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Asymmetric Organocatalytic Formal Alkynylation and Alkenylation of α,β-Unsaturated Aldehydes

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Abstract: A highly stereoselective organocatalytic one-pot protocol for the formal alkynylation and alkenylation of α,β-unsaturated aldehydes using novel chemistry based on β-keto heterocyclic sulfones is presented. The organocatalytic step is catalyzed by a prolinol derivative and allows for the formation of important optically active compounds. Further transformations of the β-keto heterocyclic sulfone moiety, based on new developments of the Smiles rearrangement through a process parallel to the Julia−Kocienski reaction, were performed leading to β-alkynylated aldehydes and 3-alkenylated alcohols. The scopes of both transformations are demonstrated by the synthesis of various optically active alkynes and alkenes. Furthermore, different transformations of the aldehyde and the alcohol functionality were performed. Finally, the proposed mechanisms for both the alkynylation and alkenylation of α,β-unsaturated aldehydes are outlined.

Introduction

The development of important and selective synthetic processes in organic chemistry is an ongoing challenge; particularly attractive are those that are both catalytic and highly stereoselective.[1] The field of organocatalysis[2] has emerged as a powerful tool in asymmetric synthesis, not only because the reactivity and selectivity of organocatalysts are competitive with more traditional metal-based catalysts, but also for practical reasons: organocatalyst are easier to handle and store, and their environmental and biological impacts are lower than their metal-based counterparts. Since its rediscovery in 2000,[3] organocatalysis has witnessed an immense increase in the number of publications and a large amount of new enantioselective protocols have emerged in this field. However, there are still chemical transformations that have not been broadly studied or developed in a stereoselective catalytic manner, of which two examples are the conjugate addition of alkynylic and alkenylic functionalities to α,β-unsaturated aldehydes.[4−7] To this day, only one example dealing with the organocatalytic alkenylation of α,β-unsaturated aldehydes has been described by Lee and MacMillan, using vinyl trifluoroborate salts as nucleophiles;[8] however, to the best of our knowledge, no stereoselective catalytic conjugate alkynylation of α,β-unsaturated aldehydes has been published until now.

The conjugate addition of alkynylic and alkenylic functionalities to α,β-unsaturated aldehydes leads to privileged classes of optically active products, which have wide applications in various fields of chemistry[9] and are precursors in the synthesis of numerous biologically active compounds[10] such as vitamin D_3[10b] and its analogues,[10c] erythromycins,[10d] prostaglandin derivatives,[10e,f] carbovir and abacavir,[10i] MMP

(1) (a) Bolm, C.; Gladysz, J. A. *Chem. Rev.* **2003**, *103*, 2761; Issue on enantioselective catalysis. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (c) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(2) See, for example: (a) Ueda, M.; Kano, T.; Maruoka, K. *Org. Biomol. Chem.* **2009**, *7*, 2005. (b) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (c) Berkessel, A., Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VHC: Weinheim, Germany, 2005. (d) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (e) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (f) *Chem. Rev.* **2007**, *107*, 5413; Issue on organocatalysis. (g) Movassaghi, M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904.

(3) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

(4) For metal-based stereoselective alkynylation of enones, see for example: (a) Nishimura, T.; Guo, X.-X.; Uchiyama, N.; Katoh, T.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 1576. (b) Kwak, Y.; Corey, E. J. *Org. Lett.* **2004**, *6*, 3385. For the addition of alkynylboronates without the presence of transition metals, see: (c) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 3244.

(5) For metal-based stereoselective alkenylation of enones, see for example: (a) Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* **2003**, *5*, 97. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (c) Lee, Y.; Akiyama, K.; Gillinghan, G. G.; Brown, M. K.; Hoveyda, A. *J. Am. Chem. Soc.* **2008**, *130*, 446. (d) Hawner, C.; Li, K.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211. For the addition of alkenylboronates, see: (e) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 4908.

(6) For metal-based stereoselective alkynylation of Meldrum's acid derivatives, see for example: (a) Knöpfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682. (b) Fujimori, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4964.

(7) For diastereoselective multistep synthesis of β-alkynylated aldehydes, see for example: (a) Hupe, E.; Calaza, M. I.; Knochel, P. *J. Organomet. Chem.* **2003**, *680*, 136. (b) Hupe, E.; Knochel, P. *Angew. Chem., Int. Ed.* **2001**, *49*, 3022. (c) Marshall, J. A.; Elliot, L. M. *J. Org. Chem.* **1996**, *61*, 4611. (d) Marshall, J. A.; Jablonowski, J. A.; Elliot, L. M. *J. Org. Chem.* **1995**, *60*, 2662.

(8) Lee, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 15438.

