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SYNTHESIS OF CHIRAL TROPOPODANDS HAVING L-AMINO ACID MOIETIES AND ABILITY OF THEIR METAL COMPLEXES AS AN ASYMMETRIC CATALYST

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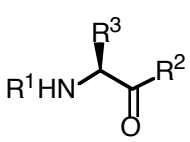
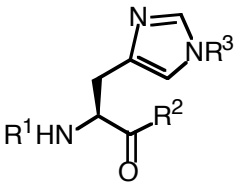
Abstract – Optical active tropopodands (**10** and **11**) having neutral L-amino acids and L-histidine moieties were synthesized. Within their metal complexes, Pd complexes of histidine-tropopodands (**11b** and **11c**) bearing bulky amide moieties showed good ability as an asymmetric catalyst in conjugate addition.

Chiral [N, O] ligand-metal complexes are well known to play a roll of asymmetric catalysts[1] and many applications to conjugate addition had been reported.[2] Aminotroponimine (ATI),[3] a nitrogen-analog of tropolone, and compounds with its unit(s) such as maclocyclic tropocoronands (TCs)[4,5] have metal coordination ability.[3,5] Although metal complexes of their optically active derivatives are also expected to be asymmetric catalysts, the investigation is few.[6] In the course of our research for ATI derivatives,[7] some asymmetrical catalytic potential of TCs bridged by L-amino acid linker chains in conjugate addition was already reported.[7d] However, the chemical and asymmetrical yields were not enough because of steric repulsion at the formation of metal complexes with a substrate. We have applied acyclic tropopodands (TPs), which could adopt more flexible conformations in their metal complex-substrate conjugates, to overcome the defect. As for chiral sources, neutral L-amino acids such as alanine (Ala), valine (Val) and phenylalanine (Phe) and basic one as histidine (His) were selected. With the efficient metal coordination at both ATI and amino acid moieties in mind, the amino acid residues were located at adjacent positions of ATI moiety in the designed chiral TPs (**10** and **11**). We describe herein the synthesis of these TPs as a novel family of non-benzenoid chiral ligands. The characteristic coordination property for Ni(Ⅱ) and Pd(Ⅱ) ions and a part of their asymmetrical catalytic ability are also reported.

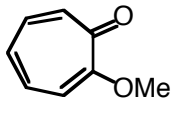
This paper is dedicated to Prof. Barry M. Trost on the occasion of his 65th birthday.



1a: R^1 = H, R^2 = OH, R^3 = Me,
1b: R^1 = H, R^1 = OH, R^3 = Pr-*i*
1c: R^1 = H, R^2 = OH, R^3 = CH_2Ph
2: R^1 = Cbz, R^2 = OH
3: R^1 = Cbz, R^2 = NHPr-*n*
4: R^1 = H, R^2 = NHPr-*n*



5: R^1 = R^3 = H, R^2 = OH
6: R^1 = R^3 = Tr, R^2 = OH
7a: R^1 = R^3 = Tr, R^2 = NHPr-*n*
7b: R^1 = R^3 = Tr, R^2 = NHPr-*i*
7c: R^1 = R^3 = Tr, R^2 = NHBu-*t*
8: R^1 = R^3 = H



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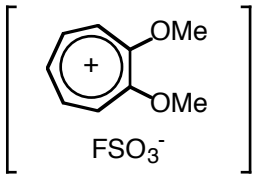
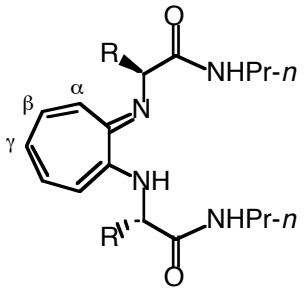
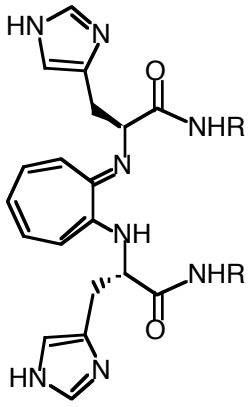


9'



