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A New Organocatalytic Concept for Asymmetric α-Alkylation of Aldehydes

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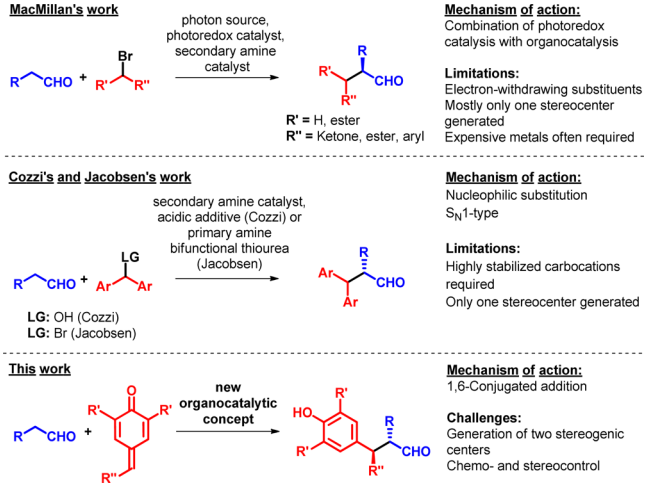
Supporting Information

ABSTRACT: The organocatalytic asymmetric α-alkylation of aldehydes by 1,6-conjugated addition of enamines to *p*-quinone methides is described. Employing a newly developed class of chiral secondary amine catalysts, α-diarylmethine-substituted aldehydes with two contiguous stereocenters have been synthesized in a simple manner with good diastereocontrol and excellent enantioselectivity.

The α-alkylation of carbonyl compounds is one of the most effective routes to establish new stereocenters and C−C bonds in organic reactions.[1] In the field of organocatalysis,[2] especially the enamine-mediated activation of aldehydes and ketones[3] by chiral amines has emerged as a reliable strategy to synthesize α-substituted carbonyl compounds with high stereoselectivity.[1,3] However, the enantioselective organocatalytic α-alkylation of aldehydes remained challenging. Recently a more general approach was realized by MacMillan et al., using organo-SOMO catalysis[4] or combined photoredox and organocatalytic strategies (Scheme 1, top).[5] Besides this, the enantioselective addition of aldehydes to electrophilic diarylmethine moieties represents a second possibility to install alkyl substituents at the α-position of carbonyl centers. Cozzi and Jacobsen discovered that diaryl alcohols[6] or diaryl halides[7] can be employed for the *in situ* generation of benzhydryl carbocations which react with carbonyl compounds via enamine activation in an S_N1-type mechanism, leading to highly enantioenriched α-alkylated products (Scheme 1, middle). Despite this successful approach, the requirement of highly stabilized carbocations represents a major limitation for this protocol. Furthermore, the simultaneous formation of diarylmethine stereogenic centers, applying unsymmetrically substituted benzhydryl carbocations, and the control of diastereoselectivity in these kind of reactions still remains a challenge.[6f,g] To address this issue, we reasoned that the α-alkylation of aldehydes with unsymmetrically substituted benzhydryl moieties and the formation of two contiguous stereocenters in one reaction might be feasible by applying *p*-quinone methides[8] as electrophiles (Scheme 1, bottom). The *p*-quinone methide scaffold exists in a variety of natural products and pharmaceuticals.[9] Moreover, these motives can also be found as highly reactive intermediates in many chemical, medicinal and biological processes.[10] Formally *p*-quinone methides are neutral molecules with a zwitterionic resonance structure that leads to a pronounced chemical reactivity as a 1,6 Michael acceptor.[11] The aromatization of the cyclohexadiene ring constitutes the driving force of this reaction and renders *p*-quinone methides more reactive toward nucleophilic addition compared to the classic conjugated enones.[8] On the other hand, the increased reactivity could also be deleterious both for the stereo- and chemoselectivity due to potential side reactions such as *N*-alkylation of the catalyst. Contrary to *o*-quinone methides that have been thoroughly investigated also in asymmetric synthesis,[12] only very few catalytic stereoselective addition reactions of *p*-quinone methides have been reported so far.[13,14]

Scheme 1. Catalytic Approaches to Chiral α-Alkylated Aldehydes



Given the high relevance for catalytic asymmetric transformations of *p*-quinone methides and stimulated by the aim to adorn the α-position of aldehydes with a diarylmethine stereocenter, we herein report the development of a new organocatalytic, stereoselective α-alkylation protocol, investigating the enamine-mediated 1,6-conjugated addition[15] of aldehydes to *p*-quinone methides.

