Asymmetric [4+2]-cycloaddition of Anthracene Derivatives *via* Hydrazone Activation

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Dedicated to Professor Miquel A. Pericàs on his retirement from the Institute of Chemical Research of Catalonia, ICIQ.

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Abstract: Enantio- and diastereoselective dearomative [4+2]-cycloaddition reaction between *N*,*N*-dimethylhydrazone derived from 9-anthracenecarbaldehyde and *α*,*β*-unsaturated aldehydes is reported. The developed strategy utilizes HOMO-rising activation of diene (*via* hydrazone formation) and aminocatalytic LUMO-lowering activation of dienophile (*via* iminium ion formation). High chemical and stereochemical efficiency have been obtained owing to the application of Jørgensen catalyst. Target cycloadducts were subjected to selected transformations aiming at unmasking the hydrazone moiety that proceeded with preservation of optical purity introduced in the organocatalytic step.

Anthracene and its derivatives constitute an important class of molecules belonging to the family of a polycyclic aromatic compounds, which are widely used in organic synthesis, biological research and in the production of dyes or other materials with interesting photochemical and photophysical properties.[1-3] Notably, the carbocyclic scaffold of anthracene cycloadducts is present in bioactive molecules, especially with antidepressant activity with maprotiline,[4] benzoctamine[4b-5] and oxaprotiline[6] being representative examples of tricyclic antidepressants (TCAs, Figure 1).

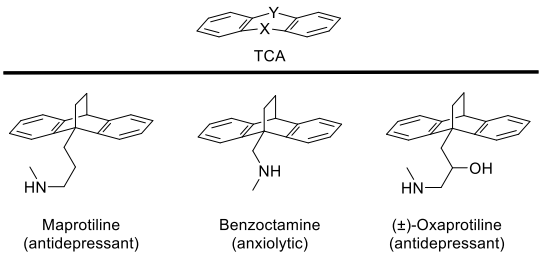
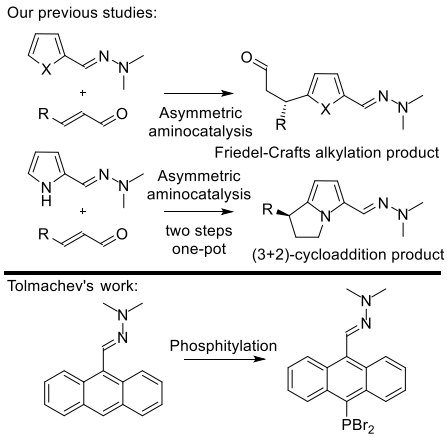


Figure 1. Application dihydro-9,10-ethaneanthracene Diels-Alder reaction in the synthesis of bioactive compounds.

One of the most interesting chemical properties of anthracene is its ability to undergo Diels-Alder reactions with various dienophiles at the 9- and 10-positions of the ring.[7] Despite the presence of a conjugated double bond system, Diels-Alder reaction of arenes such as benzene or naphthalene are generally difficult to achieve. This is due to the high energy barrier associated with the loss of aromaticity. Anthracene is an exception in this regard and is susceptible to both thermal and photochemical cycloadditions.[8] Since the products of this type of transformation with anthracene derivatives are usually optically active, asymmetric catalytic methods for their synthesis are significant importance. Several strategies are employed to reduce the high energy barrier of reactants associated with the breakage of aromaticity in the Diels-Alder reaction involving the anthracene derivatives. These include: the activation of the dienophile *via* LUMO-lowering principle, [9] the activation of the diene *via* HOMO-rising principle,[10] the *in situ* formation of anthrone enolate as a reactive diene[11] and biocatalytic methods.[12] Reversing the polarity of the carbonyl group (umpolung) is a frequently used method of creating new carbon-carbon bonds. One way to umpolung the carbonyl moiety is to convert the aldehyde to a hydrazone. The hydrazone donating effect can be transferred through the conjugated double bonds, including also heteroaromatic systems. Recently, we have demonstrated the utility of this methodology for the activation of electron-poor furan derivatives towards the Friedel-Crafts-type reaction (Scheme 1, top)[13] or (3+2)-cycloaddition leading to the formation of 2,3-dihydro-1*H*-pyrrolizine scaffold (Scheme 1, middle).[14]

