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# Enantioselective Alkynylation of 2-Trifluoroacetyl Imidazoles Catalyzed by Bis-Cyclometalated Rhodium(III) Complexes Containing Pinene-Derived Ligands

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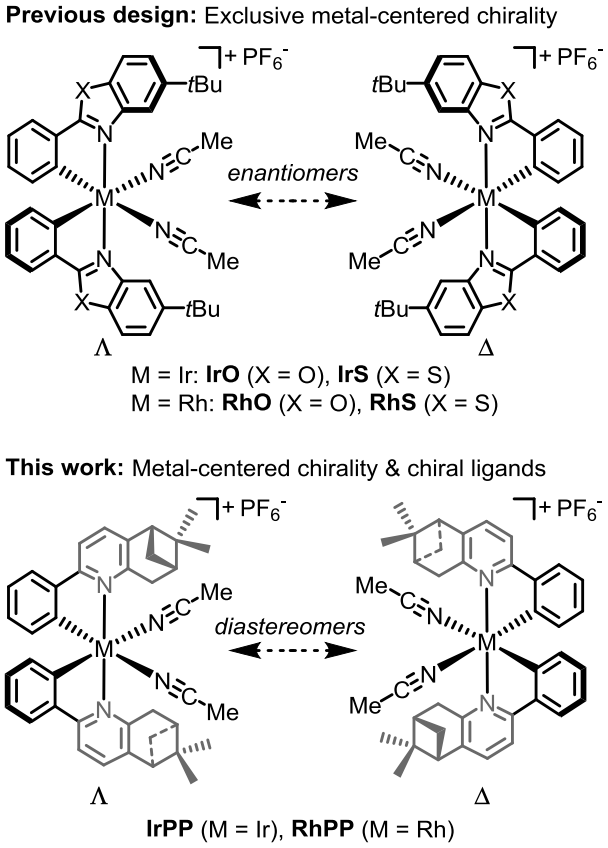
**Abstract:** Chiral rhodium(III) complexes containing two cyclometalating 2-phenyl-5,6-(*S*,*S*)-pinenopyridine ligands and two additional acetonitriles are introduced as excellent catalysts for the highly enantioselective alkynylation of 2-trifluoroacetyl imidazoles. Whereas the ligand-based chirality permits the straightforward synthesis of the complexes in a diastereomerically and enantiomerically pure fashion, the metal-centered chirality is responsible for the asymmetric induction in the course of the catalysis. Notably, the analogous iridium congeners provide only a low enantioselectivity, whereas related previously reported benzoxazole- and benzothiazole-based catalysts do not show any catalytic activity for this reaction under standard reaction conditions.

Chiral Lewis acids are indispensable tools in asymmetric catalysis and are typically composed of a main group element connected to chiral substituents or a combination out of metal salt and chiral ligand(s).[1] Recently, we introduced a new class of chiral Lewis acids in which a central iridium(III) or rhodium(III) is cyclometalated by two achiral ligands, thereby generating a propeller-type $C_2$-symmetry with metal-centered chirality[2,3] which constitutes the exclusive source of chirality (Scheme 1).[4-14] This structural element displays high constitutional and configurational stability, while two additional acetonitrile ligands are labile and provide access for substrates to coordinate to the Lewis acidic metal center. We demonstrated that these complexes are powerful chiral Lewis acid catalysts for a variety of transformations, some activated by visible light. However, all so far reported catalysts (Λ- and Δ-configured **IrO**, **IrS**, **RhO**, and **RhS**) are limited to either 2-phenylbenzoxazole or 2-phenylbenzothiazole ligands as cyclometalating components. Our objective for this study was therefore twofold: Firstly, we wanted to investigate how the catalytic properties of these cyclometalated complexes depend on the the nature of the cyclometalating unit, and secondly, we were interested in simplifying the synthesis of these chiral complexes by employing chiral cyclometalating ligands instead of achiral ones, thereby drawing from a large body of work regarding diastereoselective coordination chemistry with chiral ligands and the resolution of diastereomeric mixtures of chiral metal

complexes.[2] Here we now report our progress into this direction by introducing a new member of bis-cyclometalated chiral Lewis acids which are based on combined metal-centered and ligand-centered chirality and we demonstrate that they feature a catalytic activity that is notably distinct from our previous benzoxazole- and benzothiazole-based catalysts.