We started our investigation by screening a series of secondary amine catalysts in the reaction of *p*-quinone methide **1a** with pentanal **2a** in CH_2Cl_2 as solvent (see Supporting Information (SI) for screening of different solvents). Among the catalysts tested (Table 1, entries 1−5), only **4a** was able to complete the reaction in 24 h, delivering the product **3a**, in good conversion and high enantioselectivity, but only with poor

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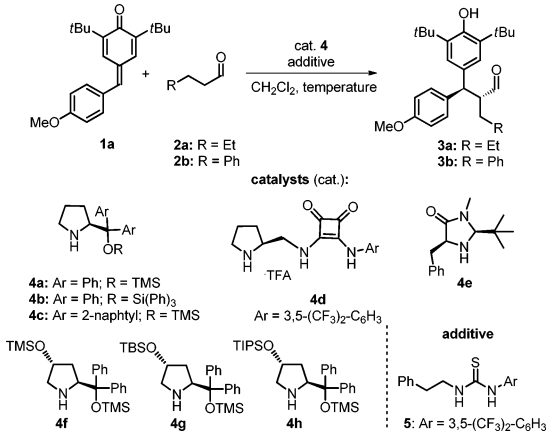
Table 1. Optimization: Screening of Catalysts and Reaction Conditions[a]



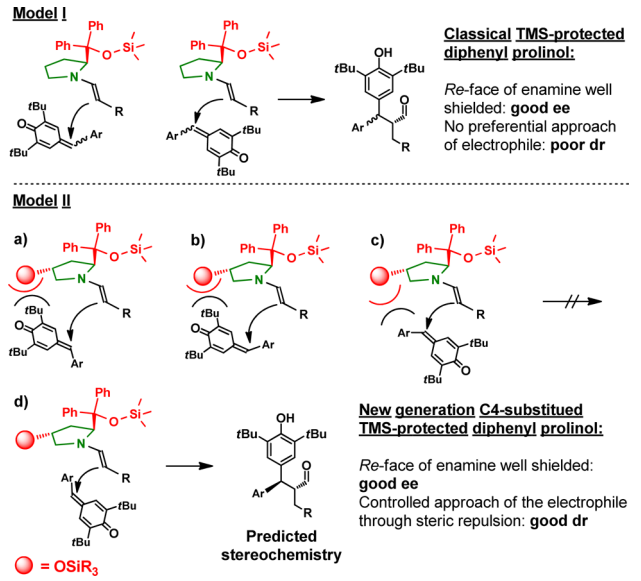
ent	2	cat. (mol%)	additive (mol%)	T (°C)	conv.[b] (%)	dr[c]	ee[d] (%)
1	**2a**	**4a** (20)	none	rt	95	1.4:1	91
2	**2a**	**4b** (20)	none	rt	58	1.2:1	88
3	**2a**	**4c** (20)	none	rt	77	2.0:1	90
4	**2a**	**4d** (20)	none	rt	31	1.1:1	nd
5	**2a**	**4e** (20)	none	rt	55	1.2:1	nd
6	**2b**	**4a** (20)	none	rt	75	1.8:1	99
7	**2b**	**4a** (20)	**5** (20)	rt	95	1.7:1	99
8	**2b**	**4f** (20)	**5** (20)	rt	90	4.7:1	99
9	**2b**	**4g** (20)	**5** (20)	rt	>95	5.1:1	99
10	**2b**	**4h** (20)	**5** (20)	rt	>95	6.8:1	99
11	**2b**	**4h** (20)	**5** (20)	4	>95	7.8:1	99
12[e]	**2b**	**4h** (20)	**5** (20)	-35	45	9.6:1	99
13[f]	**2b**	**4h** (10)	**5** (30)	4	>95	7.9:1	99

