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Enantioselective Conjugate Azidation of *α,β*-Unsaturated Ketones under Bifunctional Organocatalysis by Direct Activation of $TMSN_3$

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Abstract. An enantioselective organocatalytic conjugate azidation of α,β-unsaturated ketones is presented. A bifunctional organocatalyst activates $TMSN_3$, triggering the nucleophilic addition of the azido group to enones in absence of external promoters and avoiding the direct use or the pre-formation of highly toxic and explosive hydrazoic acid. This protocol proceeds with excellent enantiocontrol under mild conditions. DFT calculations and mechanistic trials have been performed in order to demonstrate the direct activation performed by the bifunctional organocatalyst.

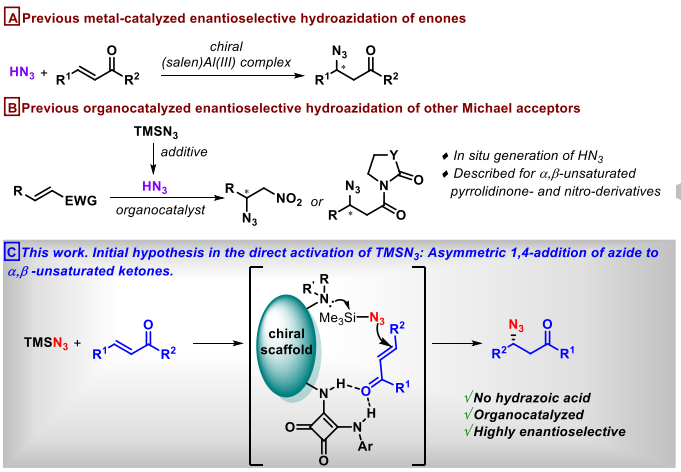
Keywords: organocatalysis • enantioselective azidation • squaramide • aza-Michael • direct activation

Introduction

The development of efficient and practical strategies for the stereoselective construction of new bonds is an ongoing objective and still holds a preferred position in organic chemistry research.[1] Organic azides have attracted the attention of organic chemists over the years as they are interesting and versatile intermediates in organic synthesis. [2] Azides provide facile and direct access to valuable functional groups (amines, amides, etc.) and heterocycles (pyrroles, pyridines, 1,2,3-triazoles and tetrazoles),[2] which stand as moieties that are difficult to install in a single operation. Moreover, the azide functionality is a prevalent structure in medicinal chemistry and chemical biology.[2]

The singularity and special reactivity of the azide moiety has led to a variety of synthetic methods centered on its installation.[3] Considering their asymmetric synthesis, enantioselective nucleophilic azidations[3b] (mainly ring opening of *meso* aziridines[4] and epoxides[5]) are among the preferred strategies for their incorporation. Although less explored, electron-deficient alkenes have also been described as platforms for the nucleophilic asymmetric *β*-azidation.[3b,6]

In this regard, the azido-Michael reaction to *α,β*-unsaturated carbonyl compounds remains a key transformation in the synthetic chemist's toolbox, as it represents a powerful tool for the rapid installation of molecular complexity.[7] Although asymmetric aza-Michael reactions have been widely explored,[8] the corresponding conjugate azidation still stands as an outstanding challenge in asymmetric catalysis.[3b] Thus, Jacobsen and coworkers reported the asymmetric hydroazidation of *α,β*-unsaturated *N*-enoylbenzamides[9] and ketones[10] catalyzed by a salen-Aluminum complex using hydrazoic acid; a toxic and explosive reagent which is not easy to handle (eq. A, Scheme 1). In pursuit of this challenging objective, other research groups have focused their attention on the



Scheme 1. Scheme 1. Previous works (equations A and B) and present work (equation C).

development of the asymmetric hydroazidation of Michael acceptors while trying to elude the use of metal-based catalysts and avoid the direct use of hydrazoic acid as nucleophilic azide source (eq. B, Scheme 1). In this context, different organocatalytic systems have been described to promote the enantioselective conjugate addition of the azide group to *α,β*-unsaturated *N*-enoylbenzamides[11] and nitroalkenes.[12] These methodologies are predicated on the *in situ* generation of hydrazoic acid from $TMSN_3$ in the presence of a carboxylic acid as additive.[13] These processes can be dramatically affected by the steric and the electronic nature of the acid.

