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Highly diastereroselective synthesis of dihydrofurans and dihydropyrroles *via* pyridine catalyzed formal [4 + 1] annulation†

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A pyridine-catalyzed ylide cyclization affording dihydrofurans and dihydropyrroles has been developed. In the presence of a catalytic amount of pyridine and Fe(Tcpp)Cl, α-ylidene-β-diketones and α,β-unsaturated imines react with diazoacetates providing dihydrofurans and dihydropyrroles respectively, in up to 96% yield with high diastereoselectivities.

Ylides can be regarded as a special cabanion with a leaving group,[1] which have proved to be good reagents for the synthesis of five-membered ring systems,[2] which are frequently encountered in biologically active compounds and are also useful as synthetic intermediates.[3,4] For example, several groups reported independently that α-ylidene-β-diketones could either react with a nitrogen ylide or a sulfur ylide giving 2,3-dihydrofurans.[2a,c–e,g–i] Unfortunately, In these reactions, a stoichiometric amount of ylide is required and the catalytic version of this transformation has not been reported. In this work it has been found that 1 mol% of pyridine can catalyze the reaction between α-ylidene-β-diketones and an alkyl diazoacetate smoothly in the presence of catalytic tetra(*p*-chlorophenyl)porphyrin iron chloride (Fe(Tcpp)Cl). Further studies showed that this method could be extended to the synthesis of dihydropyrroles by employing α,β-unsaturated imines instead of α-ylidene-β-diketones under similar reaction conditions. In this communication we report the preliminary results.

Iron carbenoids, readily available from alkyl diazo acetate, prove to be good reagents for the preparation of sulfur ylides under neutral conditions by its reaction with sulfide.[5] It was pleasing to find that the reaction of α-ylidene-β-diketone **1a** with ethyl diazoacetate, in the presence of 2 mol% of Fe(Tcpp)Cl and 20 mol% of dimethyl sulfide, proceeded smoothly affording to the desired dihydrofuran (entry 1, Table 1). As shown in Table 1, further study showed that 20 mol% of tetrahydrothiophene (THT) worked well (entry 2, Table 1). When diisobutyltelluride was used instead of dimethyl sulfide, the reaction did not work at all. Pyridine proved to be a good catalyst for such transformation (entry 4, Table 1) and DABCO gave only 50% conversion (entry 5, Table 1). Cinchonine, tridentate 2,6-bis(oxazolinyl)-pyridine ((S)-^{i}Pr-Pybox), quinine, and isoquinoline were inert to this reaction (entries 6–9, Table 1). A control experiment showed that no ylide cyclization occurred in the absence of a catalyst (entry 10, Table 1).

Since pyridine is cheap and 99% conversion could be obtained when 20 mol% of pyridine was employed (entry 4, Table 1), the effect of pyridine loading on the cyclization was next investigated using **1a** as a model substrate. As summarized in Table 2, when 1 mol% of Fe(Tcpp)Cl was employed, the loading of pyridine could be reduced from 20 mol% to 6 mol% and the conversion was still quantitative (entry 4, Table 2). Further reduction of the amount of pyridine led to low conversion under the same conditions (entries 5–6, Table 2).[6]

Under optimal conditions, the generality of this reaction was investigated using a variety of α-ylidene-β-diketone substrates. As shown in Table 3, various α-ylidene-β-diketones are good substrates for such a transformation to give dihydrofurans and no cyclopropanes are observed. For example, aromatic substrates with an electron-withdrawing group (entries 1, 2, 6, 7, 9, Table 3) as well as an electron-donating group (entries 3, 4, Table 3) all worked well to give the desired products in high yields with high diastereoselectivities (yield > 85%, dr > 50 : 1). 85% yield with excellent diastereoselectivity was obtained when 3-(furan-2-ylmethylene)pentane-2,4-dione was employed (entry 8, Table 3). Aliphatic-substituted diketones such as 3-pentylidenepentane-2,4-dione also gave high yields of cyclized products (entry 10, Table 3). Thus, this method provides an easy route to tetrasubstituted dihydrofurans under neutral conditions *via* a catalytic nitrogen-ylide process.

Diazoacetophenone was also tested and the desired dihydrofuran was isolated in 92% yield with high diastereoselectivity (eqn (1)). It is noteworthy that, under optimal conditions, loading of pyridine could be reduced to 1 mol% when the reaction was scaled up to 1.0 mmol and the concentration of **1a** was increased to 1.0 M. In this case, both the yield and diastereoselectivity were still high (eqn (2)).

