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Iron Catalyzed Enantioselective Intramolecular Inverse Electron-Demand Hetero Diels-Alder Reactions: An Access to Bicyclic Dihydropyran Derivatives

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ABSTRACT: A highly enantioselective iron-catalyzed Intramolecular Inverse Electron-Demand Hetero Diels-Alder (IIEDHDA) reaction is reported. By using a chiral semicorrin ligand in the presence of 2,6 lutidine, good isolated yields and excellent enantioselectivities were observed (up to 96% ee). Thanks to the versatile post-functionalization of the acyl-imidazole moiety, this methodology represents a unique example of the straightforward construction of highly valuable enantioenriched bicyclic dihydropyran derivatives.

Among the powerful synthetically rich Diels-Alder family reactions,¹ the intermolecular catalytic asymmetric [4+2] Inverse Electron-Demand Hetero Diels-Alder (IEDHDA) reaction gained a considerable success notably to access the prevalent 3,4-dihydropyran core.² In contrast, very few examples have been reported that demonstrate high levels of enantiocontrol in the Intramolecular Inverse Electron-Demand Hetero Diels-Alder (IIEDHDA) reaction. Narasaka first explored this transformation with unsaturated oxazolidinone **1** in the presence of a stoichiometric amount of (Taddol)TiCl₂. Unfortunately, despite high enantioselectivities, a mixture of Alder-ene **2** and IIEDHDA **3** products was formed (Scheme 1, a).³ In a series of papers, Tietze developed efficient domino Knoevenagel Hetero Diels-Alder from aldehydes and 1,3-dicarbonyl compounds.⁴ In the presence of an excess of diacetoneglucose-derived titanium catalyst, the IIEDHDA products **5** were obtained in good yields and *cis* diastereoselectivities with moderate to good enantioselectivities (30-88% ee, Scheme 1, b). Wada described a catalytic enantioselective domino transesterification/intramolecular Diels-Alder sequence affording the *trans*-fused hydropyranopyrans **6** in good yields and excellent diastereo- and enantioselectivities (69-76% yield, 97-98% ee, Scheme 1, c), with albeit narrow scope (3 examples).⁵

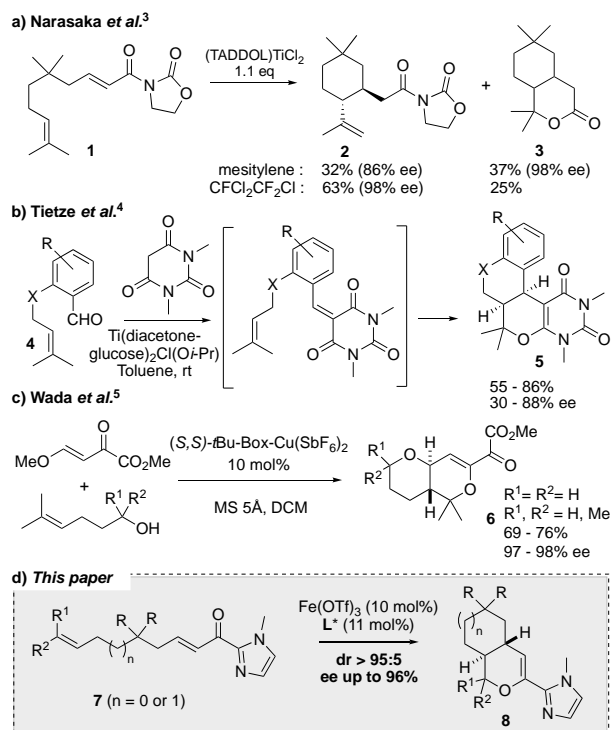
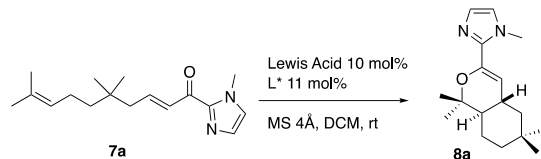


Figure 1. Enantioselective Intramolecular Inverse Electron-Demand Hetero Diels-Alder reactions.

