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

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[§]SCS Metrohm Prize for best oral presentation

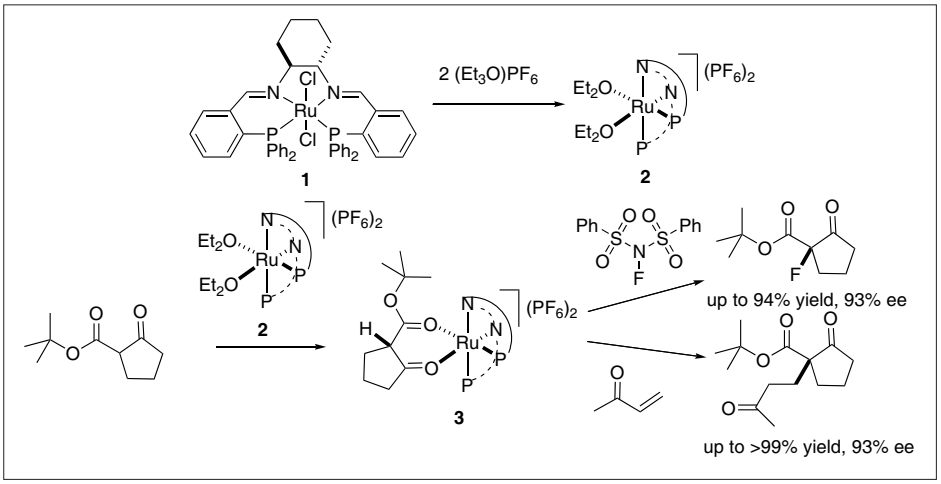
Abstract: We report here dicationic ruthenium PNNP complexes that promote the enantioselective Diels-Alder reaction of α-methylene β-ketoesters with various dienes. Complex $[Ru(OEt_2)_2(PNNP)](PF_6)_2$, formed *in situ* from $[RuCl_2(PNNP)]$ and $(Et_3O)PF_6$ (2 equiv.), catalyzes the Diels-Alder reaction of such unsaturated β-ketoesters to give novel alkoxycarbonyltetrahydro-1-indanone derivatives (nine examples) with up to 93% *ee*. The crystal structure of the substrate–catalyst adduct shows that the lower face of the substrate is shielded by a phenyl ring of the PNNP ligand, which accounts for the high enantioselectivity. The attack of the diene from the open *re* enantioface of the unsaturated β-ketoester is consistent with the absolute configuration of the product. A useful application of this method is the reaction with Dane's diene to give estrone derivatives with up to 99% *ee* and an ester-*exo*:*endo* ratio of up to 145:1 (after recrystallization). Besides the enantioselective formation of all-carbon quaternary centers, this methodology is notable because unsaturated β-ketoesters have been rarely used in Diels-Alder reactions. Furthermore, enantiomerically pure estrone derivatives are interesting in view of their potential applications, including the treatment of breast cancer.

Keywords: Asymmetric catalysis · Diels-Alder · Natural products · Polycycles · Ruthenium

1. Introduction

Ruthenium PNNP dichloro complexes such as $[RuCl_2(PNNP)]$ (**1**) were originally used by Gao, Ikariya and Noyori in asymmetric transfer hydrogenation (Scheme 1, PNNP is (1*S*,2*S*)-N,N'-bis[o-(diphenylphosphino)benzylidene]cyclohexane-1,2-diamine).[1] Discoveries made in our group have shown that the abstraction of both chloro ligands with $(Et_3O)PF_6$ leads to the elusive dicationic complex $[Ru(OEt_2)_2(PNNP)]^{2+}$ (**2**). The highly Lewis-acidic and oxophilic metal center of **2** binds bidentate oxygen donors (O–O), in particular β-ketoesters, to form complexes of the type $[Ru(O–O)(PNNP)]^{2+}$ (**3**). The coordination to the metal activates the substrate toward a number of reactions, such as Michael addition,[2] hydroxylation,[3] and fluorination[4] (Scheme 1). The complexes of type **3** are a rare example of the coordination of 1,3-dicarbonyl compounds in their neutral, non-enolized form. However, deprotonation to the corresponding enolato derivatives is easy and gives more stable monocationic enolato complexes such as **4**, which contains 2-(*tert*-butoxycarbonyl) cyclopent-1-enolate (Scheme 2). The crystal structure of **4** shows that the lower face of the substrate is shielded by one of the phenyl rings of the catalyst, which explains the high enantioselectivity observed in the catalytic reactions in Scheme 1.[2]

