Catalytic stereoselective benzylic C–H functionalizations by oxidative C–H activation and organocatalysis†

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An organocatalytic stereoselective α-alkylation reaction of aldehydes based on C–H activation is presented.

The activation of C–H bonds has attracted much attention in both the academy and industry because of its many potential advantages.[1] It is anticipated that the formation of new C–X bonds (X = C, O, N, S) *via* activation of C–H bonds will have a great impact in the field of stereoselective synthesis.[2] Asymmetric reactions based on the activation of sp^3 C–H bonds have been studied in depth,[3] particularly using the metal carbenoid insertion of sp^3 C–H bonds.[4] Recently, we have demonstrated the possibility of using the S_N1-type reaction in organocatalysis.[5] Our work combined two powerful concepts: enamine catalysis and Mayr's electrophilicity scale.[6] We have used stabilized carbocations generated by benzylic alcohols *in situ* for the enantioselective α-alkylation of aldehydes.[7] However, as carbocations can be also generated under oxidative reaction conditions by benzylic carbon-hydrogen bond activation[8] we wondered whether activation of C–H bonds of alkanes could be coupled with a direct stereoselective organocatalytic reaction.[9] This new methodology has enormous potential, as all concepts developed in organocatalytic reactions can be used in the direct functionalization of C–H bonds, with all the advantages of simple reaction conditions, and absence of metal catalysts.

In this contribution we present an organocatalytic stereoselective α-alkylation reaction of aldehydes based on C–H activation reactions. In order to set up a C–H activation reaction with organocatalytic reactions several challenges need to be addressed. In particular, water generated during the formation of the enamine *in situ* could react with the carbocation.[10] We reasoned that performing the reaction of alkyl aromatic compounds with weak C–H bonds (Fig. 1) could result in the facile generation of the carbocation, mediated by an oxidant.[11] However, the stability of the carbocation is also crucial for this type of reaction,[12] and on the basis of our previous findings concerning S_N1-type reactions, we set up a series of model reactions with xanthene **1**, octanal, and a variety of organocatalysts. We performed the model reaction choosing DDQ as the oxidant.[13] DDQ is a well-known oxidizing reagent for organic synthesis,[14] and the coupling reaction between nucleophiles and benzylic substrates mediated by DDQ have been reported.[8,15] The reaction was effectively promoted when operating in CH_3NO_2 or CH_2Cl_2. Among all the organocatalysts tested, the reaction was promoted by the MacMillan-type of catalyst **8**,[16] while chiral diphenylprolinol TBS ether catalyst[17] did not prove effective in this transformation. Catalyst **8** performed better then other MacMillan-type imidazolidinone catalysts. Selected key experiments are presented in Table 1. The enantiomeric excesses were maximized at low temperature (−25 °C) by the use of CH_2Cl_2 as the reaction solvent.

We have tested several modes of addition. DDQ was added in portions (3–4 portion), or in one portion but the enantiomeric excess was not improved. The addition of DDQ by syringe pump[18] stopped the reaction, and no conversion was observed. Other oxidants, such as $K_3Fe(CN)_6$, $Fe(acac)_3$, $K_2S_2O_8$, AgOTf, $Cu(OAc)_2$, and CAN resulted in no reaction or decomposition of the catalyst. With the optimised reaction condition, other substrates (**2–7**) and aldehydes were investigated (Table 2). A comprehensive list of the other substrates tested in the reaction is reported in the supporting information. In general, xanthene **1** reacts smoothly with different aldehydes, resulting in high yield and good stereoselection of the desired products (entries 1–5). Oxidation of 1,3,5-cycloheptatriene **2** gave the stable tropylium cation. In performing the reaction with the substrate **2** we noted that the counter ion of the catalyst was crucial in order to obtain good enantiomeric excesses (see supporting information), and by the use of catalyst **9** the alkylated product was isolated in high yield with moderate to good stereoselectivity. Other catalysts prepared *in situ* with different acids (see supporting information) gave the desired adduct with diminished stereoselectivity. Compound **3** was obtained by the reduction

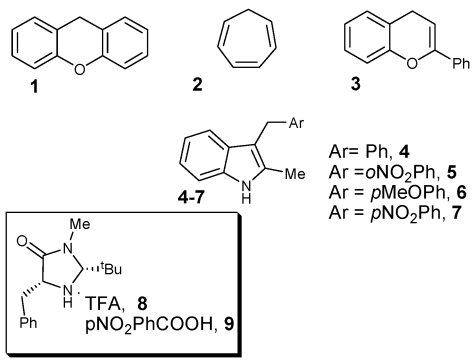

Fig. 1 Organocatalytic functionalization by C–H activation with compounds **1–7**.