[a]Unless otherwise stated all reactions were performed using **1a** (0.05 mmol), **2a** or **2b** (0.075 mmol), catalysts **4** (10–20 mol%), additive **5** (up to 30 mol%), and CH_2Cl_2 (0.20 mL), for 24 h. [b]Conversion of **1a** was determined by ^{1}H NMR. [c]Determined by ^{1}H NMR of the crude reaction mixture. [d]Determined by CSP UPC[2] and referred to the major diastereoisomer. [e]Reaction time: 72 h. [f]Reaction time: 48 h.

diastereoselectivity. Next we realized that by the employment of hydrocinnamaldehyde **2b**, product **3b** was obtained in excellent enantioselectivity and a slightly better diastereoselectivity (entry 6). Thus, **2b** was chosen as the most suitable aldehyde for further screenings. Interestingly, the readily available thiourea **5** could be used as a Lewis-acidic additive to accelerate the reaction (see SI for screening of different thioureas),[16] affording **3b** in high conversion without erosion of enantioselectivity. However, the diastereomeric ratio (dr) was not influenced by **5** (entry 7).

At this stage, it seemed that the diastereoselectivity of the reaction could not be improved only by variation of the reaction conditions. In order to understand the origin of the low diastereoselectivity, an epimerization test was carried out by treating the major diastereoisomer of **3b** with 20 mol% of (±)-**4a**. No epimerization was observed after 48 h. Hence, the catalyst cannot form an enamine species with the alkylated aldehyde which would lead to loss of stereoinformation at the α-carbon atom. Thereupon, we hypothesized that an uncontrolled approach of the *p*-quinone methide to the enamine-activated aldehyde might justify the lack of diastereoselectivity at the benzhydrylic stereocenter (Scheme 2, Model I). With the aim to tackle this challenge, we synthesized a series of secondary amine catalysts **4f–h**. Here, the (diphenylmethyl)-trimethylsiloxy group was flanked by another bulky silyloxy moiety, placed at the C4-position of the pyrrolidine ring and with opposite stereochemistry (see SI for details). We envisaged that the (diphenylmethyl)trimethylsiloxy group could effectively shield one face of the enamine providing enantiocontrol, while the other silyloxy moiety could sterically determine the approach of the *p*-quinone methide to the enamine, thus ensuring diastereocontrol (Scheme 2, Model II). Gratifyingly, the use of catalyst **4f** led to a promising enhancement of the diastereoselectivity, still maintaining high enantioselectivity (Table 1, entry 8).

Scheme 2. Models for Reaction Pathways



Speculating that a protection group larger than trimethylsilyl (TMS) at the peripheral C4-hydroxy group could have an even more positive influence on the diastereoselectivity, we installed a *tert*-butyl(dimethyl)silyl group (TBS) as well as a tri(isopropyl)silyl group (TIPS) at this site. To our delight, catalysts **4g** and **4h** could indeed further improve the diastereoselectivity, while the enantioselectivity remained excellent (Table 1, entries 9, 10). The sterically most demanding catalyst **4h** was superior to catalysts **4f** and **4g**.[17] With this catalyst a further enhancement of the diastereomeric ratio was achieved by reducing the temperature to 4 °C, although an additional decrease to −35 °C prolonged the reaction time dramatically. (entries 11, 12). Finally, by increasing the amount of thiourea **5** to 30 mol%, we were able to lower the loading of the aminocatalyst to 10 mol% upon prolonged reaction time to 48 h (entry 13).

With the optimized reaction conditions in hand, the scope of the reaction was investigated. A series of *p*-quinone methides **1a–f** bearing electron-rich, electron-neutral and electron-deficient aromatic moieties were reacted with hydrocinnamaldehyde **2b**, affording the corresponding α-alkylated aldehydes **3b–g** in good yield and high diastereo- and enantioselectivity (Table 2, entries 1–6). It is notable that the heteroaromatic substituted *p*-quinone methides **1g–i** also reacted smoothly

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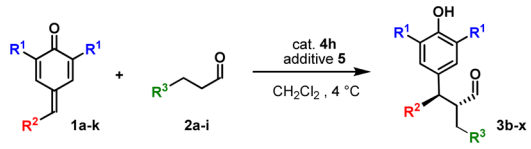
and afforded the corresponding α-alkylated aldehydes **3h–j** with similar yields and comparable enantioselectivities as their aromatic analogues (entries 7–9). Due to decomposition of the *p*-quinone methide, the reaction of **1j**, in which R^2 is a methyl substituent, afforded product **3k** in lower yield and only moderate stereoselectivity (entry 10). However, replacing the *tert*-butyl (*t*Bu) substituents R^1 for methyl groups did not change the yield and stereoselectivity of the reaction significantly (entry 11).

