Chiral Catalysts

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Integrating the Schrock and Grubbs Catalysts: Ruthenium–Binaphtholate Catalysts for Olefin Metathesis**

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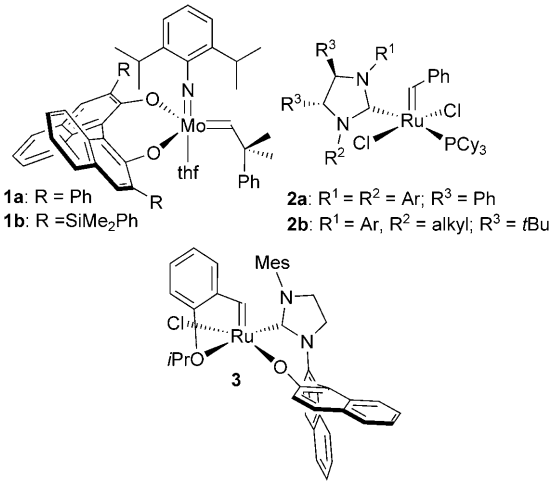
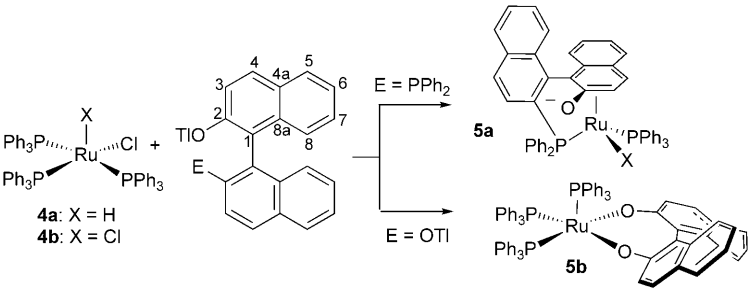
Asymmetric metathesis offers powerful opportunities for the synthesis of chiral molecules and tactic polymers.[1–3] A key series of papers by Hoveyda and Schrock showcases the fine-tuning of selectivity attainable by incorporating 1,1′-binaphthyl-2,2′-diolate (bino) and biphenolate-derived ligands within the Schrock family of Mo catalysts (**1**; Scheme 1).[4–8] Among the more readily handled ruthenium catalysts, in comparison, major advances have highlighted desymmetrization of the NHC ligand (NHC = N-heterocyclic carbene; see **2**).[9–12] A rare[13] example of an atropisomeric ligand in both the Ru systems is Hoveyda's κ^2-*C*,*O*-chelate **3**.[14] Despite the high selectivities attained in the Mo chemistry, and the ease of ligand tuning by 3,3′-functionalization of the naphthyl rings,[15] incorporation of simple bino ligands within the Grubbs class catalysts has not yet been reported. This absence is particularly notable given the commercial availability of the Ru precursors and the ligands. Herein we describe the first, facile, entry point into such systems.



Scheme 1. Representative chiral catalysts for olefin metathesis. Cy = cyclohexyl, thf = tetrahydrofuran, Mes = mesityl.

At the outset of this work, we expected that the desired [Ru(κ^2-*O*,*O*-bino)] targets would be unstable with respect to isomerization to form π-bound piano-stool structures.[16] Instances of such behavior in Ru chemistry go back thirty years.[17] The ease of isomerization is due to the donor properties of the aryl ring, in conjunction with the accessibility of three metal coordination sites (by, for example, loss of one labile ligand from a five-coordinate complex).[18] As isomerization in ruthenium–benzylidene complexes can be obscured by competing α elimination,[19] five-coordinate **4** is useful as a simple model system that yields well-defined σ- or π-OAr products (Scheme 2). Thus, reaction of **4** with phenoxide affords the piano-stool product [RuX(η^5-C_6H_5O)(PPh_3)$_2$],[18] but σ-OAr products are accessible on use of electron-deficient aryloxides,[20] or aryloxides incorporated into a rigid (e.g., five-membered) chelate ring.[21] This behavior proved an accurate predictor for the accessibility of [Ru]=CHR complexes containing electron-deficient perhaloaryloxides[19] and catecholates;[22,23] six-membered chelates are also accessible.[23–25] With more flexible, seven-membered chelate rings, π coordination of one aryl ring is expected, based on the reaction of **4a** with the heterobifunctional phosphine-phenoxide proligand M(binop) (binop = 2-diphenylphosphanyl-1,1′-binapthyl-2′-olate; Scheme 2, top).[20]



Scheme 2. Established coordination modes for ruthenium–binop complexes, and proposed coordination modes for ruthenium–bino complexes.