As a straightforward extension of this work, we have explored the possibility of using the Lewis acidity of the ruthenium/PNNP fragment to activate the double bond of unsaturated β-ketoesters **5a**–**c**.[5] This approach opens up new perspectives to the use of unsaturated β-ketoesters as dienophiles as an alternative to α,β-unsaturated aldehydes,[6] which is rather restricted because bulky unsaturated α-methylene β-ketoesters are poor dienophiles, tend to polymerize, and give keto-enol tautomery.[7] Therefore, most research projects in this area have focused on related quinone-type substrates, which are more reactive, easier to handle, and give enantioselective Diels-Adler reactions with excellent yields and enantioselectivity with a number of catalysts,[8] whereas non-quinone type unsatu-



Scheme 1. Activation of **1** and reactions of coordinated β-keto esters.

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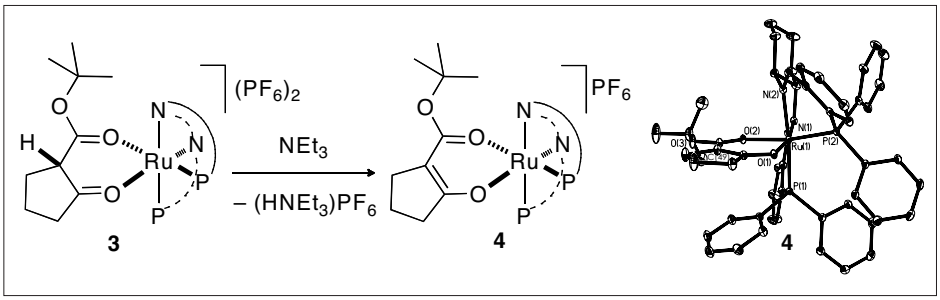
rated β-ketoesters have been scarcely investigated.[7]

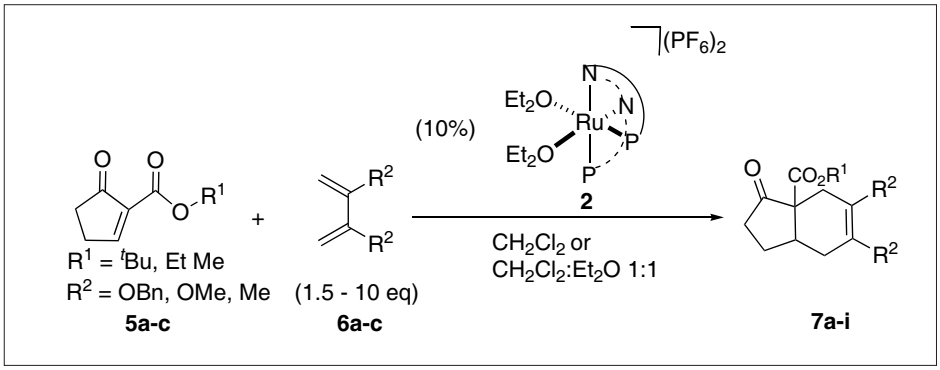
2. Catalysis Results

We recently reported that $[Ru(OEt_2)_2(PNNP)](PF_6)_2$ (**2**) catalyzes the enantioselective Diels-Alder reaction of the unsaturated β-ketoesters **5a–c** with 2,3-disubstituted butadienes (**6a–c**) (Scheme 3).[5] The reaction, which is conveniently run at room temperature overnight, yields alkoxycarbonyltetrahydro-1-indanones of the general type **7** with up to 93% *ee* (Table 1). Thus, this is an example of smooth formation of a quaternary all-carbon stereocenter, which is usually difficult to achieve in an enantioselective way.[9] The excess of the diene was optimized with each of **6a–c** to obtain high yields in all cases. The unsaturated β-ketoester is quantitatively converted overnight upon addition of 4.5 equiv. of the electron rich 2,3-(dimethoxy)-butadiene (**6b**), whereas a larger excess of the non-activated 2,3-(dimethyl)butadiene (**6c**) (10 equiv.) is necessary. The amount of reagent can be further diminished by using 2,3-(dibenzyloxy)butadiene (**6a**). We believe that this is because the larger steric bulk of the latter diene hinders its coordination to the catalyst and, thus, a successive polymerization reaction. The coordination of the oxygen-substituted dienes to the catalyst is probably also the reason why catalytic reactions involving these reagents are best performed in a 1:1 mixture of dichloromethane and diethyl ether. The large excess of ether may compete with the coordination of the diene. As product inhibition cannot be excluded either, Et_2O may displace the coordinated product and promote the coordination of a new β-ketoester molecule opening a new catalytic cycle.

