DOI: 10.1002/ejoc.201100690

Dual Secondary Amine/N-Heterocyclic Carbene Catalysis in the Asymmetric Michael/Cross-Benzoin Cascade Reaction of β-Oxo Sulfones with Enals

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Dedicated to Professor Dieter Hoppe on the occasion of his 70th birthday

Keywords: Domino reactions / Umpolung / Michael addition / Organocatalysis / Carbenes

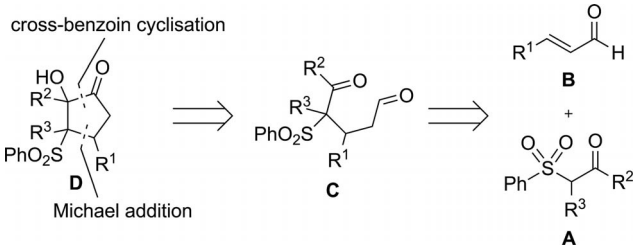
Polyfuncionalized cyclopentanones with three contiguous stereogenic centers were formed in good to excellent yields and stereoselectivities by utilizing a secondary amine/N-heterocyclic carbene catalytic system in the reaction of β-oxo sulfones with unsaturated aldehydes. In addition, the influence of the catalysts on the diastereoselectivity of the final product was studied by ^{1}H NMR spectroscopy.

Introduction

In the past two decades the field of N-heterocyclic carbenes (NHC)[1] developed rapidly to become inter alia a powerful tool in organocatalysis.[2] Recently, cascade reactions[3] received growing attention from the scientific community since they lower the cost and reduce the time needed for the synthesis of complex molecules.[4] The interlinking of these two important areas of organic chemistry provides a fast access to densely functionalized compounds difficult to prepare by other methods. Although a large number of known transformations already exists by employing the umpolung concept using NHC catalysis, publications dealing with the application of NHCs in domino reactions[5,7] are still limited. Since domino reactions solely catalyzed by an NHC appeared challenging, recent publications indicated that cooperative[6] and dual catalysis[7] could be promising alternatives.

Results and Discussion

We were intrigued by the possibilities of utilizing dual catalytic systems and hence envisioned that β-oxo sulfones **A**, which are known substrates[8,9] for the organocatalytic Michael addition, might undergo a Michael/cross-benzoin[10] cascade reaction with enals **B** to form, via the Michael adducts **C**, polyfunctionalized cyclopentanones **D** bearing three contiguous stereogenic centers (Scheme 1). Since the reaction of β-oxo carbonyl compounds with aldehydes using a secondary amine/NHC dual catalytic system has recently been published,[7a] we started our investigations by applying the reaction conditions reported. The reaction of crotonaldehyde (**1a**) with (phenylsulfonyl)acetone (**2a**) proceeded well with the aminocatalyst **4a** and the NHC precursor **5** resulting in high yields and enantioselectivities but modest diastereoselectivities of the cascade product (Table 1, Entry 1). Only two of four possible diastereomers were observed in a ratio of approximately 2:1. Unfortunately, the purification of product **3a** and separation from the excess of ketone **2a** was impossible by column chromatography, because both compounds have similar R_f values on silica gel, and therefore the reaction conditions were re-optimized. First other catalytic systems **4b/5** and **4c/5** were tested but were inferior in selectivity and reactivity (Table 1, Entries 2 and 3). After several tests using **4a/5** at low temperature in combination with higher base loadings, we achieved good conditions leading to the cascade product in virtually quantitative yield, high *ee* and moderate *dr*, while the starting materials were applied in nearly equimolar amounts (Table 1, Entry 4).



Scheme 1. Retrosynthetic analysis.

Subsequently, we focused on the scope of the reaction. First the variation of the Michael acceptor was studied (Table 2; **3a**–**c**). The long-chain leaf aldehyde (**1b**) and cinn-

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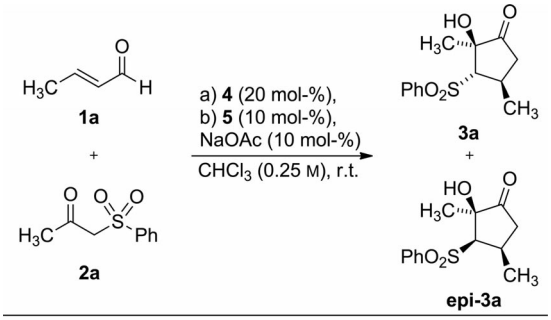
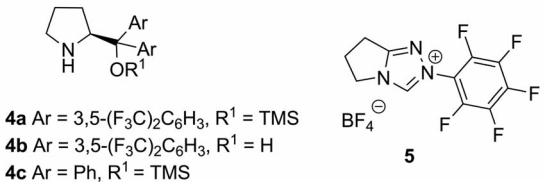
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100690.

