Ligand Design

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Olefin–Oxazolines (OlefOx): Highly Modular, Easily Tunable Ligands for Asymmetric Catalysis**

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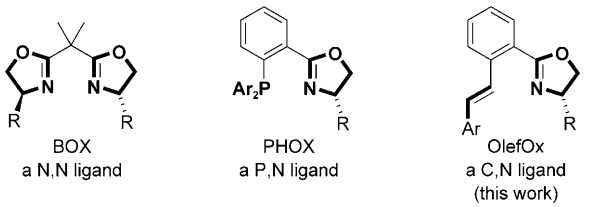
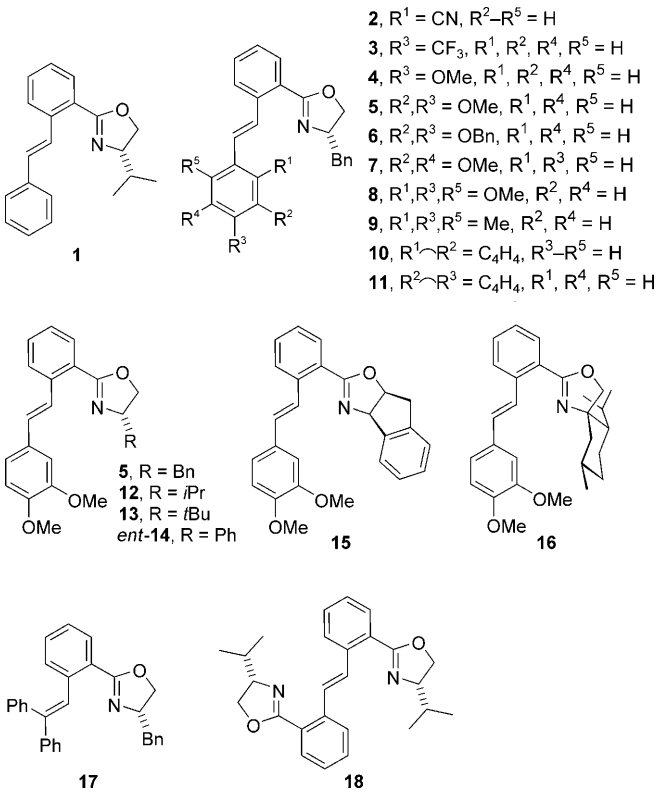
In memory of Keith Fagnou

The oxazoline moiety is a ubiquitous, privileged structural element of chiral ligands.[1] The rigid nature of the five-membered oxazoline ring, the ease of synthesis and the ready availability of many differently substituted derivatives add to their attractiveness. The most well-known oxazoline ligands are bisoxazolines (BOX)[2] and phosphine–oxazolines (PHOX),[3] but many more heterobidentate oxazoline ligands,

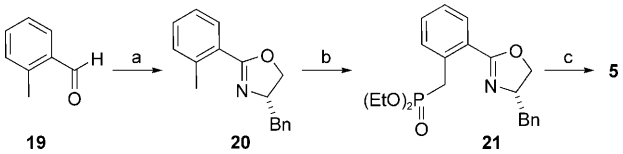


such as phosphinites,[4] phosphites,[5] pyridines,[6] phosphoramidates,[7] phenols,[8] alcohols,[9] sulfoxides,[10] sulfonamides,[11] thioethers,[12] and N-heterocyclic carbenes[13] have been successfully applied in asymmetric catalysis. Despite the structural diversity of these systems, only η^1-binding, single-donor-atom ligands have been combined with the oxazoline fragment. Inspired by the recent success of chiral olefin ligands in asymmetric catalysis,[14] we reasoned that the combination of η^2-binding olefins with oxazolines would allow new coordination geometries and possibilities. We present herein the ready synthesis of modular and easily tunable olefin–oxazoline ligands (OlefOx) and their successful application in asymmetric catalysis. We began with the preparation of a series of electronically and sterically varied olefin–oxazolines (Scheme 1).



Scheme 1. Olefin–oxazoline ligands prepared in this study.

