CHEMISTRY
AN ASIAN JOURNAL

DOI: 10.1002/asia.201000160

Organocatalytic Stereoselective α-Alkylation of Aldehydes with Stable Carbocations

Fides Benfatti, Elena Benedetto, and Pier Giorgio Cozzi*[a]

Abstract: The organocatalytic stereoselective alkylation of aldehydes is carried out with the four stable carbocations **1**–**4** in the presence of a catalytic amount (20 mol%) of MacMillan imidazolidinones **5**–**6**. In all reactions, lutidine was used as a base. The alkylation reactions are investigated at different temperatures with linear and branched aldehydes. In the case of carbocation tropylium fluoroborate, an interesting reversal of alkylation product configuration was observed, which is driven by entropic effects in the reaction. The absolute configuration of the products obtained is determined by chemical correlation and found to be in general agreement with the model proposed by MacMillan to justify the stereoselectivity obtained in the reactions promoted by catalysts of type **5**–**6**.

Keywords: alkylation · carbocations · Macmillan catalysts · Mayr's scale · organocatalysis

Introduction

The reactivity of carbocations with a nucleophile can be rationalized by Mayr's scale through the assignment of the parameter *E*.[1] Mayr's work also provided the most comprehensive nucleophilicity scale presently available. The scales are based on the reaction of benzhydrilium ions (Ar_2CH^+) and structurally related quinone methides with different n, π, and σ nucleophiles.[2] By varying the nature of the substituents present in the *para* position of diarylmethanes it is possible to alter the reactivity with an established nucleophile by up to 16 orders of magnitude, according to the linear free-energy relationship [Eq. (1)]:[3]

$$k_{(20\,^\circ C)} = s(N + E) \quad (1)$$

This relationship was established as a powerful instrument for the experimental prediction of the rate of S_N1-type reactions.[4] In Equation (1), the electrophiles are characterized by a parameter, *E*, whereas the different nucleophiles have been classified by the parameter *N* and by the nucleophilic specific slope parameter *s*. As a consequence of the Mayr generalizations, it is possible to make a quantitative prediction of a reaction between a nucleophile and an electrophile through Equation (1). As a "rule of thumb", a S_N1-type reaction could be observed at room temperature in a reasonable amount of time (3 h) if Equation (2) is satisfied:[1a]

$$E + N > -5 \quad (2)$$

Based on the suggestions of stability and reactivity of carbocations resulting from the meticolous work published by Mayr,[1,3–5] we recently reported an organocatalytic stereoselective α-alkylation of aldehydes.[6] Furthermore, we have established that the generation of stabilized carbocations coupled with organocatalysis can be realized by direct C–H bond functionalization.[7] In both the studies, the carbocations were obtained in situ, by starting from the corresponding alcohols or from the alkanes.

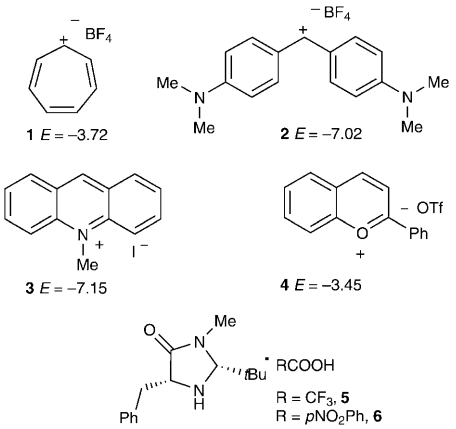
However, stable carbocations are easily generated and even commercially available.[1] In this manuscript we have investigated the organocatalyzed addition of aldehydes to easily prepared and stable carbocations **1**–**4**, providing additional useful information about the stereoselective α-alkylation of aldehydes, and showing the applicability of the present methodology with stable and isolated carbocations to access enantioenriched building blocks.

Results and Discussion

Many organocatalysis experts have long sought methodologies to enable the intermolecular α-alkylation of aldehydes,

[a] Dr. F. Benfatti, E. Benedetto, Prof. P. G. Cozzi
Dipartimento di Chimica "G. Ciamician"
Institution ALMA MATER STUDIORUM Università di Bologna
Via Selmi 2, 40126 Bologna (Italy)
Fax: (+39) 051-209-9456
E-mail: piergiorgio.cozzi@unibo.it

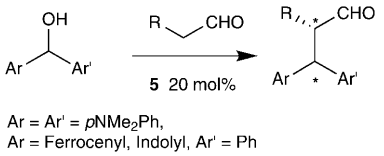
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201000160.