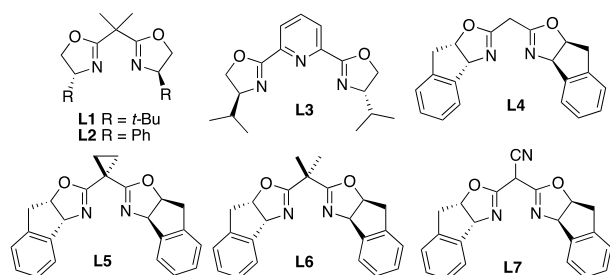
We would like to describe herein highly selective iron-catalyzed IEDHDA reactions starting from unsaturated acyl-imidazoles derivatives **7** (Scheme 1, d). Iron is an abundant, non-toxic, and inexpensive element and thus iron catalysis meets the requirements for sustainable and green chemistry.⁶

Based on our experience in asymmetric conjugate addition to unsaturated acyl-imidazoles,⁷ we were keen to exploit the unique properties of these ester/amide surrogates in IEDHDA reactions.⁸ Investigations began with the IEDHDA reaction of citral derivative **7a** using several Lewis acids in the absence of chiral ligands (see Supplementary Information, SI, for details). Among the diverse metal salts tested, Cu(OTf)₂ and Fe(OTf)₃ proved to be the more promising ones leading to the IEDHDA product **8a** as a single diastereomer in 69 and 83% yields respectively (table 1, entries 1,2). Interestingly, only traces (< 5%) of the Alder-ene product **9a** could be detected. As determined by ¹H NMR and further confirmed on X-Ray structures on post-transformed compounds (*vide infra*), **8a** adopts a bicyclic *trans* junction as expected through a sterically favored *anti* TS usually observed for *E*-dienes.^{2a-b}

Table 1. Chiral ligand optimization



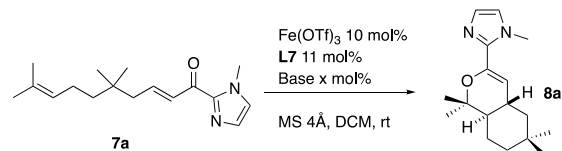
entry	LA	L*	time (h)	yield (%)	ee (%)
1	Cu(OTf) ₂	-	20	69	-
2	Fe(OTf) ₃	-	20	83	-
3	Fe(OTf) ₃	L1	19	42	0
4	Fe(OTf) ₃	L2	20	50	8
5	Fe(OTf) ₃	L3	18	35	8
6	Cu(OTf) ₂	L1	72	47	10
7	Cu(OTf) ₂	L3	20	39	5
8	Fe(OTf) ₃	L4	72	56	8
9	Fe(OTf) ₃	L5	72	48	53
10	Fe(OTf) ₃	L6	72	79	20
11	Cu(OTf) ₂	L4	72	27	14
12	Cu(OTf) ₂	L5	72	26	3
13	Cu(OTf) ₂	L6	72	48	6
14	Fe(OTf) ₃	L7	72	68	57



It is noteworthy that no reaction occurs when Weinreb amide or ethyl ester derivatives are involved, illustrating the peculiar properties of the acyl-imidazole. Indeed, acyl-imidazoles are more electron-withdrawing groups compared to esters and other ester-surrogates, and they are able via a double mode of coordination to warrant a defined transition state.⁸

Asymmetric reactions were thus next explored with Cu(OTf)₂ and Fe(OTf)₃ in the presence of most commonly used Box and Pybox **L1-L6** ligands with however disappointing results (Table 2, entries 3-13).⁹ The notable exception was observed with Fe(OTf)₃/L5 (entry 9) for which a 53% ee could be reached. All our further attempts to improve the selectivity by changing the reaction parameters (solvent, temperature, iron salts) proved anyway unsuccessful in our hands. It was anticipated that the presence of an electron withdrawing group on the bridging carbon of the bis(oxazoline) could enhance the reactivity of the metal complex.¹⁰ This was confirmed by using **L7** bearing a cyano group that produced the compound **8a** in 68% isolated yield and improved 57% ee (entry 14). Anticipating that traces of triflic acid could promote a parallel and racemic catalytic cycle, the use of a base as additive was envisioned in the presence of Fe(OTf)₃/L7 (Table 2).¹¹

