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Asymmetric Transfer Hydrogenation of 1-Naphthyl Ketones by an *ansa*-Ru(II) Complex of a DPEN-$SO_2N(Me)$-$(CH_2)_2(\eta^6$-*p*-Tol) Combined Ligand

Andrea Kišić, Michel Stephan,*,† and Barbara Mohar*

National Institute of Chemistry, Hajdrihova 19, SI-1000 Ljubljana, Slovenia

barbara.mohar@ki.si; mstephan@phosphoenix.com

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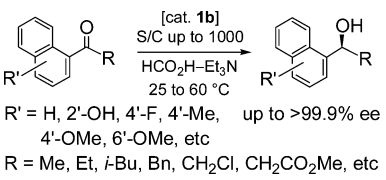
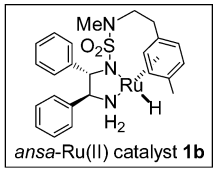
ABSTRACT





The first second-generation designer Ru(II) catalyst 1b featuring an enantiopure *N,C*-(*N*-ethylene-*N*-methyl-sulfamoyl)-tethered (DPEN-κ^2N,N')/η^6-toluene hybrid ligand is introduced. Using an S/C = 1000 in HCO_2H-Et_3N 5:2 transfer hydrogenation medium, secondary 1-naphthyl alcohols are obtained in up to >99.9% ee under mild conditions. Mechanistic factors are discussed.

Operational simplicity and safety aspects of asymmetric transfer hydrogenation (ATH) promoted by Ru(II), Rh(III), or Ir(III) complexes of chiral N-based ligands favor this cost-effective and viable alternative for the production of enantiopure bioactive ingredients or their components.[1] Noyori, Ikariya and co-workers' well-defined chiral [RuCl(TsDPEN)(η^6-arene)] complexes (in the complex, TsDPEN = 2-(*N*-tosylamido)-1,2-diphenylethylamine) have indelibly marked this technology on both the fundamental and applied levels.[1,2] With (*S,S*)- and (*R,R*)-1,2-diphenylethylenediamine (DPEN) equally commercially available, enantioenriched secondary alcohols are accessed via ketone reduction under mild conditions in the HCO_2H-Et_3N binary mixture as the H-donor source.[3]

Following novel design concepts coupled with judicious refinements of the derived original bifunctional catalyst prototype,[2] boosted catalytic systems in terms of both activity and enantioselectivity were discovered (Figure 1). The latest significant innovation was by Wills et al. who introduced *ansa*-type Ru(II) complexes wherein the enantiopure diamine-based ligands and the η^6-arene unit are either *N,C*-ethylenesulfonyl- or *N1,C*-propylene-tethered.[4] Compared to the latter design, the former was also diversified but displayed inferior results.[4f] By analogy, Ikariya et al. prepared the Ts-DENEB variant which possesses an

† Present address: PhosPhoenix SARL, 115, rue de l'Abbe Groult, 75015 Paris, France.

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"oxygen atom-doped" *N1*,*C*-3-oxabutylene-tether.[5] The presented advantage of the intracovalently tethered units (*ansa*-bridge) is a prolonged life span of the active catalytic species due to the persistent imposed coordination of the otherwise labile η^6-arene, benefiting from the strong chelation of the sulfonamido-amine anchor. This results in a reinforced collective three-point ligation of the conjugate ligand to the Ru core thereby decreasing the overall structure flexibility and rigidifies the stereoarray of the catalyst.