with simple amines catalyzing this process.[8] In fact, the α-alkylation of simple aldehydes constitutes a fundamental step in C–C bond-forming reactions. During the "gold rush" of enamine catalysis[9] by secondary amines,[10] it was assumed that α-alkylation represented an obvious and easily accessible target. However, little progress was made towards this goal prior to 2009 despite the enormous efforts of many research groups.[11] During our research devoted to establishing new compounds containing ferrocene for molecular computation, we used stabilized ferrocenyl derivatives, which generated the corresponding carbocations by Lewis acid catalysis[12] or "on water".[13] We established a fundamental correlation among the carbocations generated "on water" and their position on the Mayr scale. Based on that correlation, we developed a methodology that allows the enantioselective direct alkylation of aldehydes with unfunctionalized alcohols, only limited by the nature of the alcohol, which must stabilize the carbocationic intermediate (Scheme 1).[6]

The attack on stabilized carbocations formed in situ from the corresponding alcohols by an enamine intermediate afforded the desired alkylated adducts in good to excellent enantioselectivities. To verify the possibility of using isolated

Abstract in Italian: La reazione organocatalitica di alchilazione stereoselettiva di aldeidi è stata condotta con i quattro carbocationi stabili **1**–**4** in presenza di quantità catalitiche (20 mol%) degli imidazolidinoni di MacMillan **5**–**6**. In tutte le reazioni un equivalente di lutidina è stato usato come base. Le reazioni di alchilazione sono state investigate a diverse temperature con aldeidi lineari e ramificate. Nel caso del carbocatione **1** (tropilio tetrafluoroborato) si è osservato un interessante inversione di configurazione del prodotto di alchilazione, determinato da effetti entropici della reazione. La configurazione assoluta dei prodotti ottenuti è stata determinata attraverso una correlazione chimica ed è risultata essere in accordo al modello generale proposto da MacMillan per giustificare la stereoselezione ottenuta nelle reazioni organocatalitiche promosse dai catalizzatori del tipo **5**–**6**.



Scheme 1. Stereoselective alkylation of aldehydes by alcohols promoted by a MacMillan catalyst.

carbocations in the stereoselective alkylation reaction of aldehydes, we selected, as model carbocations, the compounds **1**–**4**. Tropylium tetrafluoroborate **1** is commercially available, whereas **2**–**4** were prepared by simple reactions described in the literature (see the Supporting Information). The carbocation **1** ($E = -3.72$ in Mayr's scale) was selected for optimization of the reaction. Tropylium tetrafluoroborate was used as received and no particular precaution was necessary for the reaction, as the carbocation is rather stable. In general, the reactions with the carbocations were run in the presence of the MacMillan imidazolidinonium organocatalysts **5**–**6**,[14] with the addition of a base for neutralizing the tetrafluoroboric acid produced during the reaction. Et_3N, iPr_2NEt, 2,6-dimethylpyridine, 2,6-di-*tert*-butylpyridine, K_2CO_3, Na_2CO_3, and K_3PO_4 were investigated. Better results in terms of yields were obtained with 2,6-dimethylpyridine (2,6-lutidine), which was used as the standard base in all reactions. However, the MacMillan imidazolidinonium catalyst **5** gave low selectivity. To improve the selectivity, we have performed the reaction in the presence of different acids by the preparation of the corresponding MacMillan catalysts as salts.[7] After several attempts and trials, we have studied the reaction of the aldehydes 7**a**–**d** in the presence of 20 mol% of the imidazolidinonium catalyst **6**, a *p*-nitrobenzoate salt, obtaining the results that are collected in Table 1. The alkylation reactions were conducted in CH_2Cl_2. Among all the MacMillan imidazolidinonium catalysts investigated, the imidazolidinonium catalyst **6** gave the best results in term of selectivity. The absolute configuration of the product **8a** was influenced by the nature of the acid. In particular, with the electron-rich 3,4,5-trimethoxybenzoic acid, the corresponding MacMillan imidazolidinonium catalyst gave the *S* product at room temperature, whereas the *p*-nitrobenzoic acid (imidazolidinonium catalyst **6**) gave, under the same conditions, the corresponding *R* product. As noted by the data collected in Table 1, the stereoselectivity of the reaction was also a function of the temperature. This peculiar behavior was already noted in organocatalytic reactions.[15] In addition, this dependency is determined by the steric hindrance of the aldehydes. We investigated the reaction at a higher temperature (40 °C) changing the solvent from CH_2Cl_2 to dichloroethane, but no increase of the selectivity was observed. Also, the base has an influence on the selectivity (Table 1, entry 8), as the employment of K_2CO_3 changed the facial selection obtained at room temperature. The results are not determined by thermodynamics, as the

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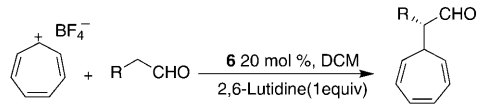
Table 1. Alkylation of aldehydes with carbocation **1** (tropylium fluoroborate).