We were therefore surprised to discover that reaction of **4b** with Tl_2(bino) affords **5b** (Scheme 2, bottom), in which the aromatic locations of the ^{1}H NMR signals imply σ coordination. Spurred by this unexpected finding, we undertook reaction of Tl_2(bino) with the "third-generation" Grubbs complexes **6a**/**b**, in which the reduced steric demand of the

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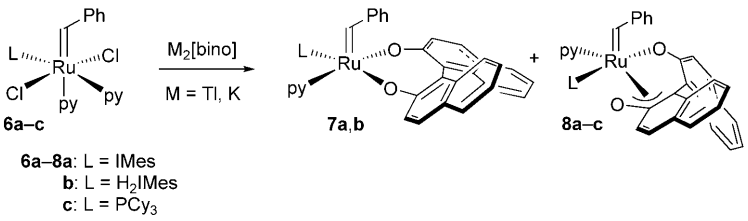
pyridine ligands helps to inhibit the α-elimination pathways noted above[19] (Scheme 3). Successful κ^2-*O*,*O* coordination of the bino ligand was inferred from NMR-scale experiments,



6a–8a: L = IMes
b: L = H_2IMes
c: L = PCy_3

Scheme 3. Synthesis of ruthenium–binaphtholate metathesis catalysts. IMes = *N*,*N*′-bis(mesityl)imidazol-2-ylidene, py = pyridine.

which revealed a new alkylidene singlet for **7a** or **7b**, and new $^{13}C\{^1H\}$ NMR signals for the bino ligand in regions characteristic of the σ-bound ligand (e.g. C2′, $\delta = 170.1$ ppm; C2, $\delta = 164.0$ ppm). Charge-transfer (CT) MALDI-TOF MS[26] revealed well-defined isotope patterns for $[M-py]^{+\bullet}$ as the highest-mass peak, consistent with replacement of both chloride atoms by bino.[27] The structures depicted were subsequently confirmed by X-ray diffraction (Figure 1): compounds **7a** and **7b** crystallize in the same space group and exhibit a very similar unit cell, but differ in the C–C and N–C bond lengths within the heterocyclic ring.[28]

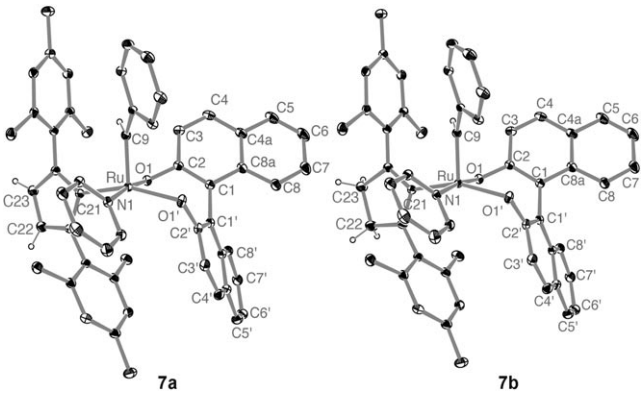


Figure 1. ORTEP diagrams of **7a** and **7b**. Nonhydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Hydrogen atoms on C22, C23, and C9 are shown with arbitrarily small thermal parameters; other hydrogen atoms are not shown.