In each case, olefin and oxazoline were attached to a benzene ring (internal ring) in a 1,2-fashion. As an illustrative example, the highly modular three-step synthesis of ligand **5** is discussed (Schemes 2 and 3). Starting from commercially available 2-methyl benzaldehyde, the oxazoline ring was



Scheme 2. Synthesis of olefin–oxazoline ligand **5**.[16] Reagents and conditions: a) (*S*)-phenylalaninol, CH_2Cl_2, room temperature, 16 h; then *N*-bromosuccinimide (NBS), room temperature, 30 min, 75%; b) *t*BuLi, $LiNCy_2$ (Cy = cyclohexyl), $ClPO(OEt)_2$, THF, −78 °C to room temperature, 16 h, 47%; c) KO*t*Bu, toluene, 3,4-dimethoxybenzaldehyde, room temperature, 15 h, 74%.

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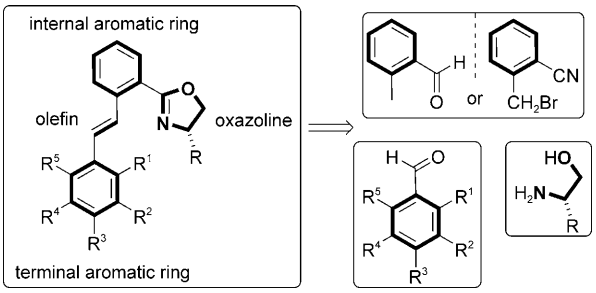
formed by a recently developed, efficient oxidative method.[15] Deprotonation and coupling of the methyl group to the corresponding phosphonate was followed by a Horner–Wadsworth–Emmons reaction with 3,4-dimethoxybenzaldehyde, providing olefin–oxazoline **5** in 26% overall yield. Alternative synthetic routes starting from 2-bromomethylbenzonitrile were also developed (Scheme 3).[16]



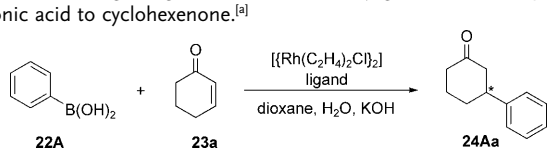
Scheme 3. Modular ligand assembly, retrosynthetic analysis.[16]

As a test reaction for this new family of ligands, we chose the rhodium-catalyzed conjugate addition of phenylboronic acid to cyclohexenone (Table 1).[14]

With the unsubstituted parent system, ligand **1**, the reaction proceeded smoothly and yielded more than 90% of the product with 75% *ee* (Table 1, entry 1). Electron-withdrawing substituents on the terminal benzene ring were detrimental to the yield and the selectivity (Table 1, entries 2, 3). The pronounced influence of *ortho*-substituents is indicated by the change of the stereochemical outcome of the reaction (Table 1, compare entries 1 and 2). An electron-donating *para*-methoxy group on the other hand increased the level of selectivity (Table 1, entry 4). Two alkoxy groups on the terminal benzene ring gave even better *ee* values (Table 1, entries 5–8), with the 3,4-dimethoxy motif derived from veratraldehyde being optimal for stereocontrol. Oxazolines derived from phenylalaninol, valinol, and aminoindanol performed almost equally well (Table 1, entries 5, 13, 16), but *tert*-leucinol- or phenylglycinol-derived ligands showed significantly lower *ee* values (Table 1, entries 14, 15).

Using 1 mol% active catalyst derived from the most selective ligand, phenylalaninol derived **5**, product **24Aa** was obtained in 93% *ee* and, using only 0.1 mol% of catalyst, 90% *ee* was still obtained (Table 1, entries 5, 6). Ligand **16**, containing a sterically more demanding oxazoline derived from (−)-menthone[17] does not give any product (Table 1, entry 17). Ligands with a doubly *ortho*-substituted terminal benzene ring (**8**, **9**), with a triphenylethylene backbone (**17**), or the potentially tridentate ligand **18** did also not provide catalytically active complexes (Table 1, entries 9, 10, 18, 19). The latter observation is in accordance with the generally accepted mechanism of the rhodium-catalyzed conjugate addition,[14] in which two of the four available coordination sites of the metal are needed for complexation of the enone and the aryl nucleophile. This large series of olefin–oxazolines with its marked reactivity and selectivity differences demonstrates the modularity, tunability, and adaptability of this new ligand class.

