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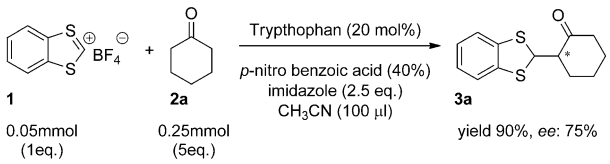
Organocatalytic Stereoselective α-Formylation of Ketones

Montse Guiteras Capdevila, Enrico Emer, Andrea Gualandi, Diego Petruzziello, Stefano Grilli, and Pier Giorgio Cozzi*[a]

Organocatalytic stereoselective α-alkylation of the carbonyl moiety represents a difficult and challenging transformation.[1] An interesting solution for this goal was presented by Jacobsen,[2] Trost,[3] Hartwig,[4] Stoltz,[5] and Braun.[6] These authors have introduced valuable chiral technologies for the enantioselective alkylation of metal enolates.[7] Despite the fact that brilliant solutions have been introduced for the stereoselective alkylation of aldehydes,[8] the enantioselective catalytic α-alkylation of simple ketones still remains a fundamental problem in chemical synthesis. Recently, MacMillan was able to translate the catalytic principle of singly occupied molecular orbital (SOMO) activation[9] into ketonic systems, providing an unprecedented direct and enantioselective α-alkylation of ketones.[10] Very recently another quite interesting approach based on Brønsted acid catalysis was reported.[11] The lacking of methodologies for the stereoselective alkylation of ketones is connected to the different steric and electronic properties with respect to catalyst interactions.[12] Particularly in organocatalysis the activation modes (enamine catalysis, iminium catalysis, SOMO catalysis) between these carbonyl subclasses is often difficult (if not achievable in many cases).[13]

Recently, we have presented a general methodology for the α-alkylation of aldehydes.[14] Our system is based on the easy reaction of enamine in S_N1-type reactions (Scheme 1).[15] In particular, we have discovered that the commercially available benzodithiolylium tetrafluoborate easily reacts with enamine formed in situ in the presence of the MacMillan catalyst.[16] The procedure is quite versatile and useful for the synthesis of natural products.[17] We wanted to extend our alkylation procedure using ketones as substrates. Therefore we set up a model reaction using cyclohexanone and benzodithiolylium as prototypical substrates (Scheme 1), in the presence of several organocatalysts (Table S1, see the Supporting Information, SI), including primary and secondary amines. Tryptophan was selected for further optimization. Many different tryptophan derivatives were investigated in the reaction (Table S2, see SI), but the enantiomeric excesses were not improved. Unfortunately, after these encouraging preliminary results (Scheme 1) we found that the conditions were not quite reproducible and the reaction was very capricious, particularly when other ketones were used.



Scheme 1. Addition to benzodithiolylium tetrafluoroborate to cyclohexanone.

The enantiomeric excesses measured varied from reaction to reaction. The major problem encountered was the quite fast background reaction. In fact, the reaction between cyclohexanone and benzodithiolylium occurred without an organocatalyst and was probably driven by traces of acids liberated during the process[18] that are able to promote the formation of the corresponding enol of the ketone.[19] The difficulties and the lack of reproducibility hampered the optimization of the process promoted by tryptophan. We reasoned that other heterocyclic substrates, such as benzoimidazolium or benzothiazolium, bearing a stabilized cationic charge, could be used in the stereoselective formylation of ketones with enamines.

In fact 3-methylbenzothiazoline hydrolysis has been reported to be accomplished in mild conditions by $AgNO_3$ in aqueous acetonitrile-phosphate buffer (0.05 M, pH 7)[20] and the use of benzothiazole as a formyl equivalent has been previously investigated in literature.[21] To test this hypothesis, we have prepared the substrates indicated in the Figure 1 and subjected them to a model reaction with cyclopentanone in the presence of different organocatalysts.

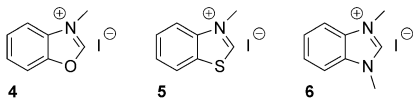


Figure 1. Formyl cation equivalents.

In the presence of L-proline, a good yield of the desired product was obtained and the adduct was isolated as a mixture of two diastereoisomers, with low enantiomeric excess. The desired product was formed with the *N*-methylbenzothiazolium iodide **5**[22] employed as formyl equivalent reagent, whereas *N*-methylbenzooxazole **4** (Figure 1) and *N*-methybenzoimidazole **6** were found to be unreactive under the explored reaction conditions.