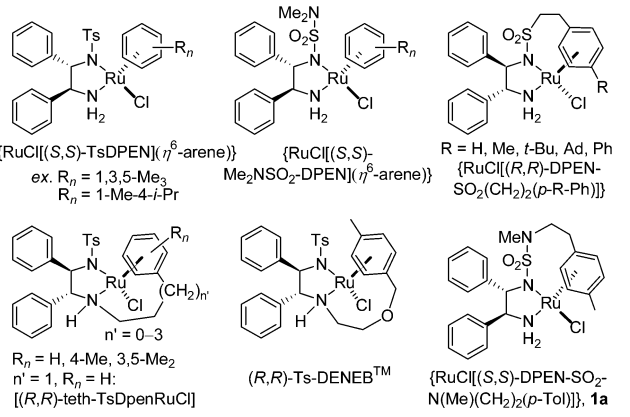

Figure 1. ATH Ru(II)-based precatalysts.

The highlight of our participation in the ATH research area was the introduction of {RuCl[*N*-(*N*,*N*-dialkylsulfamoyl)-DPEN](η^6-arene)}-type complexes, wherein *N*,*N*-dialkylsulfamoyl = Me_2NSO_2 or $(CH_2)_5NSO_2$, and the extension of the substrate scope to fluoroalkyl ketones.[6] Herein we present a *N*,*C*-(*N*-ethylene-*N*-methyl-sulfamoyl)-tethered (DPEN-κ^2N,N')/η^6-toluene version (*ansa*-Ru(II) complex **1a**), with functionalities mimicking those of original Ru(II) complexes, and its application in the ATH of the notoriously challenging 1-naphthyl ketones. Notably, (*S*)-1-(1-naphthyl)ethanol prepared via biocatalysis served as s pharma-intermediate for an HMG-CoA reductase inhibitor.[7] Hence, the corresponding enantiopure alcohols constitute potential key chiral building blocks.[8]

The active *ansa*-Ru(II) complex **1b** incorporating the new hybrid preligand **5** was readily prepared relying upon a concise strategy outlined in Scheme 1. The latter conjugate was assembled by SO_2-pairing the enantiopure (*S*,*S*)-DPEN and the Birch-reduced *N*-[2-(4-methyl-cyclohexa-1,4-dienyl)ethyl]methylamine (**2**) via an iterative stepwise activation-S_N2 displacement by the incoming amine starting from *N*,*N*′-sulfuryl-bis(2-methylimidazole).[9] Use of the 2-methyl-substituted imidazolo group was crucial as DPEN failed to react with the MeOTf-activated unsubstituted counterpart already appended to **2**. The shelf-stable μ-chlorido Ru(II) dimer **6** was prepared from the **5**·HCl salt and $RuCl_3 \cdot 3H_2O$.[10] Finally, upon admixing **6** with the transfer hydrogenation HCO_2H-Et_3N 5:2 medium, the active *ansa*-Ru(II) hydride catalyst **1b** was generated *in situ* via the presumed mononuclear precatalyst **1a**.[11] The single-pot multistep access to **1b** from precursor **6** is convenient and economical.

Upon probing Ru(II) complex **1b** in ATH, it was found to catalyze with a remarkably high rate the reduction of 1′-acetonaphthone (**S1**) in neat HCO_2H-Et_3N 5:2 azeotrope, inducing an excellent ee (Table 1). In fact, with an S/C = 1000, a full conversion and >99.9% ee ((*S*)-enantiomer formed) were reached within 20 h at 40 °C. At 60 °C, a high ee (99.1%) was maintained with a 3-fold rate enhancement (6 h). Further supplementation by fresh full portions of 1′-acetonaphthone and HCO_2H-Et_3N at the end of the reaction (3 further cycles were carried out at 60 °C), yielded the same ee with a slight increase in reaction time with each new cycle run culminating finally at 9 h. This represents the top attained literature ATH data for this challenging benchmark ketone.[12a] In parallel, the atethered-type counterpart {RuCl[(*S*,*S*)-Me_2NSO_2-DPEN](*p*-cymene)} complex[6a]

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(9) Circumventing *C*-chlorination of **2** by SO_2Cl_2 during *N*-alkyl-*N*-methyl-sulfamoyl chloride preparation,[6a] transsulfamoylation by one-by-one displacement of the 2-Me-imidazolo groups was applied. 2-Me-imidazolo *N*′-methylation methodology to promote its nucleofugality was adopted from: Beaudoin, S.; Kinsey, K. E.; Burns, J. F. *J. Org. Chem.* **2003**, *68*, 115–119.