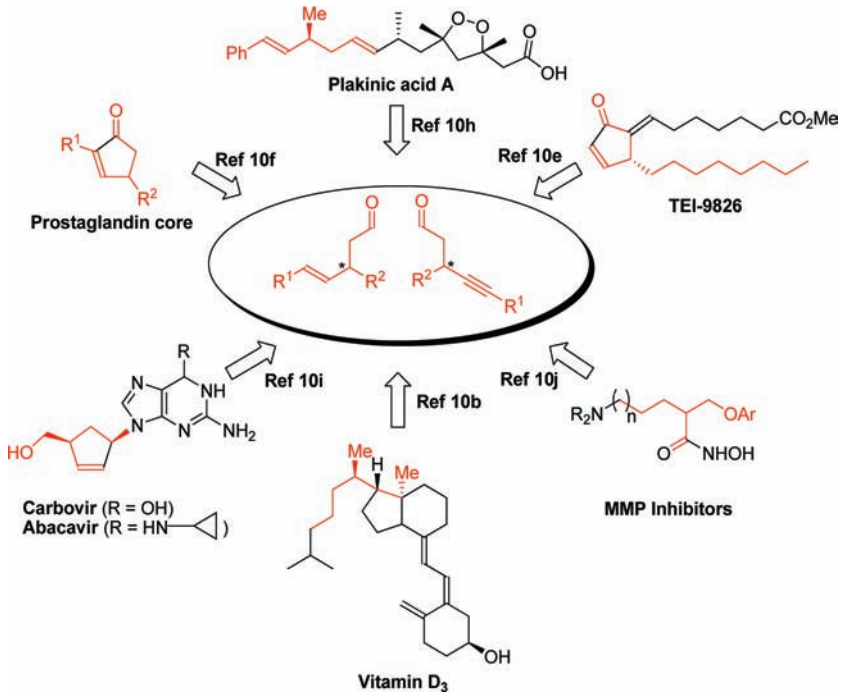
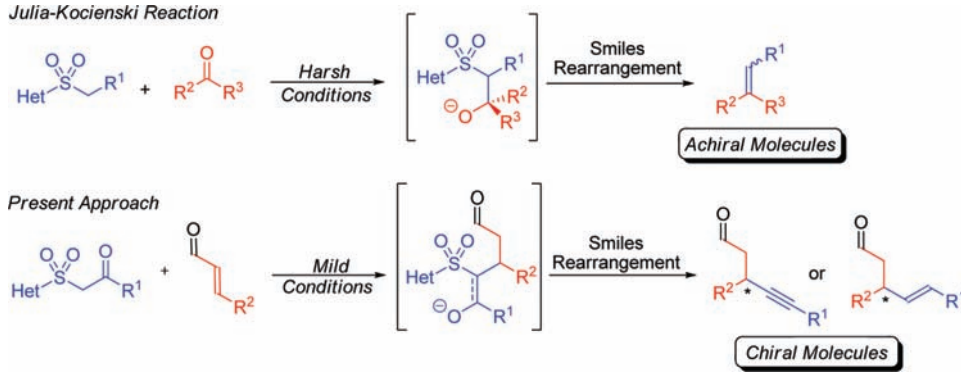


Figure 1. Examples of biologically important compounds.

Scheme 1. Mechanism of the Julia−Kocienski Olefination and the Present Approach



inhibitors,[10j] and plakinic acid A[10h] (for selected examples, see Figure 1).

The versatile utility of aryl and heterocyclic sulfones[11] for the preparation of carbon−carbon double bonds from carbonyl compounds is well-documented. One of these transformations is the Julia−Kocienski reaction,[12] where either benzothiazol-2-yl sulfones (BT-sulfones)[13a] or 1-phenyl-1*H*-tetrazol-5-yl sulfones (PT-sulfones)[13b] perform the olefination in a single and operationally simple step (Scheme 1, top). In both cases, strong bases and very polar solvents are required to form the double bond in good *E*/*Z*-selectivities. The mechanism starts with an α-deprotonation of the sulfone. Subsequent nucleophilic 1,2-addition to the carbonyl compound results in the formation of an alkoxide, which undergoes directly an irreversible rearrangement, the Smiles rearrangement,[14] through a five-membered spirocyclic intermediate. After release of the byproduct Het−OH and SO_2, the olefinic product is formed.

In the present work, we developed a new type of nucleophiles, β-keto heterocyclic sulfones, which react under mild organocatalytic conditions with α,β-unsaturated aldehydes providing the corresponding Michael intermediates with high stereoselectivity.[15] The advantage of these intermediates lies within their ability to be readily converted into important products otherwise difficult to obtain (Scheme 1, bottom); thus, in the presence of a weak base the β-keto heterocyclic sulfone moiety is transformed into a triple bond (alkynylation), while the treatment with mild reducing reagents leads to the formation of the corresponding double bond (alkenylation).