Table 2. Base as additive in the asymmetric IEDHDA reaction with 7a



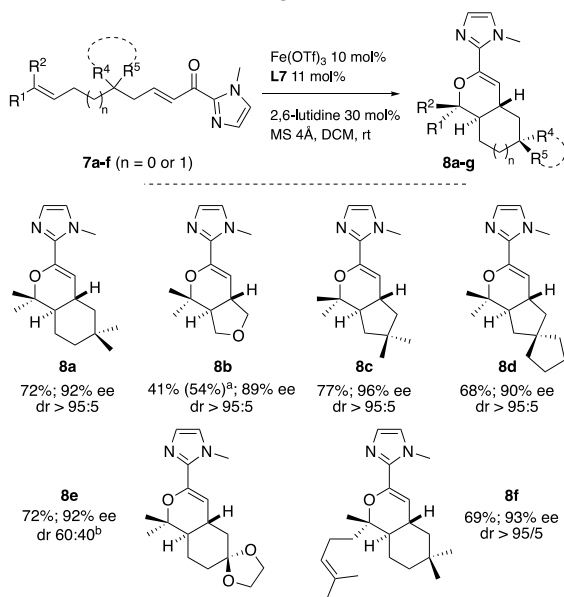
entry	base (mol %)	time (h)	yield (%)	ee (%)
1	-	72	68	57
2	DIPEA (20)	72	35	6
3	DABCO (15)	72	25	11
4	2,6-di- <i>t</i> -butylpyridine (30)	72	64	75
5	2,6-di- <i>t</i> -butyl-4-methylpyridine (30)	72	71	86
6	2,6-lutidine-4-hydroxy (30)	72	89	72
7	2,4,6-collidine (30)	72	72	85
8	2,6-lutidine (30)	72	72	92
9	2,6-lutidine (30)	72	52	52
<i>with L5</i>				
10	2,6-lutidine (30)	72	63	45
<i>without MS 4Å</i>				

After a screening of several bases, a drastic improvement of enantioselectivity was observed with pyridine derivatives (entries 4-8) reaching a maximum of 92% ee in the presence of 2,6 lutidine (30 mol%). Some other interesting observations could be drawn from the optimization study.

First, enantioselectivity dropped to 52% when using other chiral ligands such as **L5** (entry 9). Second, the molecular sieves appeared essential to maintain the enantioselection (63% yield, 45% ee, entry 10). At last, the catalyst can also be *in-situ* generated from FeCl₃ and AgOTf with similar good results (see Supplementary Information, SI, for details).

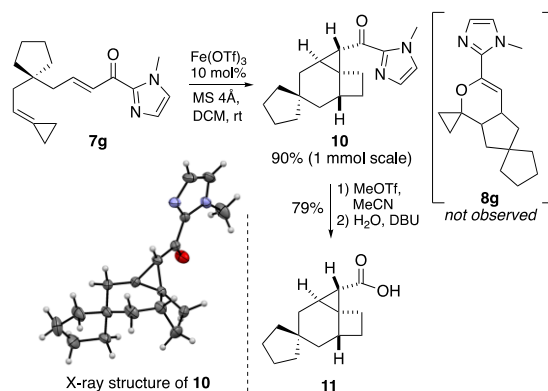
After optimization of the IIEDHDA reaction with citral derivative **7a**, the general scope was next explored (Scheme 1). When the chain length (6-6 vs 6-5 bicycles) was changed or bearing different substituents on the R⁴/R⁵ positions (alkyl chains, heteroatom or an acetal group), the reaction provided expected bicyclic compounds **8a-e** in good yields and stereoselectivities (dr >95:5; 89%-96% ee) with the exception of **8e** (dr 60:40). In this case, both separable diastereomers could be obtained in 92% ee. Concerning the 5,6-fused ring systems (compounds **8b-d**), the *trans* configuration could be ascertained by analyzing the H₄ NMR signal (H close to the double bond at the ring junction): For example in **8b**, the signal is a dddd with coupling constants of 12.1; 11.1; 7.2 and 2.0 Hz. The attribution of each coupling constant is as followed: 12.1 (H₄-H_{bicyclic}), 11.1 (H₄-CH_{trans}H'), 7.2 (H₄-CHH'_{cis}), 2.0 (H₄-H_{alkene}). The large coupling constant is consistent with a *trans* relationship along the ring junction. Finally, we also observed that substrate **7f** possessing a farnesyl chain (R¹ ≠ R²) afforded product **8f** in 69% yield as a single diastereomer (dr > 95:5) and high enantioselectivity (93% ee).