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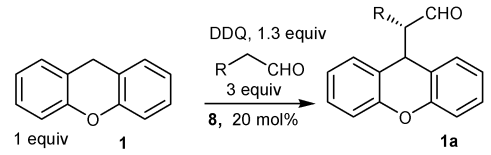
Table 1 Organocatalytic functionalization by C–H activation with compound **1**



R = nC_6H_{13}, **a**

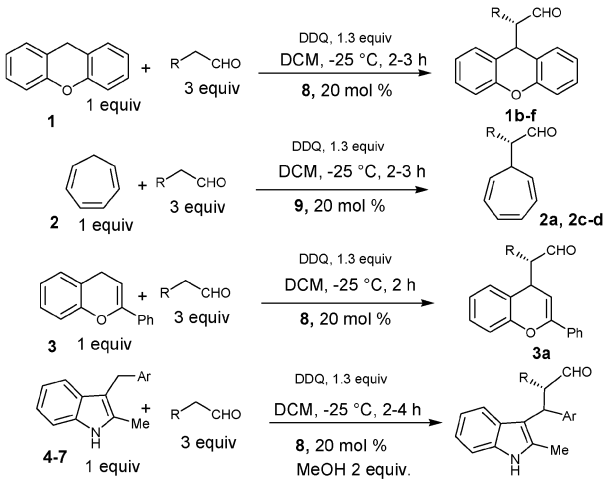
Entry[a]	T °C	Solvent	Time/h	Yield (%)[b]	ee (%)[c]
1	RT	CH_3CN	1	Traces	—
2	RT	DMF	1	—	—
3	RT	DCM	0.50	62	45
4	RT	CH_3NO_2	0.50	50	70
5	0	DCM	3	81	69
6	0	CH_3NO_2	3	55	56
7[d]	−25	DCM	4	90	79
8	−25	DCM	4	65	77
9[e]	−25	DCM	4	52	70
10[f]	−25	DCM	4	74	70

[a] All the reactions were carried out at the indicated temperature. [b] Isolated yield after chromatographic purification. [c] Evaluated by chiral HPLC analysis. [d] The reaction was carried out under nitrogen with degassed solvents and adding portion wise the oxidant. [e] The reaction was carried out using 15 mol% of MacMillan catalyst. [f] The reaction was carried out without TFA (trifluoroacetic acid) as additive.

of the corresponding flavylium salt as reported in literature.[19] A flavanoid derivative **3a** was obtained using catalyst **8** in modest yield and moderate stereoselectivity. It is worth mentioning that the addition of π-nucleophiles to a flavylium carbocation was described by Mayr.[20] Finally, the direct functionalization of indole derivatives was possible by a direct C–H activation. As carbocation derived for indolyl alcohols resulted in high ees in our S_N1-type of reaction,[5] we investigated the indole derivatives **4–7** as model substrates, prepared as reported in the literature from the reaction of 2-methylindole with aromatic aldehydes in the presence of Et_3SiH.[21] Interestingly, the reaction occurred in minutes but only when operating at low temperatures, in the presence of 2 equiv. MeOH, it was possible to obtain a moderate yield. Remarkably, we observed good stereoselection in the reaction with **5**. The major diastereoisomer obtained in this case was the *syn* isomer.[5,22]

The absolute configuration of the products **1b** and **2c** derived from xanthene **1** and from 1,3,5-cycloheptatriene **2** were established by chemical correlation through alkylation of oxazolidinone derivatives (Scheme 1).[23] 9H-Xanthen-9-ol **8** was treated with titanium enolate derived from the *N*-propionyl oxazolidinone **9**,[24] and the product was reduced with SuperHydride in THF to gave the (*R*) alcohol **11**, an enantiomer of the alcohol obtained by the reduction of **1b**. The oxazolidinone **13** was obtained by the reaction of commercially available tropylium tetrafluoroborate **12** with the lithium enolate of ethylacetate,[26] its successive hydrolysis and coupling with (*S*)-benzyloxazolidinone. Alkylation of **13** with ethyl iodide was performed in like manner to Evans,[25] and successive reduction with SuperHydride afforded the

Table 2 Organocatalytic C–H activation with compounds **1–7**



R = nC_6H_{13}, **a**
R = Me, **b**
R = Et, **c**
R = *i*Pr, **d**
R = CH_2=$CHCH_2CH_2$, **e**
R = benzyl, **f**

