Communication

Octahedral Ruthenium Complex with Exclusive Metal-Centered Chirality for Highly Effective Asymmetric Catalysis

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Octahedral Ruthenium Complex with Exclusive Metal-Centered Chirality for Highly Effective Asymmetric Catalysis

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ABSTRACT: A novel ruthenium catalyst is introduced which contains solely achiral ligands and acquires its chirality entirely from octahedral centrochirality. The configurationally stable catalyst is demonstrated to catalyze the alkynylation of trifluoromethyl ketones with very high enantioselectivity (up to >99% ee) at low catalyst loadings (down to 0.2 mol%).

Transition metal complexes represent one of the most powerful and versatile classes of homogeneous catalysts. Applied to asymmetric catalysis, metal ions are typically combined with carefully tailored chiral ligands.[1] In a more simplistic design, only achiral ligands are employed but their assembly around the central metal creates metal-centered chirality[2] which is then responsible for the asymmetric induction during catalysis.[3] We recently realized this approach with the design of bis-cyclometalated iridium[4] and rhodium[5] complexes as chiral Lewis acids which provide excellent enantioselectivities and high turnover numbers for a variety of reactions. However, at the onset of this study it was unclear to what extend this design principle is general and applicable to chiral octahedral metal complexes of other elements. In pioneering work, Fontecave reported that Λ- and Δ-[Ru(2,9-dimethyl-1,10-phenanthroline)$(MeCN)_2]^{2+}$ catalyze the oxidation of organic sulfides to their sulfoxides, albeit with a maximum of just 18% ee.[3a] Much higher enantioselectivities for the synthesis of sulfoxides were achieved by Ye using chiral-at-metal Λ- and Δ-[Ru(2,2'-bipyridine)$_2$(pyridine)$_2]^{2+}$ as recyclable chiral auxiliaries.[6] Hartung and Grubbs reported a chiral-at-ruthenium catalyst for diastereo- and enantioselective ring-opening/cross-metathesis. The complex contains additional carbon-centered stereogenicity and catalysis is supposed to occur via a trigonal bipyramidal intermediate.[7] Here we demonstrate, that ruthenium complexes featuring exclusive octahedral centrochirality can serve as highly effective asymmetric catalysts for the enantioselective alkynylation of trifluoromethyl ketones.

Our design is shown in Figure 1 and based on a structural scaffold reported by Hahn and co-workers.[8] Ruthenium in the oxidation state +2 is coordinated by two *N*-(2-pyridyl)-subsituted *N*-heterocyclic carbene (PyNHC) bidentate ligands in addition to two acetonitrile ligands.[9] The propeller-type arrangement of the two bidentate ligands provides metal-centered Λ- (left-handed propeller) or Δ-configuration (right-handed propeller).

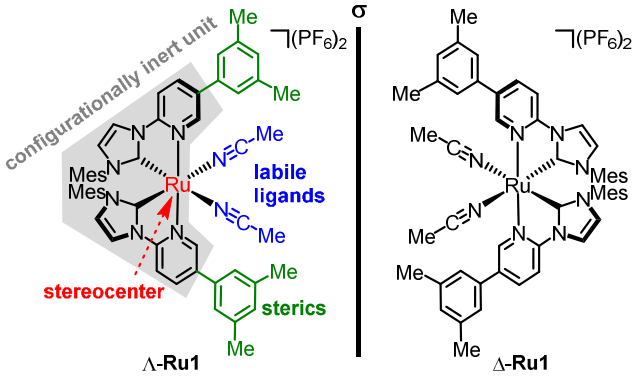


Figure 1. Design of a ruthenium-based asymmetric catalyst relying solely on octahedral centrochirality.