**Scheme 1.** Previous design and this work regarding bis-cyclometalated, chiral-at-metal iridium(III)- and rhodium(III)-based catalysts.

Our work follows stereoselective coordination chemistry developed by von Zelewsky and others using readily available pinene-modified chiral pyridine ligands.[15-19] Specifically, we reacted 2-phenyl-5,6-(*S*,*S*)-pinenopyridine[17] {(*S*,*S*)-**1**} with $RhCl_3 \cdot 3\ H_2O$ or $IrCl_3 \cdot 3\ H_2O$ in a 3:1 ethoxyethanol-water mixture at 125 °C for 36 hours to afford the respective chloro-bridged dimers

ΛΛ/ΔΔ-$\mathbf{2_{Rh}}$ and ΛΛ/ΔΔ-$\mathbf{2_{Ir}}$[19] as mixtures of diastereomers (Scheme 2). Consistent with related studies using cyclometalating pinene-derived pyridine ligands, the dinuclear complexes are mainly formed as the homochiral ΛΛ- and ΔΔ-diastereomers and within the coordination sphere the kinetically favored *trans* arrangement of the pyridine ligands is observed exclusively.[18] The diastereomers ΔΔ-$\mathbf{2_{Rh}}$ and ΔΔ-$\mathbf{2_{Ir}}$ are formed in slight excess of their ΛΛ-counterparts. Conveniently, the diastereomeric dimers can be easily resolved on silica gel chromatography using ethyl acetate:hexane (1:20) as the mobile phase. The subsequent reaction of the individual diastereomers with $AgPF_6$ in MeCN at 40 °C converts the chloro-bridged dimers into the individual monomeric bis-acetonitrile complexes Λ-**RhPP**, Δ-**RhPP**, Λ-**IrPP**, and Δ-**IrPP**. The high diastereomeric purity (>99% *dr*) of these complexes was confirmed by $^1$H-NMR and the relative and absolute configurations of all four complexes were confirmed by X-ray crystallography. Λ-**RhPP** and Δ-**RhPP** are shown in Figure 1 and reveal the propeller-type ligand arrangement with a combination of metal-centered and ligand-derived chirality. All complexes display high constitutional and configurational stability without any significant decomposition or isomerization upon leaving the complexes dissolved in $CH_2Cl_2$ on the benchtop for one week.

