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Organocatalytic Nonclassical Trienamine Activation in the Remote Alkylation of Furan Derivatives

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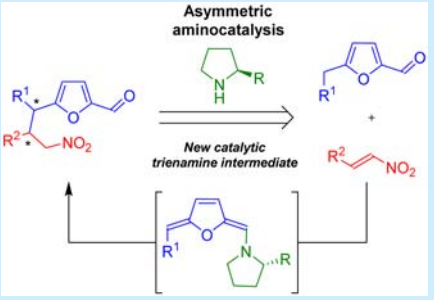
Supporting Information

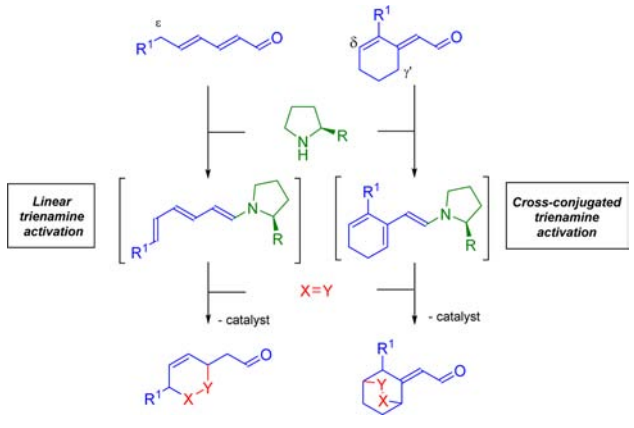
ABSTRACT: A new approach for the stereoselective remote alkylation of furan derivatives is reported. The reaction of 5-alkylfurfurals with nitroolefins as electrophilic counterparts occurs at their exocyclic ε-position and proceeds through the intermediacy of a nonclassical catalytic trienamine intermediate. The aminocatalyst bearing a H-bonding unit is used to control the stereochemical reaction outcome confirming the usefulness of such catalytic systems for the remote functionalizations of carbonyl compounds. Target products with two adjacent stereogenic centers are obtained in excellent yields and with good to moderate stereoselectivities.



Identification of new activation modes of organic compounds allowing for the discovery of new reactions constitutes one of the most significant tasks of the contemporary organic chemist. This is particularly true in the field of asymmetric catalysis where the chiral catalyst can be responsible not only for the stereochemical reaction outcome but also for the activation of a substrate through the formation of crucial synthetic intermediates exhibiting different reactivity than the starting material.[1]

Aminocatalytic trienamine activation constitutes an excellent example of such an activation strategy (Scheme 1, to the left).[2] Herein, a catalytically employed chiral secondary amine serves a dual purpose. First, it provides a chiral environment necessary in the stereodifferentiating reaction. Second, aminocatalyst transforms the $\alpha,\beta,\gamma,\delta$-diunsaturated aldehyde into the corresponding trienamine intermediate that is nucleophilic in the ε-position. It can undergo various [4 + 2]-cycloadditions with the last two double bonds of the triene system acting as the Diels–Alder diene. Importantly, the structure of the trienamine intermediate directly relates to its reactivity profile. For example, when cross-conjugated trienamine is being formed, the γ',δ-reaction occurs instead of the classical ε,β-functionalization (Scheme 1, to the right).[3]

Scheme 1. Classical Trienamines in Asymmetric Aminocatalysis



The ability of chiral amines to convert carbonyl compounds into various reactive intermediates makes them a very attractive tool in the contemporary enantioselective synthesis.[4] In addition to the two trienamine-mediated catalytic activation strategies described above, this field of chemistry started to develop in a new direction (Scheme 2). In 2011, the approach where the second double bond of $\alpha,\beta,\gamma,\delta$-diunsaturated aldehyde is a part of heteroaromatic framework was described (Scheme 2, to the left).[5] In such a setup, heterocyclic *ortho*-quinodimethanes are generated under aminocatalytic conditions that can serve as reactive dienes in a [4 + 2]-cycloaddition reaction proceeding with rearomatization of the heteroaromatic framework. An alternative strategy involves two double bonds of the furan ring as a part of trienamine intermediate enabling remote Friedel–Crafts alkylation to occur (Scheme 2, to the right).[6]