10a: R = Me
10b: R = Pr-*i*
10c: R = CH_2Ph

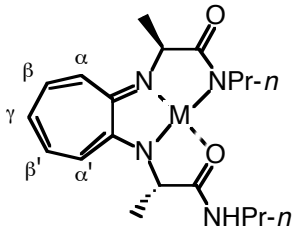


11a: R = Pr-*n*
11b: R = Pr-*i*
11c: R = Bu-*t*

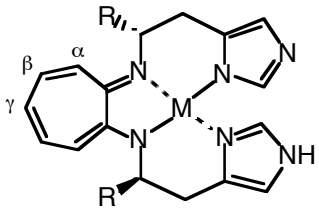
The synthesis of neutral L-amino acid-TPs (**10**) was carried out as follows. To avoid epimerization at the amino acid moieties, amide products (**3a–c**) were synthesized by the reaction of *N*-benzyloxycarbonyl-(Cbz)-amino acids (**2a–c**), derived from L-amino acids (**1a**: L-Ala, **1b**: L-Val, **1c**: L-Phe) and Cbz-Cl, with *n*-propylamine in the presence of DCC. After deprotection of the Cbz groups by hydrogenation, resulting linker chains (**4a–c**) were condensed with reactive dimethoxytropyrium ion (**9'**), prepared from tropolone methyl ether (**9**) with FSO_3Me, in methanol at room temperature to give expected TPs (**10a–c**) as yellow needles or solids in 53, 51 and 39 % yields, respectively (mp 184–186 °C for **10a**, 160–163 °C for **10b**, 95–97 °C for **10c**). The ^{1}HNMR spectrum of **10a** showed relevant protons for the moieties of alanine, *n*-propylamine and ATI. At the seven membered ring moiety, only three kinds of protons (δ: 6.32 for H-α, 6.34 for H-γ, 6.82 for H-β) were observed. This is a characteristic pattern of ATI-compounds arising from the fast equilibrium by the hydrogen bonding between adjacent NH and C=N groups. Other spectral data were also supported the proposed structure. And then the synthesis of L-histidine (His)-TPs (**11a–c**) with different amide moieties was achieved. Triphenylmethyl (Tr)-L-His (**6**),[8] prepared from L-His (**5**), was condensed with three kinds of amines (*n*-propyl-, *i*-propyl- and *t*-butylamine) by DCC method to afford protected His-chains (**7a–c**). After deprotection of the Tr groups by the reaction in hot acetic acid/H_2O, resulting diacetates of **8a–c** were reacted with **9'** to afford designed His-TPs (**11a–c**) as yellow solid in 31, 20 and 25 % yields, respectively (mp 124–125 °C for **11a**, 198–200 °C for **11b**, 117–119 °C for **11c**). Their spectral data were consistent with the proposed structures.

Neutral amino acid-TPs (**10**) have two kinds of coordination sites, that is, ATI and amide (O- and/or N-coordination) moieties, whereas His-TPs (**11**) have imidazole (Im) one furthermore. Hence the different coordination styles of **10** and **11** for transition metal ions are expected. To elucidate the coordination property for Ni(Ⅱ) and Pd(Ⅱ) ions in solution, we investigated by use of UV-VIS, MS, ^{1}HNMR and IR

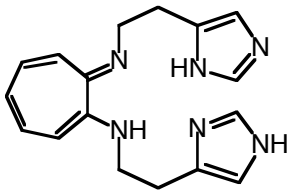
spectral data. From UV-VIS spectrum of Ala-TP (**10a**) with $Ni(OAc)_2$, the complexation was recognized (λ_{max}^{CT}: 508, 557 nm). FAB-MS spectrum of **10a**-Ni gave the molecular ion peak of mononuclear complex (MH^+: *m/z* 403, M = **10a**–1+Ni) and its isotopic peaks. All peaks of the ^{1}HNMR spectrum were shown at the region of 0 to 10 ppm, indicating the planar coordination for Ni(Ⅱ) ion (S = 0, low-spin complex).[4b] Five kinds of peaks at the seven membered ring moiety (δ: 6.14 for H-α, 6.22 for H-α', 6.33 for H-γ, 6.82 for H-β, 6.84 for H-β') suggested that the Ni(Ⅱ) ion was coordinated with an asymmetrical style. The IR spectrum indicated the split peaks at amide moieties ($\nu_{C=O}$: **10a**-Ni; 1624 for O^{amide}-coordination, 1655 for N^{amide}-coordination, **10a**; 1652 cm^{-1}). Considering the above spectral data, the **10a**-Ni complex should have the style of mononuclear, planar and [N^{ATI}, N^{ATI}, N^{amide}, O^{amide}] coordination. In the case of **10a** with Pd(Ⅱ) ion, the similar data were obtained, suggesting that **10a**-Pd complex should have the same style of **10a**-Ni. In contrast, complexes of His-TPs (**11**) showed the other style because of strong coordination ability at the Im moieties. Complexation and 1 : 1 formation of **11a** with Ni(Ⅱ) ion were confirmed by the UV-VIS and MS spectra (λ_{max}^{CT}: 470, 590 nm, MH^+: *m/z* 535, M = **11a**–1+Ni). From the IR spectrum of **11a**-Ni, not coordination at amide moieties was observed ($\nu_{C=O}$: **11a**-Ni; 1651, **11a**; 1652 cm^{-1}). The ^{1}HNMR spectral pattern revealed the planar and symmetrical coordination style (δ: **11a**-Ni; 6.49 for H-α, 6.66 for H-γ, 7.13 for H-β, **11a**; 6.32 for H-α, 6.28 for H-γ, 6.80 for H-β). Coordination with the Im groups was confirmed by comparison with proton's shifts of histamine-TP derivative (**12**-Ni) (δ: **11a**-Ni; 7.00, 7.38 for Ims, **11a**; 6.86, 7.52, **12**-Ni; 7.04, 7.36, **12**; 6.86, 7.62). From similar spectral data of **11a**-Ni and **11a**-Pd, the **11a**-M complexes (M = Ni, Pd) should have the style of mononuclear, planar and [N^{ATI}, N^{ATI}, N^{Im}, N^{Im}] coordination. The X-Ray analysis is needed to estimate these structures, however, we have not obtained their single crystals yet.