Bases and solvents were varied in order to improve yields and enantiomeric excesses, and a number of the results obtained are reported in Table 1. Slightly better results were obtained in toluene, for which inorganic bases were also tested;

[a] *M. G. Capdevila, Dr. E. Emer, Dr. A. Gualandi, D. Petruzziello, Dr. S. Grilli, Prof. P. G. Cozzi*
ALMA MATER STUDIORUM
University of Bologna
Dipartimento di Chimica "G. Ciamician"
Via Selmi 2, 40126 Bologna (Italy)
Fax: (+39) 051-2099456
E-mail: piergiorgio.cozzi@unibo.it

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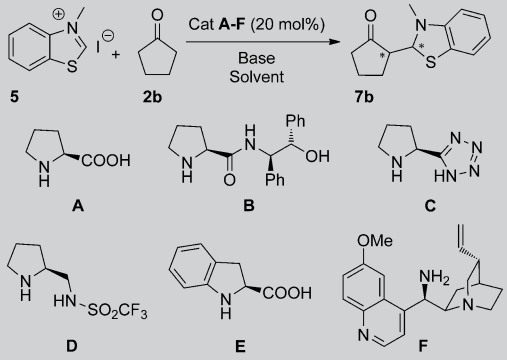
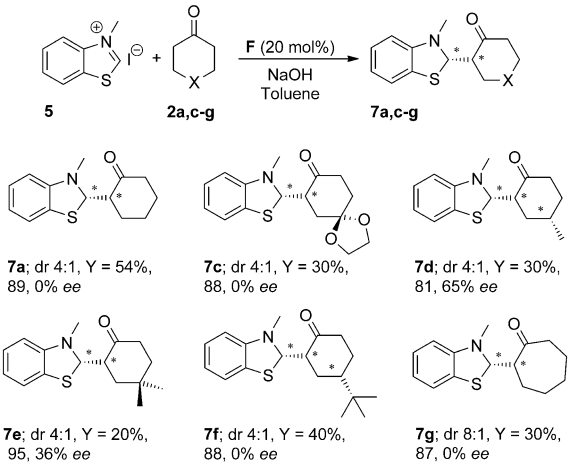
Table 1. Organocatalyst-promoted addition of cyclopentanone to the *N*-methylbenzothiazolium cation.



Entry[a]	Base	Cat	Sol	**2b** [eq.]	*dr*[b]	Yield [%][c]	*ee*[d]
1	DABCO	A	neat	20	3:1	70	30, 0
2	lutidine	A	neat	20	4:1	70	21, 0
3	DBU	A	neat	20	7:1	60	30, 0
4	K_2CO_3	A	neat	20	10:1	60	21, 0
5	Na_2CO_3	A	neat	20	10:1	70	31, 0
6	TEA	A	neat	20	8:1	75	36, 0
7	Na_2CO_3	B	tol	5	4:1	10	0, 0
8	Na_2CO_3	C	tol	5	4:1	15	25, 0
9	Na_2CO_3	D	tol	5	3:1	5	0, 0
10	Na_2CO_3	E	tol	5	–	–	–
11	Na_2CO_3	F	tol	5	6:1	25	95, 64
12	Na_2CO_3	F	tol	10	4:1	27	97, 63
13	Na_2CO_3	F	neat	10	10:1	29	92, 0
14	**NaOH**[e]	**F**	**tol**	**5**	**8:1**	**60**	**93, 56**
15	NaOH[f]	F	tol	5	–	–	–
16	-	F	tol	5	8:1	30	97, 0

[a] The reactions were performed with 1 equiv of *N*-methylbenzothiazolium iodide **5**, 5-20 equiv of cyclopentanone **2b** in the presence of 20 mol% of catalysts **A**–**F**, with 0.7 equiv of base, in 200 μL of toluene. The reactions were run until completion, as determined by TLC (24 h). [b] Determined by ^{1}H NMR analysis of the crude. [c] Yield after chromatographic purification [d] Determined by chiral HPLC analysis. [e] 0.5 equiv of base. [f] 1.0 equiv of base.

however, only low enantiomeric excesses were achieved. Consequently, different organocatalysts were examined. *Cinchona* alkaloids gave quite remarkable results in terms of enantiomeric excess and the reaction was subsequently optimized, by varying the equivalents of ketone and the base. Bases such as LiOH, $NaHCO_3$, or *t*BuOK gave reduced stereoselection. The presence of 20 or 40 mol% of TFA or other acid additives used in for many stereoselective organocatalytic processes was not necessary in our case. Finally, in the presence of 0.5 equivalents of aqueous NaOH, the product was isolated in 60% yields as a mixture of two diastereoisomers. Interestingly, the absence of base did not seem to hamper the reaction (entry 16), indeed only a reduction in the yield was observed. To improve the isolated yields, other benzothiazolium salts[23] were prepared, but in all cases quite poor results were obtained. The reaction was investigated with other experiments that explored the scope of the ketone component. Six-and seven-membered carbocycles can be employed in this asymmetric alkylation reaction (Scheme 2). Moreover, this protocol is successful with



Scheme 2. Addition of the *N*-methylbenzothiazolium **5** to ketones.

ketones that incorporate alkyl substituents at the γ ring positions. The use of 10 equivalents of ketone was necessary to observe even moderate yields. Cyclopentanone was found the more reactive when compared to the other ketones employed in the reaction, but no formation of double alkylated product was observed.[10]