We envisioned that the alternative strategy for the remote functionalization of heteroaromatic derivatives might rely on the application of 5-alkylfurfural derivatives **1** (Scheme 3). Such substrates in the presence of aminocatalyst should be able to form catalytically crucial trienamine intermediate with interesting synthetic applicability. However, certain challenges with relation to such an approach had to be addressed. First, the reactivity pattern is different from the classical trienamine activation. 5-Alkylfurfural-derived trienamine is unable to adopt *s-cis* conformation of the last two double bonds of the triene moiety. Therefore, it cannot react via a [4 + 2]-cycloaddition

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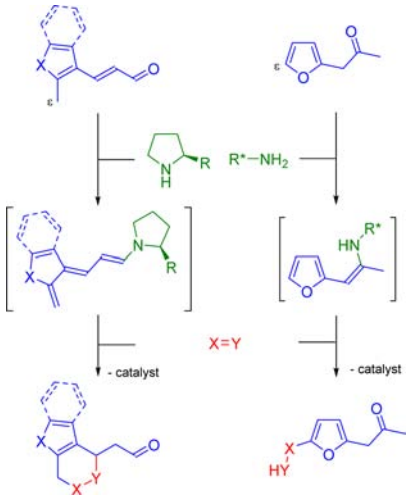
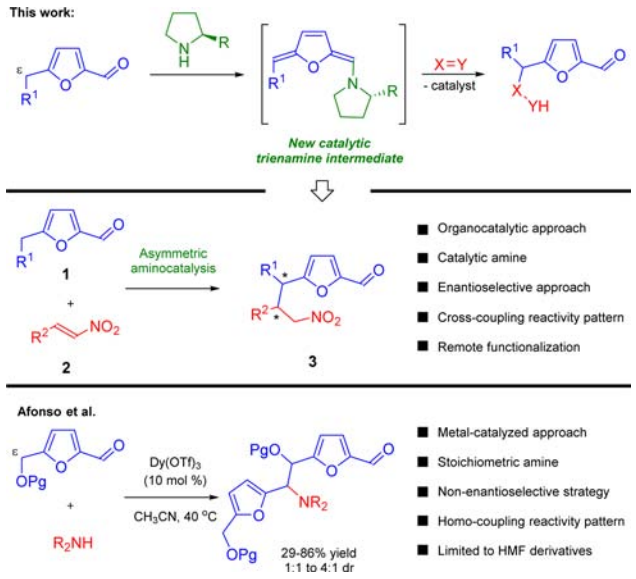
Scheme 2. Heteroaromatic Trienamines in Asymmetric Aminocatalysis



Scheme 3. Synthetic Objectives of This Work

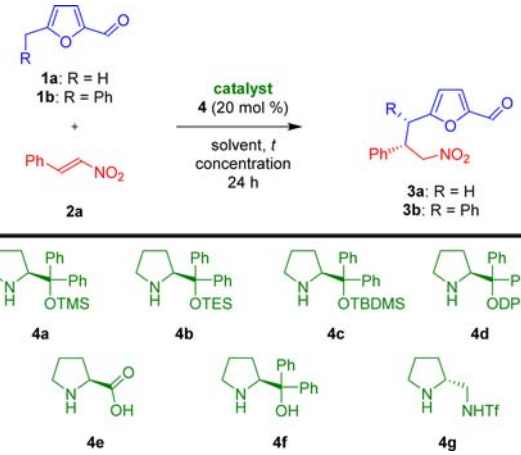


pathway, and simple alkylation should be preferred. Second, such an approach involves dearomatization of the heteroaromatic framework. Interestingly, parallel to our studies, Afonso and co-workers demonstrated that the formation of stoichiometric 5-alkylfurfural-derived trienamine intermediate is possible.[7] However, it requires the use of organometallic catalyst in order to facilitate its formation. Despite the interesting results obtained, one of the main drawbacks of the approach relates to the fact that the homocoupling reactivity pattern is observed (trienamine intermediate reacts with its precursor, the corresponding iminium ion). As a consequence, the amine is used in stoichiometric amounts and serves as a reagent. Furthermore, the reaction is not enantioselective and limited to protected hydroxymethylfurfural.

Herein, we report our work on the development of organocatalytic approach to the remote functionalization of 5-alkylfurfural derivatives **1** employing catalytic amine as the reaction promoter. The main focus of the research was on the development of the enantioselective reaction involving electrophilic reagent not derived from the starting furfural.