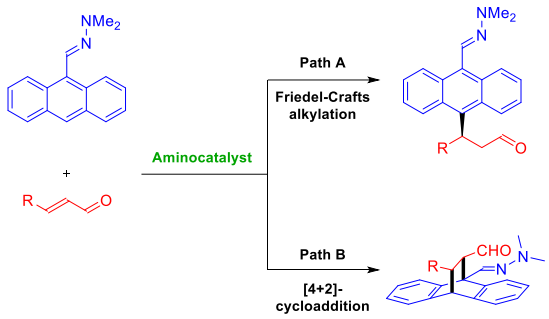


Scheme 1. The application of vinylogous hydrazone strategy in the synthesis of 2,3-dihydro-1*H*-pyrrolizines and anthracene derivatives.

Surprisingly, methods employing hydrazone strategy for the activation of aromatic hydrocarbons are highly limited. To the best of our knowledge, the research by Tolmachev and co-workers constitutes the only example of application of hydrazone activation for phosphitylation of polycyclic aromatic hydrocarbons (Scheme 1, bottom).[15]

Herein, we demonstrate the application of hydrazone strategy for the activation of anthracene derivative towards aminocatalytic

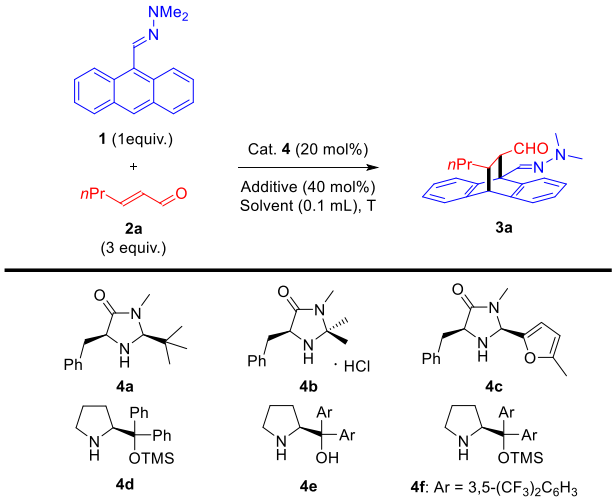
transformations. At the outset of our studies, it was anticipated that the reaction of 9-anthracenecarbaldehyde dimethyl-hydrazone could proceed following two pathways: 1) simple Friedel-Crafts reaction at the 10-position of the anthracene system (Scheme 2, path A) or 2) [4+2]-cycloaddition with the formation of polycyclic product (Scheme 2, path B).



Scheme 2. Synthetic objectives of our study.

In the first part of the optimization studies, the influence of the catalyst on the devised reactivity was evaluated. For this purpose, commercially available chiral aminocatalysts **4** were used (Table 1, entries 1-6). Reactions were carried out with (*E*)-2-hexenal **2a** and hydrazone **1** in the presence of trifluoroacetic acid (except for catalyst **4b**) in dichloromethane at room temperature for two to five days. Noteworthily, the reaction was characterized by complete chemo-, regio- and diastereoselectivity. MacMillan's catalysts **4a-c** promoted the reaction, however, the enantiomeric excess was only moderate (Table 1, entries 1-3). The best enantiocontrol of the process was provided by the Jørgensen-Hayashi catalyst **4f** (Table 1, entry 6). In the next step of studies, the effectiveness of the catalyst **4f** in the presence of selected acidic additives was investigated (Table 1, compare entries 6-8). However, among acids tested, trifluoroacetic acid (TFA) turned out to be the most beneficial (Table 1, entry 6). Subsequently, the most suited solvent for this transformation was examined (Table 1, entries 6, 9-14). The Diels-Alder reaction was carried out in 1,2-dichloroethane and diethyl ether (Table 1, entries 9-10). Unfortunately, both the yield and the enantioselectivity were lower in both cases when compared to CH_2Cl_2. The use of ethyl acetate as solvent did not provide satisfactory conversion (Table 1, entry 11). Using acetonitrile allow to achieve 28% yield and 80:20 er (Table 1, entry 12). Propionitrile provided a slightly better enantioselectivity of the process (Table 1, entry 13). The next experiment showed that the presence of water significantly increases the enantioselectivity of the reaction (Table 1, entry 14). Delightfully, increasing the concentration (Table 1, entry 15) and lowering the reaction temperature (eliminating the rapid decomposition of the aldehyde, Table 1, entry 16) enhanced the efficiency of the process, leading to a significant improvement in the conversion of substrates and identifying the final reaction parameters (Table 1, entry 16).