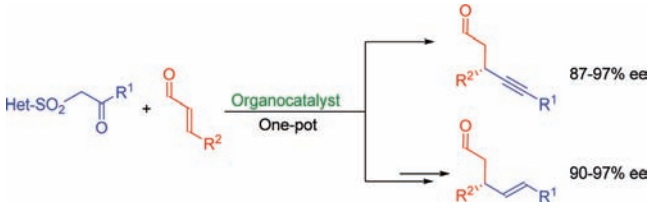
Key to these transformations is the development of new types of Smiles rearrangements and the in situ generation of the required alkoxide. While the alkenylation reaction relies on the formation of an intermediary alkoxide via a reduction step of

(9) See, for example: (a) Tanaka, K.; Hagiwara, Y.; Hirano, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2734. (b) Hartung, J. *Pure Appl. Chem.* **2005**, *77*, 1559. (c) Tanaka, K.; Hagiwara, Y.; Noguchi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7260. (d) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2003**, *125*, 30. (e) Tanaka, K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1607. (f) Csákÿ, A. G.; Contreras, C.; Mba, M.; Plumet, J. *Synlett* **2002**, 1451. (g) Hayashi, T.; Yamamoto, A.; Hagihara, T. *J. Org. Chem.* **1986**, *51*, 723. (h) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 8078. (i) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10296. (j) de Parrodi, C. A.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 4679.

the ketone functionality, the alkynylation process proceeds by a novel enolate-type Smiles rearrangement, initiated by deprotonation of the weakly acidic β-keto sulfone functionality of the key intermediate (see mechanistic details below). In contrast to the classical Julia−Kocienski reaction, where products lacking a stereocenter are formed, our method provides access to highly enantioenriched alkynylic and alkenylic functionalities. Furthermore, in contrast to the Julia−Kocienski transformation, which converts a highly valuable carbonyl group into an alkenylic compound, the present alkynylation method leaves the carbonyl untouched. In case of alkenylation, the oxidation state is simply altered into an alcohol, which can easily be reoxidized to the aldehyde using standard procedures.

Herein, we disclose the one-pot and metal-free highly stereoselective organocatalytic conjugate formal alkynylation and alkenylation of α,β-unsaturated aldehydes, as a simple process to these privileged classes of optically active compounds (Scheme 2).

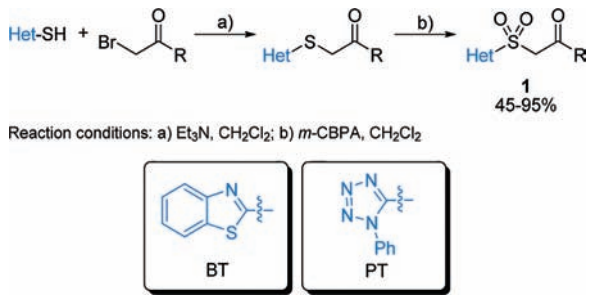
Scheme 2. Conjugate Addition of β-Keto Heterocyclic Sulfones to α,β-Unsaturated Aldehydes and Transformation into the Alkynylated or Alkenylated Products



Results and Discussion

Optimization of the Organocatalytic Conjugate Addition. The synthesis of these new nucleophilic reaction partners was achieved in a straightforward synthesis, as outlined in Scheme 3. After alkylation of the commercially available heterocyclic sulfides with different α-bromoketo compounds, the corresponding β-keto heterocyclic sulfones **1** were obtained in a range of 45−95% overall yield after oxidation with *m*-CPBA.

