Organocatalysis

DOI: 10.1002/anie.201403082

Remote Enantioselective Friedel–Crafts Alkylations of Furans through HOMO Activation**

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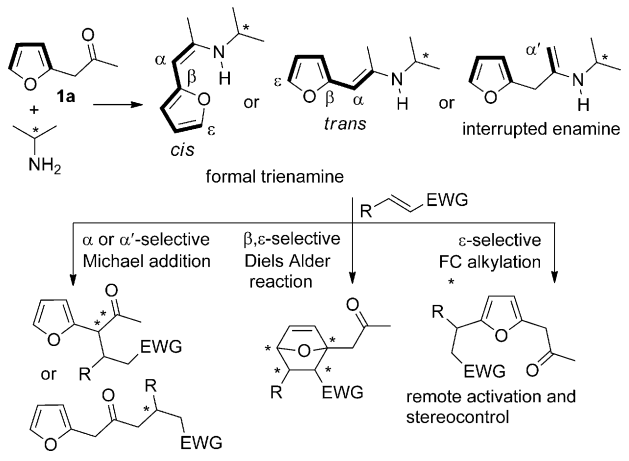
Abstract: *Catalytic asymmetric Friedel–Crafts alkylation is a powerful protocol for constructing a chiral $C(sp^2)$–$C(sp^3)$ bond. Most previous examples rely on LUMO activation of the electrophiles using chiral catalysts with subsequent attack by electron-rich arenes. Presented herein is an alternative strategy in which the HOMO of the aromatic π system of 2-furfuryl ketones is raised through the formation of a formal trienamine species using a chiral primary amine. Exclusive regioselective alkylation at the 5-position occurred with alkylidenemalononitriles, and high reactivity and excellent enantioselectivity (up to 95 % ee) was obtained by this remote activation.*

Since the seminal report by Friedel and Crafts in 1877, the Friedel–Crafts (FC) reaction remains one of the most powerful and atom-economical methods to construct a C–C bond on aromatic ring systems.[1] As a chiral benzylic center will be generated in FC alkylation reactions, the catalytic enantioselective versions trigger increasing attention in organic synthesis. The most common asymmetric FC alkylations employ the catalysis of Lewis acids coordinated to chiral ligands to activate a variety of electrophilic reagents, and abundant examples have been presented since the pioneering work of Erker et al. in 1990.[2,3] Previously less reactive allylic carbonates or alkenes also can be used as alkylation substrates with various transition-metal catalysts.[4] In contrast, organic chiral Brønsted acids have been broadly utilized in asymmetric FC alkylations through hydrogen-bonding catalysis over the past decade.[5] The covalent formation of iminium ions between a chiral secondary or primary amine with α,β-unsaturated carbonyl compounds also promote the asymmetric FC reactions with arenes.[6] In addition, an elegant organocatalytic SOMO activation mode has been used in enantioselective intramolecular FC alkylations recently.[7] Nevertheless, all of these catalytic asymmetric FC reactions proceed by lowering the LUMO energy of electrophilic partners. A conceptually different catalytic version involving the raising of the inherent electron density and nucleophilicity of aromatic substances has not been developed yet.

The HOMO activation of a carbonyl compound by in situ generation of an enamine intermediate with an amine catalyst has been extensively explored over the past decade.[8] The development of dienamine catalysis has succeeded in the activation of the γ site of α,β-unsaturated aldehydes or ketones.[9] Moreover, such an energy transfer could be further extended through the C=C bonds of polyconjugated carbonyl compounds, thus delivering trienamine species with more reactive sites.[10] Nevertheless, the reaction pattern is still limited to β,ε- or δ,ε-regioselective Diels–Alder cycloadditions.[11] As a result, the development of a new reaction mode with a trienamine-type intermediate is in high demand.

