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Cooperative Bimetallic Asymmetric Catalysis: Comparison of a Planar Chiral Ruthenocene Bis-Palladacycle to the Corresponding Ferrocene

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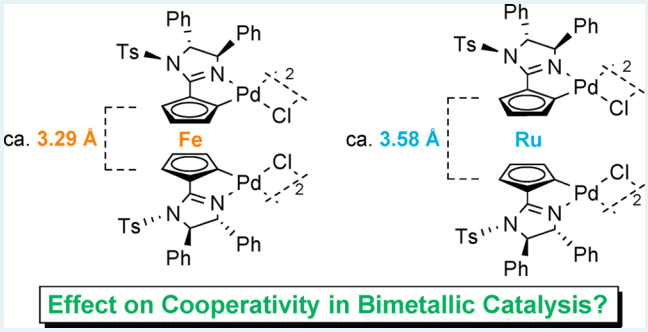
Supporting Information

ABSTRACT: Cooperative asymmetric catalysts often offer advantages in terms of activity, stereoselectivity, and generality as compared to more traditional single point activation catalysts. In cooperative bimetallic catalysis, the intermetallic distance is a crucial parameter for the outcome of a reaction and an optimal synergy of both metal centers. We have recently developed a number of catalytic asymmetric reactions, which are efficiently catalyzed by a planar chiral ferrocene based bispalladacycle and for which the cooperativity of two Pd centers has already been demonstrated. To get more insight into the role of the Pd/Pd distance in such metallocene bismetallacycles, in the present study a corresponding ruthenocene based Pd_2-complex has been prepared by the first direct diastereoselective biscyclopalladation of a chiral ruthenocene ligand. In addition, the first highly diastereoselective direct monocyclopalladation of a homochiral ruthenocene is reported. The effect of the increased Cp/Cp distance within the ruthenocene bispalladacycle has been examined in four catalytic asymmetric applications: the aza-Claisen rearrangement of *Z*-configured allylic *N*-aryltrifluoroacetimidates, the direct 1,4-addition of α-cyanoacetates to enones, a tandem azlactone formation/1,4-addition to enones and a tandem reaction to form quaternary α-aminosuccinimides by in situ azlactone formation, 1,4-addition to a nitroolefin, and a Nef-type nitro-to-carbonyl transformation as key steps. For each reaction studied, it was found that with some substrates the ferrocene based catalyst is superior, whereas for other substrates the ruthenocene backbone is more favorable. The ruthenocene based bispalladacycle can thus be considered to be a useful and complementary alternative for cooperative bimetallic catalysis.



KEYWORDS: *1,4-addition, cyclopalladation, imidazoline, rearrangement, ruthenocene*

INTRODUCTION

Inspired by the intriguing mode of action of dinuclear metalloenzymes and their impressive catalytic efficiency,[1] the synergistic cooperation of two metal centers is currently also intensively investigated for artificial catalyst systems, as it frequently offers substantial advantages in terms of catalytic activity and stereoselectivity.[2] In the context of cooperative asymmetric catalysis, our group has recently developed a planar chiral ferrocene bisimidazoline bispalladacycle (FBIP, Figure 1)[3,4] as a useful bimetallic catalyst, which enables various different catalytic asymmetric reaction types.[5−7]

A parameter of key importance for bimetallic catalysis is the intermetallic distance of both catalytically relevant metal centers.[2] In this context, a major conceptual advantage of a ferrocene (and other metallocene) backbone(s) seems to be a partial rotational freedom around the Cp−Fe (or Cp−M) axes, which allows the catalyst to adopt an appropriate distance of both cooperating metal centers to simultaneously activate two reacting substrates (or functional groups) via a bimetallic pathway.[8] The ferrocene based bismetallacycles can thus readily open and close like a pair of scissors employing only a few degrees of rotational freedom.

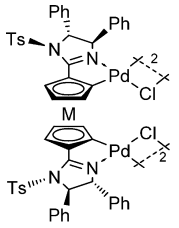


Figure 1. $[FBIP\text{-}Cl]_2$ and $[RuBIP\text{-}Cl]_2$.

Due to the significance of the intermetallic distance in bimetallic catalysis,[2] we were interested in the effect of an increased distance of both Cp-ligands in the metallocene core on the catalytic performance in enantioselective bis-Pd catalyzed reactions. Since it is known that the distance between both Cp rings is significantly larger in the parent ruthenocene

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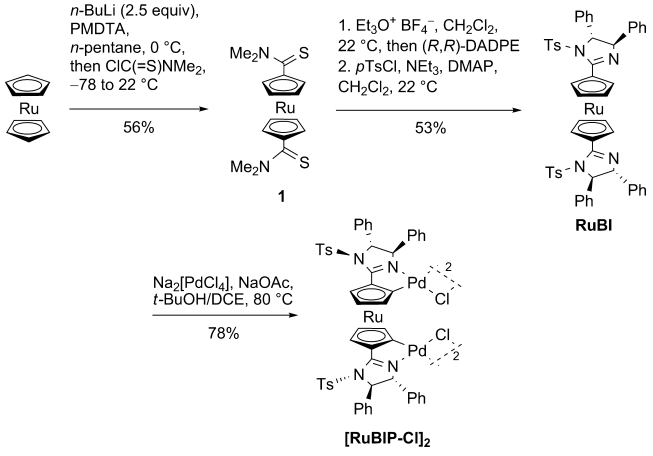
(distance of both Cp-rings ca. 3.68 Å)[9] as compared to the parent ferrocene (ca. 3.32 Å),[10] we have investigated the formation of the analogous ruthenocene bisimidazoline bispalladacycle (RuBIP) and now report its synthesis and structure as well as the catalytic performance in several reactions, in which FBIP has previously been investigated allowing for a comparison. In addition, we describe the synthesis of a related ruthenocene imidazoline monopalladacycle which represents the first highly diastereoselective monocyclopalladation of a ruthenocene. This monopalladacycle was used for control reactions.