Table 2. Scope of the Reaction[a]



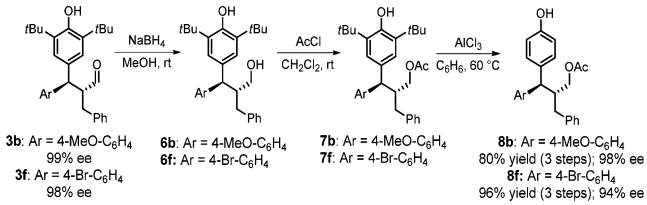
ent	**1** (R^1, R^2)	**2** (R^3)	**3**-yield[b] (%)	dr[c]	ee[d] (%)
1[e]	**1a** (*t*Bu, 4-MeO-C_6H_4)	**2b** (C_6H_5)	**3b**-79	7.9:1	99
2	**1b** (*t*Bu, C_6H_5)	**2b** (C_6H_5)	**3c**-84	9.4:1	99
3	**1c** (*t*Bu, C_6D_5)	**2b** (C_6H_5)	**3d**-78	8.3:1	99
4	**1d** (*t*Bu, 4-NO_2-C_6H_4)	**2b** (C_6H_5)	**3e**-71	7.0:1	98
5	**1e** (*t*Bu, 4-Br-C_6H_4)	**2b** (C_6H_5)	**3f**-83	10.2:1	98
6	**1f** (*t*Bu, 3,5-Me-C_6H_3)	**2b** (C_6H_5)	**3g**-90	11.0:1	99
7	**1g** (*t*Bu, 2-furanyl)	**2b** (C_6H_5)	**3h**-55	2.0:1	92
8	**1h** (*t*Bu, 2-thiofuranyl)	**2b** (C_6H_5)	**3i**-72	3.7:1	99
9[f]	**1i** (*t*Bu, 4-pyridyl)	**2b** (C_6H_5)	**3j**-67	8.2:1	99
10[g]	**1j** (*t*Bu, Me)	**2b** (C_6H_5)	**3k**-40	5.5:1	80
11	**1k** (Me, C_6H_5)	**2b** (C_6H_5)	**3l**-76	7.5:1	99
12	**1b** (*t*Bu, C_6H_5)	**2c** (4-MeO-C_6H_4)	**3m**-80	8.2:1	99
13	**1b** (*t*Bu, C_6H_5)	**2d** (4-Me-C_6H_4)	**3n**-90	9.8:1	98
14	**1b** (*t*Bu, C_6H_5)	**2e** (4-F-C_6H_4)	**3o**-81	7.8:1	99
15	**1b** (*t*Bu, C_6H_5)	**2f** (3,5-$(Me)_2C_6H_3$)	**3p**-83	8.5:1	96
16	**1b** (*t*Bu, C_6H_5)	**2g** (2-naphtyl)	**3q**-82	8.3:1	96
17	**1b** (*t*Bu, C_6H_5)	**2h** (2-thiophenyl)	**3r**-82	7.5:1	95
18	**1b** (*t*Bu, C_6H_5)	**2i** (Bn)	**3s**-72	5.8:1	98
19	**1b** (*t*Bu, C_6H_5)	**2a** (Et)	**3t**-64	4.0:1	98
20	**1e** (*t*Bu, 4-Br-C_6H_4)	**2c** (4-MeO-C_6H_4)	**3u**-80	8.5:1	88
21	**1e** (*t*Bu, 4-Br-C_6H_4)	**2d** (4-Me-C_6H_4)	**3v**-79	10.0:1	97
22	**1e** (*t*Bu, 4-Br-C_6H_4)	**2f** (3,5-$(Me)_2C_6H_3$)	**3w**-86	8.7:1	99
23	**1e** (*t*Bu, 4-Br-C_6H_4)	**2h** (2-thiophenyl)	**3x**-79	8.3:1	92

[a]Conditions: **1a–k** (0.05 mmol), **2a–i** (0.075 mmol), **4h** (0.005 mmol), **5** (0.015 mmol), and CH_2Cl_2 (0.20 mL), 4 °C, reaction time 48 h. [b]Isolated yield. [c]Determined by ^{1}H NMR of the crude reaction mixture. [d]Determined by CSP UPC^2 or CSP HPLC and referred to the major diastereoisomer. [e]Also performed on 0.5 mmol scale (82% yield, 7.8:1 dr, 99% ee). [f]Performed at rt, reaction time 72 h. [g]Performed at −35 °C.