Table 1. Asymmetric [4+2]-cycloaddition with anthracene derivative **1** – optimization studies[a]



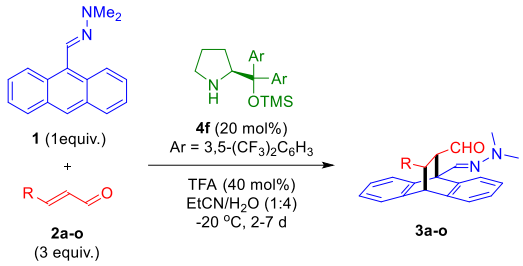
	Solvent	Cat.	Addit.	T [°C]	Conv. [%][b]	er[c]
1[d]	CH_2Cl_2	**4a**	TFA	rt	63 (42)	86:14
2[d]	CH_2Cl_2	**4b**	-	rt	3 (n.d.)	n.d.
3[d]	CH_2Cl_2	**4c**	TFA	rt	80 (73)	73:27
4	CH_2Cl_2	**4d**	TFA	rt	41 (35)	64:36
5	CH_2Cl_2	**4e**	TFA	rt	60 (36)	82:12
6	CH_2Cl_2	**4f**	TFA	rt	30 (28)	90:10
7	CH_2Cl_2	**4f**	BA	rt	3 (n.d.)	n.d.
8	CH_2Cl_2	**4f**	MCA	rt	17 (10)	86:14
9[d]	$ClCH_2CH_2Cl$	**4f**	TFA	rt	22 (19)	60:40
10	Et_2O	**4f**	TFA	rt	38 (21)	79:21
11	AcOEt	**4f**	TFA	rt	12 (n.d.)	n.d.
12	MeCN	**4f**	TFA	rt	65 (28)	80:20
13	EtCN	**4f**	TFA	rt	26 (23)	82:18
14[e]	EtCN/H_2O	**4f**	TFA	rt	42 (39)	96:4
15[f]	EtCN/H_2O	**4f**	TFA	rt	50 (46)	96:4
16[f]	EtCN/H_2O	**4f**	TFA	-20	85 (76)	98:2

[a] Reactions performed on a 0.05 mmol scale using **1** (1.0 equiv) and **2a** (3 equiv.) in 0.1 mL of the solvent for 5 days. [b] Conversion as determined by ^{1}H NMR of a crude reaction mixture. Isolated yield is given in parentheses. [c] Determined by a chiral stationary phase UPC^2. [d] Reaction performed for 2 days. [e] Reaction performed in 0.1 mL of solvents in ratio 1:4. [f] Reaction performed in 0.05 mL of solvents in ratio 1:4.

In the course of further studies, the scope and limitations of the method with regard to *α,β*-unsaturated aldehydes **2** was determined (Table 2). Initially, the usefulness of aliphatic *α,β*-unsaturated aldehydes **2a-f** was tested (Table 2, entries 1-6). Aldehydes **2b-e** containing either longer (Table 2, entries 2,3) or shorther (Table 2, entries 4,5) aliphatic chains than the model *trans*-hexenal **2a** reacted with **1** smoothly affording target products **3b-e** in good yields and an excellent enantioselectivity.