RESULTS AND DISCUSSION

Synthesis and Structural Analysis of the Dimeric Bispalladacycle [RuBIP-Cl]$_2$. Compared to the cyclopalladation of ferrocenes,[11,12] the cyclopalladation of ruthenocene derivatives has only been scarcely investigated. Most of the few known methods provide racemic[13] or achiral[14] palladacycles. To our knowledge the attempts toward direct enantioselective[15] or diastereoselective[16] cyclopalladations of ruthenocenes providing planar chiral Pd(II)-complexes always resulted in poor to moderate stereoselectivity thus far. Highly enantioenriched ruthenocene palladacycles have only very recently been reported by Kündig et al., who employed indenyl derived ruthenocene substrates already containing the element of planar chirality prior to the cyclopalladation step, thus elegantly avoiding a stereoselectivity issue upon the cyclometalation event.[17]

No examples for direct biscyclopalladations of ruthenocenes have been reported so far. For the development of a diastereoselective version of this reaction type, we have prepared the ruthenocene bisimidazoline ligand RuBI (Scheme 1). The short ligand synthesis works in close analogy to the one

Scheme 1. Diastereoselective Synthesis of the Chloride Bridged Bispalladacycle [RuBIP-Cl]$_2$



of the corresponding ferrocene ligand.[3a,b] Dilithiation of ruthenocene[18] and trapping of the resulting biscarbanion with *N*,*N*-dimethylthiocarbamoyl chloride provided bisthioamide **1**. The latter was activated by triethyloxonium tetrafluoroborate for the bisimidazoline formation by treatment with the chiral diamine (*R*,*R*)-1,2-diamino-1,2-diphenylethane ((*R*,*R*)-DADPE). Both imidazoline rings were subsequently N-tosylated to give the RuBI ligand. The direct biscyclopalladation also proceeded efficiently under conditions optimized for the synthesis of FBIP.[3c] Thus, treatment of RuBI with $Na_2[PdCl_4]$ and NaOAc in a mixture of degassed *tert*-butanol/1,2-dichloroethane at 80 °C furnished the C_2-symmetric bispalladacycle in good yield and as a single diastereomer.

The constitution and the (all-S_p)-configuration[19] of this compound were confirmed by X-ray crystal structure analysis (Figure 2).[20] The structure closely resembles the one found for the corresponding ferrocene derivative [FBIP-Cl]$_2$.[3a,b] In the dimeric structure of [RuBIP-Cl]$_2$, two chloride bridged palladium square planes are arranged in a nearly coplanar fashion, both in the upper and lower Cp planes. While chloride bridged ferrocenyl monoimidazoline palladacycle complexes and other halide bridged palladacycles usually form geometric *cis*/*trans* isomers around the Pd^{II}-centers,[12] in the case of [RuBIP-Cl]$_2$ (and also [FBIP-Cl]$_2$),[3a,b] the macrocyclic structure enforces a coordination sphere, in which the all-(S_p)-configured complexes form exclusively all-*trans*-configured isomers, meaning that both imidazoline N-donors in the same (PdCl)$_2$-plane are always placed *trans* to each other. Like expected, the most significant difference between the crystal structure of [FBIP-Cl]$_2$ and [RuBIP-Cl]$_2$ is the distance of the centroids of both Cp ligands in the same metallocene fragment with values of 3.281−3.293 Å and 3.568−3.595 Å, respectively. In contrast, the other bond lengths and also the bond angles and conformations are very similar for both complexes.[21] For example, in the case of [RuBIP-Cl]$_2$ the Pd−C/C′−Pd twist angles are between 33.1(8)° and 35.9(8)° (resulting Pd/Pd distances of 3.982(2) Å and 3.998(2) Å), while for [FBIP-Cl]$_2$ they are between 34.6(3)° and 35.8(3)° (resulting Pd/Pd distances of 3.7468(7) Å and 3.7685(7) Å).

Synthesis and Structural Analysis of Ruthenocene Imidazoline Monopalladacycle [RuIP-Cl]$_2$. The corresponding chloride bridged ruthenocene imidazoline palladacycle dimer [RuIP-Cl]$_2$ was formed by the first highly diastereoselective direct monocyclopalladation of a chiral ruthenocene ligand (Scheme 2). The synthesis started from ruthenocene and could be performed in close analogy to the corresponding ferrocene imidazoline palladacycle [FIP-Cl]$_2$.[29g,k] Monolithiation of ruthenocene[22] and subsequent trapping with CO_2 provided ruthenocene carboxylic acid **2**, which was transformed into the primary amide **3** via acid chloride formation (Scheme 2). The amide function was then activated by $[Et_3O]BF_4$ for the subsequent formation of an imidazoline, which was N-protected by tosylation. The direct cyclopalladation using $Na_2[PdCl_4]$ and NaOAc in MeOH provided the palladacycle in high yield and with high diastereoselectivity with regard to the element of planar chirality. Since the chloride bridged palladacycles form geometric *cis*/*trans* isomers around the Pd^{II}-centers resulting in relatively complex ^{1}H NMR spectra, the diastereoselectivity was estimated after formation of the monomeric acac complex RuIP-acac, which is obtained in quantitative yield by treatment of [RuIP-Cl]$_2$ with Na(acac) in MeOH/benzene (Scheme 3). The diastereomeric ratio of 20:1 is somewhat higher than for the corresponding ferrocene (*dr* = 18:1).[29k]

The expected (S_p)-configuration of this compound could be confirmed by X-ray crystal structure analysis of the chloride bridged dimer, since the *trans*-isomer selectively crystallized from a solution in CH_2Cl_2 (Figure 3).[23] The structure is nearly C_2-symmetric in the solid state. In contrast to [RuBIP-Cl]$_2$ the four-membered (PdCl)$_2$ ring is puckered with a dihedral angle Pd−Cl−Pd−Cl of around 27°. Both ruthenocene moieties are placed on the concave face of the four-membered ring, which is also in analogy to structures of halide bridged ferrocene