Scheme 1. Scope of the asymmetric IIEDHDA reaction



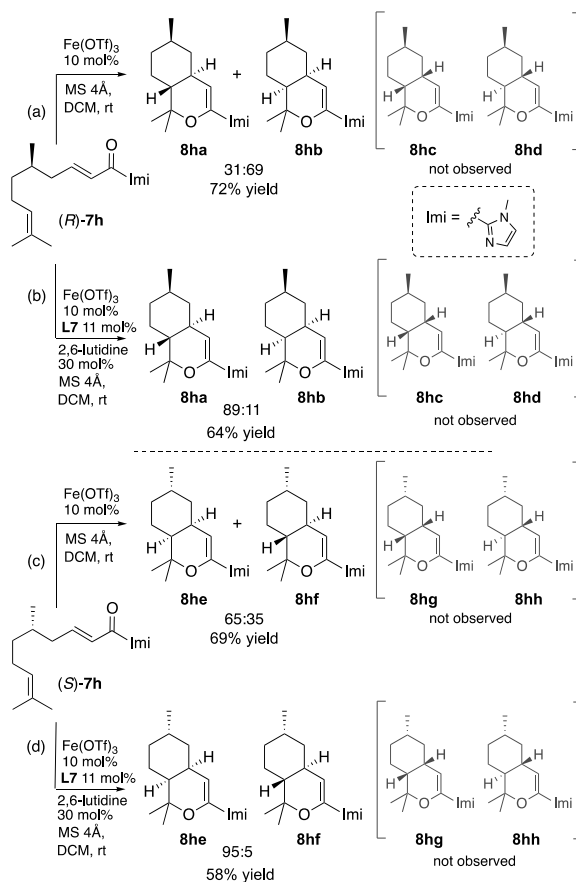
A more surprising result was observed with compounds **7g** bearing a remote cyclopropylidene unit. The IIEDHDA product **8g** was not observed and compound **10** was isolated in 90% yield (1 mmol scale) as a single diastereomer. The structure of **10** is rather complex embedding 3-, 4-, 5- (spiro) and 6-membered cycles (Scheme 2). Structural determination proved challenging and was finally ascertained using a ¹³C NMR INADEQUATE sequence (see SI).

Scheme 2. Rearrangement of **7g** in IIEDHDA reaction conditions



Its structure was unambiguously confirmed by single crystal X-Ray diffraction studies. Moreover, the acyl-imidazole was further easily transformed into the corresponding carboxylic acid **11** in 79% yield.⁸ Finally, in the presence of L7-lutidine, compound **10** could be isolated in 85% yield and 37% ee. The formation of **10** can tentatively be explained through two successive Wagner-Meerwein rearrangements (See mechanistic proposal in SI).

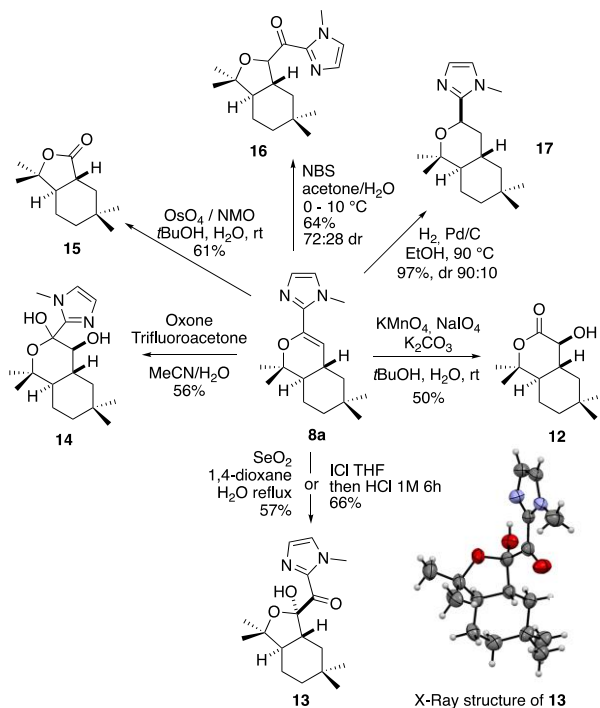
Scheme 3. IIEDHDA reaction with (*R*)- and (*S*)-enantiomer of citronellal derivative **7h**



We next turned our attention to citronellal derivatives **7h** bearing a methyl group in the δ position (Scheme 3).