1 (1 equiv) **7a–d** (3 equiv) **8a–d**

R = nC_6H_{13}, **a**
R = *i*Pr, **b**
R = Bn, **c**
R = Et, **d**

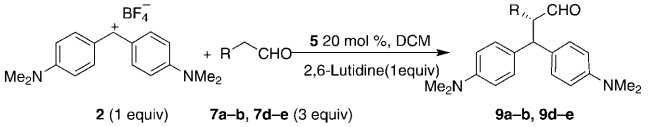
Entry	R	Product	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b] (config.)
1	nC_6H_{13}	**8a**	RT	4	65	50 (*R*)
2	nC_6H_{13}	**8a**	RT	17	67	51 (*R*)
3	nC_6H_{13}	**8a**	0	5	50	40 (*S*)
4	nC_6H_{13}	**8a**	−25	25	46	47 (*S*)
5[c]	nC_6H_{13}	**8a**	RT	4	67	51 (*S*)
6[d]	nC_6H_{13}	**8a**	4	2	50	49 (*R*)
7	nC_6H_{13}	**8a**	−25	26	37	37 (*S*)
8[e]	nC_6H_{13}	**8a**	RT	22	64	20 (*S*)
9	*i*Pr	**8b**	RT	4	55	72 (*S*)
10	*i*Pr	**8b**	0	5	30	80 (*S*)
11	*i*Pr	**8b**	−25	25	41	62 (*S*)
12	Bn	**8c**	RT	5	73	46 (*R*)
13	Bn	**8c**	0	7	65	9 (*S*)
14	Bn	**8c**	−25	25	78	30 (*S*)
15	Bn	**8c**	−25	45	92	27 (*S*)
16	Et	**8d**	RT	24	77	22 (*R*)
17	Et	**8d**	0	24	28	7 (*S*)
18	Et	**8d**	−25	24	14	20 (*S*)

[a] Yield after chromatographic purification. [b] The enantiomeric excess (*ee*) was evaluated by chiral HPLC analysis. See the Supporting Information for details. [c] The (*S*,*S*)-MacMillan catalyst *ent*-**5** was employed in the reaction. [d] Dichloroethane was employed as the reaction solvent. [e] K_2CO_3 was used as a base.

products **8a–d** are stable in solution in the presence of 20 mol% of the imidazolidinonium organocatalyst **5** or **6**.[16]

The temperature is crucial for the stereoselection, and good results were obtained at low temperature. Finally, the (*S*,*S*)-MacMillan imidazolidinonium catalyst *ent*-**5** was employed in the reaction at a low temperature, giving a comparable result (Table 1, entry 5). Then, the behavior of carbocations **2** and **3**, more stabilized than tropylium, was investigated. The bis(4-dimethylamino-phenyl)methylium tetrafluoroborate (**2**) is positioned at −7.02 of the Mayr scale and was obtained from the corresponding alcohol through the reaction with HBF_4.[17] As in the case of **1**, the compound is highly stable and the blue carbocation can be handled in open air and it is not decomposed by traces of water. It is a bench-stable product, stable for months in a flask. The temperature did not influence the stereoselectivity of the α-alkylation reaction, and slight variation of the enantiomeric excess was recorded at different temperatures (Table 2, entries 1–3). In the case of the cation **2**, isovaleraldehyde was not reactive (entry 4). The sterical hindrance among the carbocation and the enamine formed in situ was crucial, as indicated by the stereoselection obtained with linear aldehydes, which was increased when short aliphatic aldehydes were employed.

Table 2. Alkylation of aldehydes with the carbocation **2**.



