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Inverse-electron-demand Diels–Alder reactions of α,β-unsaturated hydrazones with 3-methoxycarbonyl α-pyrones†

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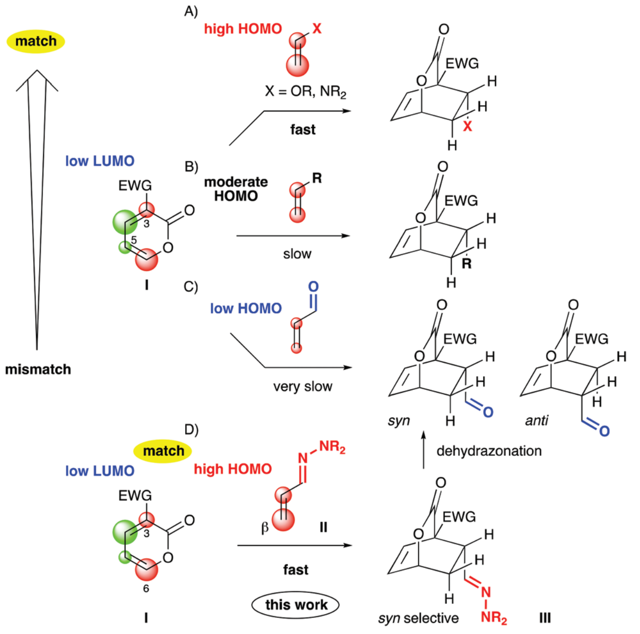
Inverse-electron-demand Diels–Alder reactions of 3-electron-withdrawing group substituted α-pyrones with α,β-unsaturated hydrazones as electron-rich counterparts are catalyzed by Eu(hfc)$_3$ to afford bicyclic lactone cycloadducts. This is an example of *umpolung* cycloaddition based on functional transformation of carbonyls to hydrazones. A subsequent dehydrazonation reaction enables indirect synthesis of carbonyl group-containing bicyclic lactones, which cannot be easily obtained by the cycloaddition of α-pyrones and enals.

An inverse-electron-demand Diels–Alder reaction is frequently used for the construction of various six-membered rings.[1] For example, cycloaddition of electron-deficient α-pyrones with electron-rich olefins has been reported[2] and applied for total synthesis of natural products.[3] Despite many reports on this type of cycloaddition of α-pyrones having an electron-withdrawing group at the 3-position **I** with enolethers and enamines having a high HOMO level owing to the presence of an electron-donating group (Scheme 1A),[4] there are few reports on cycloaddition of α-pyrones **I** with alkyl-substituted alkenes, probably because these compounds have a lower HOMO level, and the reactions often require high temperature or high pressure (Scheme 1B).[5] Furthermore, α,β-unsaturated carbonyl compounds having low HOMO levels are poorly reactive with α-pyrones **I** due to the mismatch of their frontier orbitals (Scheme 1C).[6,7] In fact, although the reaction of 3-methoxycarbonyl α-pyrones with indenones is known, this reaction required extremely high pressure conditions with very high concentrations probably due to low reactivity, selectively affording *anti* cycloadducts (head-to-tail cycloadducts) with opposite regiochemistry to that of a matched combination (A).[8] Accordingly, there is no efficient synthetic method for *syn* adducts of α-pyrones having an electron-withdrawing group at the 3-position with α,β-unsaturated carbonyl compounds.

Carbonyl *umpolung* (polarity inversion) using hydrazone, which has an electron-donating nitrogen atom in an imine functionality, is often applied in synthetic chemistry.[9] Additionally, there are a few reports on its electron-donating ability extension to conjugated olefins. For example, a Povarov-type inverse-electron-demand aza-Diels–Alder reaction of α,β-unsaturated hydrazones with aromatic imines afforded tetrahydroquinolines.[10] We focused on this *umpolung* approach to enhance the reactivity of α,β-unsaturated carbonyl compounds with α-pyrones **I** (Scheme 1D). That is, α,β-unsaturated hydrazones **II**, which have higher HOMO levels than the parent enals because of the electron-donating ability of the



Scheme 1 Cycloaddition of 3-electron-withdrawing group substituted α-pyrones.

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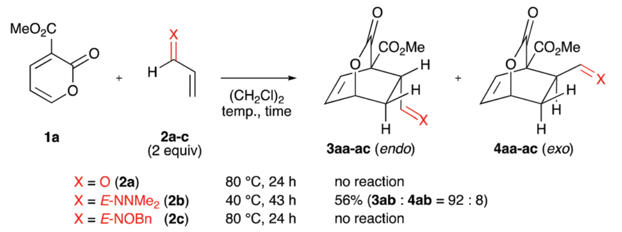
amino group, should react with electron-deficient α-pyrones **I** having low LUMO levels with matching frontier orbitals. Moreover, the regio-selectivity can be expected to be *syn*, because the orbital coefficient at the 6-position will be larger than that at the 3-position in the LUMO of α-pyrone **I** and the orbital coefficient will also be large at the β position in the HOMO of α,β-unsaturated hydrazone **II**. Here, we report inverse-electron-demand Diels–Alder reactions of electron-deficient α-pyrones **I** with α,β-unsaturated hydrazones **II** to afford cycloadducts **III** with high *syn* and *endo* selectivity.