10a-M: M = Ni (Ⅱ), Pd (Ⅱ)



11a-M: M = Ni (Ⅱ), M = Pd (Ⅱ), R = C(O)NHPr-*n*



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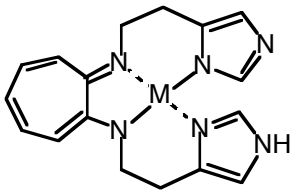
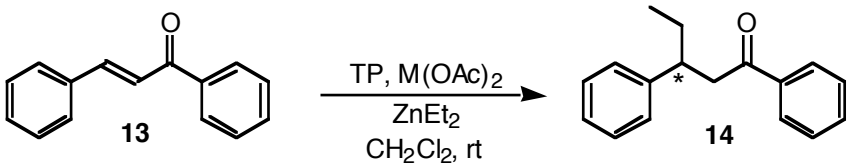


12-M: M = Ni (Ⅱ), M = Pd (Ⅱ)

The influence arising from different coordination styles of ligand-metal complexes in asymmetric reactions is of particular interest. Searching for the ability as an asymmetric catalyst, we attempted asymmetric conjugate addition of $ZnEt_2$ to chalcone (**13**)[2] with the chiral TPs (**10**, **11**)-metal complexes. In the presence of Ni and Pd complexes prepared from Val-TP (**10b**) and $M(OAc)_2$ (M = Ni and Pd), the values of enantiomer excess of the obtained **14**[9] were not high (Entries 1 and 2). The use of His-TP (**11a**) instead of **10b** resulted in acceleration of the reaction, but unfortunately, the values were still low (Entries

4 and 5). This acceleration should come from the coordination with Im moieties in the complexes. In the case of **11b** bearing bulky *i*-propyl groups at amide moieties, notwithstanding the similar low selectivity with **11b**-Ni (Entry 6), the pronounced steric effect of the Pd complex (**11b**-Pd) was indicated (75 % ee, Entry 7). More bulky *t*-butyl amide derivative (**11c**-Pd) provided the highest enantiomer excess of 81% so far (Entry 8). There is no precedent for such high enantioselective reaction using a combination of Pd and Zn. As shown in Entry 3, Pd ion is indispensable for this reaction. While the asymmetric reaction has not been optimized yet, it appears that **11b**- and **11c**-Pd complexes have considerably good potential as an asymmetric catalyst.

Table 1. Conjugate addition of $ZnEt_2$ to chalcone (**13**) in the presence of TP-metal complexes



Entry	TP	M	**13** / TP / $M(OAc)_2$ / $ZnEt_2$ (mol equiv.)	Time / h	**14** / %	% ee (*config.*)
1	**10b**	Ni	1 / 0.05 / 0.05 / 2	12	84	4 (*S*)
2	**10b**	Pd	1 / 0.01 / 0.01 / 2	13	73	8 (*S*)
3	**11a**	-	1 / 0.01 / - / 2	48	41	5 (*S*)
4	**11a**	Ni	1 / 0.01 / 0.01 / 2	3	82	4 (*S*)
5	**11a**	Pd	1 / 0.01 / 0.01 / 2	7	74	12 (*S*)
6	**11b**	Ni	1 / 0.01 / 0.01 / 2	4	56	4 (*S*)
7	**11b**	Pd	1 / 0.01 / 0.01 / 2	9	73	75 (*S*)
8	**11c**	Pd	1 / 0.01 / 0.01 / 2	3	61	81 (*S*)

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