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A general stereoselective enamine mediated alkylation of α-substituted aldehydes†

Andrea Gualandi, Diego Petruzziello, Enrico Emer and Pier Giorgio Cozzi*

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We herein present a general enamine-mediated α-alkylation of α-substituted aldehydes with carbenium ions for the stereoselective construction of quaternary stereogenic centers.

The formation of quaternary stereocenters in the synthesis of complex molecules is a rather challenging transformation.[1] Even more difficult is the control of their absolute and relative configurations. In recent years, the development of new and exciting methodologies in organocatalysis[2] has furnished new reactions for targeting the asymmetric formation of quaternary stereogenic centers.[3] All these new methodologies are appealing, in that they offer excellent stereocontrol and operate under mild operative conditions. It is also important to note that the use of transition metals is, in general, avoided.[4]

The direct asymmetric intermolecular α-alkylation of carbonyls remains a difficult and hot topic in organocatalysis.[5] The alkylation of activated carbonyl substrates was developed by Merck laboratories[6] with the invention of a quite useful asymmetric phase-transfer catalysis (PTC)[7] that was employed for preparative purposes achieving high stereoselectivity. The quaternary *cinchona* alkaloids employed at first as catalysts in asymmetric PTC were later replaced by more active and stereoselective catalysts developed by Maruoka *et al.*[8]

Although some innovative strategies have been described,[9] the development of a new general enamine-mediated α-alkylation of α-substituted aldehydes has received scarcely any attention.[9d,10]

Recently, we have established the possibility of using stable carbenium ions generated from alcohols in alkylation reactions[10] in the presence of MacMillan catalysts.[11] We have also performed enantioselective alkylation of aldehydes with 1,3-benzodithiolylium tetrafluoroborate,[12] a versatile synthon in organic chemistry. Herein we report the general and practical alkylation of α-substituted aldehydes with the 1,3-benzodithiolylium ion.

Quite recently, Aggarwal and coworkers[13] have presented a general organometallic strategy for the preparation of stereogenic centers. This outstanding procedure that starts with available enantiopure alcohol has allowed the possibility of introducing a quaternary center in a stereoselective fashion, starting from a common precursor. The idea that we want to borrow to translate in the language of organocatalysis was to apply a general and a simple methodology for preparation of an intermediate that, through practical and simple reactions, can give the possibility to introduce many different groups and to vary the chemistry.

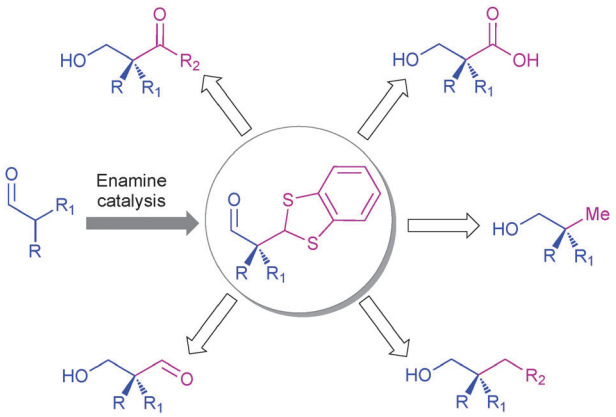


Fig. 1 Stereoselective formylation for the preparation of quaternary stereogenic centers.

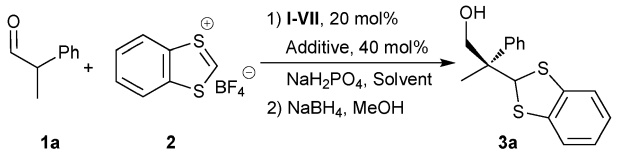
This idea can be simply pursued by the application of our benzodithiol chemistry. In fact, the introduction of the benzodithiol (Fig. 1) in a stereoselective fashion can give the possibility to construct the desired quaternary stereogenic center and to install many groups after lithiation and successive alkylation, or by reductive or oxidative cleavage of the benzodithiol group.

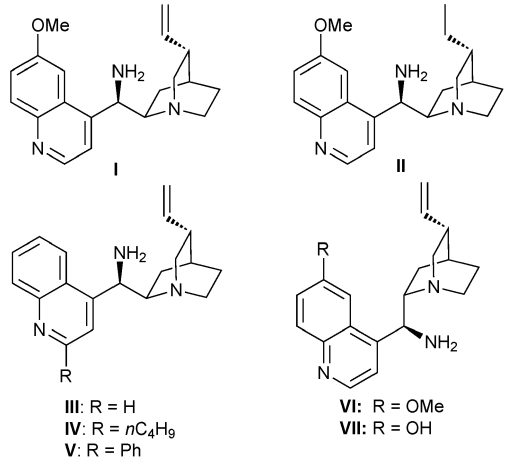
Primary amines efficiently catalyzed Michael reactions with α-substituted aldehydes.[14] In order to find the optimal reaction conditions, we started our preliminary investigation using phenylpropionaldehyde **1a** as a model substrate in the presence of a commercially available 1,3-benzodithiolylium tetrafluoroborate **2** and several aminoacids (such as L-tryptophan, proline and others). Different primary amines and imidazolidinone were also tested, all giving disappointing results (see ESI† for a complete table and all conditions screened). It is worth mentioning that Melchiorre and Bartoli have provided evidence that the catalysts derived from *cinchona* alkaloids (**I–VII**)[15] were compatible with the carbenium ion. We therefore investigated