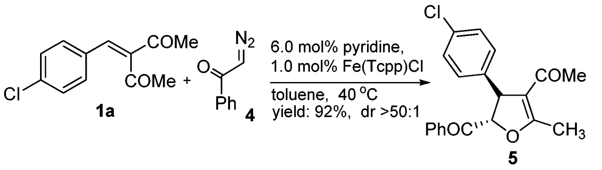

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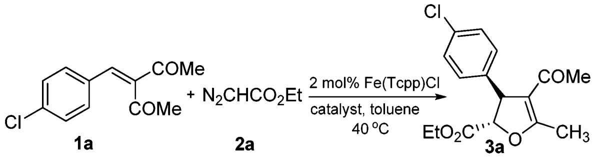
Table 1 Effects of heteroatom compounds as catalysts for the ylide cyclization[a]



1a **2a** **3a**

Entry	Cat. (20 mol%)	Conv.[b] (%)	Entry	Cat. (20 mol%)	Conv.[b] (%)
1	Dimethylsulfide	> 99	6	Cinchonine	0
2	THT	90	7	(S)-^{i}Pr-Pybox	0
3	Diisobutyltelluride	0	8	Quinine	0
4	Pyridine	> 99	9	Isoquinoline	0
5	DABCO	50	10	—	0

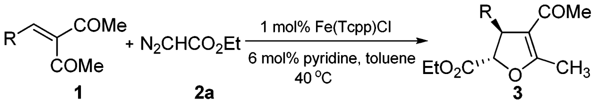
[a] **1a** (45 mg, 0.2 mmol), Fe(Tcpp)Cl (4 mg, 4 μmol), **2a** (46 mg, 0.4 mmol), toluene (2.0 mL), 40 °C. [b] Determined by ^{1}H NMR and relative stereochemistry for **3a**.

Table 2 The effect of pyridine loading on cyclization[a]

Entry	Fe(Tcpp)Cl (mol%)	Pyridine (mol%)	Time/h	Conv.[b] (%)
1	2	20	5	> 99
2	2	10	8	> 99
3	2	6	8	80
4	1	6	8	> 99
5	1	2	8	20
6	0.5	2	8	20

[a] **1a** (45 mg, 0.2 mmol), **2a** (46.0 mg, 0.4 mmol), toluene (2.0 mL), 40 °C. [b] Determined by ^{1}H NMR.

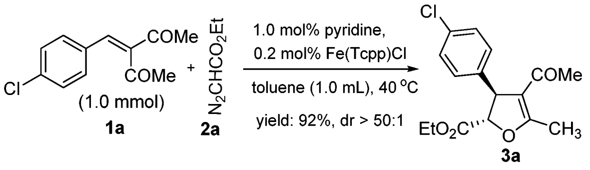
Table 3 Reaction of EDA with α-ylidene-β-diketones[a]



1 **2a** **3**

Entry	R	Yield (%)[b]	Dr[c]
1	4-Cl–C_6H_4– (**1a**)	96	> 50 : 1
2	4-Br–C_6H_4– (**1b**)	94	> 50 : 1
3	4-Me–C_6H_4– (**1c**)	88	> 50 : 1
4	4-OMe–C_6H_4– (**1d**)	85	> 50 : 1
5	Ph (**1e**)	94	> 50 : 1
6	4-NO_2–C_6H_4– (**1f**)	95	> 50 : 1
7	2-Br–C_6H_4– (**1g**)	95	> 50 : 1
8[d]	2-furanyl (**1h**)	85	> 50 : 1
9	4-CF_3–C_6H_4– (**1i**)	92	> 50 : 1
10[e]	*n*-C_3H_7– (**1j**)	85	> 50 : 1

[a] Fe(Tcpp)Cl (2.0 mg, 2 μmol), **1** (0.2 mmol), **2a** (45.6 mg, 0.4 mmol), pyridine (1.0 μL, 0.012 mmol), toluene (2.0 mL), 40 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR and relative stereochemistry for **3**. [d] Fe(Tcpp)Cl (2.0 mg, 2 μmol), **1h** (178 mg, 1.0 mmol), **2a** (228 mg, 2.0 mmol), pyridine (8.0 μL, 0.10 mmol), toluene (2.0 mL), 40 °C. [e] Fe(Tcpp)Cl (2.0 mg, 2 μmol), **1j** (154 mg, 1.0 mmol), **2a** (228 mg, 2.0 mmol), pyridine (4.0 μL, 0.05 mmol), toluene (2.0 mL), 40 °C.