Table 1. Optimization of the reaction conditions.[a]



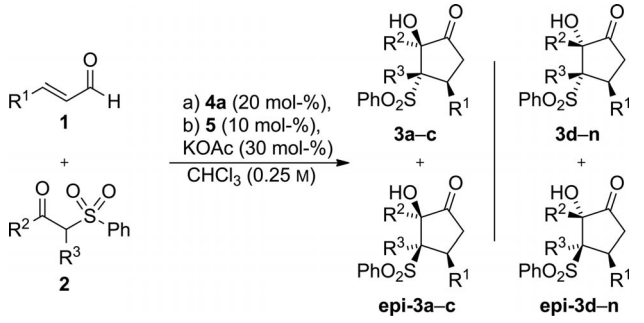


Entry	Catalysts	Yield of **3** [%][b]	*dr*[c]	*ee* [%][d]
1	**4a/5**	85	63:37	88
2	**4b/5**	8	57:43	55
3	**4c/5**	78	69:31	67
4[e]	**4a/5**	99	66:34	86

[a] Reactions (Entries 1–3) were performed by using 1 equiv. of crotonaldehyde (**1a**) (0.76 mmol scale), 2 equiv. of β-oxo sulfone **2a**, 20 mol-% of **4**, 10 mol-% of **5**, 10 mol-% of NaOAc in $CHCl_3$ (0.25 M) at room temperature; all reagents were added sequentially. [b] Sum of the yields of isolated **3a** and **epi-3a**. [c] Diastereomeric ratio of **3a** and **epi-3a** determined by ^1H NMR spectroscopy of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase; major diastereomer. [e] This reaction was performed by using 1.2 equiv. of crotonaldehyde (**1a**) (0.76 mmol scale), 1.0 equiv. of β-oxo sulfone **2a** and 20 mol-% of **4** in $CHCl_3$ (0.25 M) at room temperature; after 24 h, 10 mol-% of **5** and 30 mol-% of KOAc were added.

amic aldehyde (**1c**) showed lower reactivity towards the nucleophile **2a** than the crotonaldehyde (**1a**), although the reaction proceeded with higher enantioselectivity. Prolonging the reaction time had no effect on the yield in these cases. Therefore, the higher level of asymmetric induction may be explained with the increased steric demand, while the limited conversions are possibly caused by the deprotection of the amine catalyst leading to the less effective catalyst **4b** (Table 1, Entry 2), this being in line with what was reported by Jørgensen et al.[9a] The ratio of the two observed diastereomers was modest for **3a** and **3b**. Fortunately, they can be separated by column chromatography to yield the pure diastereomers. Furthermore, cinnamaldehyde provided only a single diastereomer of the product, possibly indicating a strong electronic or stereoelectronic influence on the diastereoselectivity here. With this observation in hand, we predicted that the change of the nucleophile to (phenylsulfonyl)acetophenones **2d**–**i** and other β-oxo sulfones bearing naphthyl or benzofuranyl groups **2j**–**k** would react in a highly diastereselective manner. As anticipated, in most cases only one diastereomer could be observed in the ^1H NMR spectra of the crude reaction mixture. Only the product **3g** bearing a nitro group and the benzofuranyl derivative **3k** contained a second isomer in a 3:1 and 4:1 ratio, respectively. In all these cases the polyfuncionalized cyclopentanones were formed in good yields and excellent enantioselectivities.[11] It is worthwhile to point out that these compounds are all crystalline solids. To our delight, they form conglomerates as shown in the case of **3d**. After a single crystallization step only one pure enantiomer of this compound was isolated with 99% *ee*. Furthermore, as was demonstrated with **3d**, this reaction could be performed on a gram scale with a comparable yield and stereoselectivity. As a further extension of the protocol α-substituted α-(phenylsulfonyl) ketones **2l**–**n** were used. As expected, the additional α-substituent decreased the reaction rate and the yield. Attempts to prolong the reaction time to 3 d still provided only modest yields. The cyclic ketones **2l**,**m** performed better than the acyclic one (**2n**). By comparison, cyclopentanone substrate **2l** resulted in a higher product yield but much lower enantio- and diastereoselectivity than the cyclohexanone substrate **2m**.