Scheme 3. Synthesis of the β-Keto Heterocyclic Sulfones **1**

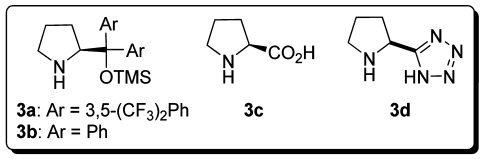


For initial screening studies, the different β-keto heterocyclic sulfones **1** were reacted with (*E*)-pent-2-enal **2a** using 10 mol % of the commercially available 2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilylanyloxymethyl]pyrrolidine **3a**[16] as catalyst and *m*-chlorobenzoic acid as additive (Table 1). We commenced with β-keto BT-sulfone **1a**, but unfortunately this substrate gave no conversion to the desired adduct (entry 1). Therefore, we turned our attention to the utilization of the β-keto PT-sulfone **1b** and were pleased to achieve full conversion after 3 h with an enantioselectivity of 83% ee in toluene as the solvent (entry 2). Changing the solvent to CH_2Cl_2 resulted in decreased enantiomeric excess (entry 3), whereas lowering the reaction concentration and temperature in toluene led to an improvement and yielded the intermediate **4** with 88 and 96% ee, respectively (entries 4−6). Other catalysts were found to be less effective for the addition reaction. The use of L-proline **3c** failed completely (entry 8), whereas catalysts **3b** and **3d** gave diminished enantioselectivity (entries 7 and 9). Ready access to both product enantiomers was possible simply by choosing the appropriate catalyst (entries 5 and 6). To state the importance of the heterocyclic moiety, we also reacted β-keto tolyl sulfone **1c** with **2a**. Full conversion was obtained in the organocatalyzed addition step; however, no product formation via the Smiles rearrangement could be observed (entry 10).

Alkynylation. With the optimized conditions in hand, we turned our attention to the envisaged transformations of the β-keto heterocyclic sulfone moiety in intermediate **4**. First attempts to form the alkynylated product under basic conditions starting from **4** resulted in unsatisfactory yields of ca. 30%, presumably due to an intramolecular reaction with the aldehyde functionality, forming an undesired and stable pyranose structure. To prevent this side reaction, the in situ protection as diethylacetal was conducted before treatment with base. To our delight, the alkyne was formed under these conditions with high conversion, and we developed a one-pot procedure for a

(10) See, for example: (a) Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239. (b) Yan, J.; Herndon, J. W. *J. Org. Chem.* **1998**, *63*, 2325. (c) Honzawa, S.; Yamamoto, Y.; Yamashita, A.; Sugiura, T.; Kurihara, M.; Arai, M. A.; Kato, S.; Kittaka, A. *Bioorg. Med. Chem.* **2008**, *16*, 3002. (d) Corey, E. J.; Trybiuski, E. J.; Melvin, L. S.; Nicolaou, K. C.; Secrist, J. A.; Lett, R.; Sheldrake, P. W.; Falck, J. R.; Brunelle, D. J.; Haslanger, M. F.; Kim, S.; Yoo, S. *J. Am. Chem. Soc.* **1978**, *100*, 4618. (e) Weaving, R.; Roulland, E.; Monneret, C.; Florent, J. *Tetrahedron Lett.* **2003**, *44*, 2579. (f) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 11492. (g) Collum, D. B.; McDonald, J. H.; Still, W. C., III. *J. Am. Chem. Soc.* **1980**, *102*, 2118. (h) Dai, P.; Trullinger, T. K.; Liu, X.; Dussault, P. H. *J. Org. Chem.* **2006**, *71*, 2283. (i) Nayek, A.; Banerjee, S.; Sinha, S.; Ghosh, S. *Tetrahedron Lett.* **2004**, *45*, 6457. (j) Chollet, A.; Diguarher, T. L.; Murray, L.; Bertrand, M.; Tucker, G. C.; Sabatini, M.; Pierré, A.; Atassi, G.; Bonnet, J.; Casara, P. *Bioorg. Med. Chem.* **2001**, *11*, 295. (k) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790. (l) Tomooka, K.; Kikuchi, M.; Igawa, K.; Suzuki, M.; Keong, P.; Nakai, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 4502. (m) Nicolaou, K. C.; Murphy, F.; Barluenga, S.; Oshima, T.; Wei, H.; Xu, J.; Gray, D. L. F.; Baudoin, O. *J. Am. Chem. Soc.* **2000**, *122*, 3830. (n) Nicolaou, K. C.; Li, Y.; Weyershausen, B.; Wei, H. *Chem. Commun.* **2000**, 307. (o) Nakatani, K.; Okamoto, A.; Matsuno, T.; Saito, I. *J. Am. Chem. Soc.* **1998**, *120*, 11219. (p) Nicolaou, K. C.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchell, H. J.; Wei, H.; Guntupalli, P.; Hepworth, D.; Sugita, K. *J. Am. Chem. Soc.* **2003**, *125*, 15433. (q) Smith, A. B.; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935. (r) Nakatani, K.; Okamoto, A.; Saito, I. *Angew. Chem., Int. Ed.* **1997**, *36*, 2794. (s) Nicolaou, K. C.; Li, Y.; Fylaktakidou, K. C.; Mitchell, H. J.; Wei, H.; Weyershausen, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3849. (t) Myers, A. G.; Glatthar, R.; Hammond, M.; Harrington, P. M.; Kuo, E. Y.; Liang, J.; Schaus, S. E.; Wu, Y.; Xiang, J. *J. Am. Chem. Soc.* **2002**, *124*, 5380. (u) Stevens, R. V.; Beaulieu, N.; Chan, W. H.; Daniewski, A. R.; Takeda, T.; Waldner, A.; Williard, P. G.; Zutter, U. *J. Am. Chem. Soc.* **1986**, *108*, 1039. (v) Mukai, C.; Kataoka, O.; Hanaoka, M. *J. Org. Chem.* **1995**, *60*, 5910. (w) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1997**, *62*, 4313. (x) Smith, A. B.; Wan, Z. *J. Org. Chem.* **2000**, *65*, 3738. (y) Chakraborty, T. K.; Thippeswamy, D.; Suresh, V. R.; Jayaprakash, S. *Chem. Lett.* **1997**, 563. (z) Drouet, K. E.; Theodorakis, E. A. *Chem.—Eur. J.* **2000**, *6*, 1987. (aa) Marshall, J. A.; Devender, E. A. V. *J. Org. Chem.* **2001**, *66*, 8037. (ab) Gopalarathnam, A.; Nelson, S. G. *Org. Lett.* **2006**, *8*, 7. (ac) Motozaki, T.; Sawamura, K.; Suzuki, A.; Yoshida, K.; Ueki, T.; Ohara, A.; Munakata, R.; Takao, K.; Tadanoi, K. *Org. Lett.* **2005**, *7*, 2261. (ad) Shao, J.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3083. (ae) Miyakoshi, N.; Mukai, C. *Org. Lett.* **2003**, *5*, 2335. (af) Shimizu, K.; Takimoto, M.; Mori, M. *Org. Lett.* **2003**, *5*, 2323. (ag) Reddy, Y. K.; Falck, J. R. *Org. Lett.* **2002**, *4*, 969. (ah) Miyakoshi, N.; Aburano, D.; Mukai, C. *J. Org. Chem.* **2005**, *70*, 6045. (ai) Organ, G. M.; Wang, J. *J. Org. Chem.* **2002**, *67*, 7847.