Dipartimento di Chimica "G. Ciamician" ALMA MATER STUDIORUM Università di Bologna, via Selmi 2, 40126 Bologna, Italy. E-mail: piergiorgio.cozzi@unibo.it; Web: www.unibo.it; Fax: +39-051-2099456; Tel: +39-051-2099511

† Electronic supplementary information (ESI) available: Optimization of the reaction, general procedure for the synthesis of aldehydes **1b–l** and catalysts **IV**, **V**, complete analytical data for products **3a–l**, **4a–7a**. See DOI: 10.1039/c2cc17482k

Table 1 Optimisation of reaction conditions[a]

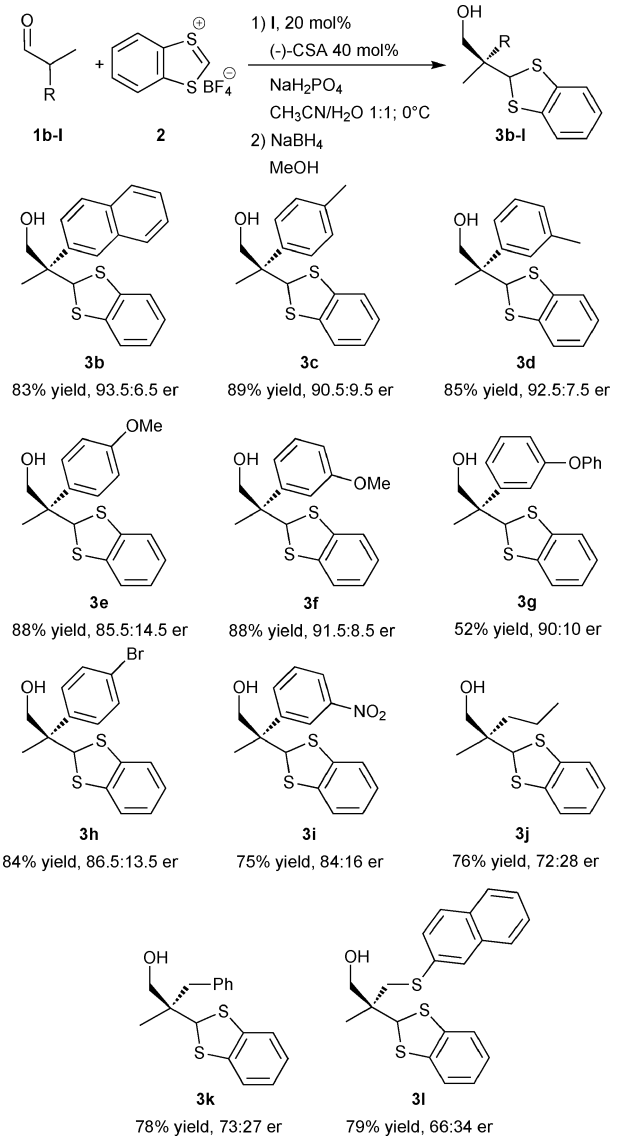




Entry	Catalyst	Additive	Solvent	Yield[b]	er[c]
1	**I**	**(−)-CSA**	**CH_3CN/H_2O**	**90**	**92 : 8**
2	**II**	(−)-CSA	CH_3CN/H_2O	84	89.5 : 10.5
3	**III**	(−)-CSA	CH_3CN/H_2O	84	90.5 : 9.5
4	**IV**	(−)-CSA	CH_3CN/H_2O	85	90 : 10
5	**V**	(−)-CSA	CH_3CN/H_2O	86	84.5 : 15.5
6	**VI**	(−)-CSA	CH_3CN/H_2O	87	11 : 89
7	**VII**	(+)-CSA	CH_3CN/H_2O	68	21 : 79
8	**VI**	(−)-CSA	CH_3CN/H_2O		nd
9	**I**	(−)-CSA	CH_2Cl_2	83	31.5 : 68.5
10	**I**	(−)-CSA	CH_3CN	86	83 : 17
11	**I**	(−)-CSA	H_2O	77	77.5 : 22.5
12	**I**	(+)-CSA	CH_3CN/H_2O	88	91 : 9
13	**VI**	PhCOOH	CH_3CN/H_2O	58	37 : 63
14	**VI**	PTSA	CH_3CN/H_2O	69	14 : 86
15	**VI**	TfOH	CH_3CN/H_2O	72	12 : 88
16	**VI**	*N*-Boc-*D*-Phe	CH_3CN/H_2O	79	12.5 : 87.5