Table 2. Substrate scope of the asymmetric Michael/benzoin domino reaction.[a]



3	R^1	R^2	R^3	Yield [%][b]	*dr*[c]	*ee* [%][d]
a	Me	Me	H	99	66:34	86
b	*n*Pr	Me	H	67	58:42	96
c	Ph	Me	H	33	99:1	94
d[e]	Me	Ph	H	72 (44)	99:1	92 (99)
e	Me	4-BrC_6H_4	H	70	99:1	90
f	Me	4-PhC_6H_4	H	85	99:1	91
g	Me	3-$O_2NC_6H_4$	H	80	74:26	83
h	Me	3-$MeOC_6H_4$	H	81	99:1	83
i	Me	3,4-$F_2C_6H_3$	H	68	99:1	97
j	Me	2-naphthyl	H	74	99:1	93
k	Me	2-benzofuryl	H	96	79:21	90
l[f]	Me	$–C_3H_6–$		53	67:33	41
m[f]	Me	$–C_4H_8–$		20	99:1	91
n[f]	Me	Me	Me	< 5[g]	n.d.	n.d.

[a] All reactions were performed by using 1.2 equiv. of crotonaldehyde (**1a**) (0.76 mmol scale), 1.0 equiv. of β-oxo sulfone **2a** and 20 mol-% of **4** in $CHCl_3$ (0.25 M) at room temperature; after 24 h, 10 mol-% of **5** and 30 mol-% of KOAc were added. [b] Sum of the yields of isolated **3** and **epi-3**. [c] Diastereomeric ratio of **3** and **epi-3** determined by ^1H NMR spectroscopy of the crude reaction mixture. [d] Determined by HPLC analysis on a chiral stationary phase; major diastereomer; values in parentheses indicate yield and *ee* after crystallization. [e] This reaction was performed on a 7.6 mmol scale. [f] The reaction time of the Michael addition step was prolonged to 3 d. [g] Estimated by ^1H NMR spectroscopy.

The absolute configuration of the cyclopentanone product **3d** was determined by X-ray crystal structure analysis (Figure 1). The structure matched well with the NOE con-

tacts for **3g** measured by NMR spectroscopy. Interestingly, this structure indicated a different configuration in the α-position to the carbonyl group than the one determined by Rovis et al.[7a] for substrates bearing a carbonyl group instead of the sulfonyl group. Additionally, NOE contacts of the products **3a** and **3n**[12] were measured, because no examples with aromatic moieties (R^2) were published. Both compounds have the (*R*) configuration here, which is consistent with the result reported in the literature.[7a]

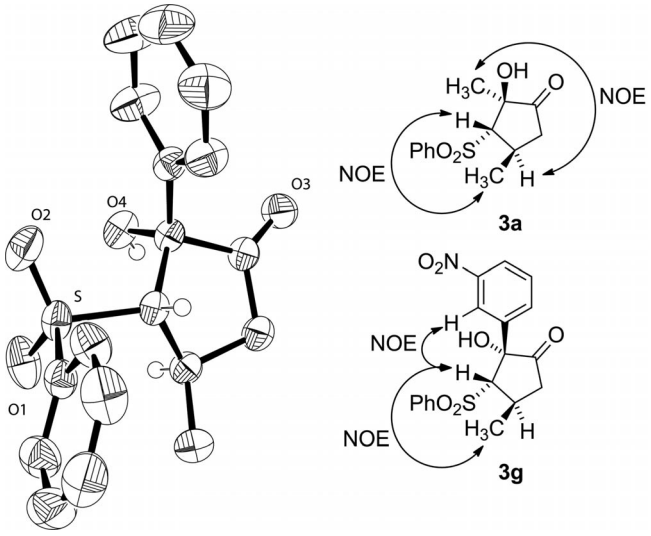


Figure 1. ORTEP plot of **3d** determined by X-ray analysis[13] and NOE measurements of **3a** and **3g**.

This interesting result led to further investigations in order to gain a deeper insight into the influences of the NHC and TMS-protected diphenylprolinol catalysts on the diastereoselectivity. Therefore, a kinetic study was undertaken in which the reaction progress for **3d** was observed directly by ^{1}H NMR spectroscopy (Figure 2). In contrast to an analysis by GC, this method makes it possible to determine the *dr* of the Michael addition product (referred to as **C** in Scheme 1) and the cross-benzoin product[14] directly in the reaction vessel (Figure 3). At the beginning of the Michael addition a moderate diastereomeric excess (*de*) of 60% was measured for the product of this first step. As the reaction progressed, this value dropped continuously. This decrease became even faster after the addition of the carbene precursor and the base. Virtually no diastereomeric excess was left after approximately 4 h, while the carbene catalyst converted only 50% of the Michael addition product. The reaction without the addition of the carbene precursor followed the same route. Thus, we assume that this epimerization is due to a deprotonation and re-protonation in the α-position to the ketone and the phenylsulfonyl group under basic conditions. This analysis was also performed with compound **3a** and resulted in a similar curve progression for the *de* of the Michael adduct.[13] It is worth mentioning that the diastereomeric ratio of **3a** during its formation remained nearly constant and is therefore independent of the *de* of the cross-benzoin reaction precursor. An explanation may be that in a dynamic kinetic process the NHC reacts faster with one Michael adduct epimer along with a rapid epimerization of the less reactive one. In summary, the diastereomeric ratio of the final product was unaffected by the amine catalyst and is completely determined by the NHC catalyst.