These substrates are more challenging because the introduction of a stereogenic center could potentially lead to 4 diastereomers and induce match/mismatch pairs. Moreover, they lack beneficial Thorpe-Ingold effect. Starting from the (*R*) enantiomer, the IIEDHDA reaction was first carried out in the absence of chiral ligand (Scheme 3, a). In this case, only two diastereomers **8ha** and **8hb** were observed in a 31:69 ratio by ¹H NMR on the crude material. Moving to the optimized enantioselective conditions, a reverse 89:11 ratio could be observed (Scheme 3, b). The structure of the major diastereomer **8ha** could be unambiguously confirmed by ¹H NMR NOESY experiments (for the determination of the structure of minor diastereomers, see SI). With the (*S*) enantiomer under achiral conditions (Fe(OTf)₃, DCM, rt), two other diastereomers **8he** and **8hf** were observed in a 65:35 ratio (determined by ¹H NMR on the crude material, Scheme 3, c). In chiral conditions (Fe(OTf)₃, **L7**, lutidine), an improved 95:5 ratio of the same two diastereomers **8he** and **8hf** could be observed with 58% isolated yield (Scheme 3, d). The structure of **8he** proved more difficult to establish. From NMR studies (see SI), it appears that **8he** adopts a bicyclic *cis* junction, with the two protons at the ring junction being *cis* to the stereogenic methyl group. These two experiences highlight the prominent role of chiral ligand **L7** in the double stereodifferentiation with these chiral substrates. The scale-up reaction was next attempted on acyl-imidazoles **7a** and (*S*)-**7h**. Moving from a 0.2 to 1.0 mmol scale was found experimentally more practical and beneficial in terms of isolated yield (84% vs 72% and 90% vs 58% respectively) with no change in the stereoselectivity (enantio- or diastereoselectivity) issues.

Scheme 4. IIEDHDA products post-functionalization



The IIEDHDA products **8** possess an usual bicyclic structure with a pending imidazolyl group and thus offer many possibilities for synthetic post-transformations. Acid-mediated direct transformation of the imidazole ring (or the imidazolium salt after methylation with MeOTf) in **8a** proved unsuccessful under various conditions. We thus next explored conditions for the double bond oxidation. In the presence of $\text{KMnO}_4/\text{NaIO}_4$, the α -hydroxy lactone **12** was obtained in 50% yield as a single diastereomer. The oxidation of **8a** in the presence of SeO_2 led to the corresponding diketone isolated as the acetal **13** as a single diastereomer. The structure was ascertained by an X-Ray analysis and also confirmed the *trans* relationship of the two hydrogens at the ring junction. Interestingly, the same compound **13** could be obtained from **8a** using ICl in 66% yield. Epoxidation of the double bond was next attempted out using oxone and trifluoroacetone,¹² but compound **14** resulting from a dihydroxylation reaction was obtained in 56% yield as a single diastereomer. By using OsO_4/NMO , lactone **15** was isolated in 61% yield. In the presence of NBS, the ring contraction product **16** was obtained in 64% yield in a 72:28 dr. Finally, the enol ether double bond could be reduced in the presence of Pd/C to give compound **17** in 97% yield (90:10 dr).