Furans are widely witnessed as key structural motifs in natural products or biologically active molecules.[12] They are electron-rich heteroarenes but generally less reactive than indoles or pyrroles in FC alkylations.[13] Accordingly, the enantioselective FC alkylations of furans have been less explored.[14] It was envisaged that the HOMO of the heteroaromatic π system could be raised by forming a conjugated enamine intermediate between 2-furylacetone (**1a**) and an amine catalyst.[15] Thus, a potential asymmetric FC alkylation with a suitable electron-deficient alkene might be realized by a previously unreported HOMO-activation strategy. However, this catalytic process via a formal trienamine species would be quite complicated and highly challenging, because not only a variety of reaction possibilities, as outlined in Scheme 1, might be involved, but also the reactive ε-site is very remote from the chiral center of amine catalyst, thus significantly diminishing the reliability of stereochemical communication.[16]



Scheme 1. HOMO activation of a furan system and the various reaction possibilities. EWG = electron-withdrawing group.

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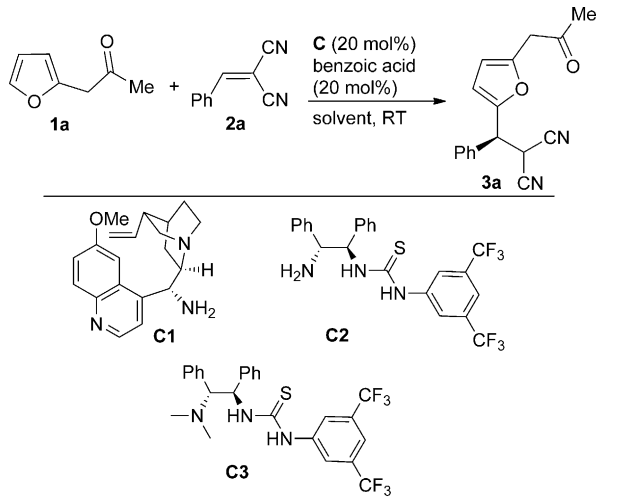
[**] We are grateful for the financial support from the NSFC (21122056, 21372160, and 21321061) and National Basic Research Program of China (973 Program, 2010CB833300). We also thank Professor Li-She Gan at Zhejiang University for helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201403082.

The initial screening reactions with 2-furylacetone (**1a**) and various electron-deficient alkenes indeed revealed some of the above-mentioned reaction patterns through the catalysis of 9-amino-9-deoxyepiquinidine (**C1**) and benzoic acid in toluene. It was pleasing that exclusive regioselective FC alkylation at the 5-position occurred to give the product **3a** in a moderate yield from the combination of **1a** and benzylidenemalononitrile (**2a**) at ambient temperature after 12 hours (Table 1, entry 1). Unfortunately, the enantioselectivity was fairly disappointing, probably because the ε site is far from the chiral amine (up to 6 or 7 bonds). After extensive exploration with a number of amine catalysts and reaction conditions,[17] it was found that the readily available bifunctional primary amine-thiourea **C2**, derived from (*R*,*R*)-1,2-diphenylethanediamine, could efficiently promote this FC alkylation and the product **3a** was obtained with high enantioselectivity, probably as a result of hydrogen-bonding interactions with the electrophile (Table 1, entry 2).[18] It should be noted that the bifunctional tertiary amine-thiourea **C3** exhibited no catalytic activity in the model reaction, thus indicating that the formation of conjugated enamine intermediate is crucial for the activation of furan system (Table 1, entry 3). A number of acid additives were investigated in combination with **C2**, but inferior results were generally obtained in comparison with that of benzoic acid.[17] Similar data were produced in other solvents (Table 1, entries 4 and 5). Gratifyingly, the reaction proceeded smoothly at 0 °C, and a slightly higher *ee* value was attained (Table 1, entry 6). However, the enantiocontrol could not be further improved at −10 °C, though the product could be isolated in good yield after 24 hours (Table 1, entry 7). Decreasing the amounts of the ketone substrate or catalyst loading required a longer reaction time so as to achieve good conversion, but high enantioselectivity was retained consistently (Table 1, entries 8–10). A reaction on a larger scale was investigated, and good results were obtained after 48 hours (Table 1, entry 11).