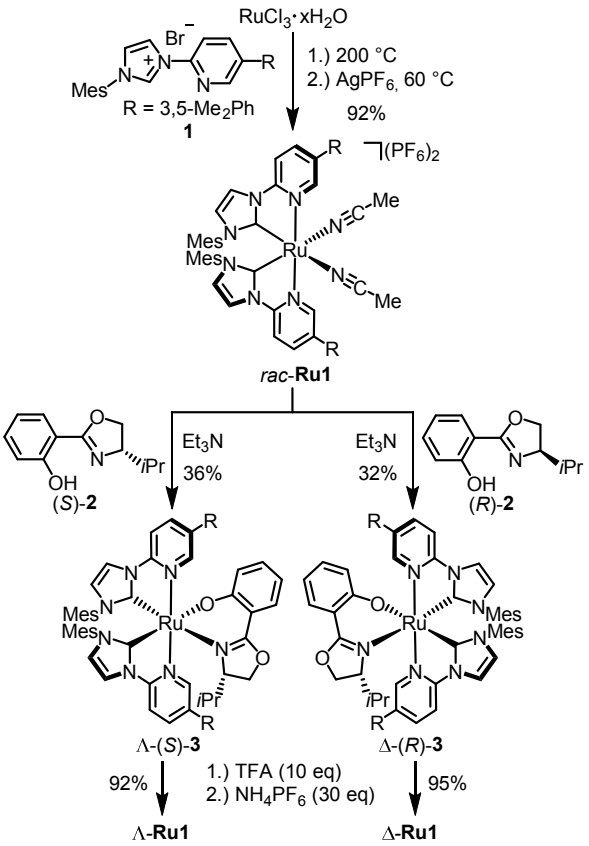


Figure 2. Synthesis of enantiopure complexes Λ- and Δ-**Ru1**.

The chiral-at-metal ruthenium complex was synthesized by reacting $RuCl_3$ hydrate with the *N*-(2-pyridyl)-imidazolium salt **1** in ethylene glycol at 200 °C followed by treatment with $AgPF_6$ to afford the racemic complex *rac*-**Ru1** in 92% yield (see Supporting Information for a single crystal X-ray structure of *rac*-**Ru1**) (Figure 2).[8] This racemic mixture was reacted with the chiral salicyloxazoline ligand (*S*)-**2** to provide Λ-(*S*)-**3** as a single diastereomer in 36% yield.[10-12] In analogy, using instead the auxiliary (*R*)-**2**, the complex Δ-(*R*)-**3** was obtained. The individual diastereomerically pure complexes were next treated with TFA in MeCN to generate **Ru1** as individual Λ- and Δ-enantiomer. CD spectra of both enantiomers are shown in Figure 3 and were used to assign the absolute configuration by comparison with related enantiopure ruthenium complexes,[13] and confirmed by an X-ray crystal structure of a derivative of Δ-**Ru1**. Revealingly, Λ- and Δ-**Ru1** are constitutionally and configurationally surprisingly stable. At a temperature of 60 °C in THF, after 72 hours no signs of isomerization or decomposition could be observed (see Supporting Information for more details).

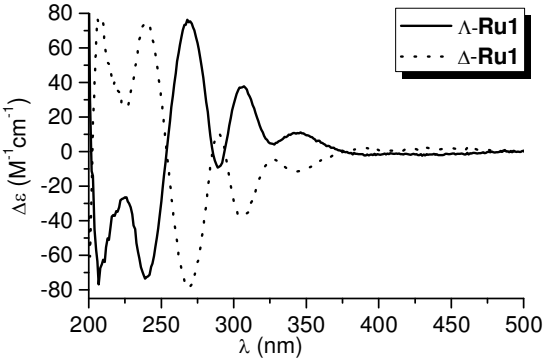
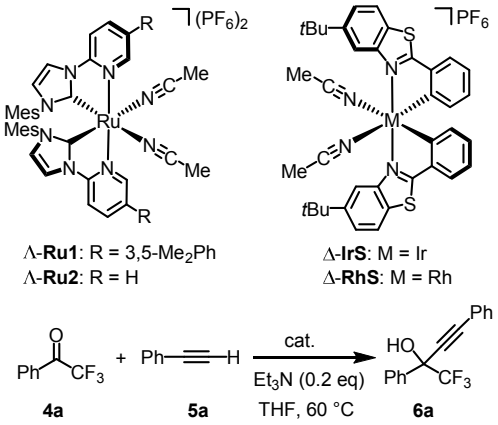


Figure 3. CD spectra (0.2 mM in CH_3OH) of Λ- and Δ-**Ru1**.