2 (1 equiv) **7a–b, 7d–e** (3 equiv) **9a–b, 9d–e**

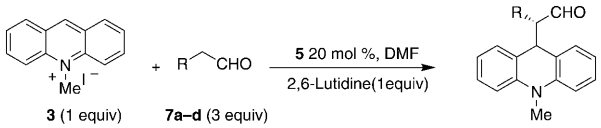
R = nC_6H_{13}, **a**
R = *i*Pr, **b**
R = Et, **d**
R= Me, **e**

Entry	R	Product	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	nC_6H_{13}	**9a**	4	4	96	34
2	nC_6H_{13}	**9a**	RT	23	86	39
3	nC_6H_{13}	**9a**	40	4	74	32
4	*i*Pr	**9b**	RT	24	–[c]	–
5	Et	**9d**	4	22	99	56
6	Me	**9e**	4	22	75	65

[a] Yield after chromatographic purification. [b] The enantiomeric excess was evaluated by chiral HPLC analysis. See the Supporting Information for details. [c] No reaction.

Methylacridinium carbocation (**3**), readily prepared by alkylation of acridine with MeI,[18] is a stable salt, positioned at −7.15 of the Mayr scale. It is a very stable cation and can be isolated by filtration and stored in air. In contrast with the reactions described for cations **1** and **2**, we used DMF as the reaction solvent, as the cation was completely insoluble in CH_2Cl_2. No reaction occurred after several days in CH_2Cl_2. The results obtained in the reaction with the aldehydes are reported in Table 3. The process conduced at 4 °C (Table 3, entry 1) was carried out with long reaction times. However, in such conditions a decrease in the enantiomeric excess was observed, relative to the reaction carried out at higher temperatures with a shorter reaction time. Particularly intriguing were the results obtained in the case of the addition of hydrocinnamaldehyde to the carbocation **3**. The

Table 3. Alkylation of aldehydes with the carbocation **3**.



3 (1 equiv) **7a–d** (3 equiv) **10a–d**

R = nC_6H_{13}, **a**
R = *i*Pr, **b**
R = Bn, **c**
R = Et, **d**

Entry	R	Product	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	nC_6H_{13}	**10a**	4	22	83	55
2	nC_6H_{13}	**10a**	RT	5	41	64
3	nC_6H_{13}	**10a**	40	4	60	64
4[c]	nC_6H_{13}	**10a**	RT	3	59	19
5	*i*Pr	**10b**	RT	3	–	–
6[c]	*i*Pr	**10b**	RT	72	–	–
7	Bn	**10c**	4	43	49	3
8	Bn	**10c**	RT	21	51	7
9	Bn	**10c**	60	7	50	7
10	Et	**10d**	50	8	66	63

[a] Yield after chromatographic purification. [b] The enantiomeric excess was evaluated by chiral HPLC analysis. See the Supporting Information for details. [c] The SbF_6^- salt was used and the reaction was performed in CH_3CN.

enantiomeric excesses obtained were quite low, and probably some π interactions among the carbocation and the aldehyde were taking place, although we do not have a detailed explanation for this behavior. We also investigated the effect of the counter-anion in the reaction by exchanging the iodide with $^{-}SbF_6$ (hexafluoroantimonate) through silver metathesis. The reaction conduced at room temperature was faster than at 4 °C (Table 3, entry 4 vs 1), but a lower enantiomeric excess was recorded.

To examine the behavior of the stereogenic carbocation, flavylium triflate (**4**) was readily synthesized by the described procedure.[19] In general, flavylium ions are basic constituents of the anthocyanin pigment in plants. Besides their use as food colorants and dyes, an increased attention over their synthesis was also determined by their biological properties.[20] Electrophilicity properties of the flavylium cation were described by Mayr.[19] The flavylium ion considered in our study is positioned at −3.45 of the Mayr scale. From the application of Equation (2), it is possible to conclude that flavylium will react with nucleophiles of $N > -1.5$.

As enamines are strong nucleophiles, positive reactivity is expected. In fact, we observed (Table 4) the formation of the desired products in the reaction of the aldehydes **7a–c** in the presence of the MacMillan imidazolidinonium catalyst **5** used in a catalytic amount (20 mol%). It is worth mentioning that the reaction of **4** with 1-(trimethylsiloxy)cyclohexene gave a low yield of adducts as a mixture of two diastereoisomers in a ratio of 79:21. The simple diastereoselection obtained in our reaction with enamines formed in situ was close to the result reported by Mayr.