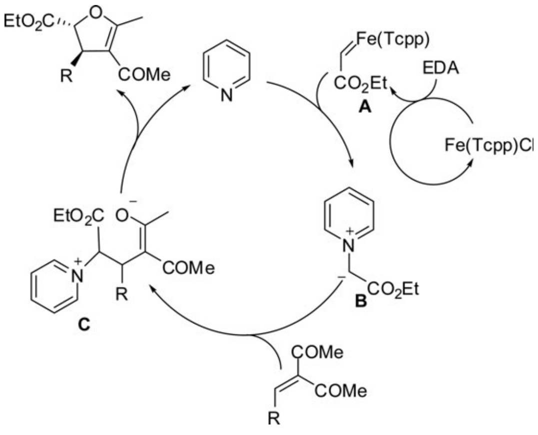
1a **2a** **3a**

(2)

A possible mechanism for this formal [4 + 1] annulation is proposed as shown in Scheme 1. Fe(Tcpp)Cl decomposes EDA to give an iron carbenoid **A**, which reacts with pyridine to generate a pyridinium ylide **B**. **B** undergoes a Michael addition, followed by intramolecular cyclization to give dihydrofurans. A clear mechanism awaits further investigation.

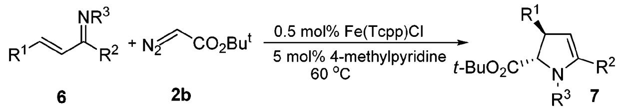
This strategy could also be extended to the synthesis of dihydropyrroles. Using 20 mol% of pyridine as the catalyst, the reaction of imine **6a** with *tert*-butyl diazoacetate worked to give dihydropyrrole **7a** in 60% conversion (entry 1 in Table 4). Further optimization showed that 4-methylpyridine is more efficient than pyridine. As shown in Table 4, under optimal conditions, α,β-unsaturated imines reacted with *tert*-butyl diazoacetate (BDA) smoothly, affording dihydropyrroles with high diastereoselectivities in the presence of 5 mol% of 4-methylpyridine and 0.5 mol% of Fe(Tcpp)Cl. Aromatic substrates bearing an electron-withdrawing group (entries 3,5) and an electron-donating group (entry 4) all gave the corresponding dihydropyrroles in high yields (> 82%) with dr > 50 : 1. Aliphatic imines are not suitable for such transformation and no desired products were observed.

In conclusion, we developed a catalytic formal [4 + 1] annulation *via* a nitrogen ylide route, providing an easy route to dihydrofurans and dihydropyrroles in good to excellent yields with high diastereoselectivities. The loading of the catalyst pyridine could be reduced to 1 mol%. The high chemoselectivity, high diastereoselectivity, the easily accessible starting material and the low amount of pyridine used in this reaction make this reaction potentially useful in organic synthesis.



Scheme 1 Possible mechanism of this annulation.

Table 4 Reaction of BDA with α,β-imines[a]



6 **2b** **7**

Entry	R^1	R^2	R^3	**7**	Yield (%)[b]	Dr[c]
1[d]	Ph	Ph	Ts	**7a**	60[e]	> 50 : 1
2	Ph	Ph	Ts	**7a**	92	> 50 : 1
3	*p*-Cl–C_6H_4	Ph	Ts	**7b**	93	> 50 : 1
4	*p*-OMe-C_6H_4	Ph	Ts	**7c**	82	> 50 : 1
5	*p*-Cl–C_6H_4	*p*-Br–C_6H_4	Ts	**7d**	92	> 50 : 1
6	Ph	Ph	*p*-$C_6H_4SO_2$	**7e**	91	> 50 : 1

[a] Fe(Tcpp)Cl (2.0 mg, 2 μmol) , **6** (0.5 mmol), **2b** (150 mg, 1.0 mmol), 4-methyl-pyridine (2.5 μL, 0.025 mmol), toluene (2.0 mL), 60 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] 20 mol% of pyridine as the catalyst. [e] Conversion by ^{1}H NMR.

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