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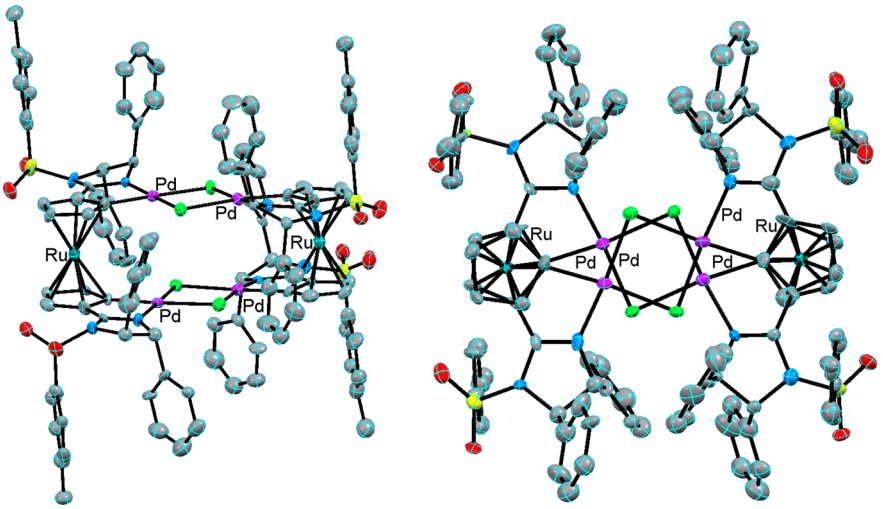
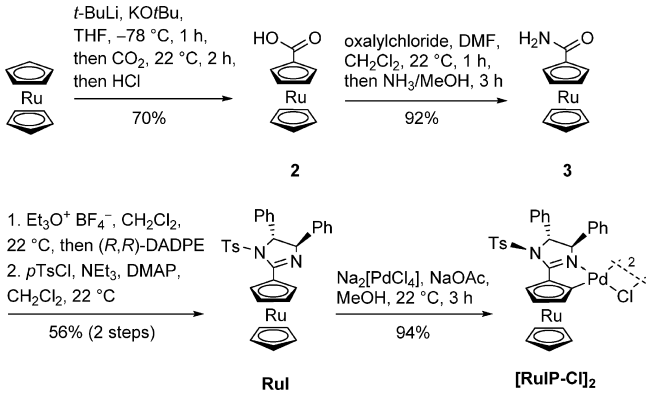
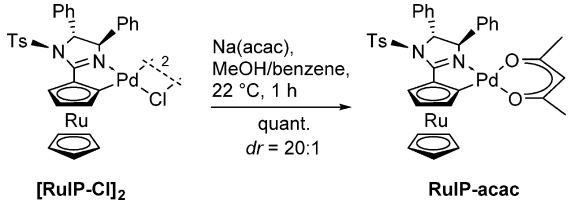


Figure 2. X-ray single crystal structure analysis of $[RuBIP\text{-}Cl]_2$ (color code: C (gray); N (blue); O (red); S (yellow); Cl (green); Ru (turquoise); Pd (magenta)). Hydrogen atoms and chloroform (7 per unit cell) are omitted for clarity in the ORTEP plot (ellipsoids at 50% probability level). Two different views are shown. Selected bond lengths (Å) and angles (deg): C−Pd, 1.914(16)−2.00(2); N−Pd, 1.977(17)−2.075(16); $Cl_{cis\text{-}to\text{-}C}$−Pd, 2.309(5)−2.329(5); $Cl_{trans\text{-}to\text{-}C}$−Pd, 2.428(5)−2.443(5); C−Pd−N, 78.7(8)−83.1(7); C−Pd−$Cl_{cis\text{-}to\text{-}C}$, 93.1(6)−95.8(6); N−Pd−$Cl_{trans\text{-}to\text{-}C}$, 93.3(4)−95.5(4); Cl−Pd−Cl, 90.48(17)−90.97(16); N−Pd−$Cl_{cis\text{-}to\text{-}C}$, 173.0(5)−175.0(4); C−Pd−$Cl_{trans\text{-}to\text{-}C}$, 172.9(6)−176.2(6).

Scheme 2. Diastereoselective Synthesis of the Chloride Bridged Palladacycle $[RuIP\text{-}Cl]_2$



Scheme 3. Formation of the Monomeric RuIP-acac for the *dr* Determination



palladacycles.[24] For the distance of the centroids of both Cp ligands in one metallocene fragment, values between 3.627 and 3.641 Å have been determined.[25]

Comparison of RuBIP to FBIP in Asymmetric Catalysis. As already mentioned above, the metal/metal distance is a crucial parameter for cooperative effects in bimetallic catalysis.[2] Since for identical Pd−C/C′−Pd′ twist angles the intermetallic distance is larger in RuBIP as compared to FBIP, we were interested in the effect of the increased Cp/Cp-distances in bimetallic asymmetric catalysis. Albeit by rotation around the Fe−Cp or Ru−Cp axes the Pd/Pd distances can adopt the same values over a relatively broad range, an identical Pd/Pd-

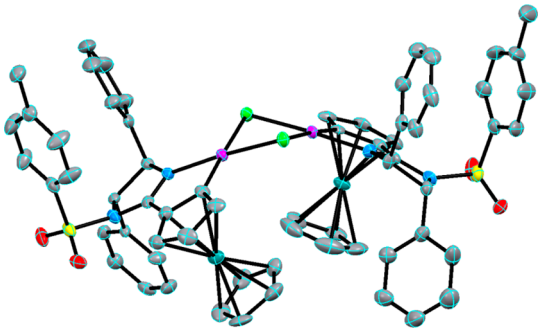


Figure 3. X-ray single crystal structure analysis of $[RuIP\text{-}Cl]_2$ (color code: C (gray); N (blue); O (red); S (yellow); Cl (green); Ru (turquoise); Pd (magenta)). Hydrogen atoms and dichloromethane (1 per unit cell) are omitted for clarity in the ORTEP plot (ellipsoids at 50% probability level). Selected bond lengths (Å) and angles (deg): C−Pd, 1.959(6)−1.967(5); N−Pd, 2.025(5)−2.042(5); $Cl_{cis\text{-}to\text{-}C}$-Pd, 2.3328(14)−2.3348(14); $Cl_{trans\text{-}to\text{-}C}$-Pd, 2.4506(13); C−Pd−N, 80.4(2)−80.6(2); C−Pd−$Cl_{cis\text{-}to\text{-}C}$, 93.35(18)−94.41(17); N−Pd−$Cl_{trans\text{-}to\text{-}C}$, 96.01(13)−97.22(13); Cl−Pd−Cl, 88.87(5)−88.92(5); N−Pd−$Cl_{cis\text{-}to\text{-}C}$, 173.59(13)−173.64(13); C−Pd−$Cl_{trans\text{-}to\text{-}C}$, 174.87(16)−176.02(17).