Table 1: Screening reaction conditions for the FC alkylation of **1a** with **2a**.[a]



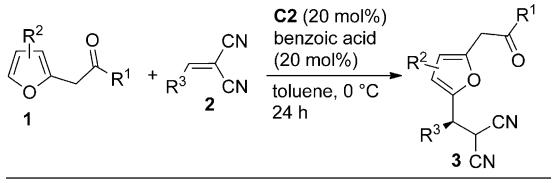
Entry	Cat.	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	**C1**	toluene	12	63	16
2	**C2**	toluene	12	85	88
3	**C3**	toluene	12	–	–
4	**C2**	CH_2Cl_2	12	74	83
5	**C2**	*m*-xylene	12	83	88
6[e]	**C2**	toluene	24	85	92
7[f]	**C2**	toluene	24	78	90
8[e,g]	**C2**	toluene	36	81	94
9[e,h]	**C2**	toluene	36	85	94
10[e,i]	**C2**	toluene	48	74	94
11[e,j]	**C2**	toluene	48	87	90

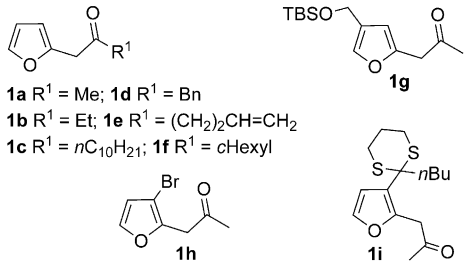
[a] Unless noted otherwise, reactions were performed with 2-furylacetone (**1a**; 0.3 mmol), benzylidenemalononitrile (**2a**; 0.1 mmol), **C** (20 mol%), and benzoic acid (20 mol%) in solvent (1.0 mL) at ambient temperature. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] With 40 mol% of benzoic acid. [e] At 0 °C. [f] At −10 °C. [g] With 0.2 mmol of **1a**. [h] With 10 mol% of **C2**. [i] With 5 mol% of **C2**. [j] With 0.5 mmol of **2a**.

With the optimal reaction conditions in hand, we then investigated the substrate scope of the 2-furfuryl ketones **1** and alkylidenemalononitriles **2**. The results are summarized in Table 2. For the reactions with **1a**, a spectrum of unsaturated malononitriles **2** having diversely substituted β-aryl groups, were well tolerated and thus afforded the FC alkylation products in high yields with good to excellent enantioselectivities (Table 2, entries 1–10). Heteroaryl-substituted acceptors showed lower reactivity, and slightly diminished *ee* values were obtained (Table 2, entries 11–13). Importantly, either linear or branched alkyl-substituted alkenes exhibited comparable reactivity, and good results were generally attained (Table 2, entries 14–18). In contrast, a number of 2-furfuryl ketones were explored with **2a**. The substrates **1b–f**, bearing various α′-alkyl substitutions, including benzyl or branched cyclohexyl groups, were compatible, thus producing the products in good yields and with high enantioselectivities (Table 2, entries 19–23). Moreover, the ketones **1g–i** having functional groups at either the 4- or 3-postion of the furan ring also exhibited similar reactivity, and excellent results were obtained for the corresponding FC products (Table 2, entries 24–26).

A diversity of activated alkenes were explored in FC alkylations with 2-furfuryl ketones using the HOMO-activation approach. As illustrated in Scheme 2, the 2-oxoindolin-3-ylidene malononitrile **4** showed good reactivity with **1a**. In this case, **C1** was a better catalyst in combination with salicylic acid, but only a fair *ee* value could be attained for the product **5** which contains a quaternary chiral center.[17] The activated alkene **6** derived from Meldrum's acid smoothly gave the desired FC products **7** by reaction with either the ketone **1a** or **1j**, which has an α′-phenyl group, and the catalyst **C4** with salicylic acid, but the enantioselectivity remained unsatisfactory after extensive screenings.[17] In contrast, completely different reaction patterns, as proposed in Scheme 1, were observed for other electrophiles. The α-regioselective Michael addition of **1a** to the less electrophilic β-nitrostyrene **8** was noticed in the presence of the amine **C2** and benzoic acid, and the adduct **9** was isolated as a diastereomeric mixture. Interestingly, the furan ring of **1a** acted as a diene moiety in the Diels–Alder cycloaddition with maleimide (**10**) under the similar catalytic conditions,[15,20] thus affording the aromatic product **11** after ring opening and elimination of a molecule of H_2O. Therefore, it seems that both electrophilicity and structural characteristics of the alkenes might