After some scouting experiments we found that **Ru1** is an excellent catalyst for the enantioselective alkynylation of trifluoromethyl ketones.[14,15] For example, the reaction of trifluoroacetophenone (**4a**) with phenylacetylene (**5a**) in the presence of Et_3N (0.2 eq), catalyzed by 3.0 mol% Λ-**Ru1**, provides the propargylalcohol (*S*)-**6a** with 97% yield and 99% ee (Table 1, entry 1). The catalyst loading can be reduced down to 0.2 mol% without any loss in yield or enantioselectivity (entries 2-4). As to be expected, mirror-imaged Δ-**Ru1** provides the mirror-imaged product (*R*)-**6a** with otherwise identical performance (entry 5). A reference catalyst devoid of the 3,5-Me_2Ph substituents (Λ-**Ru2**) leads to a reduced enantioselectivity of 97% ee (entry 6), confirming the steric role of the substituents at the pyridine ligands. Interestingly, previously reported chiral-at-metal iridium[4] and rhodium[5] catalysts only display very sluggish reactivity for the alkynylation of trifluoromethyl ketones and a diminished enantioselectivity even at catalyst loadings of 3.0 mol% (entries 7 and 8).

A substrate scope with respect to terminal alkynes is shown in Figure 4, providing the propargylalcohols (*S*)-**6b-m** in yields of 66-99% and with outstanding enantioselectivities of 96 to >99% ee. The catalyst tolerates equally well phenylacetylenes with substituents in the phenyl moiety, 2-ethynylthiophene, the conjugated alkenyl acetylene 1-ethynylcyclohexene, aliphatic acetylenes, and trimethylsilylacetylene. Typically, catalyst loadings of just 0.5 mol% Λ-**Ru1** are sufficient except for *ortho*-substituted phenylacetylenes which react more sluggish, presumably due to steric reasons.

Table 1. Initial catalysis experiments[a]



entry	catalyst	loading (mol%)	t (h)	yield (%)[b]	ee (%)[c]
1	Λ-**Ru1**	3.0	16	97	99 (*S*)
2	Λ-**Ru1**	1.0	16	93	99 (*S*)
3	Λ-**Ru1**	0.5	16	95	99 (*S*)
4	Λ-**Ru1**	0.2	30	98	99 (*S*)
5	Δ-**Ru1**	0.5	16	95	99 (*R*)
6	Λ-**Ru2**	0.5	16	93	97 (*S*)
7	Δ-**IrS**	3.0	20	15	15 (*R*)
8	Δ-**RhS**	3.0	20	28	93 (*R*)

[a] Conditions: **4a** and **5a** (3.0 eq) with catalyst (0.2-3.0 mol%) and Et_3N (20 mol%) in THF at 60 °C. [b] Isolated yields. [c] Enantiomeric excess of **6a** determined by chiral HPLC.

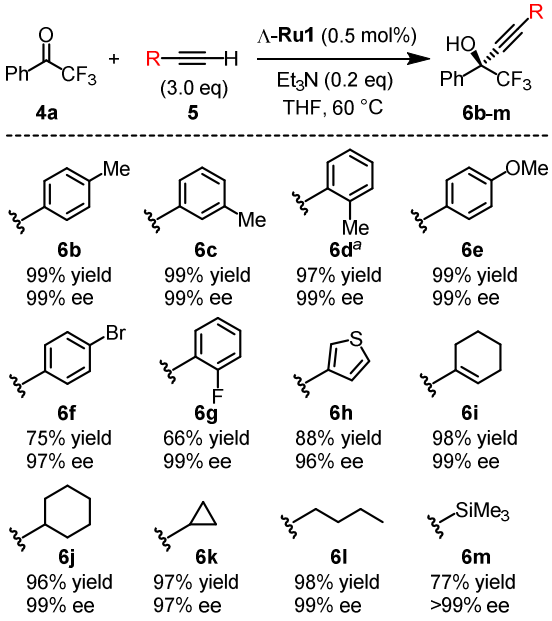


Figure 4. Substrate scope with respect to terminal alkynes. [a] 1.0 mol% catalyst loading instead.

