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Asymmetric Diels−Alder Reactions of Unsaturated β-Ketoesters Catalyzed by Chiral Ruthenium PNNP Complexes

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The enantioselective formation of all-carbon quaternary centers is an area of intense research in which Diels−Alder reactions play a major role.[1] As a possible alternative to α,β-unsaturated aldehydes, doubly activated α-methylene β-ketoesters have been employed as dienophiles.[2] However, more bulky unsaturated β-ketoesters, such as cyclic carboxypentenones, are much less reactive dienophiles and challenge the known protocols due to their tendency to polymerization and keto−enol tautomerization.[3] Additionally, the corresponding tetrahydro-1-indanones are formed in low yield under harsh conditions,[4] and to the best of our knowledge, no enantioselective synthesis has been reported yet. We report here that our dicationic ruthenium PNNP complexes,[5] which efficiently catalyze the asymmetric Michael addition,[6] hydroxylation,[7] and fluorination[8] of saturated β-ketoesters, also promote the enantioselective Diels−Alder reaction of α-methylene β-keto esters to give tetrahydro-1-indanones. In particular, we show that the methodology gives access to enantiomerically pure *ent*- (or *nat*-) estrone derivatives, which is interesting in view of the application potential of these compounds, including the treatment of breast cancer.[9]

The catalyst is formed in situ by double chloride abstraction from $[RuCl_2(PNNP)]$ (**1**) with $(Et_3O)PF_6$ (2 equiv) in dichloromethane, which gives the putative dicationic species $[Ru(OEt_2)_2(PNNP)](PF_6)_2$ (**2**).[6] Complex **2** catalyzes the Diels−Alder reaction of the unsaturated β-ketoesters of type **3** with dienes **4**−**6**, to give the alkoxycarbonyltetrahydro-1-indanone derivatives **7**−**9** (Scheme 1). This is the first enantioselective synthesis of **7**−**9**, which are versatile intermediates as they contain multiple, separately addressable reaction sites besides the β-ketoester functionality.[10] Of these products, only **9c** has been previously prepared, though with low yield and using harsh conditions.[4] Preliminary studies showed that 2,3-dimethylbutadiene (**6**) can be used as a diene, but the best results were obtained with 2,3-(dibenzyloxy)butadiene (**4**) and 2,3-dimethoxybutadiene (**5**). With diene **4**, cyclopentanone derivatives of type **7** were formed with enantioselectivity of up to 93% ee (Table 1).[11]

A useful application of this method is the synthesis of the estrone derivative **11** from **3a** (or **3c**) and the unsymmetrical Dane's diene **10** (Scheme 2). Catalyst **2** gave crude **11a** as a single regioisomer of the ester-*exo* diastereoisomer (as determined by X-ray; see Supporting Information) in quantitative yield and 86% ee. Enantiomerically pure **11a** was obtained in 85% yield (based on **3a**, after recrystallization from 2-PrOH). The *exo*/*endo* ratio of crude **11a** is 27:1 (145:1 after one crystallization) as compared to methyl analogue **11c** (3:1), which indicates that the ^{t}Bu ester moiety on **3a** is pivotal to give excellent diastereoselectivity for the ester *exo* product. The absolute configuration of **11a** was shown to be 8*R*,13*S*,14*S* by reducing the enantiomerically pure product with $NaBH_4$ to the corresponding alcohol **13**. Esterification with (1*S*,4*R*)-(−)-camphanic chloride gave (1*S*,4*R*,8′*R*,13′*S*,14′*S*,17′*S*)-**14**, whose X-ray structure was determined (Scheme 3).[12]

Scheme 1. Diels−Alder Reactions of Unsaturated β-Ketoesters

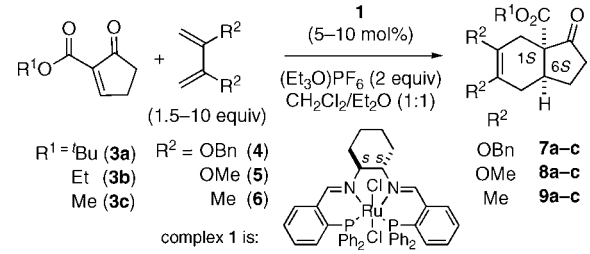
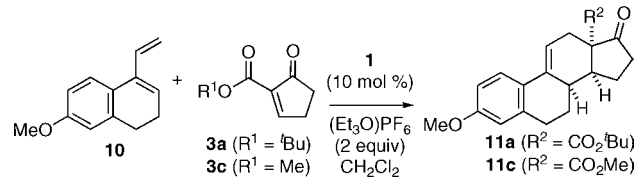