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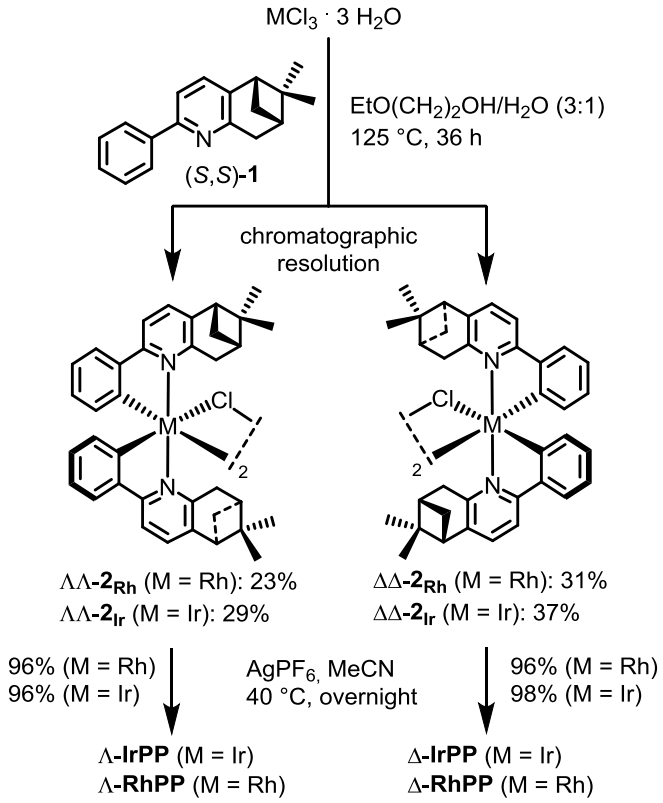
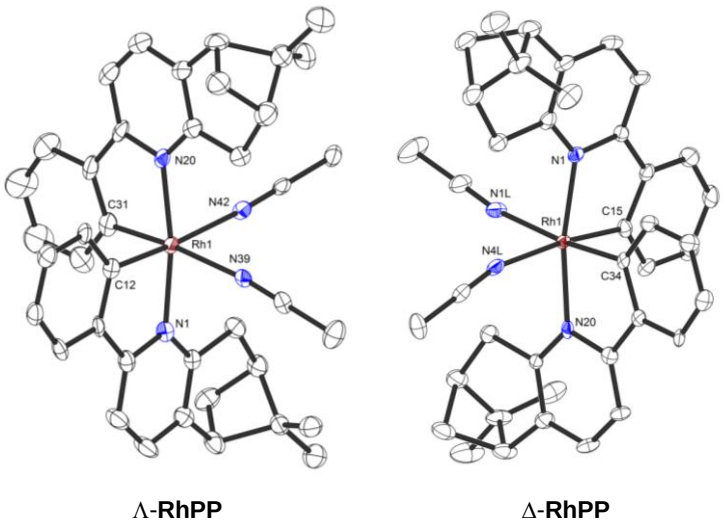



**Scheme 2.** Synthesis of enantiomerically and diastereomerically pure chiral-at-metal iridium(III) and rhodium(III) complexes containing pinene-derived chiral ligands.

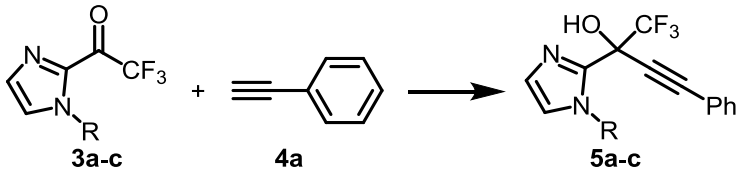



Λ-**RhPP** Δ-**RhPP**

**Figure 1.** Crystal structures of Λ-**RhPP** and Δ-**RhPP**. The hexafluorophosphate counterions are omitted for clarity. ORTEP drawings with 50% probability thermal ellipsoids.