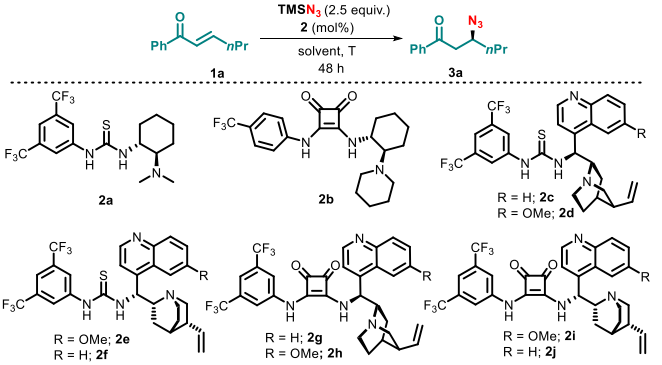
In spite of these particular achievements, we believe there is still great room for improvement in the challenging *β*-azidation of *α,β*-unsaturated carbonyl compounds. Considering our experience in the field,[14] we envisioned that a neutral coordinate organocatalyst would be able to directly activate the organosilyl nucleophile ($TMSN_3$). This would trigger the enantioselective conjugate addition of the azide group to the *α,β*-unsaturated ketone.[15]

Herein, we describe an enantioselective conjugate azidation of *α,β*-unsaturated ketones. The asymmetric process is promoted by a bifunctional organocatalyst which is able to synergistically activate both the enone and the $TMSN_3$ in absence of the carboxylic acid additive (eq. C, Scheme 1), avoiding the pre-formation of the highly toxic and explosive hydrazoic acid.

Results and Discussion

Based on our experience in bifunctional catalysis, [14] we began our investigations by studying the reaction of *α,β*-unsaturated ketone **1a** as model substrate with trimethyl silyl azide in the presence of different bifunctional organocatalysts based on thiourea and squaramide cores (Table 1) and tertiary amines, which may act as Lewis base sites. At first, all catalysts were examined in toluene at room temperature (entries 1-10). All of them showed the ability to promote the reaction featuring good levels of reactivity. Squaramide **2g** showed the best result, leading to the desired conjugate adduct (**3a**) with the highest enantiomeric excess (47% *ee*). Different solvents were then studied, using **2g** as optimal catalyst (entries 11-12 and see Supporting Information). Only hexafluorobenzene (HFB) and hexane displayed increased performance, enhancing the selectivity up to 53% and 50% *ee*, respectively. These results were improved at lower temperatures (4 ºC), and already reasonably high enantioselectivities were observed (entries 13 and 14), although the reactivity was diminished and longer reaction times were required. To our delight, a mixture of hexane and hexafluorobenzene (1:1) significantly improved the enantioselectivity to 93% *ee* when the initial amount of water was controlled and set at 0.5 equiv.[16] However, the low reactivity observed under such reaction conditions led to the desired product in low yields (entry 15). By changing the stoichiometry of the reaction and increasing the catalyst loading (20 mol%), the *β*-keto azide (**3a**) was isolated in 66% yield and 94% *ee* (entry 16).

Table 1. Optimization of the conjugate azidation of enones.[a)]