Table 1: Screening of ligands **1**–**18** in the conjugate addition of phenylboronic acid to cyclohexenone.[a]



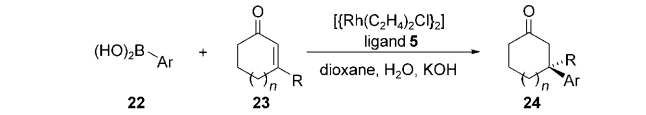
22A **23a** **24Aa**

Entry	Ligand	Yield[b] [%]	*ee*[c] [%]
1[d,e]	**1**	91	75 (*S*)
2[d,e]	**2**	60	51 (*R*)
3	**3**	50	69 (*S*)
4	**4**	78	81 (*S*)
5	**5**	88	93 (*S*)
6[f]	**5**	88	90 (*S*)
7[g]	**6**	92	80 (*S*)
8	**7**	97	85 (*S*)
9	**8**	0	–
10	**9**	0	–
11	**10**	83	50 (*S*)
12	**11**	86	86 (*S*)
13	**12**	97	89 (*S*)
14	**13**	74	30 (*S*)
15	**14**	91	64 (*R*)
16	**15**	93	85 (*R*)
17	**16**	0	–
18	**17**	0	–
19	**18**	0	–

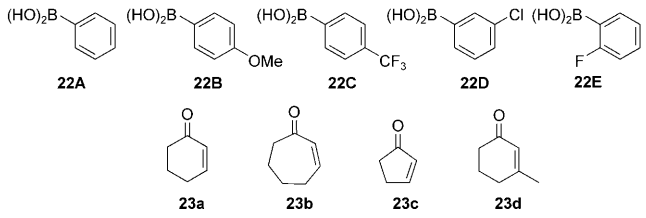
[a] General procedure: 0.005 mmol $[\{Rh(C_2H_4)_2Cl\}_2]$ and 0.011 mmol ligand were stirred at 40°C with 1.5 mmol $PhB(OH)_2$, 1 mmol cyclohexenone, and 0.3 mmol KOH in dioxane/H_2O 10:1 until GC-MS showed the absence of starting material. [b] Yield of isolated product. [c] Determined by HPLC on chiral stationary phases. [d] 5 mol% $[\{Rh(C_2H_4)_2Cl\}_2]$ and 11 mol% ligand were used. [e] Reaction run on 0.3 mmol scale. [f] Reaction run with 0.1 mol% catalyst at 60°C. [g] Reaction run at 60°C.

Especially interesting is the unprecedented coordination mode of this new ligand class. The ^1H NMR spectrum of a Rh complex of ligand **5** and $[Rh(C_2H_4)_2Cl]$ revealed a strong coordination between olefin and rhodium, as shown by the upfield shifts of the olefinic protons from $\delta = 8.85$ ppm and 7.11 ppm ($J = 16$ Hz) in the free ligand to $\delta = 5.49$ and 4.49 ppm ($J = 12$ Hz) in the complex. Furthermore, the olefin–rhodium interaction was unequivocally demonstrated by single-crystal X-ray analysis of crystals obtained by slow diffusion of pentane into a dioxane solution of a complex derived from ligand **12** and $[Rh(C_2H_4)_2(acac)]$ (Figure 1; acac = acetylacetone).[19] In this complex, ligand **12** and acac were both found to act as bidentate, chelating ligands to give a pseudo-square-planar coordinated Rh^I center. The Rh–C bond lengths (2.088 Å and 2.097 Å) are typical for olefin

Table 2: Substrate scope of olefin–oxazoline ligand **5** in the conjugate addition reaction.[a]



22 23 24



22A 22B 22C 22D 22E

23a 23b 23c 23d

Entry	Boronic acid	Enone	Product	Yield[b] [%]	*ee*[c] [%]
1	**22A**	**23a**	**24Aa**	90	93 (*S*)
2[d]	**22B**	**23a**	**24Ba**	75	77 (*S*)
3	**22C**	**23a**	**24Ca**	89	90
4	**22D**	**23a**	**24Da**	88	89
5	**22E**	**23a**	**24Ea**	65	85
6	**22A**	**23b**	**24Ab**	85	85 (*S*)
7	**22A**	**23c**	**24Ac**	81	97 (*S*)
8	**22B**	**23c**	**24Bc**	79	85
9	**22C**	**23c**	**24Cc**	81	97
10	**22D**	**23c**	**24Dc**	83	97
11[e]	**22A**	**23d**	**24Ad**	36	85 (*S*)