With the four diastereomerically and enantiomerically pure transition metal complexes in hand we next investigated their catalytic activity. After some orientational experiments we found that **RhPP** is an excellent catalyst for the enantioselective alkynylation of 1-phenyl-2-trifluoroacetyl imidazole (**3a**).[20-23] For example, using 3 mol% of Δ-**RhPP** in the presence of 1.2 equivalents of $Et_3N$, the reaction of ketone **3a** with phenylacetylene (**4a**) for 24 hours at room temperature provided the propargyl alcohol (*R*)-**5a** in 89% yield and with 95% *ee* (Table 1, entry 1). Replacing the *N*-phenyl substituent with an isopropyl group (**3b**) improved the yields of (*R*)-**5b** to 94% and enantioselectivity to 97% *ee* (entry 2). However, the best results were achieved with 1-methyl-2-trifluorocetyl imidazole (**3c**), providing the propargyl alcohol (*R*)-**5c** with 92% yield and >99% *ee* (entry 3). Noteworthy, using the diastereomeric catalyst Λ-**RhPP** afforded the mirror-imaged product (*S*)-**5c** with an identical enantioselectivity of >99% *ee* and only with a slightly reduced yield of 90% (entry 4). This comparison of Δ-**RhPP** with Λ-**RhPP** unambiguously demonstrates that the asymmetric induction in the course of the catalysis is mainly controlled by the metal-centered chirality and not the chirality of the ligand. Control experiments confirm that both the catalyst and a base are necessary for achieving a conversion (entries 5 and 6). Reduced loadings of Δ-**RhPP** (entries 7 and 8) and the base triethylamine (entry 9) do not affect the enantioselectivity but the reaction rate. Conveniently, the catalytic reaction can even be performed in an open flask since it is not sensitive to air and water (entries 10 and 11). Furthermore, the iridium congeners Δ- and Λ-**IrPP** (entries 12 and 13) provide inferior results, whereas our previously developed catalysts **RhO**, **IrO** or **IrS** are not able to catalyze the conversion **3c**+**4a**→**5c** at all (entries 14-16). Thus, although the absolute configuration at the ligand does not effect the rate and degree of asymmetric induction, the nature of the ligand is obviously crucial for an effective catalysis as cyclometalated phenylbenzoxazoles (**RhO** and **IrO**) or phenylbenzothiazoles (**IrS**) do not provide active catalysts.

**Table 1.** Initial Experiments.[a]




R = Ph (**3a**, **5a**), *i*Pr (**3b**, **5b**), Me (**3c**, **5c**)

| Entry | Catalyst[b] | Substrate | Base | Conditions | *t* (h) | Yield (%)[c] | *ee* (%)[d] |
|---|---|---|---|---|---|---|---|
| 1 | Δ-**RhPP** (3.0) | **3a** | $Et_3N$ (1.2 eq) | nitrogen | 24 | 89 | 95 (*R*) |
| 2 | Δ-**RhPP** (3.0) | **3b** | $Et_3N$ (1.2 eq) | nitrogen | 24 | 94 | 97 (*R*) |
| 3 | Δ-**RhPP** (3.0) | **3c** | $Et_3N$ (1.2 eq) | nitrogen | 24 | 92 | >99 (*R*) |
| 4 | Λ-**RhPP** (3.0) | **3c** | $Et_3N$ (1.2 eq) | nitrogen | 24 | 90 | >99 (*S*) |
| 5 | Δ-**RhPP** (3.0) | **3c** | none | nitrogen | 24 | 0 | n.a. |
| 6 | none | **3c** | $Et_3N$ (1.2 eq) | nitrogen | 24 | 0 | n.a. |
| 7 | Δ-**RhPP** (2.0) | **3c** | $Et_3N$ (1.2 eq) | nitrogen | 24 | 80 | >99 (*R*) |
| 8 | Δ-**RhPP** (1.0) | **3c** | $Et_3N$ (1.2 eq) | nitrogen | 24 | 51 | >99 (*R*) |
| 9 | Δ-**RhPP** (3.0) | **3c** | $Et_3N$ (0.3 eq) | nitrogen | 24 | 60 | >99 (*R*) |
| 10 | Δ-**RhPP** (3.0) | **3c** | $Et_3N$ (1.2 eq) | air | 24 | 93 | 99 (*R*) |
| 11 | Δ-**RhPP** (3.0) | **3c** | $Et_3N$ (1.2 eq) | air, 1% $H_2O$ | 24 | 88 | 99 (*R*) |
| 12 | Δ-**IrPP** (3.0) | **3c** | $Et_3N$ (1.2 eq) | nitrogen | 24 | 37 | 29 (*R*) |
| 13 | Λ-**IrPP** (3.0) | **3c** | $Et_3N$ (1.2 eq) | nitrogen | 24 | 84 | 15 (*S*) |
| 14 | Λ/Δ-**RhO** (3.0) | **3c** | $Et_3N$ (1.2 eq) | nitrogen | 24 | 0 | n.a. |
| 15 | Λ/Δ-**IrO** (3.0) | **3c** | $Et_3N$ (1.2 eq) | nitrogen | 24 | 0 | n.a. |
| 16 | Λ/Δ-**IrS** (3.0) | **3c** | $Et_3N$ (1.2 eq) | nitrogen | 24 | 0 | n.a. |