Our studies began with examination of the reactions of methyl 2-oxo-2*H*-pyran-3-carboxylate (**1a**) with acrolein derivatives without any additive, in order to compare their reactivities (Scheme 2). Firstly, α-pyrone **1a** failed to react with acrolein (**2a**) at 80 °C. In contrast, the reaction with the corresponding dimethylhydrazone derivative **2b**[11] proceeded at 40 °C to produce only *syn* cycloadducts, as expected, in moderate yield as a 92 : 8 mixture of *endo*-adduct **3ab** and *exo*-adduct **4ab**. The structures of the two isomers were determined by means of NOESY experiments, as shown in Fig. 1. The *syn* selectivity can be explained in terms of frontier orbital theory as described above. We also examined the reaction with oxime derivative **2c** as another polarity-inverted enal,[12] but no reaction occurred.

Next, we investigated whether a Lewis acid catalyst would improve the conversion (Table 1). Although the use of $ZnCl_2$ or $AlCl_3$ resulted in degradation (runs 1 and 2), lanthanide catalyst $Eu(fod)_3$ increased the product yield to 76% (run 3). Furthermore, $Eu(hfc)_3$, which is occasionally used for the cycloaddition of α-pyrone-3-carboxylate,[13] afforded cycloadducts in 90% yield with perfect *endo* selectivity (run 4).[14] These results can be explained by the oxophilic nature of hard lanthanide catalysts.[15] Next, we examined whether the catalyst loading could be lowered. The *endo* cycloadduct **3ab** was obtained in high yield and selectivity by using 10 mol% $Eu(hfc)_3$ (run 5), whereas 5 mol% $Eu(hfc)_3$ resulted in a slight reduction of the yield (run 6). Gradual lowering of the *endo*-selectivity was observed when the amount of the catalyst was reduced. Taking into account the yield, selectivity, and catalyst loading, we chose 10 mol% $Eu(hfc)_3$ in dichloroethane as the optimum conditions.[16]



Scheme 2 Cycloaddition with acrolein derivatives without a Lewis acid.

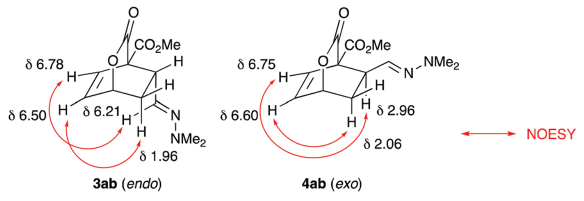
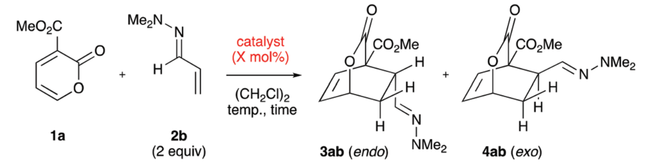


Fig. 1 Structure determination by means of NOESY experiments.

Table 1 Optimization of Lewis acid for α-pyrone activation



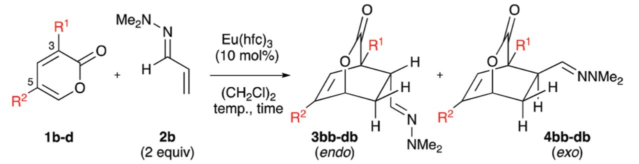
Run	Catalyst	Mol%	Temp.	Time	Yield	3 : 4
1	$ZnCl_2$	30	rt	30 h	33%	80 : 20
2	$AlCl_3$	30	rt	50 h	27%	89 : 11
3	$Eu(fod)_3$	30	0 °C	4 h	76%	94 : 6
4	$Eu(hfc)_3$	30	rt	17 h	90%	97 : 3
5	$Eu(hfc)_3$	10	rt	26 h	86%	92 : 8
6	$Eu(hfc)_3$	5	rt	20 h	75%	90 : 10

Recovery of α-pyrone **1a**: 7% (run 1), 43% (run 2).

Next, the substrate scope of this reaction for α-pyrones was studied (Table 2). The reaction of 3-*p*-toluenesulfonyl-substituted α-pyrone **1b**[17] with acrolein dimethylhydrazone (**2b**) catalyzed by 10 mol% of $Eu(hfc)_3$ successfully afforded cycloadducts **3bb** and **4bb** quantitatively with good *endo* selectivity (run 1). In contrast, the reaction of 5-methoxycarbonyl-substituted α-pyrone **1c** was slow, and gradual decomposition was observed (run 2). This result can be explained in terms of the lower affinity of 5-methoxycarbonyl α-pyrone **1c** for the Lewis acid catalyst, as compared with 3-methoxycarbonyl α-pyrone **1a**, due to its lack of bidentate chelation ability with the Eu complex. In this reaction, only a trace amount of *exo*-adduct **4cb** was isolated from the complex mixture. As the reaction of non-substituted α-pyrone **1d** was very slow even at 80 °C (run 3), as expected, this cycloaddition reaction appears to be an inverse-electron-demand Diels–Alder reaction.