Table 2: Substrate scope for the asymmetric FC reactions of 2-furfuryl ketones (**1**) and alkylidenemalononitriles (**2**).[a]



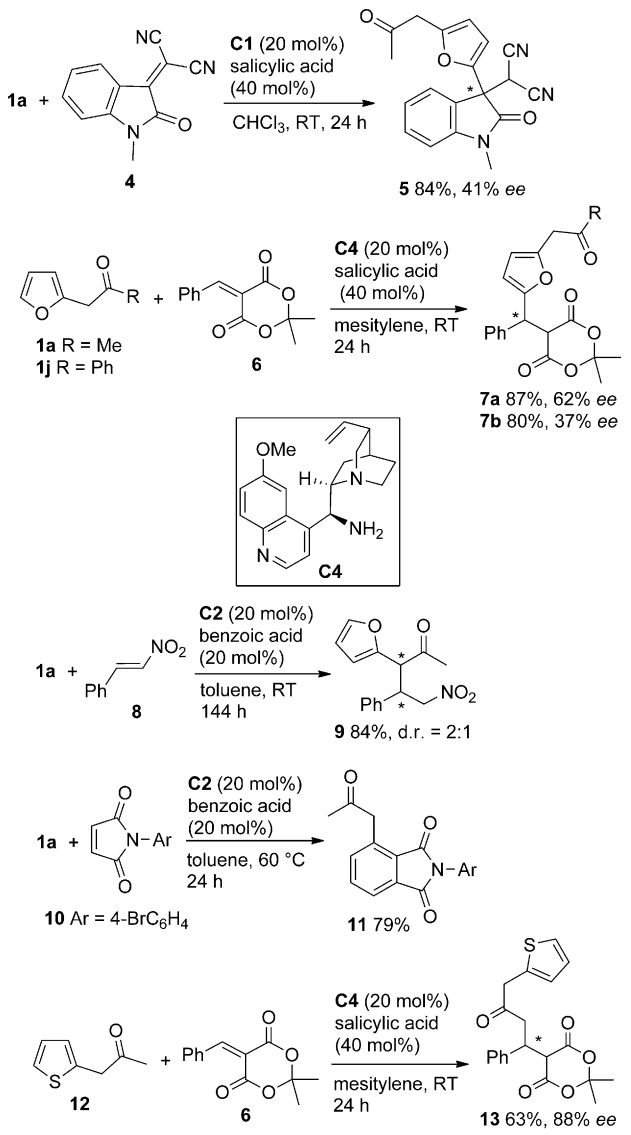


Entry	**1**	R^3	Yield [%][b]	*ee* [%][c]
1	**1a**	Ph	**3a**, 85	92
2	**1a**	3-MeC_6H_4	**3b**, 88	90
3	**1a**	4-MeC_6H4	**3c**, 89	90
4[d]	**1a**	3-MeOC6H_4	**3d**, 82	86
5	**1a**	3-ClC_6H_4	**3e**, 89	92[e]
6	**1a**	3-$NO_2C_6H_4$	**3f**, 92	86
7	**1a**	4-$CF_3C_6H_4$	**3g**, 90	88
8[f]	**1a**	3,5-$(CF_3)_2C_6H_3$	**3h**, 92	84
9[d]	**1a**	1-naphthyl	**3i**, 75	90
10	**1a**	2-naphthyl	**3j**, 84	91
11[d]	**1a**	2-furyl	**3k**, 77	75
12	**1a**	2-thienyl	**3l**, 81	80
13[f]	**1a**	3-pyridyl	**3m**, 83	82
14	**1a**	Et	**3n**, 86	89
15	**1a**	$Ph(CH_2)_2$-	**3o**, 87	90
16	**1a**	$BnO(CH_2)_3$-	**3p**, 82	81
17	**1a**	cyclohexyl	**3q**, 90	92
18	**1a**	*t*Bu	**3r**, 80	86
19	**1b**	Ph	**3s**, 79	94
20	**1c**	Ph	**3t**, 84	93
21	**1d**	Ph	**3u**, 79	90
22	**1e**	Ph	**3v**, 81	92
23[d]	**1f**	Ph	**3w**, 78	93
24	**1g**	Ph	**3x**, 83	93
25	**1h**	Ph	**3y**, 81	90
26	**1i**	Ph	**3z**, 75	95