The scope of this reaction with respect to trifluoromethyl ketones is outlined in Figure 5. Trifluoroacetophenone with different substituents in the phenyl moiety provided the corresponding propargylalcohols in high yields and with almost perfect enantioselectivity except for *ortho*-methyl trifluoroacetophenone which reacts sluggish, reinforcing that the catalyst is sensitive to steric effects. It is also noteworthy that an aliphatic trifluoromethyl ketone and ethyl trifluoropyruvate are not suitable substrate for this catalysis. However, replacing one fluorine of the trifluormethyl group with chlorine by using 2-chloro-2,2-difluoroacetophenone as the substrate yields the corresponding propargyl alcohol in 99% yield and 99% ee.

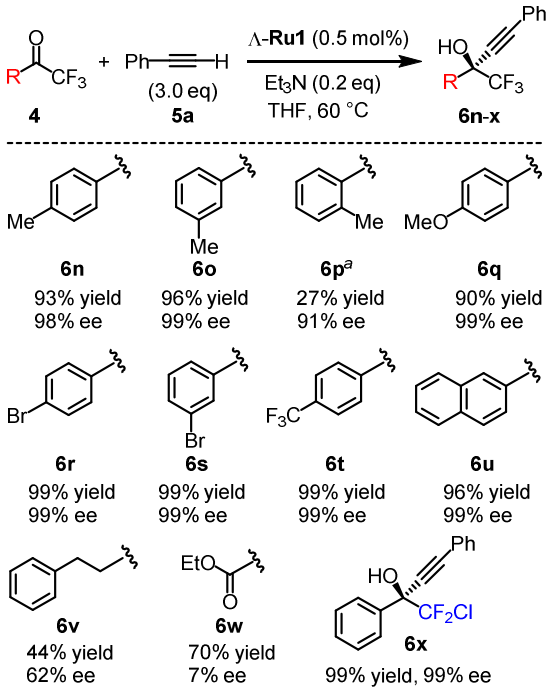


Figure 5. Substrate scope with respect to trifluoromethyl ketones. [a] 1.0 mol% catalyst loading instead.

The here introduced synthetic methodology should be very valuable because propargylic alcohols constitute highly versatile synthetic building blocks and furthermore fluorinated compounds play an increasingly important role in drug development.[16,17] Searching for an application, we turned our attention to Efavirenz,[18] a potent HIV-1 reverse transcriptase inhibitor and a key drug for the treatment of AIDS, which contains a quaternary stereocenter bearing a CF_3 and alkynyl group. Carreira reported the first catalytic asymmetric conversion of the trifluoroacetylanilide **7** into the key intermediate (*S*)-**8**.[19,20] However, the reaction requires a complicated cocktail out of Et_2Zn, chiral ligand, and the chiral product. Instead, reacting **7** with an excess of cyclopropylacetylene with 3 mol% Δ-**Ru1** under otherwise standard conditions provided (*S*)-**8** in a yield of 58% and with 92% ee. Thus, our novel chiral-at-ruthenium catalyst provides a very convenient access to the chiral building block (*S*)-**8**.

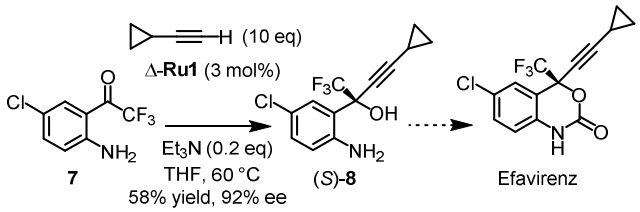


Figure 6. Catalytic asymmetric synthesis of (*S*)-**8**, a key intermediate in the synthesis of Efavirenz.

Mechanistically, we propose that the reaction proceeds through an intermediate ruthenium acetylide which then tranfers the acetylide to the presumable ruthenium-coordinated trifluoroketone.[16] The observed fluoromethyl ketone substrate coordinates to the ruthenium ahead of the acetylide transfer. During this transfer, the metal-centered chirality provides a suprisingly high asymmetric induction, thus reinforcing our catalyst design strategy. The rigidity of the propeller-type coordination sphere most likely contributes to the observed excellent enantioselectivities but is also responsible for sensitivity to steric effects. It is worth noting that catalytic amounts of base are necessary in this reaction,[21] which apparently serves as a proton shuttle.