It should be noted that only one product of the alkoxycarbonyltetrahydro-1-indanone class has been previously prepared as racemate, with low yield, and under harsh conditions.[10] Therefore, this is the first enantioselective synthesis of compounds **7a–i**, which are versatile intermediates as they contain multiple, separately addressable reaction sites apart from the still intact β-ketoester functionality.[11] More general, standard, non-quinone type unsaturated β-ketoesters have been rarely used as dienophiles, and only one catalytic system has been previously reported to accomplish enantioselective Diels-Alder reactions with such substrates.[7] However, this magnesium bisoxazoline system requires high catalyst loadings and an extremely low temperature of –90 °C to achieve good yields and enantioselectivity. Apart from this example, standard achiral, Lewis acidic catalysts have been reported,[12] but yields are, at best, only moderate due to the tendency of the substrates to polymerize. In contrast, the coordination of the unsaturated β-ketoesters **5a–c** to the dicationic ruthenium PNNP fragment enhances their reactivity without promoting polymerization at a detectable level. Therefore, ruthenium PNNP complexes seem specially suited for catalyzing Diels-Alder reactions of these difficult dienophiles.



Scheme 2. Deprotonation of complex **3** to obtain enolate complex **4**.



Scheme 3. Asymmetric Diels-Alder reaction with **5a–c** and dienes **6a–c**.

Table 1. Asymmetric Diels-Alder reaction with **5a–c** and dienes **6a–c**.

Entry	dienophile	diene	product	R^1	R^2	yield [%]	*ee* [%]
1	**5a**	**6a**	**7a**	^{t}Bu	OBn	91	93
2	**5b**	**6a**	**7b**	Et	OBn	99	77
3	**5c**	**6a**	**7c**	Me	OBn	90	76
4	**5a**	**6b**	**7d**	^{t}Bu	OMe	86	64
5	**5b**	**6b**	**7e**	Et	OMe	92	84
6	**5c**	**6b**	**7f**	Me	OMe	62	66
7[a]	**5a**	**6c**	**7g**	^{t}Bu	Me	82	67
8[a]	**5b**	**6c**	**7h**	Et	Me	87	60
10[a]	**5c**	**6c**	**7i**	Me	Me	88	69

[a]In pure CH_2Cl_2.

3. Application in Natural Product Synthesis

Estrone derivatives are of biomedical interest, in particular for potential application in breast cancer treatment.[13] Corey has recently reported the synthesis of an enantiomerically enriched estrone methyl ether whose key step is an enantioselective Diels-Alder reaction of 2-methylcyclopent-2-enone and Dane's diene **8**.[14] Although estrone derivatives are accessible from natural estrone, the introduction of functionalizable substituents at the C(18) position is difficult.[15] Therefore, only few derivatives of this class are synthetically available as compared to the large number of differently substituted estrones. We realized that replacing 2-methylcyclopent-2-enone with the unsaturated β-ketoesters **5a–c** would give estrone derivatives that bear an ester group as a synthetic handle at C(18) (Scheme 4). In fact, Dane's diene reacted with the unsaturated β-ketoester **5a** according to our protocol to give crude **9a** as a single regioisomer of the ester-*exo* diastereoisomer in excellent yield, an ester-*exo*:*endo* ratio of 27:1, and 86% *ee*. Recrystallization from 2-PrOH gave enantiomerically pure **9a** (R^1 = ^{t}Bu) with an ester-*exo*:*endo* ratio of 145:1 (Scheme 4). Interestingly, when the less bulky methyl derivative **5c** is used as dienophile, the dia-

stereoselectivity drops considerably, which we will discuss in the following section.