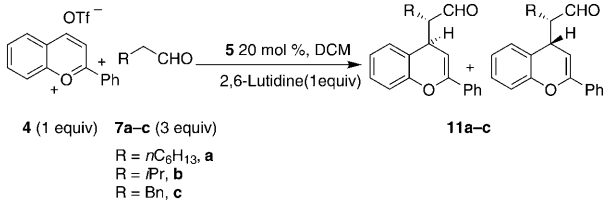
The simple stereoselection and the enantioselectivity increased when the reaction was carried out at −25 °C (Table 4, entries 2, 5, and 8). Yields of isolated product were moderate to good with linear aldehydes, whereas the yields were reduced when operating with hindered aldehydes.

The results in terms of stereoselectivity of the process can be rationalized in relation to the different reactivity of the carbocations. With the less electrophilic carbocations **2** and **3**, moderate to low selectivity was obtained at room temperature. The reaction became more selective at low temperatures with the more electrophilic carbocations **1** and **4**. The inversion of absolute configuration of the products isolated with linear aldehydes in the case of the carbocation **1** is particularly intriguing. The results are kinetically controlled. In fact the isolated product **8a** of *S* configuration, obtained in the reaction at −25 °C, is not equilibrated to the *R* enantiomer in the presence of the MacMillan imidazolidinonium catalyst **6** at room temperature, and the enantiomeric excess does not change over 6–8 h. It is commonly assumed that the MacMillan imidazolidinone catalyst forms selectively *E* enamine isomer **I** with aldehydes, which avoids sterical interaction with the *tert*-butyl group (Scheme 2.[21] The small facial preference showed by carbocation **1**, a function of the temperature, could be related to the smaller size of the carbocation, relative to the others.

The attack on the *Si* face is favored at low temperature with linear aldehydes. With a more hindered aldehyde (Table 1, entry 9–11), the carbocation cannot approach from both sides of the nucleophile, at low temperatures and at room temperature. The peculiar behavior of the tropylium cation arises from a nonideal temperature effect,[22] a phenomenon that was recently described in organocatalytic reactions.[23]

The proposed catalytic cycle for the reaction is depicted in Scheme 2. As a first step, we propose the formation of the enamine by reaction of the MacMillan catalyst as a salt with the corresponding aldehydes. The stoichometric amount of acid (HX) formed during the reaction is trapped by 2,6-lutidine (B). Water formed during the catalytic step is necessary to the process and it is a possible nucleophile, able to react with the carbocations. As a matter of fact, when the bis-bis(4-methoxy-phenyl)methylium cation, positioned at point 0 of the Mayr's scale, was reacted with octanal and the catalyst **5** in the usual reaction conditions, only the corresponding alcohol was isolated. Water ($N = 5.2$ in Mayr scale)[24] generated during the catalytic cycle reacted very fast with the unstable carbocation, hampering the reaction with the enamine.

Table 4. Alkylation of aldehydes with the carbocation **4**.



4 (1 equiv) **7a–c** (3 equiv) **11a–c**

R = nC_6H_{13}, **a**
R = *i*Pr, **b**
R = Bn, **c**

Entry	R	Product	*T* [°C]	*t* [h]	Yield [%][a]	d.r.[b]	*ee* [%] (major)[c]	*ee* [%] (minor)[d]
1	nC_6H_{13}	**11a**	0	2	90	4:1	78	2
2	nC_6H_{13}	**11a**	−25	2.5	68	9:1	80	10
3[e]	nC_6H_{13}	**11a**	−25	3	13	1.1:1	22	11
4	*i*Pr	**11b**	0	24	34	4:1	77	64
5	*i*Pr	**11b**	−25	21	51	4:1	92	62
6	*i*Pr	**11b**	0	74	41	2.3:1	71	76
7	Bn	**11c**	0	22	97	2.3:1	52	16
8	Bn	**11c**	−25	22	88	7:3	69	24

[a] Yield after chromatographic purification. [b] d.r. = diastereomeric ratio. Determined by ^1H NMR spectroscopy on the crude reaction mixture. The *syn*/*anti* ratio was not assigned and is indicated as the major versus minor diastereoisomer. [c] The enantiomeric excess was evaluated by chiral HPLC analysis. See the Supporting Information for details. The enantiomeric excess values are indicated for the major diiastereoisomer. [d] Enantiomeric excess values for the minor diastereoisomer. [e] The BF_4^- salt was used.