[a] Unless noted otherwise, reactions were performed with the 2-furfuryl ketone **1** (0.3 mmol), alkylidenemalononitrile **2** (0.1 mmol), amine **C2** (20 mol%), and benzoic acid (20 mol%) in toluene (1.0 mL) at 0°C for 24 h. [b] Yield of isolated product. [c] Determined by HPLC analysis using a chiral stationary phase. [d] For 48 h. [e] The absolute configuration of **3e** was determined by X-ray analysis after derivatization; see the Supporting Information.[19] The other products were assigned by analogy. [f] At −10°C for 48 h. TBS = *tert*-butyldimethylsilyl.

play an important role in the reactions with 2-furfuryl ketones when operating under the formal trienamine catalysis. Unexpectedly, the α′-regioselective Michael addition was observed with 2-thienylacetone (**12**) and **6** when catalyzed by **C4**, thus giving the product **13** with good enantiocontrol.[21]

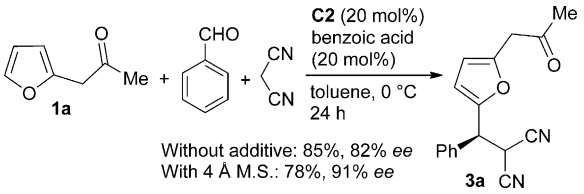
Finally, it was pleasing that the three-component reaction of **1a**, benzaldehyde, and malononitrile took place effectively under the same catalytic conditions, thus directly producing the FC product **3a** but with a decreased *ee* value, probably



Scheme 2. More reactions of activated alkenes and either the 2-furfuryl ketones **1** or 2-thienylacetone (**12**).

because the generated H_2O affects the hydrogen-bonding interactions of the catalyst **C2** (Scheme 3). Fortunately, the addition of some 4 Å molecular sieves dramatically improved the enantiocontrol.

In conclusion, we have presented an efficient and enantioselective Friedel–Crafts alkylation of furans with activated alkenes using a previously unreported HOMO-activation strategy. These reactions rely on in situ generation of a formal trienamine species from 2-furfuryl ketones and is catalyzed by a chiral primary amine, and thus enriches the



Scheme 3. Catalytic three-component reaction.

electron density of heteroaromatic π system and subsequently facilitates the Friedel–Crafts alkylation with electrophiles. Exclusive regioselective alkylation at the remote 5-position was observed in the reactions of diversely structured 2-furfuryl ketones and alkylidenemalononitriles, and moderate to excellent enantioselectivity was obtained by employing a simple bifunctional primary amine-thiourea derived from chiral 1,2-diphenylethanediamine. Such a HOMO-activation strategy should stimulate the investigation of a broad range of other valuable asymmetric Friedel–Crafts alkylation reactions.

Received: March 7, 2014
Published online: April 22, 2014

Keywords: alkylation · heterocycles · organocatalysis · regioselectivity · synthetic methods

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[19] CCDC 992909 (a derivative of **3e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[20] Much lower reactivity was observed in the absence of amine catalyst, thus indicating the HOMO activation of the aromatic π system is important to this cycloaddition, as noted in Ref. [15].

[21] 2-Pyrrolylacetone was unstable under the current catalytic conditions.