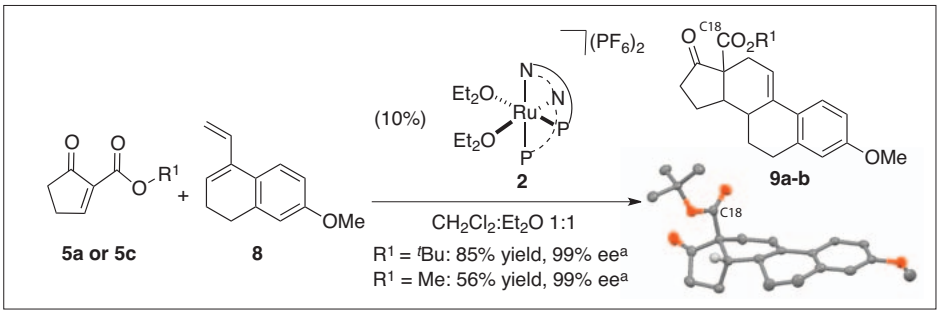
4. Stereochemical Analysis

Analogously to the saturated analogues, the unsaturated β-ketoesters **5a–c** coordinate to the rigid dicationic ruthenium PNNP framework to form [Ru(**5a–c**)(PNNP)]$(PF_6)_2$ complexes. The crystal structure of [Ru(**5a**)(PNNP)]$^{2+}$ (**11**) shows close similarity to that of enolato complex **4**, including the protection of the lower face of the coordinated substrate by one of the phenyl rings of the ligand (Fig. 1). Accordingly, the diene attacks from the top face of the unsaturated β-ketoester as proposed for the electrophilic transformations performed with their saturated analogues (Scheme 1).[2–4] To verify this stereochemical model, the absolute configuration of two catalysis products, **7i** and **9a**, was determined by reduction of the ketone moiety with sodium borohydride, followed by esterification with (1*S*,4*R*)-(–)-camphanic chloride (Scheme 5) and crystallization by slow evaporation of diethyl ether. The crystal structures indicate that the absolute configuration at the bridgehead positions is *S*,*S* in both cases,[16] which is consistent with the expected attack from the unshielded top face of the substrate.

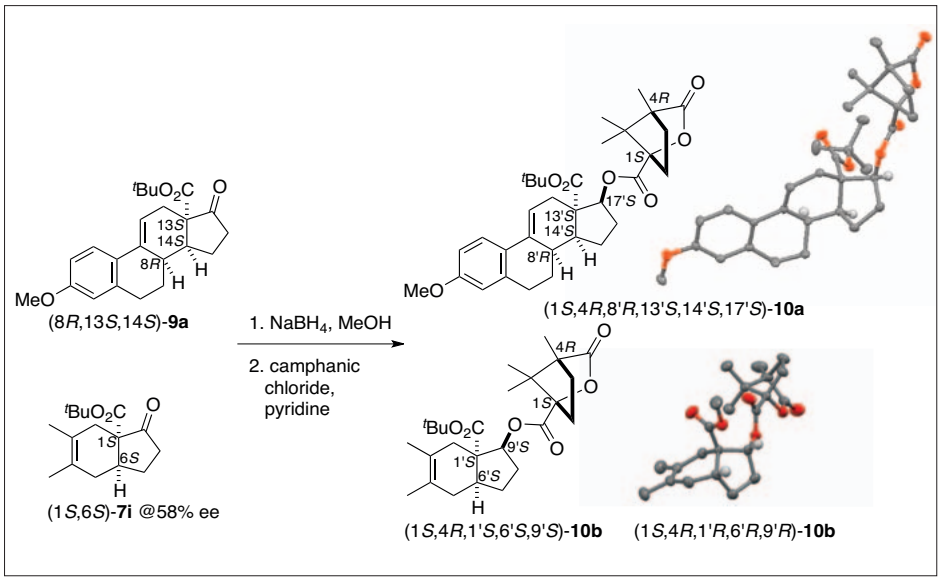
In contrast to the symmetrical dienes **6a–c**, Dane's diene (**8**) enables the formation of two diastereoisomers, usually described as the ester-*exo* and the ester-*endo* isomer. Both **5a** and **5c** favor the ester-*exo* product, but the diastereomeric ratio is highly dependent on the ester moiety, and drops from 27:1 for the *tert*-butyl ester to 3:1 for the methyl ester. In order to understand these results, both steric and electronic factors have to be taken into account.

The observed diastereoselectivity is a direct result of the approach of the diene to the catalyst-bound substrate (Fig. 1). If the diene approaches over the cyclopentenone ring, the favored ester-*exo* product is formed, while an approach over the ester moiety results in the formation of the unfavored ester-*endo* product. Clearly, the approach *via* the more bulky *tert*-butyl ester moiety of **5a** is very difficult, so this residue is likely to point away from the forming ring in the pericyclic transition state, which is in agreement with the observed high ester-*exo* selectivity. In the less bulky methyl ester derivative **5c**, the approach over the ester group is less disfavored than in **5a**, which results in lower *endo*/*exo* selectivity.

Electronic factors influence the diastereoselectivity of Diels-Alder reactions *via* secondary orbital overlaps (SOO). In addition to the bond-forming primary orbital overlaps (bold lines), secondary orbital



Scheme 4. Asymmetric Diels-Alder reaction with **5a** or **5c** and Dane's diene **8**; [a]yields and enantioselectivities after recrystallization.



Scheme 5. Absolute configuration of the Diels-Alder products.