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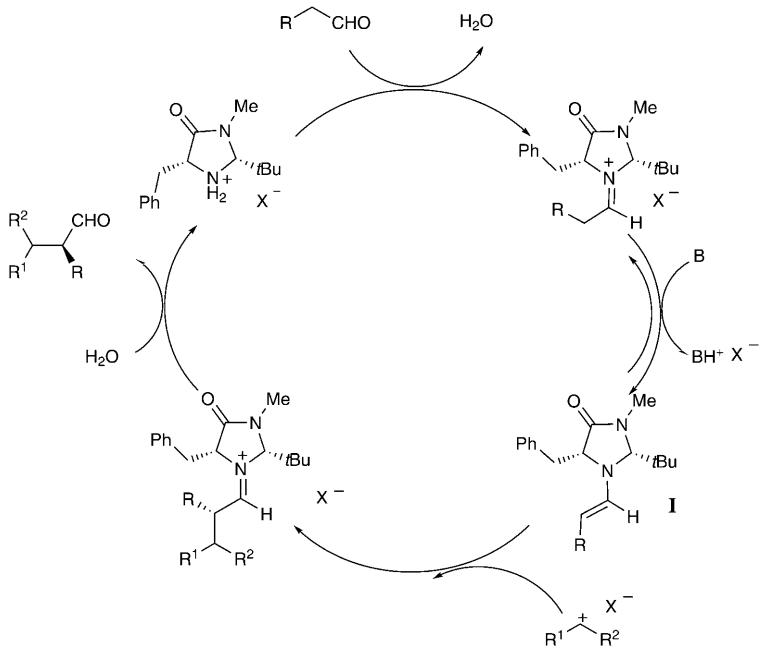
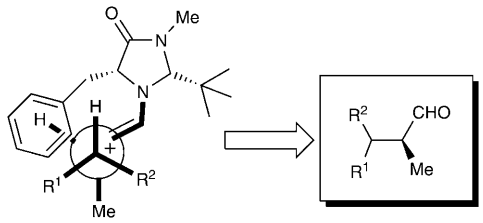


Scheme 2. Proposed catalytic cycle for the stereoselective alkylation of stabilized cations.

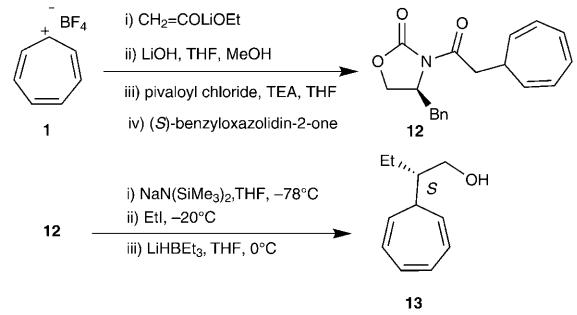
The stereoselectivity of the process can be explained by considering the model illustrated in Scheme 3, in which the less hindered face of the enamine is attacking the carbocation.[25]



Scheme 3. Sterochemical model for the addition of enamine to the carbocation.

This model was confirmed in our precedent studies[6,7] by correlation with a product of established absolute configuration. However, as the behavior of the tropylium cation was very different from other cations, we established the absolute configuration of the product **8d**, isolated by the attack of butanal on the carbocation **1** at −25 °C. The product was correlated to a known compound, obtained by a reaction sequence (Scheme 4). The synthetic sequence started with the reaction of the tropylium fluoroborate (**1**) with the enolate of ethyl acetate.

After a successful hydrolysis, the resulting acid was treated with (*S*)-benzyl oxazolidin-2-one, and the derivative **12** was alkylated according to Evans procedure.[26] Reduction of the compound with superhydride gave the alcohol **13**, identical for the sign of optical rotation and HPLC traces to the alcohol obtained by reduction with $NaBH_4$ of the product **8d** obtained at −25 °C.



Scheme 4. Absolute configuration of the product **8** through an established reaction sequence. TEA = triethylamine.

Conclusions

We have investigated, with four model carbocations, the α-alkylation of aldehydes promoted by the MacMillan catalyst salts **5**–**6**. In general, the reaction of isolated and stable carbocations is possible, and takes place with moderate to good selectivity in the presence of a stoichiometric amount of 2,6-lutidine as a base. Steric hindrance of the carbocation and of the enamine formed in situ by condensation of the aldehyde with the MacMillan catalyst salts **5**–**6** is influencing the process. With less hindered carbocations, the reaction with hindered aldehydes takes place. Temperature is also a controlling factor in the selectivity of the process. In particular, we have discovered an interesting entropic effect within the reaction of tropylium tetrafluoroborate with enamine. The facial selectivity is temperature-dependent and one MacMillan catalyst, operating at a different temperature, is able to furnish both enantiomers of the compounds, although in modest selectivity. Even if the chemical correlation for the isolated product **13** confirms the proposed model of attack, much work is still necessary to enhance the generality of our reaction by the use of less stabilized carbocations and by a more profound understanding of the selectivity of organocatalytic S_N1-type reactions.