[a] The reactions were carried out with 1 equiv. of **2**, 3 equiv. of **1a** in the presence of 20 mol% of catalysts **I–VII**, 40 mol% of additive and with 2 equiv. of NaH_2PO_4 in 500 μL of solvent at 0 °C. [b] Determined by ^1H NMR. [c] (*R*)-**3a** : (*S*)-**3a** ratio determined by HPLC (see ESI for details).

these primary amines and were pleased to find out that these catalysts were able to transmit the chiral information in a better way (Table 1). However, still the results were not useful, a series of conditions, such as: solvent, temperature and additive, were screened. Under the optimized conditions the reactions were performed in a 1 : 1 mixture of CH_3CN/H_2O as reaction solvent, at 0 °C, in the presence of NaH_2PO_4 as a base. It is noteworthy that the solvent controls the enantiofacial selectivity of the reaction (entry 9 *vs.* entry 10), as a result of the delicate conformation of the *cinchona* alkaloid framework.[16] After testing several acidic additives able to enhance both reactivity and selectivity, we have observed that (−)-CSA as chiral acid[17] gave the best results in terms of stereoselectivity. We have also prepared and tested the primary amines **IV** and **V** following the procedure developed by Hintermann *et al.*,[18] but the enantiomeric excess was not increased.

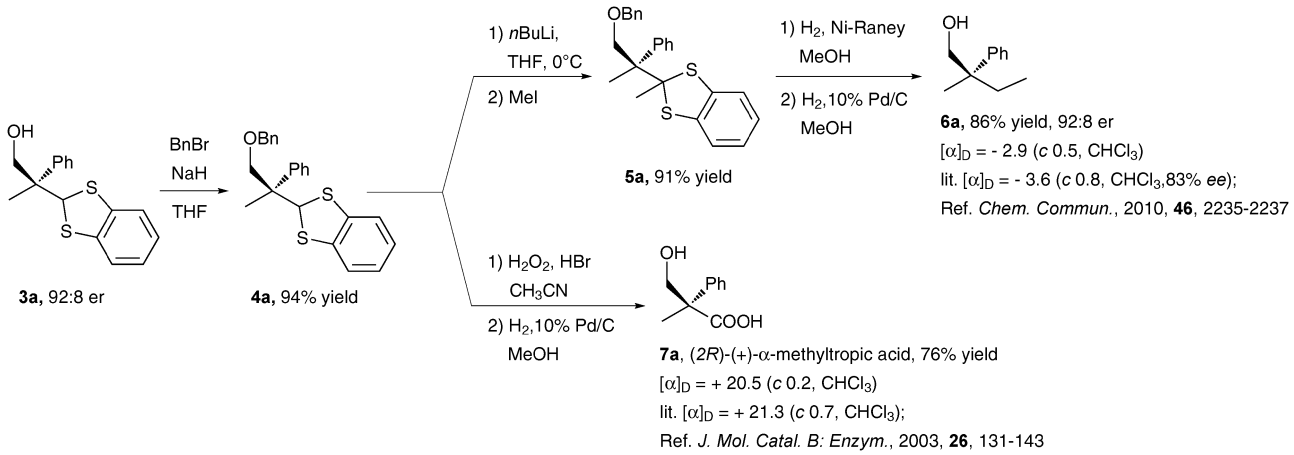


Scheme 1 Scope of the reaction with different α-substituted aldehydes.

The optimized reaction conditions were applied to a series of aldehydes (Scheme 1). The hindrance of the starting aldehydes is crucial in order to obtain the reaction. *Ortho* substituted aldehydes were not reactive under the optimized reaction conditions, however a series of α-branched aldehydes were alkylated in good yield and with good enantiomeric excess. Interestingly, moderate enantiomeric excesses were obtained with α,α-dialkyl aldehydes (**3j–l**). The absolute configuration of the newly formed quaternary center was established by chemical correlation.

The advantage of benzodithiol as a versatile and chameleonic synthetic group was fully explored in a series of transformations performed on the derivative **3a** with previous protection of the alcoholic function as a benzyl ether. The resulting **4a** was treated with *n*-BuLi at 0 °C and alkylated with MeI. Finally, by treatment with Ni-Raney[19] compound **6a** was obtained without loss of enantiopurity, and the absolute configuration of the product was determined.

We have applied our chemistry to the synthesis of a natural product. Compound **4a** can be straightforwardly transformed



Scheme 2 Synthesis of (2*R*)-(+)-α-methyltropic acid from compound **4a**.

in (2*R*)-(+)-α-methyltropic acid,[20] by direct oxidation of the benzodithiol to the corresponding acid and debenzylation of the hydroxyl group (Scheme 2). In conclusion, we have reported a simple and general methodology for the enamine-mediated α-alkylation of α-substituted aldehydes, previously an unresolved problem in organocatalysis. Synthetic work is in progress towards the synthesis of more hindered carbenium ions, in order to improve the stereoselection of this synthetic methodology.

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