In summary, we here reported the first example of an octahedral chiral-only-at-metal ruthenium complex with high catalytic activity and excellent enantioselectivity. Key components of this new class of asymmetric catalysts are the two *N*-(2-pyridyl)-subsituted *N*-heterocyclic carbene (PyNHC) chelate ligands.[8,9] First, the PyNHC ligands are tightly coordinating ligands which provide a strong ligand field important for the constitutional and configurational stability of the bis-(PyNHC)Ru unit. Second, the propeller shape and high rigidity of the bis-(PyNHC)Ru provides an excellent asymmetric induction. And third, the strong σ-donating NHC-ligands[22] in trans to the coordinated acetonitrile ligands are crucial for labilizing the coordinated acetonitrile ligands (trans-effect[23]) thereby ensuring a high catalytic activity.[24] The application of this novel class of chiral-at-metal ruthenium-based catalysts to other catalytic, enantioselective reactions is underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental details and chiral HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Walsh, P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis*; University Science Books: Sausalito, California, 2009.

(2) For reviews on different aspects of metal-centered chirality, see: (a) Pierre, J.-L. *Coord. Chem. Rev.* **1998**, *178-180*, 1183. (b) Knof, U.; von Zelewsky, A. *Angew. Chem. Int. Ed.* **1999**, *38*, 302. (c) Fontecave, M.; Hamelin, O.; Ménage, S. *Top. Organomet. Chem.* **2005**, *15*, 271. (d) Meggers, E. *Eur. J. Inorg. Chem.* **2011**, 2911. (e) Bauer, E. B. *Chem. Soc. Rev.* **2012**, *41*, 3153 (f) Crassous, J. *Chem. Commun.* **2012**, *48*, 9684. (g) Gong, L.; Chen, L.-A.; Meggers, E. *Angew. Chem. Int. Ed.* **2014**, *53*, 10868. (h) Cao, Z.-Y.; Brittain, W. D. G.; Fossey, J. S.; Zhou, F. *Catal. Sci. Technol.* **2015**, *5*, 3441.

(3) For precedence of asymmetric, octahedrally coordinated catalysts featuring solely metal-centered chirality, see: (a) Chavarot, M.; Ménage S.; Hamelin, O.; Charnay, F.; Pécaut, J.; Fontecave, M. *Inorg. Chem.* **2003**, *42*, 4810. (b) Hamelin, O.; Rimboud, M.; Pécaut, J.; Fontecave, M. *Inorg. Chem.* **2007**, *46*, 5354. (c) Ganzmann, C.; Gladysz, J. A. *Chem. Eur. J.* **2008**, *14*, 5397. (d) Chen, L.-A.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.* **2013**, *135*, 10598.

(4) (a) Huo, H.; Fu, C.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2014**, *136*, 2990. (b) Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L.-A.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature* **2014**, *515*, 100. (c) Shen, X.; Huo, H.; Wang, C.; Zhang, B.; Harms, K.; Meggers, E. *Chem. Eur. J.* **2015**, *21*, 9720. (d) Wang, C.; Qin, J.; Shen, X.; Riedel, R.; Harms, K.; Meggers, E. *Angew. Chem. Int. Ed.* **2016**, *55*, 685.

(5) (a) Wang, C.; Chen, L.-A.; Huo, H.; Shen, X.; Harms, K.; Gong, L.; Meggers, E. *Chem. Sci.* **2015**, *6*, 1094. (b) Tan, Y.; Yuan, W.; Gong, L.; Meggers, E. *Angew. Chem. Int. Ed.* **2015**, *54*, 13045. (c) Shen, X.; Harms, K.; Marsch, M.; Meggers, E. *Chem. Eur. J.* **2016**, *22*, 9102. (d) Huo, H.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2016**, *138*, 6936.

(6) (a) Li, Z.-Z.; Yao, S.-Y.; Wu, J.-J.; Ye, B.-H. Chem. Commun. **2014**, *50*, 5644. (b) Li, Z.-Z.; Yao, S.-Y.; Ye, B.-H. *ChemPlusChem* **2015**, *80*, 141. (c) Li, Z.-Z.; Wen, A.-H.; Yao, S.-Y.; Ye, B.-H. *Inorg. Chem.* **2015**, *54*, 2726. (d) Li, Z.-Z.; Yao, S.-Y.; Wen, A.-H.; Ye, B.-H. *Eur. J. Inorg. Chem.* **2015**, 4335.