Acknowledgements

The European Commission through the project FP7-201431 (CATAFLU.OR), PRIN (Progetto Nazionale Stereoselezioni in Chimica Organica: Metodologie ed Applicazioni), and Bologna University are acknowledged for financial support for this research.

[1] a) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77; b) M. F. Gotta, H. Mayr, *J. Org. Chem.* **1998**, *63*, 9769–9775; c) H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512; d) A. R. Ofial, H. Mayr, *Macromol. Symp.* **2004**, *215*, 353–367; e) M. Hofmann, N. Hampel, T. Kanzian, H. Mayr, *Angew. Chem.* **2004**, *116*, 5518–5521; *Angew. Chem. Int. Ed.* **2004**, *43*, 5402–5405; f) H. Mayr, A. R. Ofial, H. Schimmel, *Macromolecules* **2005**, *38*, 33–40; g) H. Mayr, A. R. Ofial, *Pure Appl. Chem.* **2005**, *77*, 1807–1821; h) A. D. Dilman, S. L. Ioffe, H. Mayr, *J. Org. Chem.* **2001**, *66*, 3196–3200; i) S. Lakhdar, T. Tokuyasu, H. Mayr, *Angew. Chem.* **2008**, *120*, 8851–8854; *Angew. Chem. Int. Ed.* **2008**, *47*, 8723–8726; j) H. Mayr, A. R. Ofial, *Angew. Chem.* **2006**, *118*, 1876–1886; *Angew. Chem. Int. Ed.* **2006**, *45*, 1844–1854; k) L. Shi, M. Horn, S. Kobayashi, H. Mayr, *Chem. Eur. J.* **2009**, *15*, 8533–8541.

[2] M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096–1122; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070.

[3] H. Mayr, M. Patz, *Angew. Chem.* **1994**, *106*, 990–1010; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 938–957.

[4] R. Lucius, R. Loos, H. Mayr, *Angew. Chem.* **2002**, *114*, 97–102; *Angew. Chem. Int. Ed.* **2002**, *41*, 91–95.

[5] Recently, Mayr has studied the electrophilicity (*E* parameter) of intermediates in organocatalytic reactions, see: a) M. Baidya, M. Horn, H. Zipse, H. Mayr, *J. Org. Chem.* **2009**, *74*, 7157–7164; b) S. Lakhdar, R. Appel, H. Mayr, *Angew. Chem.* **2009**, *121*, 5134–5137; *Angew. Chem. Int. Ed.* **2009**, *48*, 5034–5037; c) D. Richter, H. Mayr, *Angew. Chem.* **2009**, *121*, 1992–1995; *Angew. Chem. Int. Ed.* **2009**, *48*, 1958–1961; d) S. Lakhdar, T. Tokuyasu, H. Mayr, *Angew. Chem.* **2008**, *120*, 8851–8854; *Angew. Chem. Int. Ed.* **2008**, *47*, 8723–8726.

[6] P. G. Cozzi, F. Benfatti, L. Zoli, *Angew. Chem.* **2009**, *121*, 1339–1342; *Angew. Chem. Int. Ed.* **2009**, *48*, 1313–1316.

[7] F. Benfatti. M. G. Capdevila, L. Zoli, E. Benedetto, P. G. Cozzi, *Chem. Commun.* **2009**, 5919–5921.

[8] a) N. Vignola, B. List, *J. Am. Chem. Soc.* **2004**, *126*, 450–451; b) I. Ibrahem, A. Còrdova, *Angew. Chem.* **2006**, *118*, 1986–1990; *Angew. Chem. Int. Ed.* **2006**, *45*, 1952–1956; c) A. Fu, B. List, W. Thiel, *J. Org. Chem.* **2006**, *71*, 320–326; d) H. Xie, L. Zu, H. Li, J. Wang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 10886–10894; e) R. Rios, H. Sunden, J. Vesely, G.-L. Zhao, P. Dziedzic, A. Còrdova, *Adv. Synth. Catal.* **2007**, *349*, 1028–1032; f) D. Enders, C. Wang, J. W. Bats, *Angew. Chem.* **2008**, *120*, 7649–7653; *Angew. Chem. Int. Ed.* **2008**, *47*, 7539–7542.