distance would require different Pd−C/C′−Pd′ twist angles and thus different reactive conformations for both catalyst systems, which should result in different reactivities and stereoselectivities. To allow for a first comparison, we have selected several catalytic asymmetric reactions,[26] for which we have previously already demonstrated that a bimetallic catalyst is either essential for sufficient reactivity or high enantioselectivity or for the formation of a certain stereoisomer.

One of these applications is the catalytic asymmetric [3,3]-rearrangement of (*Z*)-configured allylic *N*-aryltrifluoroacetimidates, which is known as Overman or aza-Claisen rearrangement.[27] The bis-Pd catalyst FBIP[3a,b] and the corresponding heterodinuclear Pd−Pt catalyst[28] are the most active enantioselective catalysts known so far for the rearrangement of $Z_{C=C}$-configured allylic *N*-aryltrifluoroacetimidates. The allylic imidate rearrangement catalyzed by chiral palladacycles

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is known to proceed stereospecifically, i.e., $E_{C=C}$- and $Z_{C=C}$-configured substrates in general provide different enantiomers in excess.[29] As *Z*-olefins are often more readily available in geometrically pure form (avoiding the need for a tedious separation of isomers), the use of the $Z_{C=C}$-configured substrates is synthetically attractive. On the other hand though, the $Z_{C=C}$-substrates are much less reactive than the corresponding $E_{C=C}$-substrates in the allylic imidate rearrangements. This is due to an unfavorable axial orientation of the *Z*-olefin substituent in the accepted halfchair-like transition state of the rate determining C−N bond formation and the ensuing cyclic σ-alkyl-Pd intermediate.[30] With the above-mentioned bimetallic complexes, a catalytic activity has been found that is at least 1−2 orders of magnitude higher than with the most active mono-Pd complexes using this difficult substrate class.[29] This points to a synergistic action of both metal centers, which has been explained by an initial bimetallic precoordination of the substrate.[28,27d]

Table 1 shows a comparison of the performance of the $[FBIP\text{-}Cl]_2$[3a,b] and $[RuBIP\text{-}Cl]_2$ activated by silver tosylate for chloride/tosylate ligand exchange (to facilitate the substrate coordination) under identical reaction conditions previously optimized for $[FBIP\text{-}Cl]_2$.[3a,b] With substrate **4a** carrying an *n*Pr residue as R^Z, the ruthenocene based catalyst showed at room temperature a slightly lower reactivity than the FBIP complex (entries 1 and 2), but still provided the product with a very high enantiomeric excess. In contrast, at 55 °C employing only 0.05 mol % of the precatalysts, RuBIP was more active than FBIP (entries 3 and 4).

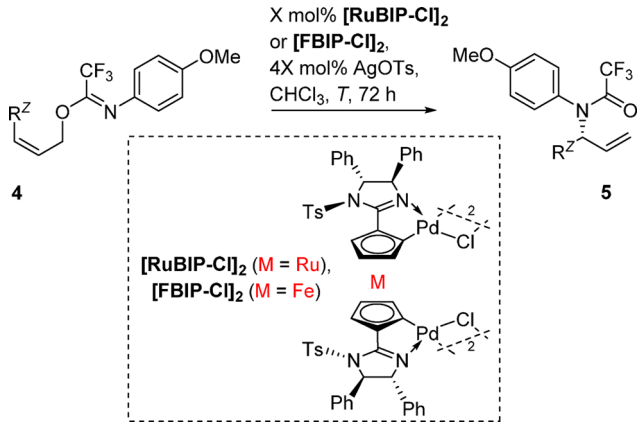
Very similar results were also obtained for substrate **4b** carrying a phenethyl residue R^Z, either at room temperature with a higher activity of FBIP (entries 5 and 6) or at 55 °C with RuBIP being more active, in particular at a precatalyst loading of only 0.1 mol % (87% vs 43% yield, entries 9 and 10). The opposite behavior was noticed for the branched substrate **4c** (R^Z = *i*Bu, entries 11−14) with a slightly higher activity of RuBIP at room temperature compared to FBIP, whereas at 55 °C working with low catalyst loadings, the FBIP system was found to be more active.

The conversion was monitored in the case of the rearrangement of substrate **4a** at 55 °C via ^{1}H NMR (Figure 4). This comparison shows a higher activity of the RuBIP system in particular at higher conversions. Using 0.05 mol % of precatalyst, after 24 h, 88% of the rearrangement products are formed with RuBIP, whereas with FBIP the yield is just 65% after that time (69% after 72 h). This might either indicate a higher catalyst stability for the ruthenocene based bispalladacycle or a lower level of product inhibition.

Control experiments were performed with the ruthenocene monopalladacycle under the conditions of Table 1, entry 3, but using 0.1 mol % of $[RuIP\text{-}Cl]_2$ to allow for the same Pd loading as with 0.05 mol % of $[RuBIP\text{-}Cl]_2$. After the catalyst activation by 0.2 mol % of AgOTs, the product was formed in just 31% yield with an *ee* of 68%. As expected, the monopalladacycle is thus significantly less active and enantioselective in comparison to the bispalladacycles supporting a cooperation of both metal centers in RuBIP.