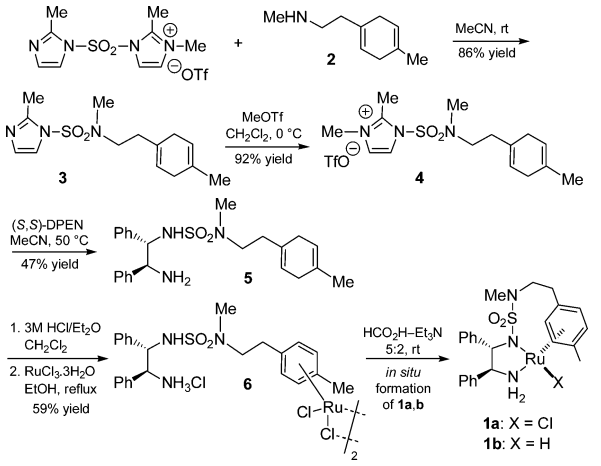
(10) Ru(II) complex **6** was characterized by ^1H and ^{13}C NMR; ^1H NMR revealed characteristic signals at 5.5–6.0 ppm corresponding to a dimeric structure.

(11) We assume the formation of the monomeric Ru(II) structure **1a** (and subsequently **1b**) from dimer **6** following a coordination-induced proximity effect by analogy to Wills et al. *N*,*C*-ethylenesulfonyl-tethered-type Ru(II) complexes.[4a,f] Our attempts to isolate **1a** were unfruitful; nonetheless ^1H NMR analysis revealed the disappearance of **6** upon HCO_2H-Et_3N 5:2 treatment at rt, and the high activity of the generated complex bears proof for the indicated monomeric structure. Besides, a mononuclear Ru species ($[M_{\mathbf{1a}}-Cl]^+$) was detected during HRMS (ESI) analysis of **6**.

(12) For literature examples of ATH of 1′-acetonaphthone, see the Supporting Information (Comparison Tables 1 and 2). (a) Ms-DENEB (S/C = 1000, HCO_2H-Et_3N 5:2, 60 °C, 24 h) gave a 96% conversion and 97% ee with **S1**.[5a] (b) [Ru(TsDPEN)(*p*-cymene)] (S/C = 100, 0.2 HCO_2H-Et_3N, 40 °C, 7 h) gave a 91% yield and 86% ee with **S9**. For this, see: Zhou, X.; Wu, X.; Yang, B.; Xiao, J. *J. Mol. Catal. A: Chem.* **2012**, *357*, 133–140. (c) [Ru(TsDPEN)(*p*-cymene)] (HCO_2H-Et_3N 5:2, 25 °C) gave a 4% conversion and 86% ee with **S10**, and [Ru(TsDPEN)-(mesitylene)] gave a 15% conversion and 71.0% ee with **S17**. For this, see: Slungard, S. V.; Krakeli, T.-A.; Thvedt, T. H. K.; Fuglseth, E.; Sundby, E.; Hoff, B. H. *Tetrahedron* **2011**, *67*, 5642–5650.

provided an excellent enantioselectivity as well (> 99.9% ee), albeit with a relatively fast catalyst deactivation with conversion stagnating at ~10% despite a high-load catalyst (S/C = 200). As a corollary, the Ru-catalyst robustness integrity during catalysis is clearly preserved by the two-in-one merge of its organic components.