[a] Conditions: trifluoromethyl ketone (0.20 mmol), phenylacetylene (0.60 mmol) and catalyst ( 3.0 mol%) in THF (0.2 mL) were stirred at room temperature for 24 hours. [b] Catalyst loading in mol% provided in brackets. [c] Isolated yields. [d] Determined by chiral HPLC analysis. Enantiomeric excess ≥ 99.5% *ee* designated as >99% *ee*. n.a. = not applicable.

After these promising initial results regarding the enantioselective alkynylation with Δ-**RhPP**, we performed a substrate scope under optimized conditions with the trifluoroketone **3c** and a variety of arylacetylenes. As shown in Scheme 3, our method tolerates a variety of substituted phenylacetylenes, containing alkyl, aryl, electron-donating, and electron-withdrawing substituents. Heteroarylacetylenes such as 2-pyridylacetylene and 3-thiophenylacetylene are also suitable substrates. Overall, yields range from 79-99% and enantioselectivities from 97 to >99% *ee* for the propargyl alcohols (*R*)-**5d-p**. Δ-**RhPP** also catalyzes the reaction of trifluoroketone **3c** with aliphatic acetylenes as shown in Scheme 4 to provide the propargyl alcohols (*R*)-**5q-v** in satisfactory yields (55-88%) and with excellent enantioselectivity (94% to >99% *ee*). However, it is important to note that satisfactory yields and excellent enantioselectivity of this reaction is limited to ketones which contain both the $CF_3$ group as well as the imidazole moiety. For example, replacing the imidazole moiety with a phenyl or the $CF_3$ group with an ethyl group completely abolishes the conversion. Replacing the imidazole moiety with a less strongly coordinating group such as ethylcarboxylate or benzoyl leads to reduced yields and reduced enantioselectivities (see Supporting Information for more details). These results imply that a successful catalysis relies on a strong electronic activation of the carbonyl group by a neighboring $CF_3$ in combination with the efficient coordination of the substrate to the rhodium catalyst.