The above results demonstrate that both FBIP and RuBIP are excellent catalysts for this reaction type, allowing for excellent levels of enantioselectivity. It somewhat depends on the substrate and the conditions, which of both catalysts show the better catalytic performance.

Table 1. Comparison of RuBIP and FBIP in the Catalytic Asymmetric Rearrangement of (*Z*)-Configured Allylic Imidates 4



entry	M	4	R^Z	precatalyst loading: X mol %	*T* [°C]	yield (%)[a]	*ee* (%)[b]
1	**Ru**	**a**	*n*Pr	1.0	20	**88**	**96**
2[3b]	Fe					96	98
3	**Ru**	**a**	*n*Pr	0.05	55	**87**	**96**
4[28]	Fe					68	97
5	**Ru**	**b**	$Ph(CH_2)_2$	1.0	20	**88**	**98**
6[3b]	Fe					99	96
7	**Ru**	**b**	$Ph(CH_2)_2$	0.2	55	**98**	**94**
8[3b]	Fe					90	95
9	**Ru**	**b**	$Ph(CH_2)_2$	0.1	55	**87**	**95**
10[28]	Fe					43	87
11	**Ru**	**c**	*i*Bu	1.0	20	**90**	**98**
12[3b]	Fe					87	98
13	**Ru**	**c**	*i*Bu	0.2	55	**71**	**96**
14[3b]	Fe			0.1		86	98

[a]Yield of isolated product. [b]Determined by HPLC after hydrolysis of the amide.

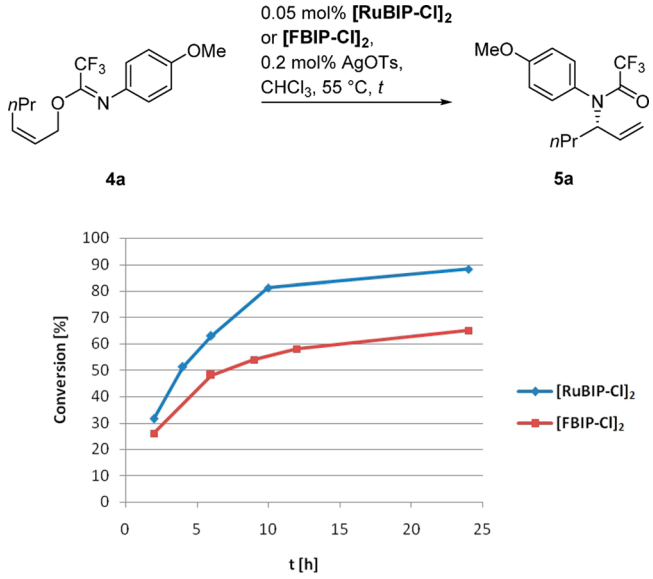


Figure 4. Comparison of the reactivity using the bis-Pd precatalysts $[RuBIP\text{-}Cl]_2$ (blue curve) and $[FBIP\text{-}Cl]_2$ (red curve)—activated by AgOTs—for the rearrangement of substrates **4a** by monitoring via ^{1}H NMR (conditions of Table 1, entries 1 and 2).

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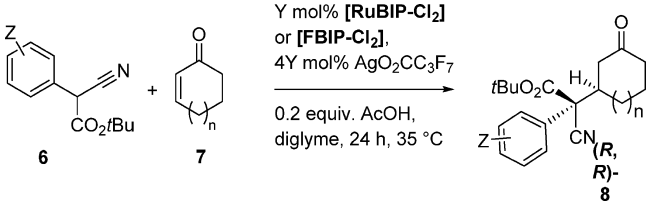
The second application that has been studied is the direct 1,4-addition[31] of α-cyanoacetates **6** to enones, which generates all-C-substituted quaternary stereocenters[32] in densely functionalized products. The latter are synthetically attractive chiral building blocks, e.g., toward enantioenriched α- and β-amino acid derivatives.[33] Our previous studies have shown that mono- and bispalladacycles can be employed for stereodivergent access to the addition products: while the use of vinylketones as Michael-acceptors resulted in the preference of different enantiomers using either FBIP or a pentaphenylferrocene monopalladacycle catalyst, the use of cyclic ketones as Michael-acceptors resulted in epimeric products possessing vicinal quaternary and tertiary stereocenters.[6b] While (S_p)-configured FBIP generated the (*R*,*R*)-configured products as the major diastereomers with high enantioselectivity, the (S_p)-configured pentaphenylferrocene monopalladacycle preferentially provided highly enantioenriched (*R*,*S*)-diastereomers in excess. Kinetic studies strongly support a bimetallic reaction pathway with the dinuclear Pd-complex, in which both substrates are simultaneously activated by the two Pd-centers within one catalyst molecule, culminating in an extraordinarily fast C−C bond formation elementary step.[6] Table 2 shows results obtained with RuBIP and FBIP[6b] for comparison. In general, it can be stated that both the RuBIP and the FBIP system usually provide good activity and enantioselectivity. In terms of diastereoselectivity FBIP is usually superior with only one exception found (entries 11 and 12). In terms of enantioselectivity it depends on the substrate which of both systems is more efficient. A cooperativity of both Pd-centers like in FBIP is also likely in RuBIP. This is supported by a control experiment with the mono-Pd catalyst RuIP, which is significantly less efficient in comparison to RuBIP. Under the conditions of Table 2/entry 1, but using 1 mol % of $[\text{RuIP-Cl}]_2$ instead of 0.5 mol % of $[\text{RuBIP-Cl}]_2$, the product was formed in a moderate yield of 55% and with only poor diastereoselectivity (*dr* = 1.2:1) and low enantioselectivity (45% *ee* for the major diastereomer).