The studies were initiated with the goal of finding the optimal conditions for the reaction (Table 1, for detailed screening results, see Supporting Information). β-Nitrostyrene **2a** was selected as a model electrophile. Initial attempts involved the use of diphenylprolinol trimethylsilyl ether **4a**[8] as a catalyst and commercially available 5-methylfurfural **1a** as the corresponding trienamine precursor (Table 1, entry 1). However, under the employed conditions no reaction was observed. We hypothesized that the lack of reactivity might be related to the problems with dearomatization of the furan moiety. Therefore, the corresponding 5-benzylfurfural **1b** was synthesized. We anticipated that the presence of the phenyl ring on the exocyclic carbon atom should facilitate the dearomatization process due to the formation of a highly conjugated π-system. To our delight,

Table 1. Enantioselective Remote Alkylation of 5-Alkylfurfurals: Optimization Studies[a]



entry	solv.	cat. (prod.)	t [°C]	conv [%][b]	dr[c]	er[d]
1	$CHCl_3$	**4a** (**3a**)	rt	<5	nd	nd
2	$CHCl_3$	**4a** (**3b**)	rt	>95	2:1	65:35
3	$CHCl_3$	**4b** (**3b**)	rt	>95	2:1	65:35
4	$CHCl_3$	**4c** (**3b**)	rt	>95	1.5:1	65:35
5	$CHCl_3$	**4d** (**3b**)	rt	>95	1.3:1	60:40
6	$CHCl_3$	**4e** (**3b**)	rt	<5	nd	nd
7	$CHCl_3$	**4f** (**3b**)	rt	<5	nd	nd
8	$CHCl_3$	**4g** (**3b**)	rt	15	5:1	75:25
9	CH_2Cl_2	**4g** (**3b**)	rt	33	3:1	75:25
10[e]	1,4-dioxane	**4g** (**3b**)	rt	53	4.5:1	80:20
11[e]	CH_3CN	**4g** (**3b**)	rt	83	6:1	77:23
12	hexane	**4g** (**3b**)	rt	<5	nd	nd
13	CH_2Cl_2	**4g** (**3b**)	10	15	5:1	82:18
14[f]	CH_2Cl_2	**4g** (**3b**)	10	70	5:1	82:18
15[g]	CH_2Cl_2	**4g** (**3b**)	10	82	5:1	82:18
16[h]	CH_2Cl_2	**4g** (**3b**)	10	95 (91)	5:1	82:18

[a]Reactions performed on 0.1 mmol scale using **1** (1 equiv) and **2a** (1.2 equiv) in 0.36 mL of the solvent (see Supporting Information for detailed reaction conditions). [b]Conversion as determined by ^{1}H NMR of a crude reaction mixture. In parentheses isolated yields are given. [c]Determined by ^{1}H NMR of a crude reaction mixture. [d]Determined by a chiral stationary phase HPLC. Enantiomeric ratios reported for a major diastereomer. [e]The formation of side-products was observed. [f]Reaction was performed using **1b** (0.2 mmol) and **2a** (0.1 mmol) in 0.54 mL of CH_2Cl_2 for 3 days. [g]Reaction was performed using **1b** (0.2 mmol) and **2a** (0.1 mmol) in 0.27 mL of CH_2Cl_2 for 3 days. [h]Reaction was performed using **1b** (0.2 mmol) and **2a** (0.1 mmol) in 0.18 mL of CH_2Cl_2 for 3 days.