Table 1. Asymmetric Diels−Alder Reaction with **3a**−**c** and Dienes **4**−**6**[a]

entry	dienophile	diene	product	R^1	R^2	yield	ee
1	**3a**	**4**	**7a**	^{t}Bu	OBn	91	93
2	**3b**	**4**	**7b**	Et	OBn	99	77
3	**3c**	**4**	**7c**	Me	OBn	90	76
4[b]	**3a**	**5**	**8a**	^{t}Bu	OMe	86	64
5[b]	**3b**	**5**	**8b**	Et	OMe	92	84
6[b]	**3c**	**5**	**8c**	Me	OMe	62	66
7[c]	**3a**	**6**	**9a**	^{t}Bu	Me	82	67
8[c]	**3b**	**6**	**9b**	Et	Me	87	60
10[c]	**3c**	**6**	**9c**	Me	Me	88	69
11	**3a**	**10**	**11a**	^{t}Bu		85[d]	99[d]
12	**3c**	**10**	**11c**	Me		56[d]	99[d]

[a] A Et_2O solution (1 mL) of **3a**−**c** (0.12 mmol) and, after 10 min, the diene **4** or **6** (0.13−1.2 mmol) were added to catalyst **2** (prepared from **1** (12.1 μmol) and Et_3OPF_6 (25.0 μmol) overnight in CH_2Cl_2 (1 mL)). All reactions were quenched after 24 h by addition of Bu_4NCl and were run at least twice with identical results (within experimental error). [b] Diene **5** was added in three portions of 0.12 mmol (see Supporting Information). [c] In pure CH_2Cl_2. [d] After crystallization from 2-propanol.

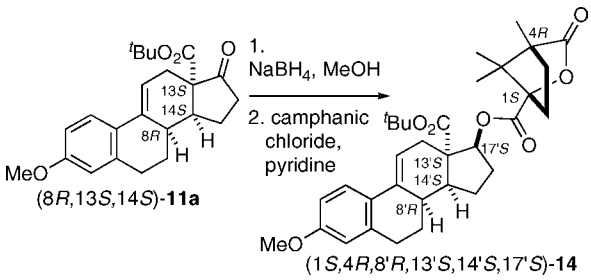
Scheme 2. Synthesis of the Estrone Precursor **11**



As Corey has recently reported a procedure to convert the 18-C-methyl analogue of **11** (R^2 = Me) (prepared with high enantioselectivity via a chiral boron catalyst) to estrone methyl ether,[13] the reaction in Scheme 2 is potentially useful in the synthesis of enantiomerically pure estrone derivatives functionalzed at the α-carbonyl bridghead position, which are of biomedical interest. Although such molecules are known from nature, the difficulty of introducing substituents at the bridgehead position, as opposed to other locations in the molecule, has restricted the number of synthetically available estrones of this class in comparison to those in other steroid classes.[14]

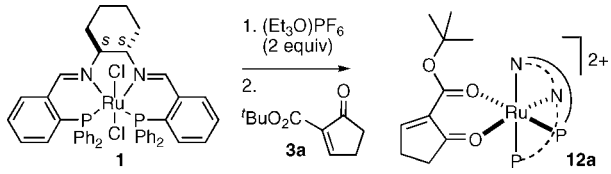
10.1021/ja910039e

Scheme 3. Determination of the Absolute Configuration of **11a**



To gain mechanistic insight into the reaction, we studied the coordination of substrates **3a**−**c** (1 equiv) to the ruthenium/ PNNP moiety. Double chloride abstraction from **1** with $(Et_3O)PF_6$ (2 equiv), followed by addition of the β-keto ester (1 equiv), yields the dicationic ruthenium(II) complexes $[Ru(\mathbf{3},\kappa O,O)(PNNP)]^{2+}$ (**12**). We isolated and fully characterized **12a**,[15] which is formed from substrate **3a** as a single diastereoisomer (Scheme 4).[16]

Scheme 4. Dicationic Adduct **12a** of β-Ketoester **3a**



The X-ray structure of **12a** shows that the lower face of the substrate is shielded by one of the phenyl rings of the PNNP ligand (Figure 1).[17] In combination with the absolute configurations of **9c** and **11a**, we conclude that the diene attacks the open *re* enantioface of the metal-bound dienophile in a higly enantioselective fashion. An analogous shielding of the *si* enantioface of the coordinated substrate has been observed in the ruthenium/PNNP complexes of saturated β-keto esters.[6,8]