Table 1. Conjugate Addition of β-Keto Sulfones to (*E*)-Pent-2-enal Optimization[a]



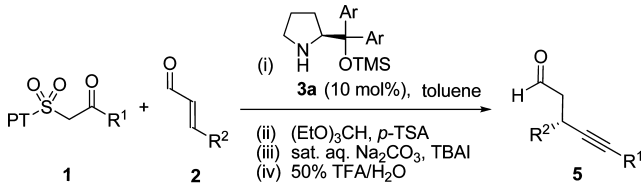
1 2a 4

entry	R[b]	catalyst	solvent [M]	temp	conversion[c]	ee (%)[d]
1	BT (**1a**)	**3a**	toluene [0.5]	rt	0	–
2	PT (**1b**)	**3a**	toluene [0.5]	rt	full	83
3	PT (**1b**)	**3a**	CH_2Cl_2 [0.5]	rt	full	80
4	PT (**1b**)	**3a**	toluene [0.1]	rt	full	88
5	PT (**1b**)	**3a**	toluene [0.1]	−30 °C	full	96
6[e]	PT (**1b**)	**3a**	toluene [0.1]	−30 °C	full	–94
7	PT (**1b**)	**3b**	toluene [0.1]	−30 °C	full	86
8	PT (**1b**)	**3c**	toluene [0.1]	−30 °C	14	nd
9	PT (**1b**)	**3d**	toluene [0.1]	−30 °C	full	63
10	tolyl (**1c**)	**3a**	toluene [0.5]	rt	full	–

[a] All reactions were performed with **1** (0.20 mmol), **2a** (0.40 mmol), **3** (0.02 mmol), and *m*-Cl-$PhCO_2H$ (0.02 mmol) for 12 h. [b] BT = benzothiazol-2-yl; PT = 1-phenyl-1*H*-tetrazol-5-yl. [c] Determined by ^1H NMR spectroscopy. [d] Determined by chiral stationary-phase HPLC of the alkenylated product **9a**. [e] The enantiomer of the catalyst **3a** was employed.

protection−alkynylation−deprotection protocol. Thus, the one-pot formation of the β-alkynylated carbonyl compound **5** took place by reacting β-keto phenyltetrazole sulfones **1** with α,β-unsaturated aldehyde **2** in the presence of catalyst **3a**, in situ protection with ethyl orthoformate, treatment with an aqueous Na_2CO_3 solution in the presence of TBAI, and subsequent deprotection with TFA. The results for the alkynylation of α,β-unsaturated aldehydes are presented in Table 2.