Table 2. Comparison of RuBIP and FBIP in the Direct 1,4-Addition of α-Cyanoacetates to Cyclic Enones

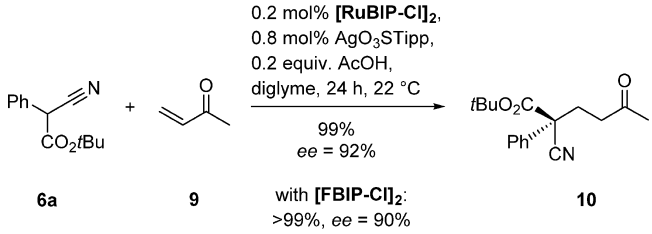


entry	M	Y	Z	*n*	8	yield (%)[a]	*dr*[b]	*ee* (%) (*R*,*R*)-8[c]
1	**Ru**	0.5	H	1	**a**	**82**	**5.2:1**	**81**
2[6b]	Fe					99	8.0:1	94
3	**Ru**	0.5	H	0	**b**	**84**	**4.5:1**	**95**
4[6b]	Fe					99	4.6:1	90
5	**Ru**	0.5	4-Me	1	**c**	**90**	**7.3:1**	**97**
6[6b]	Fe					75	11.5:1	94
7	**Ru**	0.25	4-Cl	1	**d**	**99**	**3.3:1**	**87**
8[6b]	Fe					99	7.3:1	99
9	**Ru**	0.5	3-OMe		**e**	**90**	**5.9:1**	**91**
10[6b]	Fe					99	8.0:1	93
11	**Ru**	0.5	3-Me		**f**	**81**	**8.1:1**	**94**
12[6b]	Fe					85	6.7:1	95
13	**Ru**	0.25	3-Cl		**g**	**90**	**3.5:1**	**80**
14[6b]	Fe					97	4.9:1	87

[a]Yield of isolated product. [b]*dr* = (*R*,*R* + *S*,*S*):(*S*,*R* + *R*,*S*), determined by HPLC. [c]Determined by HPLC.

The use of RuBIP for the significantly more reactive methylvinylketone (MVK, **9**) as Michael acceptor in combination with α-cyanoacetate **6a** resulted in a nearly quantitative yield (99%) and high enantioselectivity (*ee* = 92%, Scheme 4)

Scheme 4. Comparison of RuBIP and FBIP in the Direct 1,4-Addition of α-Cyanoacetate 6a to MVK



with a precatalyst loading of 0.2 mol %. A comparison with FBIP under identical reaction conditions (>99% yield, *ee* = 90%)[6a] reveals that the enantioselectivity is slightly better for RuBIP in that case. A control experiment using 0.4 mol % of $[\text{RuIP-Cl}]_2$ provided the 1,4-adduct in 43% yield and as a racemate, again supporting the cooperativity of both Pd centers in RuBIP.

The third application is the 1,4-addition of in situ generated azlactones[34] to enones, which is an attractive step-economic reaction providing access to masked and functionalized highly enantioenriched quaternary α-amino acid derivatives of biological interest.[7a−c] The azlactones are produced in the reaction mixture from racemic *N*-benzoylated α-amino acids and acetic anhydride, which is used as a cosolvent in combination with acetic acid as a solvent. Our previous investigations have shown that $[\text{FBIP-Cl}]_2$ activated by silver triflate is capable of forming the tandem reaction product in good yields and with high enantioselectivity, if NaOAc is used as a Brønsted base cocatalyst.[7a,c] In contrast, pentaphenylferrocene monopalladacycles showed poor activity in this reaction type in control experiments supporting a bimetallic mechanism for FBIP, in which both Pd-centers cooperate.[7a,c,35] This synergy has been explained by simultaneous activation of the enone electrophile and the azlactone pronucleophile by different Pd centers.[7c] Table 3 shows a comparison of results obtained with $[\text{FBIP-Cl}]_2$[7a,c] and $[\text{RuBIP-Cl}]_2$.

Our previous studies with FBIP had shown that the use of the racemic N-benzoylated alanine (R^1 = Me) is relatively difficult in terms of enantioselectivity.[7a,c] A comparison with RuBIP shows that FBIP is clearly superior for this intricate example (entries 1 and 2). For the other investigated substrates the differences are much less pronounced. In the other examples (entries 3−10) FBIP was found to be always somewhat superior regarding the enantioselectivity, but the latter is still high with RuBIP. However, in terms of reactivity RuBIP was found to be superior for four out of six examples (entries 1, 5, 7, 11).[36]

A related reaction has been investigated as a fourth application, in which nitroolefins **14** are reacted with the racemic *N*-benzoylated amino acids **11** and acetic anhydride in the presence of manganese(II)acetate and acetic acid (Table 4).[7e] Using the bimetallic RuBIP and FBIP[7e] systems,

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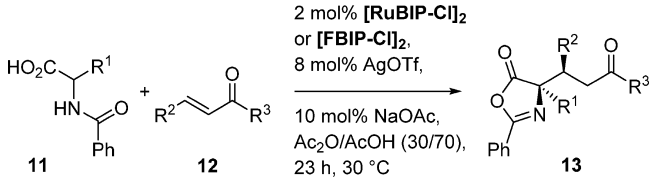
Table 3. Comparison of RuBIP and FBIP in the Domino Azlactone Formation/Michael Addition

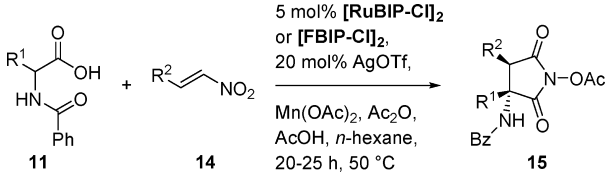


11 12 13

entry	precatalyst	13	R^1	R^2	R^3	yield (%)[a]	*dr*[b]	*ee* (%)[c]
1	**[RuBIP-Cl]$_2$**	**a**	Me	Ph	Me	**97**	**>98:2**	**46**
2[7c]	[FBIP-Cl]$_2$					95	>98:2	76
3	**[RuBIP-Cl]$_2$**	**b**	*n*Pr	Ph	Me	**81**	**>98:2**	**97**
4[7c]	[FBIP-Cl]$_2$					89	>98:2	98
5	**[RuBIP-Cl]$_2$**	**c**	Bn	Ph	Me	**45**	**>98:2**	**74**
6[7c]	[FBIP-Cl]$_2$					41	>98:2	81
7	**[RuBIP-Cl]$_2$**	**d**	*n*Pr	4−Cl-C$_6$H$_4$	Me	**98**	**>98:2**	**94**
8[7c]	[FBIP-Cl]$_2$					85	>98:2	98
9	**[RuBIP-Cl]$_2$**	**e**	*n*Pr	Ph	Ph	**83**	**>98:2**	**83**
10[7c]	[FBIP-Cl]$_2$					87	>98:2	90
11	**[RuBIP-Cl]$_2$**	**f**	*n*Pr	2-furyl	Me	**93**	**>98:2**	**92**
12[7c]	[FBIP-Cl]$_2$					88	>98:2	96

[a]Yield of isolated product. [b]Determined by ^{1}H NMR of the isolated product. [c]Determined by HPLC.