(7) (a) Hartung, J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 10183. (b) Hartung, J.; Dornan, P. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2014**, *136*, 13029.

(8) Kaufhold, O.; Hahn, F. E.; Pape, T.; Hepp, A. *J. Organomet. Chem.* **2008**, *693*, 3435.

(9) For selected Ru-PyNHC complexes, see: (a) Son, S. U.; Park, K. H.; Lee, Y.-S.; Kim, B. Y.; Choi, C. H.; Lah, M. S.; Jang, Y. H.; Jang, D.-J.; Chung, Y. K. *Inorg. Chem.* **2004**, *43*, 6896. (b) Cheng, Y.; Sun, J.-F.; Yang, H.-L.; Xu, H.-J.; Li, Y.-Z.; Chen, X.-T.; Xue, Z.-L. *Organometallics* **2009**, *28*, 819. (c) Dakkach, M.; Fontrodona, X.; Parella, T.; Atlamsani, A.; Romero, I.; Rodríguez, M. *Adv. Synth. Catal.* **2011**, *353*, 231. (d) Norris, M. R.; Concepcion, J. J.; Harrison, D. P.; Binstead, R. A.; Ashford, D. L.; Fang, Z.; Templeton, J. L.; Meyer, T. J. *J. Am. Chem. Soc.* **2013**, *135*, 2080. (e) Leigh, V.; Ghattas, W.; Lalrempuia, R.; Müller-Bunz, H.; Pryce, M. T.; Albrecht, M. *Inorg. Chem.* **2013**, *52*, 5395. (f) Barbante, G. J.; Francis, P. S.; Hogan, C. F.; Kheradmand, P. R.; Wilson, D. J. D.; Barnard, P. J. *Inorg. Chem.* **2013**, *52*, 7448. (g) Saha, B.; Sengupta, G.; Sarbajna, A.; Dutta, I.; Bera, J. K. *J. Organomet. Chem.* **2014**, *771*, 124. (h) Olguín, J.; Díaz-Fernández, M.; La Cruz-Cruz, J. I. de; Paz-Sandoval, M. A. *J. Organomet. Chem.* **2016**, *824*, 33.

(10) For related auxiliary-mediated syntheses of enantiopure transition metal complexes, see for example: (a) Gong, L.; Mulcahy, S. P.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2009**, *131*, 9602. (b) Chepelin, O.; Ujma, J.; Wu, X.; Slawin, A. M. Z.; Pitak, M. B.; Coles, S. J.; Michel, J.; Jones, A. C.; Barran, P. E.; Lusby, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 19334. (c) Davies, D. L.; Singh, K.; Singh, S.; Villa-Marcos, B. *Chem. Commun.* **2013**, *49*, 6546. (d) Ma, J.; Shen, X.; Harms, K.; Meggers, E. *Dalton Trans.* **2016**, *45*, 8320.

(11) For the auxiliary-mediated synthesis of enantiopure ruthenium polypyridyl complexes, see: Gong, L.; Wenzel, M.; Meggers, E. *Acc. Chem. Res.* **2013**, *46*, 2635.

(12) The chiral ligand (*S*)-**2** apparently only reacts with Λ-**Ru1** to form Λ-(*S*)-**3** since the diastereomer Δ-(*S*)-**3** was not detected. In fact, reisolated, unreacted **Ru1** is enriched in Δ-**Ru1** and can be subsequently reacted with the chiral ligand (*R*)-**2** to provide Δ-(*R*)-**3** in 22% yield, although the purity of this compound is slightly diminished.

(13) (a) Watson, R. T.; Jackson, J. L.; Harper, J. D.; Kane-Maguire, K. A.; Kane-Maguire, L. A. P.; Kane-Maguire, N. A. P. *Inorg. Chim. Acta* **1996**, *249*, 5. (b) Gong, L.; Mulcahy, S. P.; Devarajan, D.; Harms, K.; Frenking, G.; Meggers, E. *Inorg. Chem.* **2010**, *49*, 7692.