Table 2. Organocatalytic Enantioselective One-Pot Alkynylation of α,β-Unsaturated Aldehydes[a]



1 2 5

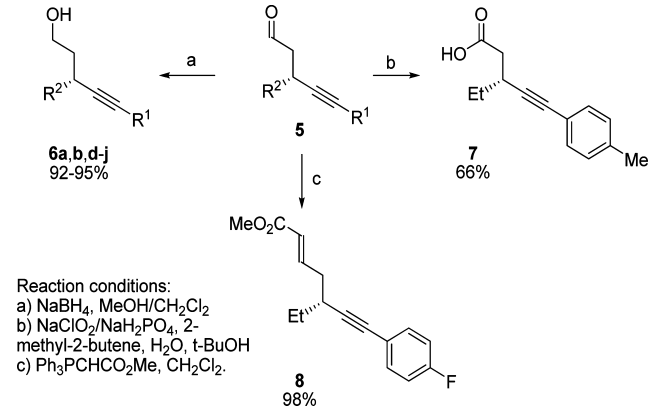
entry	R^1	R^2	yield (%)[b]	ee (%)[c]
1	Ph (**1b**)	Et (**2a**)	**5a** (81)	95
2	*p*-Me-C_6H_4 (**1d**)	Et (**2a**)	**5b** (76)	94
3	*p*-F-C_6H_4 (**1e**)	Et (**2a**)	**5c** (74)	96
4[d]	*m*-Cl-C_6H_4 (**1f**)	Et (**2a**)	**5d** (50)	93
5	2-naphthyl (**1g**)	Et (**2a**)	**5e** (62)	94
6	$Ph(CH_2)_2$ (**1h**)	Et (**2a**)	**5f** (41)	95
7	Ph (**1b**)	Me (**2b**)	**5g** (77)	87
8	Ph (**1b**)	*n*-heptyl (**2c**)	**5h** (81)	95
9	Ph (**1b**)	*cis*-hex-3-enyl (**2d**)	**5i** (72)	95
10	Ph (**1b**)	$BnOCH_2$ (**2e**)	**5j** (76)	97

[a] All reactions were performed with **1** (0.20 mmol), **2** (0.40 mmol), **3a** (0.02 mmol), and *m*-Cl-$PhCO_2H$ (0.02 mmol) in 2 mL of toluene. [b] Isolated yield. [c] Determined by chiral stationary-phase HPLC. [d] *m*-Cl-$PhCO_2H$ (0.04 mmol) was used.

As shown in Table 2, various substrates were examined; aromatic nucleophiles **1b**,**d**−**g**, with different substitution patterns, different ring sizes and both electron-rich and electron-poor character, were well-tolerated. In all cases, the corresponding alkynylated aldehydes **5a**−**e** were isolated in good yields and enantioselectivities up to 96% ee (entries 1−5). The reaction also proceeds for an aliphatic-substituted nucleophile **1h**, which resulted in the formation of alkyne **5f** with 95% ee; however, the yield obtained was slightly lower (entry 6). It was also demonstrated that linear-saturated and -unsaturated substituted α,β-unsaturated aldehydes of different lengths all furnished the desired optical active alkynylated products **5g**−**i** in good yield (72−77%) and high enantioselectivity in the range of 87−95% ee (entries 7−9). Moreover, aldehydes carrying functionalities, such as a benzyloxy moiety, also underwent the desired transformation, as shown for the formation of the alkynylic compound **5j** (entry 10).

The obtained optically active alkynylated products **5** were set up for a range of transformations, presented in Scheme 4. Both reduction and oxidation of the aldehyde unit into the corresponding alcohol and acid derivatives **6a**,**b**,**d**−**j** and **7**, respectively, could be obtained in good yield. Thus, all oxidation states of the carbonyl moiety could be accessed, which is of great interest from a synthetic point of view. Furthermore, a Wittig reaction with (methoxycarbonylmethylen)triphenylphosphoran furnished the α,β-unsaturated ester **8** in 98% yield as the *E*-isomer.

Scheme 4. Transformations of the Optically Active Alkynylated Products **5**



Alkenylation. Next, we examined the transformation of the β-keto phenyltetrazole sulfone moiety into the corresponding alkenylic products **9**. To our delight, by treatment of the reaction mixture, obtained after performing the organocatalytic addition step, with $NaBH_4$ in MeOH, the corresponding 3-alkenylated alcohols **9** were formed in good yields and high *E*/*Z*-selectivities. The results are outlined in Table 3.