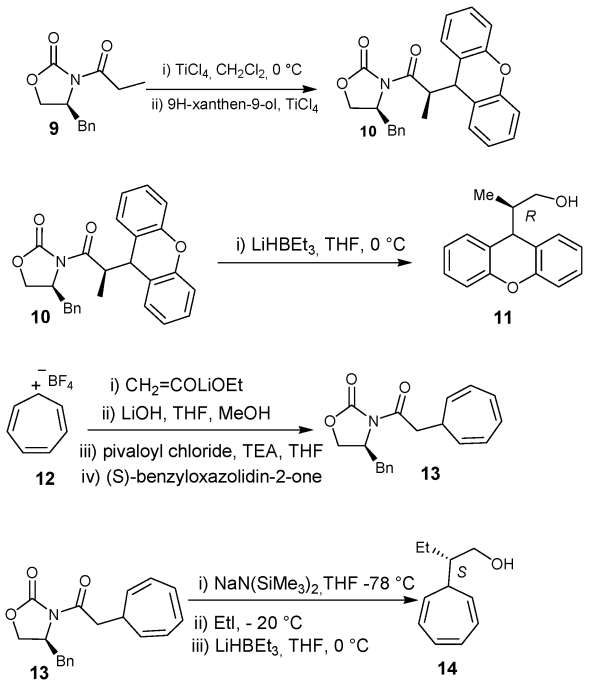
Ar = Ph, **4**
Ar = oNO_2Ph, **5**
Ar = *p*MeOPh, **6**
Ar = pNO_2Ph, **7**

Entry	Product	Yield[b]	d.r.[c]	e.e (%)[d]
1	**1b**	75	—	68
2	**1c**	50	—	78
3	**1d**	66	—	68
4	**1e**	90	—	78
5	**1f**	30	—	74
6	**2a**	90	—	46
7	**2c**	30	—	38
8	**2d**	30	—	70
9	**3a**	30	2 : 1[e]	min 10; maj 62
10	**4a**	50	1 : 1	anti **82**; syn 62
11	**4f**	40	1 : 1	anti 69; syn 59
12	**5a**	57	1 : 9	anti;[f] syn **86**
13	**5f**	57	1 : 9	anti 60; syn 77
14	**6a**	33	1 : 1	anti 66; syn 65
15	**6f**	55	3 : 1	anti 74; syn 50
16	**7a**	40	1 : 1	anti **86**; syn 79

[a] All the reactions were carried out at −25 °C under nitrogen under strictly anaerobic conditions. Catalyst aldehyde and substrates were mixed at RT, then DDQ was added at −25 °C. [b] Isolated yield after chromatographic purification. [c] Estimated by ^{1}H NMR on the crude product. The ratio is indicate *anti vs. syn*, assigned on the basis of ^{1}H NMR and HPLC, see ref. 8. The absolute and relative configuration for products **4a**, **4f**, **5a**, **5f**, **6a**, **6f**, and **7a** was assigned on the basis of HPLC retention time, ^{1}H NMR spectra, and comparison with *syn* products obtained with a different synthetic procedure; see ref. 5. [d] Evaluated by chiral HPLC analysis (see ESI for details†). [e] The diastereoisomer ratio was not assigned. The indicated values are major diastereoisomer against minor. [f] The ee of the minor diastereoisomer was not determined.

alcohols **14**, identical to the (*S*) alcohol obtained by reduction of **2c**. In both cases the configurations of the isolated products were in agreement with the addition of carbocation from the less hindered face of the enamine (Fig. 2).[27]

In summary, we have reported a stereoselective alkylation of benzylic C–H merging an oxidative C–H activation reaction with organocatalysis. Further work to improve yields and stereoselectivity of the present reaction by tailored



Scheme 1 Assignment of absolute configuration by chemical correlation.

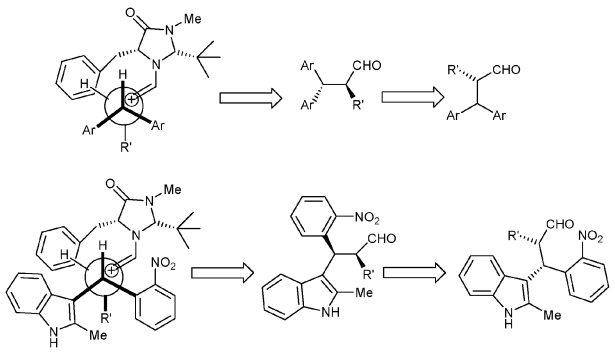


Fig. 2 Stereochemical models for the oxidative organocatalytic reaction.

modification of the MacMillan catalysts is in progress and will be reported in due course.

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