Next, we examined the scope of α,β-unsaturated hydrazones (Table 3). The reaction of methacrolein hydrazone **2d**[11] gave

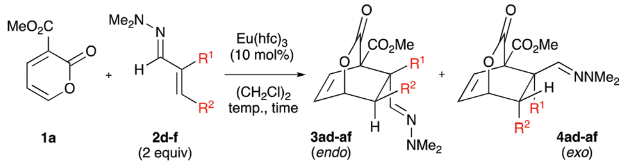
Table 2 Substrate scope: α-pyrones



Run	R^1	R^2	Temp.	Time	Yield	3 : 4
1	SO_2*p*-tol	H	50 °C	10 h	99%	83 : 17
2	H	CO_2Me	rt	48 h	2%	Only **4cb**
3	H	H	80 °C	40 h	9%	Only **3db**

Recovery of α-pyrone **1d**: 78% (run 3).

Table 3 Substrate scope: α,β-unsaturated hydrazones

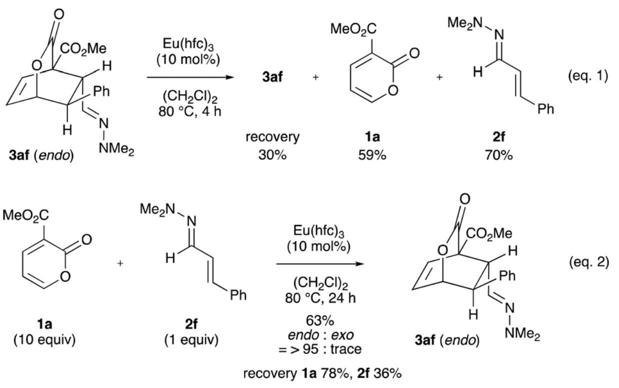


Run	R^1	R^2	Temp.	Time	Yield	3 : 4
1	Me	H	rt	4.5 h	67%	52 : 48
2	H	Me^a	50 °C	16 h	72%^{b}	96 : 4
3	H	Ph	80 °C	26 h	17%	>95 : trace

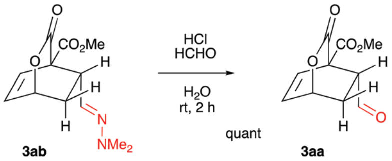
^{a} *trans* : *cis* = 89 : 11. ^{b} *cis*-Alkene derived isomer (4%) was excluded.

cycloadducts in moderate yields with poor stereoselectivity (run 1). In contrast, the cycloaddition with crotonaldehyde hydrazone **2e** selectively afforded the *endo* adduct in good yield (run 2). Surprisingly, the cycloaddition of cinnamaldehyde hydrazone **2f**[18] was not complete even after 26 hours at 80 °C, and the *endo*-cycloadduct **3af** was obtained in low yield concomitantly with gradual decomposition of **1a** (run 3). We established that the reason why the reaction did not proceed to completion was the occurrence of retrocycloaddition (Scheme 3). When the cycloadduct **3af** was treated under the same reaction conditions, α-pyrone **1a** (59%) and α,β-unsaturated hydrazone **2f** (70%) were obtained along with the starting cycloadduct **3af** (30%) (eqn (1)). This experiment clearly showed the occurrence of equilibration of the cycloaddition with **2f**. Therefore, we tried to improve the yield by loading an excess amount of α-pyrone to move the equilibrium. The cycloaddition of α-pyrone **1a** (10 equiv.) and cinnamaldehyde hydrazone **2f** (1 equiv.) gave *endo* cycloadduct **3af** in moderate yield with high selectivity, accompanied by the recovery of the starting materials (eqn (2)).

Finally, we examined the indirect synthesis of aldehyde **3aa**, which is the equivalent of the *syn*–*endo*-cycloadduct between α-pyrone-3-carboxylate **1a** and acrolein (**2a**), by dehydrazonation of cycloadduct **3ab** (Scheme 4). Under hydrazone exchange conditions (HCl and aq. HCHO), **3ab** gave aldehyde **3aa** quantitatively.



Scheme 3 Retrocycloaddition and improvement of the yield.



Scheme 4 Dehydrazonation of cycloadduct **3ab**.

Conclusions

We have developed an inverse-electron-demand Diels–Alder reaction of α-pyrones bearing a 3-electron-withdrawing group with α,β-unsaturated hydrazones as a new type of electron-rich olefin. The reaction was catalysed by the oxophilic lanthanide complex Eu(hfc)$_3$ and showed high *endo* selectivity. This method enabled us to synthesize a hydrazone-containing cycloadduct that can undergo hydrazone-specific reactions.[9] To our knowledge, this is the first report of an all-carbon inverse-electron-demand Diels–Alder reaction using α,β-unsaturated hydrazone as a dienophile apart from the reactions of 1,2-diazepine.[19] We also succeeded in dehydrazonation to afford the corresponding aldehyde, which cannot be easily obtained by the cycloaddition of α-pyrone and enal. Studies to develop an asymmetric version of this cycloaddition are ongoing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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