In all the cases the major diastereoisomer was obtained from good to excellent enantiomeric excess, while the minor diastereoisomer was isolated with low or no enantiomeric excess. The diastereoselection of the reaction is dependent on the approaching mode of the cation to the enamine. However, suggesting a preferential conformation of the enamine derived by *Cinchona* alkaloids is still troublesome.[24] Chiral 3-tosyl-oxalkyl oxazolines were employed as chiral formyl equivalents with enamines[25] and with enolsilanes.[26] Similarly to the studied addition of the chiral formyl cation equivalent, the bulky benzothiazoline substituent is locked in a single chair conformation. We have performed ^{1}H NMR analysis on product **7d** in order to attribute the relative configuration of the most abundant diastereoisomer. From the multiplicity of the H^2 proton signal it was possible to establish the equatorial position of the benzothiazole group. The positive NOE response experienced by the four H^3 and H^5 protons, when the methyl frequency was irradiated, confirmed the *syn* relative configuration between the methyl in the γ position and the benzothizole (Figure 2, see the SI for further details).

Unfortunately, the direct long range NOEs between the H^2 and H^4 in 1,3-diaxial position was not clear, owing to the over-

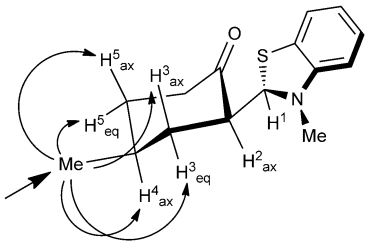


Figure 2. Observed NOEs for the analyzed diastereoisomer.

lap of the H^3_{eq} and H^5_{eq} signals. The analysis was less clear for the compound **7 f**, in which some protons were seen to overlap in the ^{1}H NMR spectra; this has been attributed to the presence of the *tert*-butyl substituent. Considering the partial results obtained and that the *tert*-butyl group is more bulky when compared to the methyl, we can assume that again for the compound **7 f**, a *syn* product was obtained with both the *tert*-butyl and benzothiazolyl groups in equatorial positions. For the derivatives **7 d**,**f** only two of the possible four diastereoisomers were observed, and the more stable *syn* diequatorial diastereoisomer was obtained in both cases.[27] We have followed the reaction by sampling amounts of the crude reaction mixture over the time and studying the *dr* of the reaction by ^{1}H NMR and HPLC analysis. We saw no evidence of diastereoisomeric equilibration or changes in the *dr* over the reaction time.

The stereochemical outcome of the reaction was probably determined by the hindrance of the *N*-methylbenzothiazolium iodide in the approach to the primary enamine. At this time we can only suggest the speculative model for interpreting the result of the reaction that is depicted in the Figure 3.

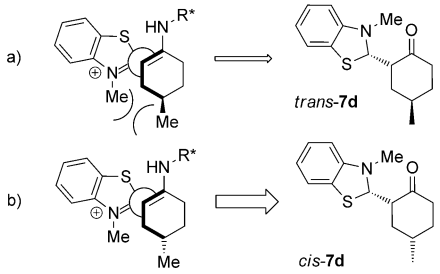
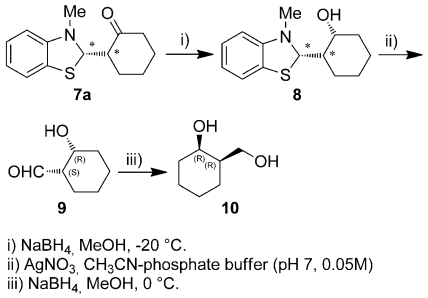


Figure 3. Model for the stereochemical course of the reaction.

The absolute configuration of the newly formed stereogenic center was established through chemical correlation to a known product (Scheme 3), and the absolute configuration of the major diastereoisomer was assigned by analogy to all products **7 a**–**g**.

The reduction with $NaBH_4$ of **7 a**, at 0 °C, was completely diastereoselective and only the *syn* product was isolated. The presence of the bulky benzothiazolyl group at the 2-position resulted in an equatorial attack by the hydride.[28] The relative *syn* configuration between the benzothiazoline and the OH bond was assigned on the basis of the NOE ^{1}H NMR analysis. The hydrolysis of the benzothiazoline group to the corresponding aldehyde was accomplished in accordance with the procedure reported by Chikashita[29] and resulted in a high yield of the almost pure, but unstable, aldehyde **9**, which was immediately reduced by $NaBH_4$ to the known (1*R*, 2*R*)-2-hydroxycyclohexanemethanol **10**.[30]



Scheme 3. Determination of the absolute configuration of product **7 a** through chemical correlation.

In conclusion we have described the first organocatalytic stereoselective formylation of ketones accomplished by the use of *N*-methybenzothiazolylium iodide. The benzothiazolium salt, generally used as a masked formyl group or as precursor of carbenes,[31] is quite electrophilic and react with enamines formed in situ. Both moderate yield and high stereoselectivity were obtained with different ketones. The general application of S_N1 type reactions in organocatalysis and the stereoselective reaction of the carbenium ion with nucleophiles are under active investigation in our laboratory.

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Keywords: cinchona alkaloid · enantioselective · formylation · ketones · organocatalysis

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