[9] a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840–3864; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748; b) B. List, *Tetrahedron* **2002**, *58*, 5573–5590; c) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248–5286; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; d) A. Berkessel, H. Gröger, Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in *Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2004**; e) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724; f) B. List, *Chem. Commun.* **2006**, 819–824; g) C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042–8046; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876–7880; h) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; i) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44–50; *Angew. Chem. Int. Ed.* **2008**, *47*, 42–47; j) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232–6265; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171; for a commentary on the advent of asymmetric organocatalysis, see: k) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308.

[10] a) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; b) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.

[11] P. Melchiorre, *Angew. Chem.* **2009**, *121*, 1386–1389; *Angew. Chem. Int. Ed.* **2009**, *48*, 1360–1363, and references therein.

[12] P. Vicennati, P. G. Cozzi, *Eur. J. Org. Chem.* **2007**, 2248–2253.

[13] P. G. Cozzi. L. Zoli, *Green Chem.* **2007**, *9*, 1292–1295.

[14] G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79–87; for recent applications of the imidazolininoe catalysts, see: a) C. Conrad, J. Komg, B. N. Laforteza, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 11640–11641; b) E. Wilson , A. D. Casarez, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 11332–11334; c) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877; d) M. Amatore, T. D. Beeson, S. P. Brown, D. W. C. MacMillan, *Angew. Chem.* **2009**, *121*, 5223–5226; *Angew. Chem. Int. Ed.* **2009**, *48*, 5121–5124; e) B. Simmons, A Walji, D. W. C. MacMillan, *Angew. Chem.* **2009**, *121*, 4413–4417; *Angew. Chem. Int. Ed.* **2009**, *48*, 4349–4353.

[15] M. Bartók, *Chem. Rev.* **2010**, *110*, 1663–1705.

[16] Racemization of enantioenriched α-chloro aldehydes by MacMillan imidazolidinonium catalysts has been observed, and are presumably determined by the equilibrium iminium–enamine, see reference [14d]. In the case of our products, we have not observed racemization of products in solution or after purification. Probably, in our case, the sterical hindrance of the alkylated aldehydes is preventing the equilibration in the presence of the MacMillan imidazolidinonium catalyst.

[17] J. Burfeindt, M. Patz, M. Müller, H. Mayr, *J. Am. Chem. Soc.* **1998**, *120*, 3629–3634.

[18] A. K. Colter, C. C. Lai, T. W. Williamson, R. E. Berry, *Can. J. Chem.* **1983**, *61*, 2544–2551.

[19] C. Fichtner, G. Remennikov, H. Mayr, *Eur. J. Org. Chem.* **2001**, 4451–4456.

[20] a) F. H. Sarkar, Y. Li, *Cancer Metastasis Rev.* **2002**, *21*, 265–280; b) N. Jain, R. M. Kanojia, J. Xu, J.-Z. , Gou. E. Pacia, M.-T. Lai, F. Du, A. Musto, G. Allan, D. Hahn, S. Lundeen, Z. Sui, *J. Med. Chem.* **2006**, *49*, 3056–3059; c) S.-Y. Fwu, C.-Y. Chang, L.-J. Huang, C.-M. Teng, J.-P. Wang, S.-C. Chen, S.-C. Kuo, *Chin. Pharm. J.* **1999**, *34*, 255–359.

[21] I. K. Mangion, A. B. Northrup, D. W. C. MacMillan, *Angew. Chem.* **2004**, *116*, 6890–6892; *Angew. Chem. Int. Ed.* **2004**, *43*, 6722–6724. NOE analysis of an enamine–imidazolidinone derivative has revealed a preference for the *E* configuration about the N–C(sp^2) bond, see: T. J. Peelen, Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2005**, *127*, 11598–11599.

[22] D. Heller, H. Buschmann, H.-D. Sharf, *Angew. Chem.* **1996**, *108*, 1964–1967; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1852–1854.

[23] E. Emer, P. Galletti, D. Giacomini, *Eur. J. Org. Chem.* **2009**, 3155–3160.

[24] S. Minegishi, S. Kobayashi, H. Mayr, *J. Am. Chem. Soc.* **2004**, *126*, 5174–5181.

[25] For computational models of the addition of nucleophiles to benzhydrylic carbocations, see: C. Wang, Y. Fu, Q.-X. Guo, L. Liu, *Chem. Eur. J.* **2010**, *16*, 2623–2633.

[26] D. A. Evans, M. D. Ennis, D. A. Mathre, *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739.

Received: February 26, 2010
Revised: March 23, 2010
Published online: July 6, 2010