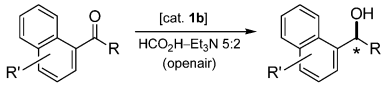
Scheme 1. Synthesis of the Active *ansa*-Type Ru(II) Complex **1b**



Next, a large series of commercially available or prepared 1-naphthyl ketones **S2**–**S17** was profiled. Accordingly, 95% ee was obtained with 2′-hydroxy-1′-acetonaphthone (**S2**) at 60 °C and the outcome was upgraded to 97.2% ee operating at 40 °C (with a comparable full-conversion time as that for **S1**). Moreover, various 4′-substituted acetonaphthones **S4**–**S7** possessing either an electron-withdrawing or -donating group and 9-acetylphenanthrene (**S9**)[12b] afforded good enantioselectivities (up to > 99.9%) along with full conversions within 6–12 h, except the 4′-methoxy-substituted derivative **S6** which demonstrated a marked resistance and led to 92.3% ee (S/C = 200). Interestingly enough, the 6′-methoxy-substituted analog **S7** furnished 97.6% ee within a relatively short reaction time. By contrast, the structurally related 2′-methoxy-1′-acetonaphthone (**S3**) and 9-acetylanthracene (**S8**) were completely unreactive under the adopted reaction conditions hinting to some clues regarding the catalyst functioning mode. Also, competition experiments (S/C = 200, 60 °C) employing a 1:1 mixture of 1′-acetonaphthone (**S1**) and **S3** or **S8** indicated a total conversion of **S1** (1 h, 99.1% ee) while **S3** and **S8** remained intact. Consequently, the origin of **S3** and **S8** inertness is their conformational geometry as the (shielded) acetyl group is noncoplanar with the aromatic nucleus inhibiting their conjugation.

Further on, reduction of an α-substituted or α-functionalized set of **S1** composed of ethyl (**S10**),[12c] isobutyl (**S11**), benzyl (**S12**), (*E*)-β-styryl (**S13**), CH_2Cl (**S14**), and CH_2CO_2Me (**S15**) 1-naphthyl ketones afforded the corresponding (*S*)-alcohols ((*R*) with **S14**)[13] in 97–99% ee. Noteworthy, a longer reaction time (10 h) and an S/C = 100 were required for complete conversion at 60 °C of the bulky isobutyl homologue **S11**. With 1-cinnamoylnaphthalene (**S13**), the saturated 1-(1-naphthyl)-3-phenyl-1-propanol was obtained tinted by 5% of (*E*)-1-(1-naphthyl)-3-phenyl-2-propen-1-ol.[14] Interestingly, the

Table 1. Transfer Hydrogenation of 1-Naphthyl Ketones[a]



S1: R = Me, R′ = H
S2: R = Me, R′ = 2′-OH
S3: R = Me, R′ = 2′-OMe
S4: R = Me, R′ = 4′-F
S5: R = Me, R′ = 4′-Me
S6: R = Me, R′ = 4′-OMe
S7: R = Me, R′ = 6′-OMe
S8: 9-Anth-C(O)Me
S9: 9-Phen-C(O)Me
S10: R = Et, R′ = H
S11: R = *i*-Bu, R′ = H
S12: R = CH_2Ph, R′ = H
S13: R = (*E*) CH=CHPh, R′ = H
S14: R = CH_2Cl, R′ = H
S15: R = CH_2CO_2Me, R′ = H
S16: R = Ph, R′ = H
S17: R = CF_3, R′ = H

ketone	S/C	temp (°C)	time (h)	yield (%)[b]	ee (%)[c] (conf)
S1	200	40	5	100	>99.9 (*S*)
	1000	40	20	100	>99.9 (*S*)
	1000	60	6	100	99.1 (*S*)
S2	1000	40	22	100	97.2 (*S*)
	1000	60	6	100	95.0 (*S*)
S3	200	60	20	0	–
S4	1000	40	20	75	97.8 (*S*)
	1000	60	6	100	97.2 (*S*)
S5	1000	60	15	100	98.4 (*S*)
S6	200	60	15	100	92.3 (*S*)
S7	1000	60	15	100	97.6 (*S*)
S8	200	60	20	0	–
S9	1000	40	22	100	>99.9 (*S*)
	1000	60	6	100	98.1 (*S*)
S10	1000	60	20	100	97.8 (*S*)
S11	100	60	10	100	97.0 (*S*)
S12	1000	40	20	85	99.0 (*S*)
	1000	60	6	100	98.5 (*S*)
S13	1000	60	10	100[d]	97.5 (*S*)
S14	1000	40	15	70[e]	88.4 (*R*)
	1000[f]	40	15	100	98.0 (*R*)
S15	200	25	20	100	98.5 (*S*)
	1000	40	10	100	98.2 (*S*)
	1000	60	6	100	98.1 (*S*)
S16	100	60	15	70	35.3 (*R*)
S17	1000	25	15	100	69.4 (*S*)
	1000	60	0.5	100	51.0 (*S*)