An accompanying, minor coproduct is **8a/b** (ca. 10%), for which we propose an η^3-enolate coordination mode, by analogy to the structure of the PCy_3 complex **8c** described below. More problematic for synthetic purposes is the extensive decomposition (probably of **6a/b**) revealed by decreases in the total integrated intensity of the benzylidene signals, relative to internal standard. We thus explored a range of optimization strategies with **6a** (Table 1). Use of CH_2Cl_2 (entry 2), THF, (entry 3) or aromatic solvents (entry 4), or shorter reaction times at slightly elevated temperatures (entries 5 and 6), effected minimal improvement. A breakthrough, however, was achieved by use of pyridine as the reaction medium (entry 7). This switch inhibits pyridine dissociation, retards decomposition, and proves the key to high conversions (ca. 85% conversion to the desired **7a** over 20 h at 25 °C; entry 10). Importantly, we were then able to replace the toxic[29] thallium salt with potassium, a switch that fails in aromatic solvents (compare entries 8 and 9 vs. entries 10 and 11). Preparative-scale reactions afforded green **7a** in 72% yield after purification, some losses being incurred by its partial solubility in hexanes. The H_2IMes analogue **7b** was obtained in 85% yield. Comparable yields are attained with greater convenience by one-pot ligand exchange of

Table 1: Optimizing the synthesis of **7a**.

Entry	Solvent	M	*t* [h]	*T* [°C]	Conv. [%][a]	Yield of **7a** [%][a]	Yield of **8a** [%][a]	Decomp. [%][a,b]
1	$CDCl_3$	Tl	5	RT	91	49	11	30
2	CH_2Cl_2	Tl	5	RT	85	53	12	20
3	THF	Tl	5	RT	70	35	7	28
4	benzene	Tl	5	RT	54	30	8	16
5	benzene	Tl	3	40	77	50	13	14
6	toluene	Tl	3	40	77	56	5	16
7	pyridine	Tl	3	40	>99	73	18	9
8	benzene	Tl	20	RT	>99	53	16	31
9	benzene	K	20	RT	91	37	14	40
10	pyridine	Tl	20	RT	>99	87	6	7
11	pyridine	K	20	RT	>99	83	8	9

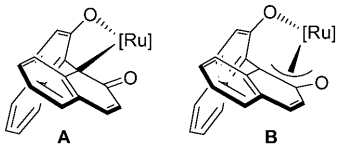
[a] Conversions, in situ yields, and decomposition assessed by ^1H NMR analysis, by integration of the benzylidene protons against the internal standard (1,3,5-trimethoxybenzene).[27] [b] Refers to the formation of unwanted non-alkylidene by-products.

$[RuCl_2(NHC)(PCy_3)(=CHPh)]$ with pyridine (5 min, RT), followed by salt metathesis.

In parallel experiments, we sought access to the corresponding PCy_3 complex **7c**, which would expand the capacity for steric and electronic tuning. Reaction of **6c** with K_2(bino) in pyridine is much faster than reaction of **6a/b**. After 2 hours at room temperature, ^1H NMR analysis indicates complete loss of **6c**. New benzylidene doublets ($\delta = 17.45$ ppm, $J = 4$ Hz; $\delta = 20.14$ ppm, $J = 11$ Hz; $CDCl_3$), the ratio of which depends on the extent of drying, are assigned to **8c** and pyridine-bound **9**, respectively (for identification of **9**, vide infra). After workup, solely **8c** is present; 90% yield after purification. We identify **8c** as an η^3-enolate on the basis of detailed NMR analysis, supplemented by CT-MALDI MS (which reveals a clean isotope pattern for $[M-py]^{+\bullet}$ as the highest-mass peak) and elemental analysis. Circular dichroism spectra of (*R*)-**8c** (as well as (*R*)-**7a**, (*R*)-**7b**) show no evidence of racemization over time.[27]

Unorthodox binding modes are well established in late-transition-metal complexes of bino derivatives,[30,31] as well as binap (2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl)[32,33] and mop (2-diphenylphosphanyl-2′-methoxy-1,1′-binaphthyl).[32–34] That **8c** is not a simple κ^2-*O*,*O*-bino complex is indicated by

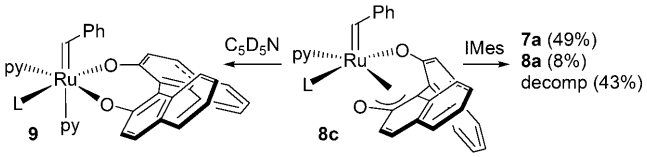
the upfield shift of the C1 signal (CD_2Cl_2: ca. $\delta = 96$ ppm, cf. $\delta = 124$ ppm in **7a**; bino numbering given in Scheme 2), which suggests a Ru–C1 interaction. More telling is the location of the C2 signal (ca. $\delta = 154$ ppm, cf. $\delta = 164$ ppm in **7a**). Significant double-bond character in the C–O bond (see **A**, Scheme 4) would effect a dramatic downfield shift for C2,