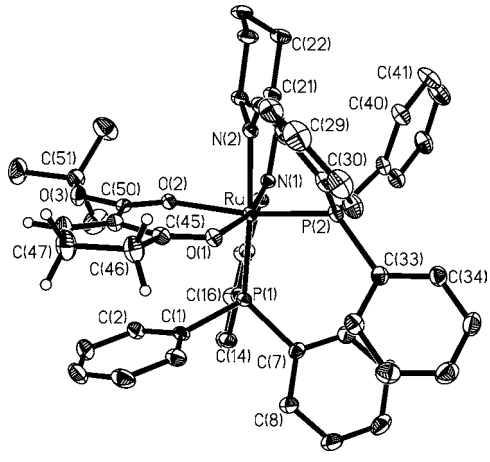


Figure 1. ORTEP drawing of **12a**. Selected distances (Å): Ru−P(1) 2.2973(8), Ru−P(2) 2.2692(8), Ru−N(1) 2.047(3), Ru−N(2) 2.083(3), Ru−O(1) 2.107(2), Ru−O(2) 2.172(2), C(48)−C(49) 1.339(5) Å.

The highly regio- and diastereoselective formation of **11a** indicates that diene **10** approaches with the bicyclic moiety directed away from the PNNP ligand and away from the bulky ^{t}Bu group of the dienophile. This arrangement in the pericyclic transition state leads to the observed ester *exo* product.

In conclusion, we have described a ruthenium/PNNP-catalyzed asymmetric Diels−Alder reaction that converts unsaturated β-ketoesters into multifunctional tetrahydro-1-indanone derivatives, most of which have not been reported before, under mild conditions and with high regio-, diastereo-, and enantioselectivity. This approach allows the first enantioselective synthesis of both *nat*- and *ent*-entiomers of an estrone derivative bearing an ester functionality at the α-carbonyl bridgehead position.

Acknowledgment. We thank Dr. Martin Althaus for the synthesis and characterization of complex **12a** and Mrs. Katrin Niedermann, Mr. Pietro Butti, and Mr. Raphael Aardoom for the X-ray structure determinations.

Supporting Information Available: Detailed experimental procedures and CIF files of **12a** and (1*S*,4*R*,8′*R*,13′*S*,14′*S*,17′*S*)-**14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Preliminary tests with cyclopentadiene gave racemic Diels−Alder products along with poly- or oligomers of the diene (see Supporting Information).
(12) The absolute configuration of **9c** was determined similarly (see Supporting Information); those of the remaining products are assigned by analogy.
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(15) Data of **12a**: 31P NMR (101.3 MHz, CH_2Cl_2): δ 63.4 (*d*, 1P, $J_{P,P'} = 31.2$ Hz), 52.5 (*d*, 1P, $J_{P,P'} = 31.2$ Hz). Analysis calcd for $C_{54}H_{55}F_6N_2O_3P_3Ru$: C, 59.61; H, 5.09; N, 2.57. Found: C, 59.86; H, 5.20; N, 2.54.
(16) Addition of **3b** or **3c** to a solution of **2** results in the formation of one additional species, which is believed to be a different diasteroisomer of the corresponding complexes **12b** and **12c** (see Supporting Information).
(17) Crystal data of **12a**: $C_{56}H_{88}Cl_4F_{12}N_2O_3P_4Ru$, triclinic, $P\bar{1}$, $a = 11.5110(7)$ Å, $b = 13.8903(8)$ Å, $c = 20.6616(12)$ Å, $\alpha = 96.886(1)°$, $\beta = 93.755(1)°$, $\gamma = 113.085(1)°$, $V = 2994.2(3)$ Å^3, $Z = 2$, $T = 200$ K, $D_c = 1.555$ Mg/m^3, $\mu = 0.630$ mm^{-1} (Mo K_α, graphite monochromated), $\lambda = 0.710\,73$ Å, $F(000) = 1424$, 26 500 data collected at 200 K on a Bruker AXS SMART APEX platform in the θ range 1.00°−26.02°, 11 770 independent reflections ($R_{int} = 0.0252$), $R_1 = 0.0504$ (for 10 527 reflections with $I > 2\sigma(I)$) and $wR_2 = 0.133724$ (all data), GOF = 1.021. Max and min difference peaks +1.26 and−0.76 eÅ^{-3}, largest and mean $\Delta/\sigma = 0.001$ and 0.000.

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