate scope, well functional group tolerance, good yields and high enantioselectivity, readily available starting materials, easy scale-up and application in late stage modification of bioactive compounds make this method extremely attractive. The obtained products can be readily transformed into useful chiral 1, 3-aminoalcohols.

Acknowledgements

We gratefully acknowledge the funding support of NSFC (21425205, 21672067, 21702063), 973 Program (2015CB856600), the Program of Eastern Scholar at Shanghai Institutions of Higher Learning and the Innovative Research Team of Ministry of Education.

Conflict of interest

The authors declare no conflict of interest.

Keywords: palladium catalyzed • xiang-Phos • alkenyl oximes • carboetherification • chiral isoxazolines

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[14] (*S*, *R*s)-**NMe-X2** (CCDC: 1946327), **3g** (CCDC:1946328) and **4c** (CCDC: 2946329)

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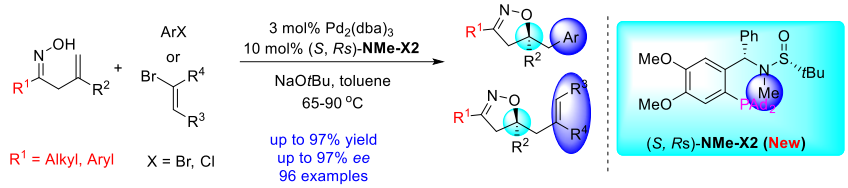

♥ **General substrate scope, mild reaction conditions**

♥ **Good yields and high enantioselectivity**

♥ **Gram-scale synthesis and late-stage modification**

♥ **Quaternary stereocenters**

A new robust Pd/Xiang-Phos catalytic system for the asymmetric carboetherification of *β*, *γ*-unsaturated ketoximes with aryl halides. The sterically bulky and electron-rich ligand (*S*, *R*s)-**NMe-X2** is responsible for the excellent reactivity and enantioselectivity. The salient features of this transformation include mild reaction conditions, general substrate scope, well functional group tolerance, good yields, high enantioselectivity, easy scale-up and application in late stage modification of bioactive compounds.

*Lei Wang, Kenan Zhang, Yuzhuo Wang, Wenbo Li, Mingjie Chen, Junliang Zhang**

Page No. – Page No.

Chiral Isoxazolines Enabled by Palladium/Xiang-Phos–Catalyzed Enantioselective Carboetherification of Alkenyl Oximes