Various substituted aromatic nucleophiles **1b**,**d**−**g** were employed, and in all cases the corresponding alkenylic products **9a**−**e** were obtained in good yield and excellent enantioselectivity in the range of 94−97% ee (Table 3, entries 1−5). Independent of the substitution pattern and the electronic character of the functional group attached to the aromatic ring, the double bond was formed in high selectivity in favor of the *E*-isomer (*E*/*Z* 10:1) (entries 1−4) and in the

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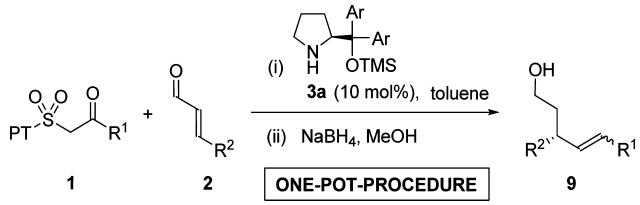
Table 3. Organocatalytic Enantioselective One-Pot Alkenylation of α,β-Unsaturated Aldehydes[a]



1 2 9

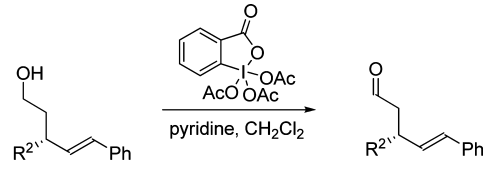
entry	R^1	R^2	yield (%)[b]	*E*/*Z*[c]	ee (%)[d]
1	Ph (**1b**)	Et (**2a**)	**9a** (79)	10:1	96
2	*p*-Me-C_6H_4 (**1d**)	Et (**2a**)	**9b** (72)	10:1	96
3	*p*-F-C_6H_4 (**1e**)	Et (**2a**)	**9c** (74)	10:1	96
4	*m*-Cl-C_6H_4 (**1f**)	Et (**2a**)	**9d** (72)	10:1	94
5	2-naphthyl (**1g**)	Et (**2a**)	**9e** (79)	20:1	97
6[e,f]	$Ph(CH_2)_2$ (**1h**)	Et (**2a**)	**9f** (52)	3:1	95
7	Ph (**1b**)	Me (**2b**)	**9g** (76)	10:1	90
8	Ph (**1b**)	*n*-heptyl (**2c**)	**9h** (71)	10:1	96
9	Ph (**1b**)	*cis*-hex-3-enyl (**2d**)	**9i** (68)	9:1	94
10	Ph (**1b**)	$BnOCH_2$ (**2e**)	**9j** (72)	9:1	95
11[g]	Ph (**1b**)	$Ph(CH_2)_2$ (**2f**)	**9k** (73)	10:1	96

[a] All reactions were performed with **1** (0.20 mmol), **2** (0.40 mmol), **3a** (0.02 mmol), and *m*-Cl-$PhCO_2H$ (0.02 mmol) in 2 mL of toluene. [b] Isolated yield. [c] Determined by ^1H NMR spectroscopy. [d] Determined by chiral stationary-phase HPLC. [e] Aldehyde **2a** (2.0 mmol) was used. [f] The reduction was performed using 0.40 mmol $LiBH_4$ in THF. [g] Yield based on ^1H NMR spectroscopy.

case of the more bulky naphthylic substituent in a ratio of 20:1 (entry 5). Again, it should be noted that aliphatic nucleophile **1h** proved to be efficient in terms of enantioselectivity (95% ee) but both yield and *E*/*Z*-selectivity were slightly diminished (entry 6). Moreover, it has been shown that this procedure is applicable to linear α,β-unsaturated aldehydes with different lengths (entries 7 and 8). Functional groups such as double bonds, benzyloxy groups, or aromatic rings were well-tolerated, and the corresponding alkenylic products **9i**−**k** were isolated in good yields (68−73%) with 94−96% ee as major *E*-configurated isomer (entries 9−11).

To demonstrate the potential of the obtained 3-alkenylated alcohols **9**, the transformation into the corresponding aldehyde derivatives via Dess−Martin oxidation was performed (Scheme 5) and both β-alkenylated aldehydes **10g** and **10j** were obtained in good yield. By chemical correlation[8] of the aldehyde **10g**, the absolute configuration was determined to be (*R*). The remaining configurations were assumed by analogy.

Scheme 5. Reoxidation of the 3-Alkenylated Alcohols **9**



R^2 = Me (**9g**)
R^2 = $BnOCH_2$ (**9j**)

10g - 67%
10j - 71%

Mechanism. The proposed mechanisms for the formation of β-alkynylated aldehydes and 3-alkenylated alcohols are outlined in Scheme 6. Both reactions are initiated by the organocatalytic conjugate addition cycle, with condensation of catalyst **3a** and α,β-unsaturated aldehyde **2** leading to the formation of the reactive iminium-ion species **11**. Addition of the β-keto phenyltetrazol sulfone **1** occurs favorably from the Re-face because of the sterical shielding of the Si-face by the chiral catalyst,[15e] resulting after hydrolysis in the formation of the key intermediate **4**. This intermediate can be transformed following two pathways. (i) Upon in situ protection of the aldehyde unit and subsequent treatment with base the enolate **12** is formed, which undergoes directly rearrangement via a five-membered spirocyclic transition state, by attack of the enolate alkoxide to the imine functionality of the tetrazole ring (Smiles rearrangement, **13**). Elimination of the byproduct SO_2 and phenyltetrazole hydroxide, followed by acidic workup for the cleavage of the protective group, gives rise to the β-alkynylated compound **5** (Scheme 6, top). (ii) Via treatment with reducing reagents the alkoxide **14** is formed, which rearranges in the same manner (**15**), yielding after release of the byproduct the alkenylated compound **9**.