(14) For precedence on enantioselective, catalytic alkynylations of trifluoromethyl ketones, see: (a) Motoki, R.; Tomita, D.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 8083. (b) Motoki, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2007**, *9*, 2997. (c) Aikawa, K.; Hioki, Y.; Mikami, K. *Org. Lett.* **2010**, *12*, 5716. (d) Zhang, G.-W.; Meng, W.; Ma, H.; Nie, J.; Zhang, W.-Q.; Ma, J.-A. *Angew. Chem. Int. Ed.* **2011**, *50*, 3538. (e) Ohshima, T.; Kawabata, T.; Takeuchi, Y.; Kakinuma, T.; Iwasaki, T.; Yonezawa, T.; Murakami, H.; Nishiyama, H.; Mashima, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 6296. (f) Wang, T.; Niu, J.-L.; Liu, S.-L.; Huang, J.-J.; Gong, J.-F.; Song, M.-P. *Adv. Synth. Catal.* **2013**, *355*, 927. (g) Dhayalan, V.; Murakami, R.; Hayashi, M. *Asian J. Chem.* **2013**, *25*, 7505. (h) Cook, A. M.; Wolf, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 2929. (i) Ito, J.-i.; Ubukata, S.; Muraoka, S.; Nishiyama, H. *Chem. Eur. J.* **2016**, *22*, 16801.

(15) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455.

(16) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963.

(17) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315.

(18) Vrouenraets, S. M. E.; Wit, F. W. N. M.; van Tongeren, J.; Lange, J. M. A. *Expert Opin. Pharmacother.* **2007**, *8*, 851.

(19) Chinkov, N.; Warm, A.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 2957.

(20) For other asymmetric catalytic procedures to implement this quaternary carbon stereocenter, see: (a) Kawai, H.; Kitayama, T.; Tokunaga, E.; Shibata, N. *Eur. J. Org. Chem.* **2011**, 5959. (b) Okusu, S.; Kawai, H.; Yasuda, Y.; Sugita, Y.; Kitayama, T.; Tokunaga, E.; Shibata, N. *Asian J. Org. Chem.* **2014**, *3*, 449. (c) Okusu, S.; Hirano, K.; Yasuda, Y.; Tanaka, J.; Tokunaga, E.; Fukaya, H.; Shibata, N. *Org. Lett.* **2016**, *18*, 5568.

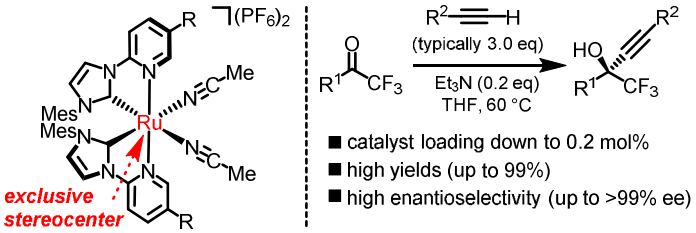
(21) No product is observed in the absence of Et_3N but catalytic amounts are sufficient. See Supporting Information for reactions with other bases.

(22) (a) Díez-González, S.; Nolan, S. P. *Coord. Chem. Rev.* **2007**, *251*, 874. (b) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612.

(23) Coe, B. J.; Glenwright, S. J. *Coord. Chem. Rev.* **2000**, *203*, 5.

(24) This trans-effect becomes apparent when comparing **Ru1** with the related complex $[Ru(2,2'\text{-bipyridine})_2(MeCN)_2]^{2+}$. **Ru1** features both longer Ru-N bonds to the coordinated MeCN ligands (structural trans-effect) which are at the same time more labile as revealed by ligand exchange measurements (kinetic trans-effect). See the Supporting Information for more details.

TOC graphic: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(PF6)2
Me
Mes
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R
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R2
H
(typically 3.0 eq)
O
R1
CF3
Et3N (0.2 eq)
THF, 60 °C
HO
R2
R1
CF3
catalyst loading down to 0.2 mol%
high yields (up to 99%)
high enantioselectivity (up to >99% ee)