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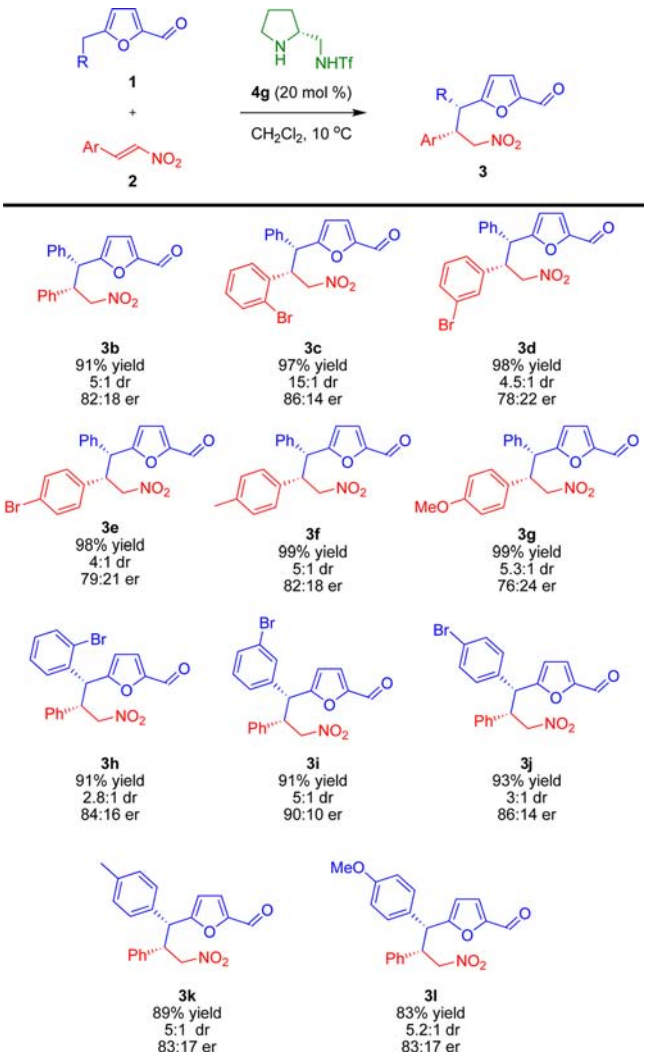
when **1b** was employed in the trienamine-mediated reaction, the remote alkylation was found to occur efficiently at room temperature yielding **3b** as a sole product (Table 1, entry 2). Notably, no formation of the homocoupling product was observed under these conditions. However, the stereochemical reaction outcome was not satisfactory (2:1 dr, 65:35 er). Attempts to improve the result by increasing the bulkiness of the catalyst failed (Table 1, compare entries 2−5). At this point we postulated that the sterically demanding substituent present in the 2-position of aminocatalysts **4a−d** prefers to position itself away from the triene moiety adopting the *anti*-conformation around the C−N bond. Consequently, control of the asymmetric induction process taking place at the remote ε-position is almost impossible. Therefore, an alternative approach was devised. It utilized H-bonding catalysts[9] to control stereochemical reaction outcome. It was anticipated that a proper choice of the catalyst in terms of distances between amine moiety and H-bonding unit will be crucial. Initial attempts using **4e** or **4f** as catalysts were unsuccessful (Table 1, entries 6,7). To our delight, a significant improvement of the reaction stereoselectivity was observed using **4g** as the catalyst (Table 1, entry 8). Further optimization studies were focused on finding the optimal solvent for the reaction (Table 1, entries 9−12). Interestingly, the improvement of the enantioselectivity of the remote functionalization was observed in the polar solvents such as 1,4-dioxane and acetonitrile (Table 1, entries 10,11). However, under these conditions the reaction lost its chemoselectivity as the formation of side-products arising from the homoaldol and subsequent poly homoaldol reactivity was observed. As we were unable to separate the product **3b** from the impurities by means of flash chromatography, dichloromethane became a solvent of choice. Further optimization studies (Table 1, entries 13−16) revealed that the best results were obtained when the reaction was performed at 10 °C, 0.56 M concentration, and using 2:1 ratio of **1b** to **2a** for 3 days (Table 1, entry 16).

With the optimized reaction conditions in hand, the scope of the method was studied. Initially, the scope with regard to the nitroolefin counterpart **2** was evaluated (Scheme 4, compounds **3b−g**). Gratifyingly, the reaction proceeded efficiently in all of the cases (91−99% yield). The stereochemical reaction outcome was found independent from the position of the substituent on the aromatic ring in **2** (compare results for the synthesis of **3c-e**). Interestingly, the highest diastereoselectivity (>15:1) was observed for the reaction leading to *ortho*-substituted derivative **3c**. Furthermore, the electronic properties of the substituent had no pronounced influence on the stereoselectivity of the alkylation and both electron-poor and electron-rich substituents could be present on the aromatic moiety in **2** (compare results for the synthesis of **3e−g**). Subsequently, the reaction scope of the furfural substrate **1** was studied (Scheme 4, compounds **3h−l**). To our delight, in this case the reaction was also found to be of general character as high yields (91−99% yield) were observed in all cases. The enantioselectivity of the reaction was found to be unbiased toward both the substitution pattern (compare results for the synthesis of **3h−j**) and to the electronic properties of the substituents present on the phenyl ring in **1** (compare results for the synthesis of **3j−l**). Furthermore, control of the diastereoselectivity of the process was on a similar level. However, the introduction of the substituent in the *ortho*-position of this aromatic moiety led to slight deterioration of the result. Notably, in all of the cases major diastereomer could be separated by means of flash chromatography.