Scheme 4. Representative bino bonding modes (other than κ^2-*O*,*O* coordination) considered for **8**. Of C1 and C1′, the former is designated as interacting with the metal center

to nearly $\delta = 200$ ppm.[33,35] Rather, we identify **8** as an example of the class **B** η^1,η^3-enolate very recently reported by Li and co-workers for [Ru(bino)(*p*-cymene)],[31] for which C1 and C2 appear at ca. $\delta = 85$ and 142 ppm, respectively. Consistent with assignment of **8c** as a skewed type-**B** system is the doublet multiplicity of the C1 and C2 signals ($^2J_{CP} = 11$ and 3 Hz, respectively; cf. their single multiplicity in **9**, as discussed below): these collapse to singlets on decoupling on ^{31}P as well as ^1H.

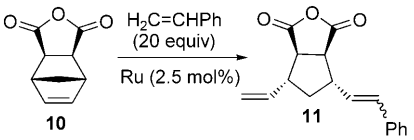
The Li report highlighted the dynamic nature of the η^1,η^3-binding mode, and its capacity to interconvert with the conventional *O*,*O*-bound structure at room temperature. Complex **8c**, in comparison, does not spontaneously equilibrate with its κ^2-*O*,*O* isomer **9** (Scheme 5, left) over 5 hours in



Scheme 5. Dynamic behavior of **8c**. L = PCy_3.

CD_2Cl_2, but signals for **9** emerge upon addition of even 1% v/v pyridine, indicating that the coordination mode of the bino ligand in **8c** is sensitive to the steric pressure exerted by the other ligands present. The alkylidene proton in **9** gives rise to a doublet at $\delta = 20.16$ ppm ($^3J = 11.4$ Hz), confirming that this is the second species observed during synthesis of **8c** (see above). At 10% v/v pyridine, the ratio of **8c** to **9** is 1:3. In [D_5]pyridine, solely **9** is present. Loss of the direct Ru···[C1=C2] interaction is confirmed by the singlet multiplicity of the NMR signals for C1 and C2, which appear significantly downfield (C1: $\delta = 127.3$ ppm; C2: $\delta = 167.9$ ppm) from their values in **8c**. Loss of one pyridine ligand and isomerization to the η^1,η^3-bino structure occurs during workup. Attempts to isolate **9** by precipitation from pyridine/hexanes (1:5) afforded **8c**, with only about 10% **9** present. Finally, addition of IMes to **8c** in benzene effected transformation into κ^2-*O*,*O* product **7a**, accompanied by minor amounts of enolate **8a** and decomposition (Scheme 5, right), just as in our unoptimized synthesis of **7a** (Table 1).

Preliminary studies of the performance of the bino catalysts in ring-opening-metathesis/cross-metathesis (ROM/CM) reactions (Scheme 6) indicated an order of activity **7b** > **7a** > **8c**. In all cases, however, enantioselectivities are low, indicating the need for functionalization at these positions of the binaphthol ring. It may be noted that rather bulky substituents at the 3,3′-positions are required for high enantioselectivities in the Schrock–Hoveyda catalysts.[2–8]



Cat.	Conv. [%]	Yield of **11** [%]	*ee* [%] (*E*/*Z*)
7a	72	38	5 (1.3:1)
7b	quant	78	2 (1:1)
8c	33	9	9 (3.4:1)

Scheme 6. ROM/CM of **10** with styrene (10 mM **10**, THF, 50°C, 2 h).

In conclusion, reaction of K_2(bino) with the third-generation Grubbs catalysts enables, for the first time, direct incorporation of the important binaphtholate ligand within the Ru family of olefin-metathesis catalysts. As well as κ^2-*O*,*O*-bino derivatives, a η^1,η^3-bino form is accessible, a variant on the originally-expected π-OAr motif. Importantly, exchange between the two indicates that the latter does not represent a deactivation product in this chemistry. Rather, it may represent a resting state for low-coordinate species. Exploration of this hypothesis, and of more extensively functionalized ligands, is under way, and will be reported in due course.