Moreover, the use of aldehyde **2f**,**g** bearing a functional group (double bond or protected hydroxyl group) in the aliphatic chain proved possible affording **3f**,**g** with excellent or good results (Table 2, entries 6,7). Subsequently, the cycloaddition of hydrazone **1** with cinnamaldehyde **2h** was performed (Table 2, entry 8). The desired compound **3h** was obtained in 53% yield and 99:1 er.

Table 2. Asymmetric [4+2]-cycloaddition with anthracene derivative **1 –** scope studies[a]

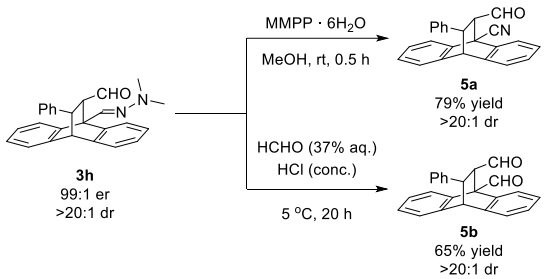


Entry	R	Yield [%]	*E*/*Z*[b]	er[c]
1[d]	*n*Pr	76	>20:1	98:2
2[e]	*n*Bu	48	>20:1	>99:1
3[e]	*n*-Pentyl	61	>20:1	>99:1
4[e]	Me	61	>20:1	99:1
5[e]	Et	56	>20:1	>99:1
6[e]	(*E*)-3-Hexenyl	76	>20:1	>99:1
7[e]	$BnOCH_2$	47	>20:1	92:8
8[f]	Ph	53	>20:1	99:1
9[d]	3-$MeOC_6H_4$	68	>20:1	88:12
10[d]	2-$MeOC_6H_4$	70	>20:1	83:17
11[g]	4-$NO_2C_6H_4$	35	>20:1	90:10
12[f]	4-$CF_3C_6H_4$	68	>20:1	98:2
13[g]	4-ClC_6H_4	58	>20:1	84:16
14[g]	2,4-$Cl_2C_6H_3$	86	>20:1	68:32
15[d]	2-Furyl	62	>20:1	97:3

[a] Reactions performed on a 0.05 mmol scale using **1** (1.0 equiv) and **2a-o** (3 equiv.) in 0.05 mL of the solvent. [b] Determined by ^{1}H NMR of a crude reaction mixture. [c] Determined by a chiral stationary phase UPC^2 or HPLC.[d] Reaction performed for 5 days. [e] Reaction performed for 2 days. [f] Reaction performed for 4 days. [g] Reaction performed for 7 days

Encouraged by this excellent result, we decided to conduct additional experiments to determine the influence of the electronic steric effects of substituents on the phenyl ring in **2** on the cycloaddition outcome (Table 2, entries 9-14). The introduction of electron-rich substituents did not influence the reactivity (Table 2, entries 9,10), but had an effect on the stereoselectivity of the process that was particularly pronounced for the *ortho*-substituted derivative **2j** presumably for steric reasons (Table 2, entry 10). Cinnamaldehydes **2k-m** bearing electron-withdrawing substituents proved also useful substrates for the reaction (Table 2, entries 11-13). However, in the case of nitro-group-substituted enal **2k** and cinnamaldehydes bearing chlorine atom **2m** deteriorated results were obtained (Table 2, entries 11,13). Disubstitution pattern was also tolerated in the reaction as demonstrated in the synthesis of **3n** with a 2,4-dichlorophenyl substituent (Table 2, entry 14). Disappointingly, the reaction proceeded with only moderate enantioselectivity presumably for steric reasons. The possibility of employing heteroaromatic-ring-substituted substrate **2o** was also demonstrated and **3o** containing the 2-furyl substituent was obtained with very good results (Table 2, entry 15).