Next we turned our attention to the aldehyde scope. A series of aldehydes **2c–i** bearing differently substituted aromatic rings was tolerated and furnished products **3m–s** in good yield under high stereocontrol (Table 2, entries 12–18). Interestingly, an aliphatic aldehyde such as pentanal **2a** afforded a slightly decreased but still decent diastereoselectivity, while the enantioselectivity remained excellent (entry 19). This indicates that bulky substituents at the aldehyde, such as a phenyl ring, contribute to the diastereocontrol of the reaction. Finally, the aldehyde scope was expanded to the brominated *p*-quinone methide **1e**. Also in these cases the reactions proceeded smoothly, delivering compounds **3u–x** in good yield and high stereoselectivity (entries 20–23).

In most of these examples the bulky *t*Bu groups were installed to stabilize the *p*-quinone methide.[18] Utilizing a three steps procedure, consisting of the reduction of the aldehyde, acetyl-protection of the corresponding alcohol and $AlCl_3$ mediated de-*tert*-butylation[13,18] the stereomerically pure aldehydes **3b** and **3f** were converted into the de-*tert*-butylated compounds **8b** and **8f** in high yield and without loss of stereoinformation (Scheme 3). Notably, in product **8b** we were able to obtain a stereocenter which is only derived from a methyl substituent at one of the hydroxy functionalities of the diphenolmethine scaffold.

Scheme 3. De-*tert*-butylation Reactions



3b: Ar = 4-MeO-C_6H_4 99% ee
3f: Ar = 4-Br-C_6H_4 98% ee

6b: Ar = 4-MeO-C_6H_4
6f: Ar = 4-Br-C_6H_4

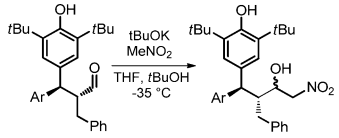
7b: Ar = 4-MeO-C_6H_4
7f: Ar = 4-Br-C_6H_4

8b: Ar = 4-MeO-C_6H_4 80% yield (3 steps); 98% ee
8f: Ar = 4-Br-C_6H_4 96% yield (3 steps); 94% ee

The absolute configuration of products **3** was unambiguously assigned by single-crystal X-ray analysis of compound **7f** (see SI).[19] The observed 2*R*,3*S* configuration is in agreement with the predicted stereochemical outcome of the reaction (Scheme 2, Model II-d). Therefore, Model II-d very possibly constitutes the approach of the *p*-quinone methide to the enamine in the asymmetric α-alkylation reactions investigated herein.

The possibility to further functionalize the obtained α-alkylated aldehydes was briefly explored. By treatment of **3b** with nitromethane in the presence of potassium *tert*-butoxide another stereocenter could be introduced. Nitroalcohol **9b**, which could be a valuable precursor for the synthesis of novel optically active β-aminoalcohols, was isolated in good yield and acceptable diastereoselectivity (Scheme 4).[20]

Scheme 4. Functionalization of Alkylated Aldehydes



3b: Ar = 4-MeO-C_6H_4

9b: Ar = 4-MeO-C_6H_4 84% yield, 3.5:1 dr

In conclusion, we have developed a new and easy-to-conduct organocatalytic strategy for the α-alkylation of aldehydes. For the first time, enamine-activated aldehydes have been added to *p*-quinone methides, providing α-diarylmethine-substituted aldehydes with two contiguous stereocenters in high yield and broad substrate scope. Employing new chiral secondary amine catalysts, the stereochemistry of these reactions could be very well controlled, leading to highly diastereo- and enantio-enriched products, which could be readily functionalized further.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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