Table 4. Comparison of RuBIP and FBIP in the Asymmetric Synthesis of α-Aminosuccinimides 15 by Tandem Azlactone Formation/Michael Addition/Nef Type Reaction



11 14 15

entry	precatalyst	15	R^1	R^2	yield (%)[a]	*dr*[b]	*ee* (%)[c]
1	**[RuBIP-Cl]$_2$**	**a**	Me	Ph	**83**	**>50:1**	**58**
2[7e]	[FBIP-Cl]$_2$				95	>50:1	82
3	**[RuBIP-Cl]$_2$**	**b**	*n*Pr	Ph	**49**	**9:1**	**81 and 87**[d]
4[7e]	[FBIP-Cl]$_2$				91	>50:1	93
5	**[RuBIP-Cl]$_2$**	**c**	*n*Pr	*i*Pr	**58**	**>50:1**	**94**
6[7e]	[FBIP-Cl]$_2$				46	>50:1	95
7	**[RuBIP-Cl]$_2$**	**d**	$(CH_2)_2CO_2Me$	3-MeOC$_6$H$_4$	**21**	**>50:1**	**57**
8[7e]	[FBIP-Cl]$_2$				67	>50:1	93

[a]Yield of isolated product. [b]Determined by ^{1}H NMR of the isolated product. [c]Determined by HPLC. [d]For the minor diastereomer.

biologically interesting α-aminosuccinimides are generated. Our previous investigations suggest a bimetallic reaction pathway also in this case, because related ferrocene monopalladacycles provided either no product at all (pentaphenylferrocene core) under the standard conditions or led to significantly lower enantioselectivity (ferrocene core).[7e]

A comparison between the RuBIP and FBIP catalyst in this tandem reaction,[37] which involves an in situ azlactone formation, a 1,4-addition of the generated azlactone to the nitroolefin, and a Nef-type-reaction as key steps,[38] reveals that the FBIP catalyst is superior in three out of four cases investigated in terms of activity and enantioselectivity. Only with a branched aliphatic nitroolefin, which provided the lowest reactivity in our previous study using the FBIP catalyst, was the RuBIP catalyst somewhat superior in terms of reactivity, and a comparably high enantioselectivity was attained (entries 5 and 6). For this latter example, a control experiment was performed under identical reaction conditions but with RuIP (10 mol % [RuIP-Cl]$_2$, activated by 20 mol % AgOTf) providing the product with lower enantioselectivity (*ee* = 83%).[39]

CONCLUSION

In conclusion, we have reported the first highly diastereoselective direct mono- and biscyclopalladations of chiral enantiopure ruthenocene derivatives. With *N*-tosylated imidazolines as *ortho*-directing groups the cyclopalladation conditions previously optimized for the corresponding ferrocene ligands could be employed and resulted—in contrast to earlier investigations on diastereoselective cyclopalladations of chiral ruthenocenes—in nearly diastereomerically pure palladacycles. The bispalladacycle [RuBIP-Cl]$_2$ was studied (after activation by a chloride ligand exchange) as a bimetallic catalyst in a number of different synthetic applications, in which the intramolecular cooperation of two Pd centers is likely to play a crucial role for the reaction outcome. In RuBIP, the Cp/Cp distance is increased by ca. 10% as compared to FBIP, thus resulting in larger Pd/Pd distances for identical Pd−C/C′−Pd′ twist angles. Since the intermetallic distance constitutes an important parameter in bimetallic catalysis, the results obtained with RuBIP in catalysis were directly compared to results

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previously reported for the corresponding ferrocene [FBIP-Cl]$_2$. From all four reaction types studied, it is obvious that the catalytic outcome is influenced by the metallocene Cp/Cp distance. For each reaction studied, it was found that with some of the investigated substrates the ferrocene based catalyst is superior, whereas for other substrates the ruthenocene backbone is more favorable, even though the catalytic applications have only been optimized for the FBIP system, but not for RuBIP. Based on the above investigations, we consider RuBIP to be a useful and complementary alternative to FBIP.

EXPERIMENTAL SECTION

General Considerations. All reactions were performed in oven-dried glassware under a positive pressure of nitrogen. THF, acetonitrile, and dichloromethane were dried under N_2 over molecular sieves in a solvent purification system. The solvents chloroform, methanol, and ethyl acetate were used as purchased from commercial suppliers. Solvents were usually removed at 30−40 °C by rotary evaporation at 600−10 mbar pressure, and nonvolatile compounds were dried in vacuo at 0.1 mbar. Yields refer to isolated, pure compounds and are calculated in mol % of the used starting material. NMR spectra were recorded at 21 °C operating at 300 or 500 MHz (^{1}H), 125 MHz (^{13}C), and 235 MHz (^{19}F). Chemical shifts are referred to in terms of parts per million, and *J*-coupling constants are given in hertz. Abbreviations for multiplicities are as follows: *s* (singulet), *d* (doublet), *t* (triplet), *m* (multiplet), and *b* (broad signal). IR spectra were recorded on an ATR unit, and the signals are given by wavenumbers (cm^{-1}). Optical rotation was measured at the sodium D line in a cell with 100 mm path length. Melting points were measured in open glass capillaries and are uncorrected. Mass spectra were measured on an ESI spectrometer. Single crystal X-ray analysis was performed by Dr. Wolfgang Frey (Universität Stuttgart).