[a] Reaction conditions (S/C = 1000): (i) (*S*,*S*)-DPEN-derived dimer **6** (1.26 mg, 0.002 mmol based on Ru atom), HCO_2H–Et_3N 5:2 azeotrope (1.0 mL), rt, 30 min; (ii) ketone (2.0 mmol). [b] Determined by ^1H NMR of extracted crude. Isolated yields after silica gel chromatography were 1–3% lower. [c] Determined by chiral GC or HPLC analysis. The major enantiomer was assigned by optical rotation or on the basis of the general observed trend of enantioselectivity. For further details, see the Supporting Information. [d] 1-(1-Naphthyl)-3-phenyl-1-propanol was obtained tinted by 5% of (*E*)-1-(1-naphthyl)-3-phenyl-2-propen-1-ol. Ee corresponds to the further Pd–C hydrogenation product. [e] 2-Hydroxy-2-(1-naphthyl)ethyl formate was also formed (30% yield). [f] EtOAc (7 mL) used as cosolvent.

(13) Due to CIP stereochemistry rules, the absolute configuration is reversed for the **S14** reduction product.

(14) Racemic (*E*)-1-(1-naphthyl)-3-phenyl-2-propen-1-ol was chemoselectively obtained (100% yield) by $NaBH_4$ reduction of **S13** in MeOH without use of $CeCl_3$.

solvent effect was pronounced in the case of α-chloro-1′-acetonaphthone (**S14**) reduction, as using EtOAc as a cosolvent, quantitatively afforded 2-chloro-1-(1-naphthyl)-ethanol in 98.0% ee versus 88.4% ee (70% yield) accompanied by 2-hydroxy-2-(1-naphthyl)ethyl formate (30% yield) in the neat HCO_2H-Et_3N medium. Also, reduction of the β-keto ester **S15** with the current ATH system occurred with high enantioselectivity (98.1−98.5% ee) surpassing its reduction result via asymmetric hydrogenation.[12]

From what preceded, the primary origin of the observed high enantioselection in ATH of 1-naphthyl ketones with the current catalytic system stems from dual synergistic stereoelectronic matches of the substrate structure and the substrate−catalyst affinity. A putative 6-membered pericyclic mechanism in ATH involving concerted Ru−H (hydride) and N−H (proton) transfers to the C=O function was first proposed by Noyori et al.[2f] In opposition to this process implicating gas phase quantum chemical computation, a recent DFT study of a solution of acetophenone ATH with [RuH(TsDPEN)(mesitylene)] suggested a two-step mechanism which more likely involves neutralization of the formed chiral alkoxide by a protic solvent molecule.[2i] In fact, the inherent vicinal congestion (and *peri*-interaction) of the carbonyl group of these hydrophobic 1-naphthyl ketones imposes a determined C=O orientation in the highly polar reaction medium which affects in turn its approach dynamics to the catalyst (Figure 2). Also, a stronger stabilizing edge-to-face $CH_{\eta^6\text{-arene}}-\pi(Ar_{ketone})$ attractive interaction in the transition state is believed to manifest itself.[15] The existence of such an attractive electrostatic interaction was first rationalized by Noyori et al. for atethered-type Ru(II) complexes,[2g,h] and then by Wills et al. for *N*1,*C*-alkylene-tethered-type ones.[4e] In addition, stereocontrol exercised by an oriented peripheral η^6-arene-branching versus a minimalist benzene ligand is well-recognized in atethered-type systems. Finally, it appears that the [Ru catalyst]···1′-acetonaphthone intermolecular binding interaction in particular is more beneficial with a *N*-sulfamoyl- over a *N*-sulfonyl-functionalized DPEN ligand for tethered or atethered systems.[12] Alteration of the sterics and electronics of this critical differentiator effectively modulates catalysis.