Experimental Section

Synthesis of **7a**, **7b**, and **8c**:[27] Racemic and (*R*)-(+)-bino derivatives were prepared similarly (99% (*R*)-(+)-binol). Pyridine (1.5 mL) was added to [$RuCl_2$(IMes)(PCy_3)(=CHPh)] (194 mg, 0.268 mmol) under N_2, causing an immediate color change from pink to green. Solid K_2(bino) (107 mg, 0.292) was added, then a further 1 mL of pyridine. After stirring at 25°C (17 h: **7a**, **7b**; 2 h: **8c**) the solvent was removed under vacuum, and trace pyridine was removed azeotropically with toluene (3 mL). The residue was redissolved in THF (2 mL), filtered (Celite), washed through (2 × 2 mL THF; 2 mL CH_2Cl_2) then concentrated, precipitated (hexanes), washed (hexanes, Et_2O) and reprecipitated (**7a**, **7b**: CH_2Cl_2/hexanes (1:6); **8c**: THF/hexanes (1:4). Yield of **7a**: 142 mg, 72%. Key NMR chemical shifts: ^1H NMR (CD_2Cl_2): $\delta = 19.18$ ppm (s, R=C*H*Ph, 1H); ^{13}C NMR (CD_2Cl_2): $\delta =$ 306.0 (C9), 170.1 (C2′), 164.0 (C2), 124.2 (C1), 123.86 ppm (C1′); CT-MALDI MS (pyrene matrix) calcd for *m*/*z*: ([*M*−py]$^+$): 780.2; found: 780.0; elemental analysis calcd for $C_{53}H_{47}N_3O_2Ru$: C, 74.10; H, 5.51; N, 4.89; found: C, 74.32; H, 5.66; N, 5.16.

7b: Yield 85%. Key NMR chemical shifts: ^1H NMR (CD_2Cl_2): $\delta = 18.93$ ppm (s, Ru=C*H*Ph, 1H); ^{13}C NMR (CD_2Cl_2): $\delta = 307.1$ (C9), 170.3 (C2), 164.0 (C2′), 123.94 (C1 or C1′), 123.87 ppm (C1 or C1′); CT-MALDI MS (pyrene) calcd for *m*/*z*: ([*M*−py]$^+$): 782.2;

found: 782.2; elemental analysis calcd for $C_{53}H_{49}N_3O_2Ru{\cdot}CH_2Cl_2$: C, 68.56; H, 5.43; N, 4.44; found: C, 68.95; H, 5.39; N, 4.52.

8c: Yield 92%. Key NMR chemical shifts: ^{1}H NMR (CD_2Cl_2): $\delta = 17.55$ ppm (d, $^3J_{HP} = 4.5$ Hz, Ru=C*H*Ph, 1H); ^{13}C NMR (CD_2Cl_2): $\delta = 302.1$ (s, C9), 174.1 (d, C2′, $^3J_{CP} = 5$ Hz), 154.1 (d, C2, $^2J_{CP} = 2.6$ Hz), 116.8 (C1′), 95.6 ppm (d, C1, $^2J_{CP} = 11$ Hz); ^{31}P{^{1}H} NMR (CD_2Cl_2): $\delta = 46.8$ (s, Ru*P*Cy$_3$); CT-MALDI MS (pyrene) calcd for m/z: ([M−py]$^+$): 756.3; found: 756.4; elemental analysis calcd for $C_{50}H_{56}NO_2PRu$: C, 71.92; H, 6.76; N, 1.68; found: C, 71.65; H, 6.59; N, 2.10.

Representative procedure for ROM/CM: Compound **7b** (100 μL, 0.60 mg, 7.0×10^{-4} mmol, obtained from a stock THF solution) was added to a stirred mixture of **10** (4.6 mg, 0.028 mmol) and styrene (58 mg, 0.56 mmol) in THF (300 μL) under N_2. The reaction mixture was heated at 50°C for 2 h, then cooled, quenched with KTp (Tp = hydrotris(pyrazolyl)borate),[36] and analyzed by calibrated GC-FID.

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[27] For details, including full spectra, see the Supporting Information.
[28] CCDC 755131 (**7a**) and 755132 (**7b**) contain 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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