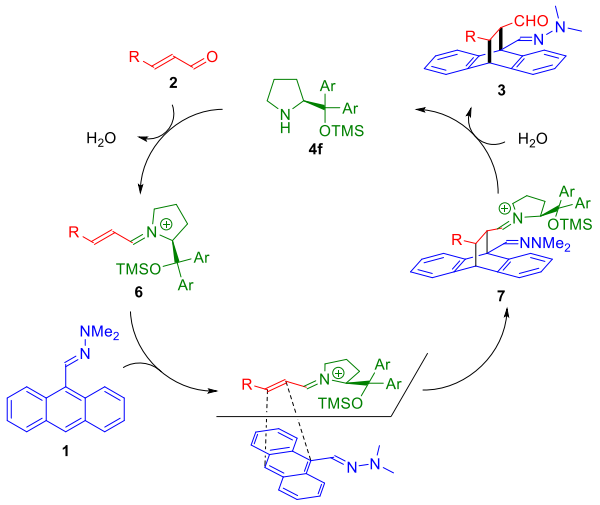
To demonstrate the usefulness of the developed synthetic method, experiments aiming at unmasking the hydrazone moiety in the product **3h** were performed (Scheme 3). The reaction of **3h** with magnesium bis(monoperoxyphthalate) hexahydrate in methanol at room temperature afforde the corresponding nitrile **5a** in 79% yield (Scheme 3, top). Furthermore, when concentrated hydrochloric acid and 37% solution of formaldehyde in THF were employed the corresponding dialdehyd **5b** was obtained in 65% yield (Scheme 3, bottom). Notably, both transformations proceeded with retention of optical purity of **3h**.



Scheme 3. Transformations of compound **3h**.

The absolute configuration of the product (11*S*,12*R*)-**3h** has been unequivocally confirmed on the basis of X-ray structure analysis of a single crystal obtained by its crystallization from a mixture of cyclohexane/ethyl acetate (for datails, see SI).[16] Since the same enantiomer of the catalyst was used for the synthesis of all cycloadducts **3a-o**, the absolute configuration of the remaining products was assigned by analogy.

The developed synthetic strategy utilizes both HOMO-rising and LUMO-lowering activations. The introduction of a hydrazone moiety into compound **1** increases the energy of the HOMO orbital of the aromatic anthracene system, making it electron-rich diene for the Diels-Alder reaction, more reactive than anthracene or anthracene-9-carbaldehyde. Furthermore, the condensation of diarylprolinol silyl ether **4f** with *α*,*β*-unsaturated aldehyde **2** results in the formation of the iminium ion **6**. It is characterized by a lower energy of the LUMO orbital in comparison to the starting aldehyde and can act as excellent dienophile in the reaction (Scheme 4).[17] Notably, the observed stereochemical effect of the [4+2]-cycloaddition is governed by steric interactions ensuring the diene approach from the side opposite to the sterically demanding substituent in the 2-position of the pyrrolidine ring. The presence of water exhibited beneficial effects on both reaction rate and selectivity as it is required for the final hydrolysis step, resulting in the formation of product **3** with simultaneous regeneration of the aminocatalyst **4f**.



Scheme 4. Proposed mechanism of asymmetric [4+2]-cycloaddition of anthracene **1**.

In conclusion, we have developed a new activation of anthracene-9-carbaldehyde towards the [4+2]-cycloaddtition. Its conversion into the corresponding *N*,*N*-dimethylhydrazone results in HOMO-rising activation making it a highly reactive electron-rich diene for the Diels-Alder reaction. Aminocatalytic LUMO-lowering activation of *α*,*β*-unsaturated aldehydes enables the [4+2]-cycloaddtition to occur in a highly enantio- and diastereoselective manner. High chemical and stereochemical efficiency has been obtained owing to the application of Hayashi-Jørgensen aminocatalyst. Further transformations of target cycloadducts aiming at unmasking the hydrazone moiety proceeded with preservation of optical purity introduced in the organocatalytic step.

Acknowledgements

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Keywords: asymmetric organocatalysis • iminium activation • [4+2]-cycloaddition• umpolung strategy • anthracene

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