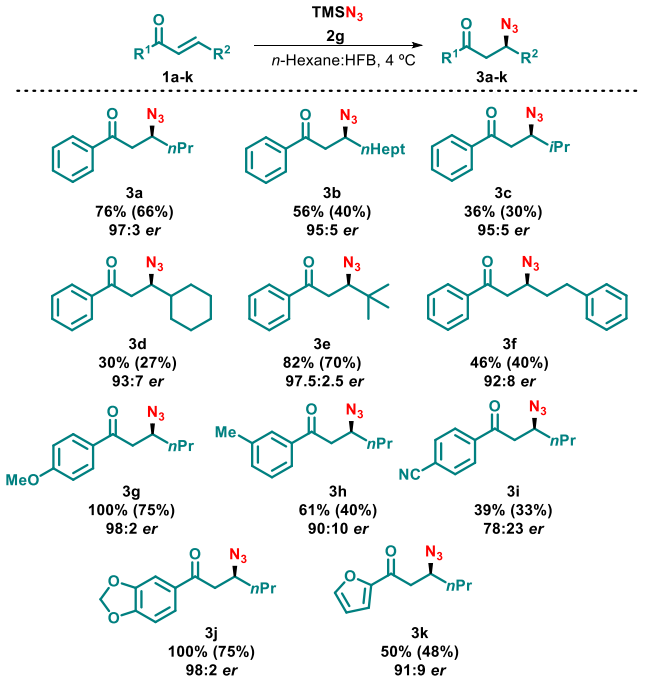
	Cat.	Solvent	T (ºC)	Conv.[b)]	*ee* [c)]
1	**2a**	Toluene	rt	66	5
2	**2b**	Toluene	rt	50	9
3	**2c**	Toluene	rt	90	40
4	**2d**	Toluene	rt	90	20
5	**2e**	Toluene	rt	87	27
6	**2f**	Toluene	rt	80	14
7	**2g**	Toluene	rt	94	47
8	**2h**	Toluene	rt	87	21
9	**2i**	Toluene	rt	93	12
10	**2j**	Toluene	rt	95	11
11	**2g**	HFB	rt	100	53
12	**2g**	*n*Hexane	rt	100	50
13	**2g**	HFB	4	74	70
14	**2g**	*n*Hexane	4	67	75
15[d)]	**2g**	*n*Hexane:HFB	4	54 (32)[e)]	93
16[f)]	**2g**	*n*Hexane:HFB	4	100(76)[e)] (66)[g)]	94

[a)] All the reactions were performed on a 0.1 mmol scale in the presence of **2** (10 mol%) in 0.6 mL of solvent with a determined residual amount of water (250 ppm, determined by Karl-Fisher titration). [b)] The conversion was determined by ^{1}H-NMR. [c)] The enantiomeric excess (*ee*) was measured by SFC. [d)] The reaction was performed in a mixture of *n*-hexane:HFB (1:1, 0.17 M) (0.5 equiv. H_2O) for 72 h. [e)] NMR yield in brackets using trimethoxybenzene as internal standard. [f)] The reaction was performed in the presence of 20 mol% of **2g**, 1.2 equiv. of **1a** and at 0.04 M concentration (0.5 equiv. H_2O) for 72 h. [g)] Isolated yield.

Once the reaction conditions had been optimized (entry 16, Table 1), we studied the scope of the reaction considering differently substituted *α,β*-unsaturated ketones (Table 2). The conjugate azidation embraced a variety of aromatic *α,β*-unsaturated ketones bearing alkyl substituents. The reaction proceeded smoothly employing enones substituted with a linear aliphatic chain, achieving excellent enantiocontrol with **3a**, **3b** and **3f**. Bulkier carbon chain substituents such as *iso*-propyl (**3c**), cyclohexyl (**3d**) and *tert*-butyl (**3e**) were

very well tolerated, reaching the desired adducts with excellent enantioselectivities. The stereoelectronic nature of the aromatic ring was also studied. Differently substituted electron-rich aromatic rings in *para* and *meta* positions led to the desired *β*-keto azide with very good results in both yield and enantioselectivity (**3g**, **3h** and **3j**). Electron-deficient systems were not tolerated (**3i**) and low levels of enantioinduction were observed. Gratifyingly, the protocol enabled access to the corresponding *β*-azido substituted adduct in the presence of heterocyclic enones with high enantioselectivities (**3k**). Aromatic *α,β*-unsaturated ketone bearing an aryl substituent was not suitable for this transformation.

Table 2. Scope of the reaction for the enantioselective conjugate azidation of enones.