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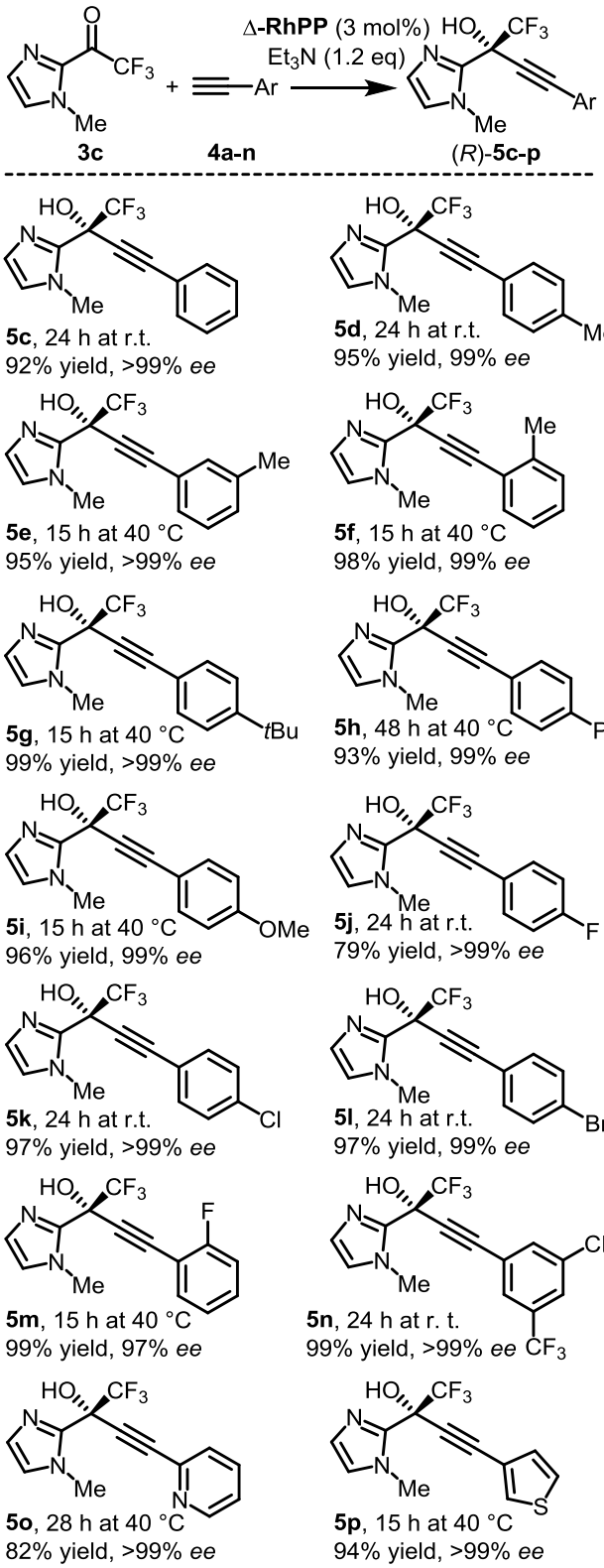
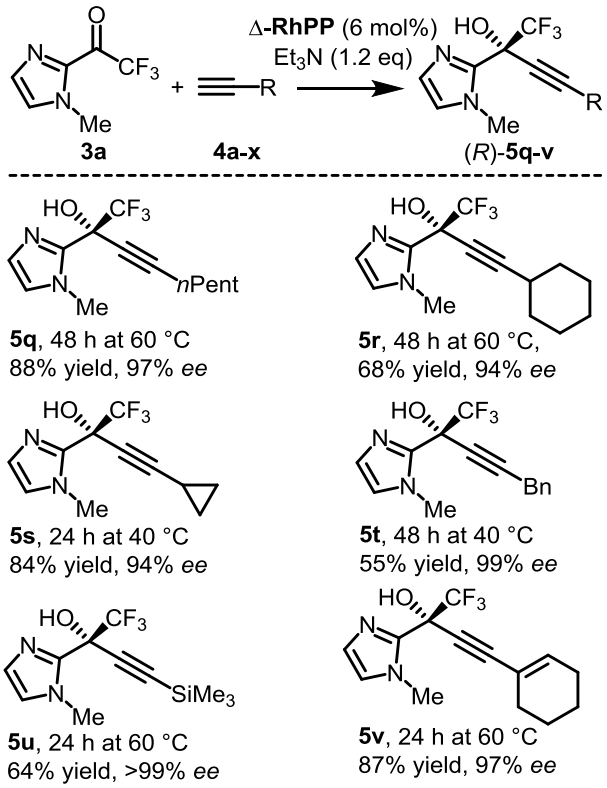



**Scheme 3.** Substrate scope with respect to arylacetylenes.




**Scheme 4.** Substrate scope with respect to alkylacetylenes and trimethylsilylacethylene.

Fluorine substituents play a prominent role in medicinal chemistry.[24] For example, the reverse transcriptase inhibitor Efavirenz, which is used for the treatment of HIV infections, contains a $CF_3$ group attached to a stereocenter, indicating a demand of methods for the asymmetric construction of stereogenic centers containing $CF_3$ substituents.[22] The enantioselective alkynylation of trifluoromethyl ketones constitutes an attractive strategy into this direction considering the versatility of propargyl alcohols as synthetic building blocks.[25] However, catalytic enantioselective methods for the alkynylation of trifluoromethyl ketones are still limited. Shibasaki reported copper(I) complexes for the direct alkynylation of trifluoromethyl ketones, albeit with very moderate enantioselectivities,[20a,b] Mikami reported the enantioselective alkynylation of ethyl trifluoropyryvate with alkynylsilanes using a palladium(II)-BINAP catalyst,[20c] whereas Ohshima, Mashima and Nishiyama,[20e] and independently Gong and Song,[20f] were able to employ terminal alkynes in using rhodium(III)-pincer complexes. Ma