Scheme 4. Enantioselective Remote Alkylation of 5-Alkylfurfurals: Scope of the Method[a]



[a]Reactions performed on 0.1 mmol scale (see Supporting Information for detailed reaction conditions). Enantiomeric ratios reported for a major diastereomer.

The absolute configuration of the remotely alkylated furfural **3i** was unambiguously assigned by the single crystal X-ray analysis (Scheme 5, top).[10] The absolute configuration of the remaining furfurals **3b−h**, **3j−l** was assigned by analogy. On the basis of the configurational assignments, the reaction mechanism explaining the observed stereochemistry of the products was proposed (Scheme 5, bottom). The reaction is initiated through the condensation of aminocatalyst **4g** with the corresponding 5-alkylfurfural **1**. Subsequent deprotonation from the remote ε-position yields the key trienamine intermediate **5**. It is postulated that the reaction proceeds through the intermediacy of thermodynamically stable *Z,Z,Z*-configured trienamine intermediate **5**. Furthermore, *anti*-conformation around the C−N bond in **5** is assumed. In the next step the reaction with electrophile **2** takes place. As the catalyst **4g** is employed, H-bonding interaction with nitroolefin **2** is essential and responsible for the control of stereochemical reaction outcome. Therefore, the trienamine **5** is approached from the upper-side. The diastereoselectivity is a consequence of the shown alignment of nitroolefin **2** with respect to **1** in which the π-stacking

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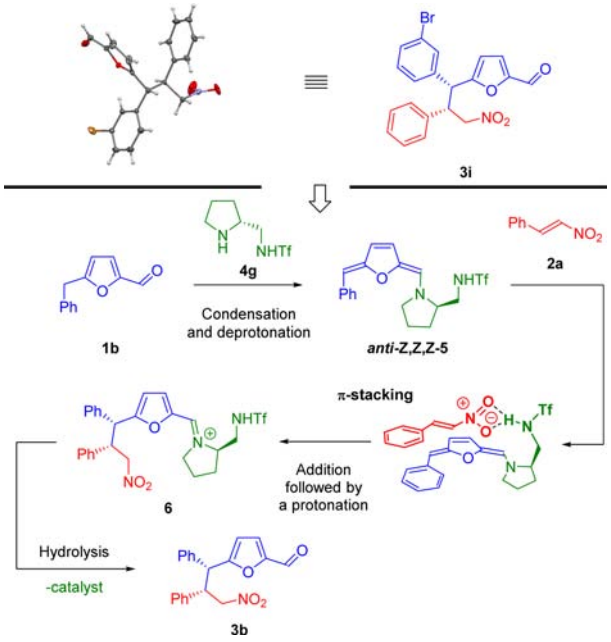
Scheme 5. Enantioselective Remote Alkylation of 5-Alkylfurfurals: Mechanistic Considerations



interactions of the aromatic rings in **2** and **1** can occur. The addition reaction proceeds with the rearomatization of the furan moiety and leads to the formation of the iminium ion **6**. Subsequent hydrolytic cleavage of the catalyst **4g** furnishes the catalytic cycle to yield remotely alkylated furfural **3** in high yield and in a stereocontrolled fashion. Importantly, in order to better understand the principles governing this nonclassical reactivity pattern, further mechanistic investigations on this reaction by means of both experimental and computational methods are currently ongoing in our laboratory.

In summary, we have developed a novel organocatalytic approach for the remote functionalization of furan derivatives. It employs 5-alkylfurfurals as precursors of nonclassical catalytically obtained trienamines that undergo efficient alkylation at the remote ε-position with nitroolefins as electrophilic counterparts. The developed methodology utilizes H-bonding aminocatalyst in order to control stereochemical reaction outcome and benefits from high efficiency and moderate to good stereoselectivity. Based on the absolute configuration assignments a plausible reaction mechanism was proposed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02979.

Screening details, experimental procedures, characterization of the products, and NMR data (PDF)
CIF information (CIF)

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Notes

The authors declare no competing financial interest.

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(10) See Supporting Information for details. CCDC 1431276 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.

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