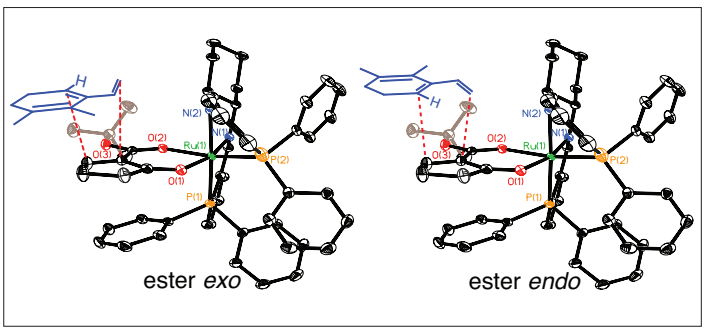


Fig. 1. Ester-*exo* vs. ester-*endo* approach of the diene, cartoon based on the X-ray structure of **11**.

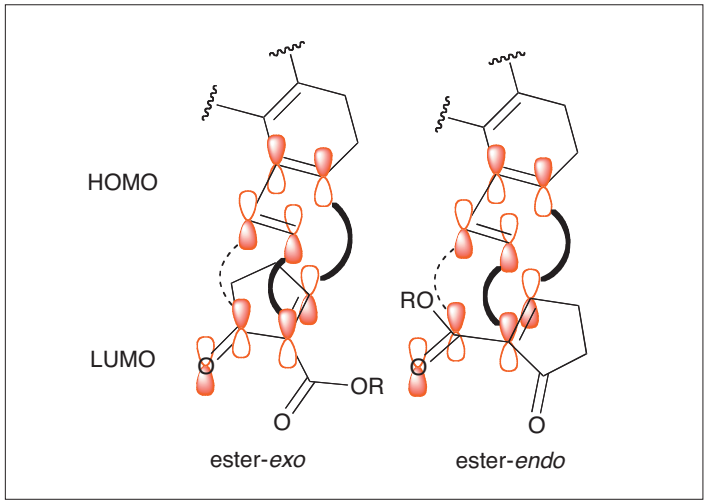


Fig. 2. Secondary orbital overlaps in ester-*exo* and ester-*endo* transition state. Non-interacting orbitals omitted for clarity.

overlaps (dashed lines) can be present in both transition states (Fig. 2). In the ester-*exo* transition state, there is a secondary overlap of the HOMO with the LUMO component located at the ketone moiety of the cyclopentenone ring. In the case of the unfavored ester-*endo* transition state, this interaction involves the carbonyl group of the ester moiety instead. As β-ketoesters are rarely used in Diels-Alder reactions, it is not known – to the best of our knowledge – whether ketones or esters give larger effects. However, it has been shown that secondary orbital overlaps are crucial only if the HOMO-LUMO gap between diene and dienophile is small, which results in a very close transition state.[17] In systems with large HOMO-LUMO gaps, steric factors dominate the stereoselectivity even at the expense of having no secondary overlaps at all. Therefore, as in the case of the unsaturated β-ketoesters **5a**–**c** there is merely a competition between two slightly different secondary overlaps, we suggest that steric effects are pivotal. Similarly, Welker has shown that steric influences entirely dominate the diastereoselectivity of Diels-Alder reactions with β-ketoesters when a large substituent is present on the diene.[18]

Finally, it should be noted that the more commonly used quinone derivatives[8] are not directly comparable to standard unsaturated β-ketoesters, as their LUMO energy is lowered due to the conjugation with an additional carbonyl group. As a result, their HOMO-LUMO gap is considerably smaller (in agreement with their stronger reactivity), and secondary orbital overlaps play the major role. A strong ester-*endo* selectivity is often observed for these substrates.

5. Conclusion

We have described herein 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. Mild reaction conditions and high regio-, diastereo-, and enantioselectivity are key features of this reaction. This approach opens the way for the first enantioselective synthesis of both *nat*- and *ent*-enantiomers of estrone derivatives that bear an ester functionality at the α-carbonyl bridgehead position, which should act as a useful synthetic handle for further derivatization.

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[16] Due to the moderate enantiomeric purity of **7i**, the camphanic ester derivative was obtained as a mixture of the (1*S*,4*R*,1'*S*, 6'*S*,9'*S*)-**10b** (major) and (1*S*,4*R*,1'*R*,6'*R*,9'*R*)-**10b'** (minor) diastereoisomers, which were separated *via* preparative HPLC. Only the minor diastereoisomer **10b'** crystallized, and its X-ray structure was determined (Scheme 5).
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