General Procedure for the Enantioselective Aza-Claisen Rearrangement (GP1). Silver *p*-toluenesulfonate (4.00 equiv) was dissolved in MeCN (0.1 mL/mg), and the solvent was subsequently removed by a stream of dinitrogen. A solution of [RuBIP-Cl]$_2$ (1.00 equiv) in CH_2Cl_2 (0.1 mL/mg) was then added under a dinitrogen atmosphere. The mixture was stirred overnight at room temperature and subsequently filtered through Celite/CaH_2. The filter cake was extracted with CH_2Cl_2 until the organic solution was colorless. The solvent was removed by a steady stream of dinitrogen and finally by high vacuum. A stock solution of the activated catalyst was prepared by dissolving the solid in dry $CHCl_3$ (20 mmol/L). The required amount of this solution was added to the substrate (prepared according to Overman et al.[29a]) under an air atmosphere. The reaction tube was sealed, and the reaction mixture was stirred for the indicated time at the indicated temperature. Afterward, the reaction mixture was suspended in petroleum ether/ethyl acetate (10/1) and subsequently purified by filtration over silica gel.

General Procedure for the Catalytic Asymmetric Michael Addition of α-Cyanoacetates to Cyclic Enones (GP2). Silver heptafluorobutyrate (4.0 equiv) was dissolved in acetonitrile (0.1 M), and the solvent was then removed under reduced pressure. A solution of the precatalyst [RuBIP-Cl]$_2$ in CH_2Cl_2 (1 mL/5 mg silver salt) was added, and the suspension was stirred for 1 h at room temperature. Afterward, the suspension was filtrated over Celite, and the solvent was removed by a steady flow of dinitrogen followed by high vacuum. A stock solution was prepared in diglyme. To the corresponding α-aryl-α-cyanoacetate (1 equiv) in diglyme were added acetic acid as a stem solution in diglyme (0.2 equiv), the indicated amount of the activated catalyst as a stem solution in diglyme (total amount of solvent: 0.34 mL for 0.18 mmol substrate), and finally the corresponding enone (2.0 equiv). The reaction mixture was stirred for 24 h at 35 °C. Afterward *n*-pentane was added to precipitate the catalyst, and the mixture was subjected to column chromatography (silica, pentane/EtOAc, 4:1).

General Procedure for the Catalytic Asymmetric Tandem Azlactone Formation/Michael Addition (GP3). A solution of [RuBIP-Cl]$_2$ and silver triflate (4.0 equiv per [RuBIP-Cl]$_2$) in acetonitrile (1 mL/5 mg silver salt) was stirred for 6 h at room temperature under dinitrogen. The mixture was then filtered through a pad of Celite, and the solvent was removed under reduced pressure. A stock solution of the activated catalyst was subsequently prepared in HOAc/Ac_2O (7/3).

To the corresponding *N*-benzoyl amino acid (1.0 equiv), the corresponding enone (2.0 equiv) was added under a dinitrogen atmosphere. To this mixture, stem solutions of NaOAc (0.1 equiv) and the above prepared activated catalyst (starting from 2 mol % [RuBIP-Cl]$_2$) in HOAc/Ac_2O (7/3, total amount of solvent: 0.325 mL for 0.27 mmol substrate) were successively added. The mixture was heated to 30 °C while shaking at 450 rpm. After 23 h the reaction mixture was cooled to room temperature and was subjected to column chromatography (silica, pentane/Et_2O, 4:1).

General Procedure for the Catalytic Asymmetric Synthesis of α-Alkyl-α-Amino Succinimides 15 (GP4). [RuBIP-Cl]$_2$ and silver triflate (4 equiv per dimeric precatalyst molecule) were dissolved in acetonitrile (1 mL per 5 mg [RuBIP-Cl]$_2$). The solution was placed in a supersonic bath at room temperature for 30 min. The mixture was subsequently filtered through Celite, and free acetonitrile was removed under reduced pressure. A stock solution in acetic acid (3.7 mg [RuBIP-Cl]$_2$ in 100 μL HOAc) was subsequently prepared.

The corresponding *N*-benzoyl amino acid (**11**, 1.2 equiv., 0.30 mmol), the corresponding nitroolefin (**14**, 1.0 equiv., 0.25 mmol), and manganese acetate (5.0 equiv., 1.25 mmol, 216.3 mg) were charged into a vial. A vacuum was then applied, and the vial was subsequently flushed with nitrogen (3 times repeated). *n*-Hexane (0.25 mL) and the activated catalyst (prepared from 0.05 equiv., 12.5 μmol, 31.6 mg [RuBIP-Cl]$_2$ as described above) as a stock solution in acetic acid (0.85 mL) were added. After acetic anhydride (225 μL) was added, the mixture was directly warmed to 50 °C. After 25 h at this temperature, the mixture was cooled to room temperature, and chloroform (ca. 12 mL) was added. The resulting mixture was washed with water (ca. 50 mL) twice. The aqueous phases were extracted with chloroform (ca. 10 mL). The combined organic phases were then dried over Na_2SO_4. After filtration and concentration, the crude material was used for silica gel chromatography (PE:EE 1.5:1) to isolate the targeted compound.

ASSOCIATED CONTENT

Supporting Information

Characterization data and CIF files. 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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(20) Supplementary crystallographic data for this compound have been deposited with the Cambridge Crystallographic Data Centre as deposition 988586. This material is available free of charge *via* the Internet at http://pubs.acs.org and http://www.ccdc.cam.ac.uk/products/csd/request/.
(21) Like for $[FBIP\text{-}Cl]_2$, the sulfonylated N atoms of $[RuBIP\text{-}Cl]_2$ are pyramidalized, but to a lower degree. The pyramidality at a given atom can be expressed by the difference between 360° and the sum of the three bond angles at that atom. For the present analysis, corresponding values at the N centers are between ca. 1.8° and ca. 5.9° (for $[FBIP\text{-}Cl]_2$, these values are between ca. 13° and 16°).[3b]
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