Upon shifting to 1-benzoylnaphthalene (**S16**) and 1-naphthyl trifluoromethyl ketone (**S17**), a 35.3% ee ((*R*)-enantiomer) and 51.0% ee ((*S*)-enantiomer; 69% ee at 25 °C)[16] were obtained respectively at 60 °C, wherein the major H-delivery occurred from the opposite ketone face (*si*) compared to the case of the alkyl 1-naphthyl ketone series **S1**, **S2**, **S4**−**S7**, and **S9**−**S15**. In fact, in these two extreme polar cases, with the reduction of **S16** being the most sluggish and **S17** the fastest but both yielding low ee's, the major enantiomer ensues from a favored competing $CH_{\eta^6\text{-Tol}}-\pi$(Ph) or $CH_{\eta^6\text{-Tol}}-F$ attractive interaction, respectively, with $CH_{\eta^6\text{-Tol}}-\pi$(Naph).

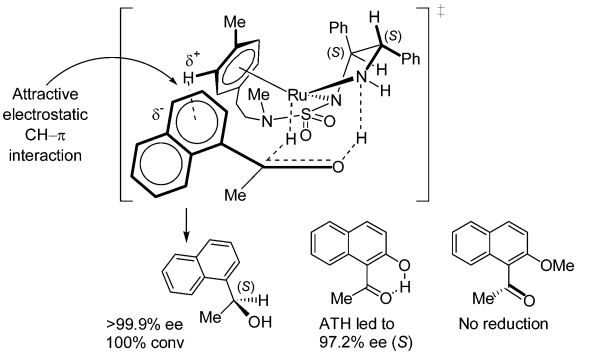


Figure 2. Assumed *trans* orientation of 1′-acetonaphthone (**S1**) in the transition-state adduct with the Ru-hydride catalyst **1b** leading to >99.9% ee (*S*), and ATH profile of **S1** derivatives having an enforced H-bonding (**S2**) or a nonplanar (**S3**) conformation.

In summary, we have presented the first (DPEN-κ^2N,N')/η^6-arene tethered-type ruthenium complex (**1b**) possessing a *N*,*C*-(*N*-ethylene-*N*-methyl-sulfamoyl) linkage. Its preliminary investigation in ATH demonstrated its high efficiency for the reduction under the practical mild reaction conditions of 1-naphthyl ketones compared to the current state-of-the-art catalyst systems. Enantioselectivities up to >99.9% coupled with 100% conversions were attained employing an S/C = 1000 in HCO_2H-Et_3N 5:2 medium. Such catalyst performance in this case clearly illustrates significant potential, including the turnover-rate enhancement offered by *ansa*-type catalysts over the atethered-type version. Challenges in the discovery−development continuum in this area reside in catalysts with added efficiency and ease of synthesis.

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Supporting Information Available. Experimental procedures and characterization data associated with this article. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(15) Noteworthy, the reduction data using Ru(II) dimer **6** for "vicinally nonbulky" basic acetophenone and 2′-acetonaphthone were somewhat inferior, as a decreased enantioselectivity (~96% ee) and a longer reaction time (6 h at 40 °C with S/C = 200) were observed.

(16) Due to CIP stereochemistry rules, the group's priority reverses going from 1-(1-naphthyl)ethanol to 2,2,2-trifluoro-1-(1-naphthyl)ethanol.