[a] General procedure: see Table 1. [b] Yield of isolated product. [c] Determined by HPLC or GC on chiral stationary phases. The absolute configuration of the products was unambiguously determined only in the indicated cases. [d] Reaction performed in 1,2-dimethoxyethane. [d] 0.05 mmol $[\{Rh(C_2H_4)_2Cl\}_2]$ and 0.11 mmol ligand were used.

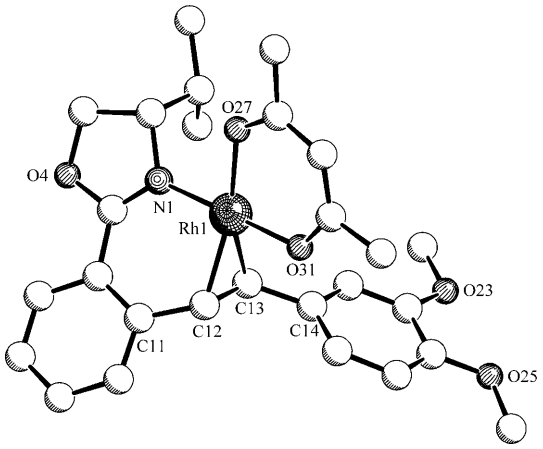


Figure 1. Crystal structure of the complex derived from **12** and $[Rh(C_2H_4)_2(acac)]$. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]: Rh1–N1 2.015(3), Rh1–O27 2.049(2), Rh1–O31 2.015(2), Rh1–C12 2.088(4), Rh1–C13 2.097(3), C11–C12 1.482(5), C12–C13 1.414(5), C13–C14 1.483(5); N1-Rh1-O27 88.2(1), N1-Rh1-O31 177.4(1), N1-Rh1-C12 90.6(1), N1-Rh1-C13 91.1(1), O27-Rh1-O31 90.6(1), O27-Rh1-C12 162.6(1), O27-Rh1-C13 157.9(1), O31-Rh1-C12 89.8(1), O31-Rh1-C13 90.9(1), C12-Rh1-C13 39.5(1), C11-C12-C13 120.6(3), C12-C13-C14 124.3(3).

complexes and the distance between the two olefinic carbon atoms (1.414 Å) is about 7% longer than in related uncomplexed olefins.[20]

Remarkably, although either one of the two diastereotopic olefin π-faces could bind to the rhodium center, only one coordination mode was observed. In the complex, the oxazoline and the internal benzene ring are almost in the same plane, whereas the coordinating olefin unit is rotated out of this plane pointing in the same direction as the *i*Pr substituent on the oxazoline ring (Figure 1).

In conclusion, we have introduced the new class of olefin–oxazoline ligands into asymmetric catalysis and demonstrated both modularity and versatility. In contrast to many other classes of chiral ligands, the ability to easily vary the steric and electronic properties of the olefin component over a wide range is especially appealing. Expanding the scope and synthesis of ligands with tailor-made electronic properties for distinct reaction are currently under investigation.

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[19] X-ray data of the complex derived from **12** and [Rh(C_2H_4)$_2$-(acac)]: $C_{27}H_{32}NO_5Rh$, $M_r = 553.45$, red crystal $0.30 \times 0.15 \times 0.03$ mm, $a = 8.4910(1)$, $b = 13.2944(2)$, $c = 22.3959(4)$ Å, $V = 2528.11(7)$ Å^3, $\rho_{calcd} = 1.454$ g cm^{-3}, $\mu = 0.712$ mm^{-1}, $Z = 4$, orthorhombisch, space group $P2_12_12_1$ (No. 19), $\lambda = 0.71073$ Å, $T = 223(2)$ K, ω and ϕ scans, 20704 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.66$ Å^{-1}, 5989 independent ($R_{int} = 0.060$) and 4735 observed reflections [$I \geq 2\sigma(I)$], 313 refined parameters, $R = 0.038$, $wR^2 = 0.082$. CCDC 748087 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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