Conclusions

In summary, we developed a highly stereoselective organocatalytic one-pot protocol for the formal alkynylation and alkenylation of α,β-unsaturated aldehydes using novel chemistry based on β-keto heterocyclic sulfones as donors for the alkyne and alkene functionalities. The enantioselective alkynylation reaction proceeds for a variety of α,β-unsaturated aldehydes and provides the corresponding optically active alkynes, having a broad range of aromatic and alkyl substituents in moderate to good yields and with enantioselectivities up to 97% ee. For the enantioselective alkenylation reactions the same range of α,β-unsaturated aldehydes is applied and the alkene functionality is introduced with high *E*/*Z*-ratio and enantioselectivities in the range 90−97% ee. A number of transformations are also

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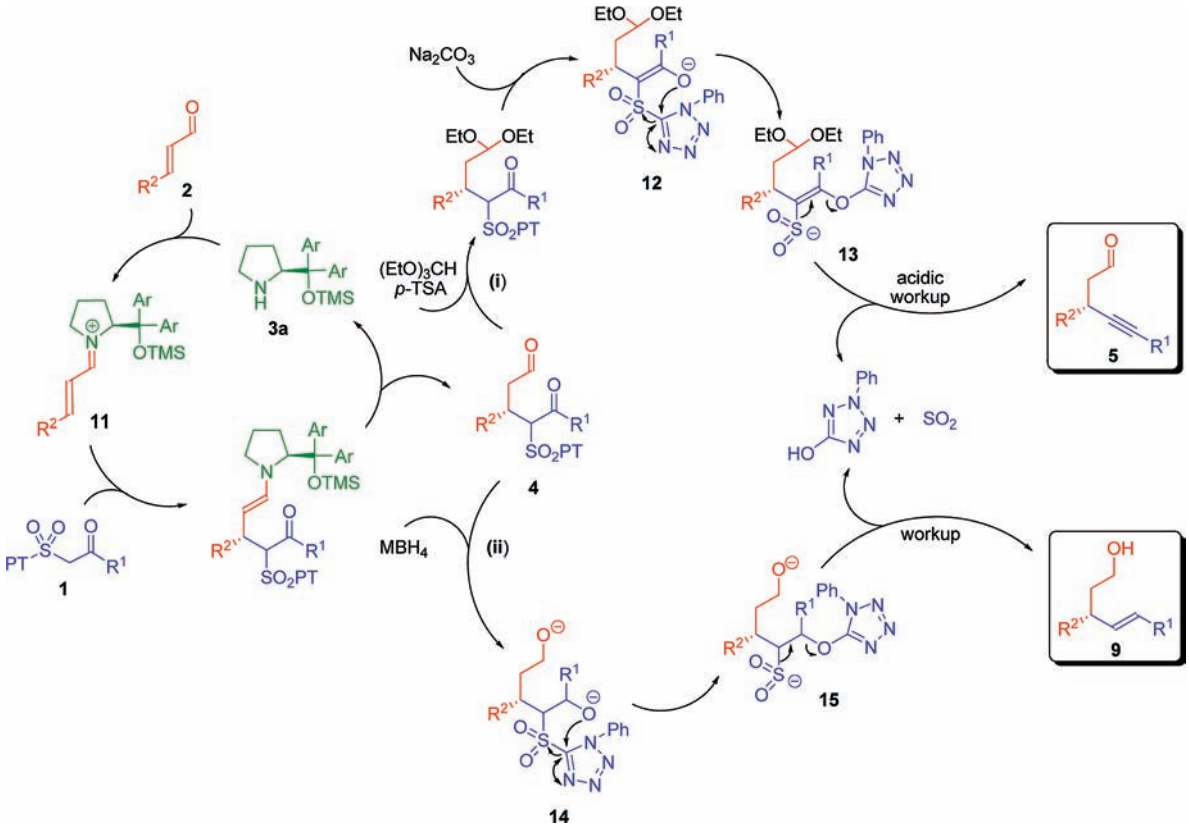
Scheme 6. Proposed Mechanisms for the Transformations of Key Intermediate **4** into Alkyne Product **5** and Alkene Product **9**



demonstrated, and mechanistic proposals for these novel reactions are outlined.

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Supporting Information Available: Complete experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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