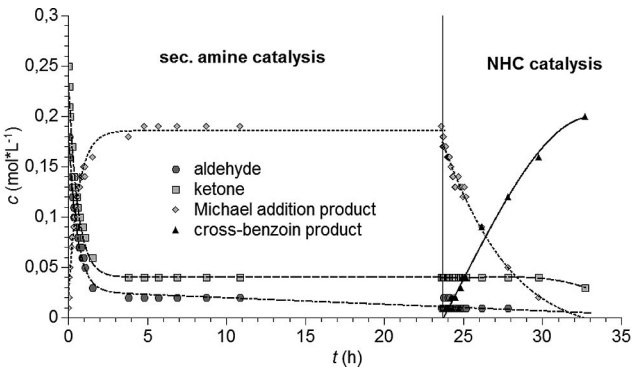


Figure 2. Direct observation of the reaction progress for **3d** by ^{1}H NMR spectroscopy; for details see Supporting Information; all curves are polynomial plots of the data points.

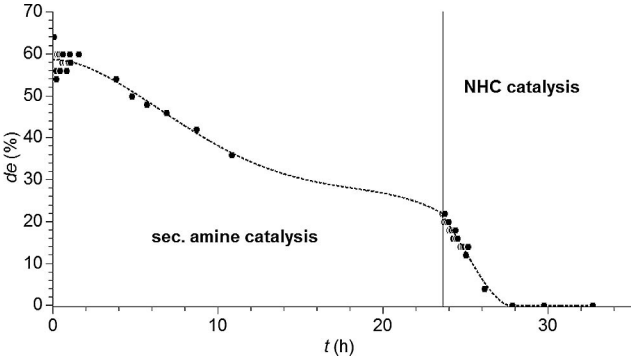


Figure 3. Development of the diastereomeric ratio of the cross-benzoin reaction precursor of **3d**; for details see Supporting Information; the curve is the polynomial plot of the data points.

Conclusions

We developed an organocatalytic cascade reaction between β-oxo sulfones and enals by utilizing a dual secondary amine/N-heterocyclic carbene catalytic system. The polyfuncionalized cyclopentanones bearing a synthetically useful β-(phenylsulfonyl) group, an α-hydroxy function and three contiguous stereocenters are formed mostly in good yields, modest to excellent diastereoselectivities and very good enantiomeric excesses. Further improvement of the *ee* value can be achieved by re-crystallization. Kinetic studies revealed that the carbene catalyst solely controls the observed diastereoselectivity.

Experimental Section

General Procedure for the Synthesis of Polysubstituted Cyclopentanones: A solution of β-oxo sulfone **2** (1 equiv.) and the aldehyde **1** (1.2 equiv.) in $CHCl_3$ (0.25 M) was cooled to –35 °C and then charged with the catalyst **4a** (20 mol-%). After the mixture had

been stirred for 24 h, the carbene precursor **5** (10 mol-%) and KOAc (30 mol-%) were consecutively added in one portion. While the reaction mixture was stirred for additional 24 h it slowly reached room temperature. The crude product was directly purified by column chromatography to afford **3** as a colourless solid.

Supporting Information (see footnote on the first page of this article): Complete experimental details and spectroscopic data for all new compounds.

Acknowledgments

This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (SeleCa – international research training group).

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[11] Compounds **3g** and **3h** showed low solubility in most organic solvents. Therefore, it was difficult to obtain reproducable *ee* values by HPLC analysis. The values in Table 2 are the lowests that were measured. Since these two compounds also form conglomerates, we assume that the variation in the *ee* values is due to partial crystallisation on the HPLC column. The average of the measured values for **3g** was 92%.

[12] For the NOE measurements of **3n**, see Supporting Information.

[13] CCDC-819238 contains the supplementary crystallographic-data for the compound **3d** reported in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] For the corresponding diagrams of **3a**, see Supporting Information.

Received: May 17, 2011
Published Online: June 15, 2011
Minor changes have been made since publication in Early View.