reported an efficient titanium(IV)-catalyzed enantioselective alkynylation of trifluoromethyl ketones using chiral cinchona alkaloids as chiral ligands.[20d] Hayashi introduced an enantioselective alkynylation of trifluoromethyl ketones catalyzed by chiral Schiff bases in the presence of $Me_2Zn$, albeit with only very modest enantioselectivity.[20g] Finally, Wolf recently reported the enantioselective zinc(II)-catalyzed addition of terminal ynamides to trifluoromethyl ketones.[20h] Alltogether, it can be concluded that each reported method contains limitations with respect to substrate scope and enantioselectivity. Taking into account the limitation that our here reported method requires an imidazole substituent next to the carbonyl group, very high enantioselectivities at low catalyst loadings are achieved for terminal alkynes with aryl and alkyl substituents. Furthermore, the method is technically undemanding since it does not require precautions with respect to moisture or air.

In conclusion, we here disclosed a new bis-cyclometalated rhodium(III) complex as a highly effective catalyst for the catalytic enantioselective alkynylation of 2-trifluoroacetyl imidazoles. The rhodium complex contains pinene-derived chiral ligands which permit the straightforward synthesis of the complexes as enantiomerically pure single diastereomers. Interestingly, although the asymmetric induction in the course of the catalysis is mainly controlled by the metal-centered chirality, the synthesized rhodium complexes feature a catalytic activity that is surprisingly distinct from our previous benzoxazole- and benzothiazole-based catalysts.

**Acknowledgements:**

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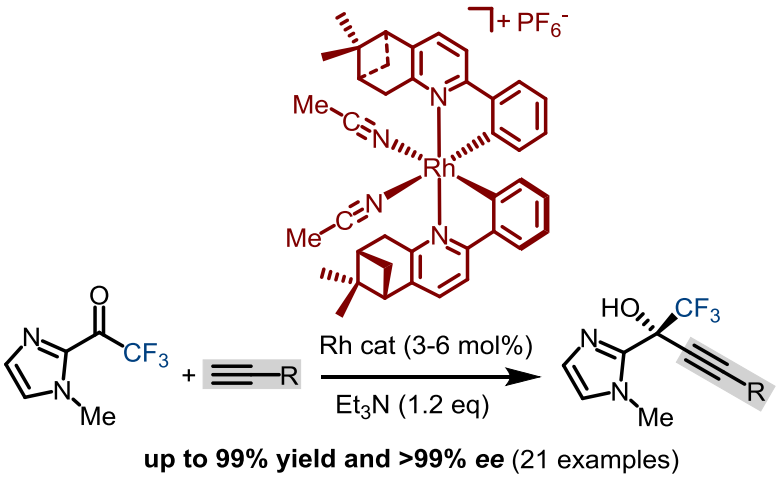
**Keywords:** Chiral-at-metal, rhodium, cyclometalation, asymmetric catalysis, alkynylation, trifluoromethyl.

**TOC graphic:**




A chiral rhodium(III) complex containing two cyclometalating 2-phenyl-5,6-(*S*,*S*)-pinenopyridine ligands and two additional acetonitriles catalyzes the highly enantioselective alkynylation of 2-trifluoroacetyl imidazoles. Whereas the ligand-based chirality permits the straightforward synthesis of the complexes in a diastereomerically and enantiomerically pure fashion, the metal-centered chirality is responsible for the asymmetric induction in the course of the catalysis.