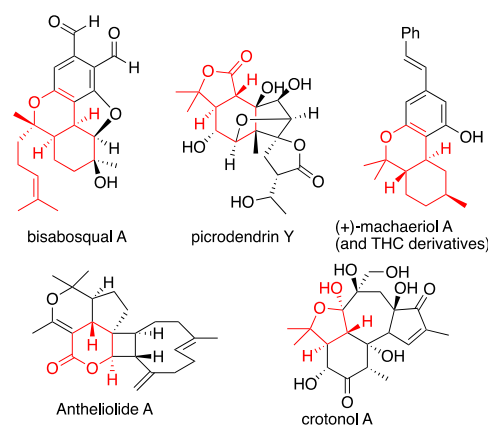
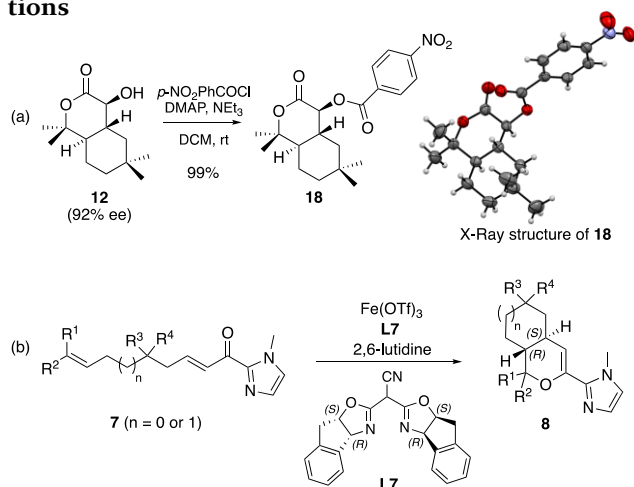


Figure 2. Natural Products embedding dihydropyran derivatives **8b** and post-transformed products **12-17**.

It should be emphasized that bicyclic dihydropyran derivatives **8** and post-transformed products **12-17** are present in a wide range of bioactive natural products, as illustrated in figure 2.¹³

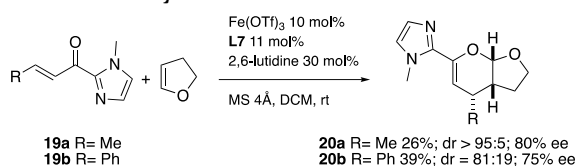
Scheme 5. Determination of the absolute configurations



The determination of absolute configurations of IEDHDA products **8** could be finally obtained via the derivatization of enantiomerically enriched **12** (92% ee) to the corresponding *p*-NO₂ phenyl ester **18** allowing the formation of a crystalline compound (Scheme 5, a). An X-ray structure for **18** was obtained confirming the relative stereochemistry determined by ¹H NMR but also establishing absolute configurations. It should be emphasized that this experiment confirms the absolute configurations observed in **8ha** (obtained from (*R*)-**7h**). Accordingly, the absolute stereochemistries for compounds **8** obtained from Fe(OTf)₃/L7 (obtained from (1*R*, 2*S*)-(+)-*cis*-1-amino-2-in-danol)) were thus tentatively assigned by analogy (Scheme 5, b).

Finally, an intermolecular version of the hetero Diels-Alder reaction of acyl-imidazoles **19** (R = Me or Ph) with dihydrofuran led to the Diels-Alder products **20** in low yields but promising enantioselectivities (Scheme 6).

Scheme 6. Asymmetric intermolecular reactions



In summary, we have developed a highly enantioselective iron-catalyzed Intramolecular Inverse Electron-Demand Hetero Diels-Alder (IEDHDA) reaction using C₂-symmetric semicorrin ligand and 2,6-lutidine. This iron-catalyzed reaction generates enantioenriched bicyclic dihydropyran derivatives in good yields and excellent diastereo- and enantio-selectivities. These compounds can be further easily transformed into a large range of valuable bicyclic heterocycles. Further mechanistic investigations and DFT calculations are currently ongoing in our laboratory to unveil the role of the base in these transformations, and determine the stepwise vs concerted character of this [4+2] cycloaddition, as we envision that this catalytic system will

inspire future studies in iron-catalyzed asymmetric transformations.

ASSOCIATED CONTENT

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interests.

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(11) The exact role of the added base is not yet understood. Efforts to crystallize the Fe(OTf)₃/L7 or Fe(OTf)₃/L7/2,6-lutidine catalytic systems were unsuccessful in our hands only leading to the crystalline L7·TfOH salt, catalytically inactive in the absence of iron.

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