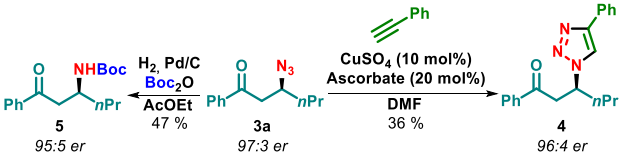


[a] Reaction conditions: To a solution of the catalyst **2g** (20 mol%) in *n*-hexane (1.2 mL), the corresponding enone **1** (1.2 equiv.) was added. The reaction was cooled to 4 °C. Then, the azidotrimethylsilane (0.075 mmol, 1 equiv.) and hexafluorobenzene (1.2 mL) were sequentially added. H_2O content was 0.0035 mmol (0.5 equiv.). The reaction was stirred for 48 hours at 4 °C. Isolated yields are in brackets.

The absolute configuration of product **3a** was assigned by correlation and was determined as *S* (see Supporting Information). The same stereochemical outcome was assumed for the rest of compounds **3**.

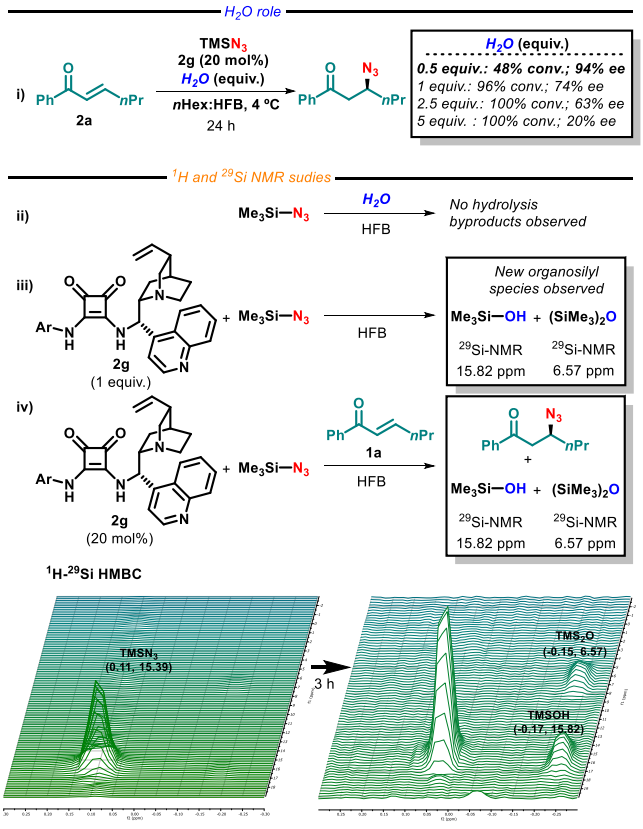
As stated before, azides are powerful and versatile building blocks in organic chemistry due to their inherent and special reactivity.[2] Notably, Pd/C mediated selective hydrogenation of the azido group efficiently led to the *β*-amino ketone derivative **5** with no significant loss of stereochemical information (Scheme 2).[9] Moreover, the enantioenriched *β*-azido derivative **3a** was transformed to triazole derivative **4**.

To our delight, no erosion in the enantiomeric purity was observed, despite of reports on the racemization of enantioenriched azides in the presence of multiple Lewis acids. [17] It should be noted that N1–functionalized triazole derivatives are difficult to access by direct addition of 1,2,3-triazole in a conjugated fashion, as they tend to react through the central nitrogen atom (N2) of the heterocycle.[18]



Scheme 2. Derivatization of β-azido ketone **3a**.

In order to gain insight into the reaction mechanism, we performed a series of experiments, including NMR studies (^{1}H and ^{29}Si NMR) (Scheme 3, see Supporting Information for full details). The role of water in the reaction was studied through analysis of the side-products generated in the reaction, which unequivocally result from the reaction of enone **1a**, $TMSN_3$ and water.



Scheme 3. Mechanistic investigation. Reactions carried out in presence of different amounts of H_2O (i). NMR studies showing silicon species detected (ii, iii and iv).

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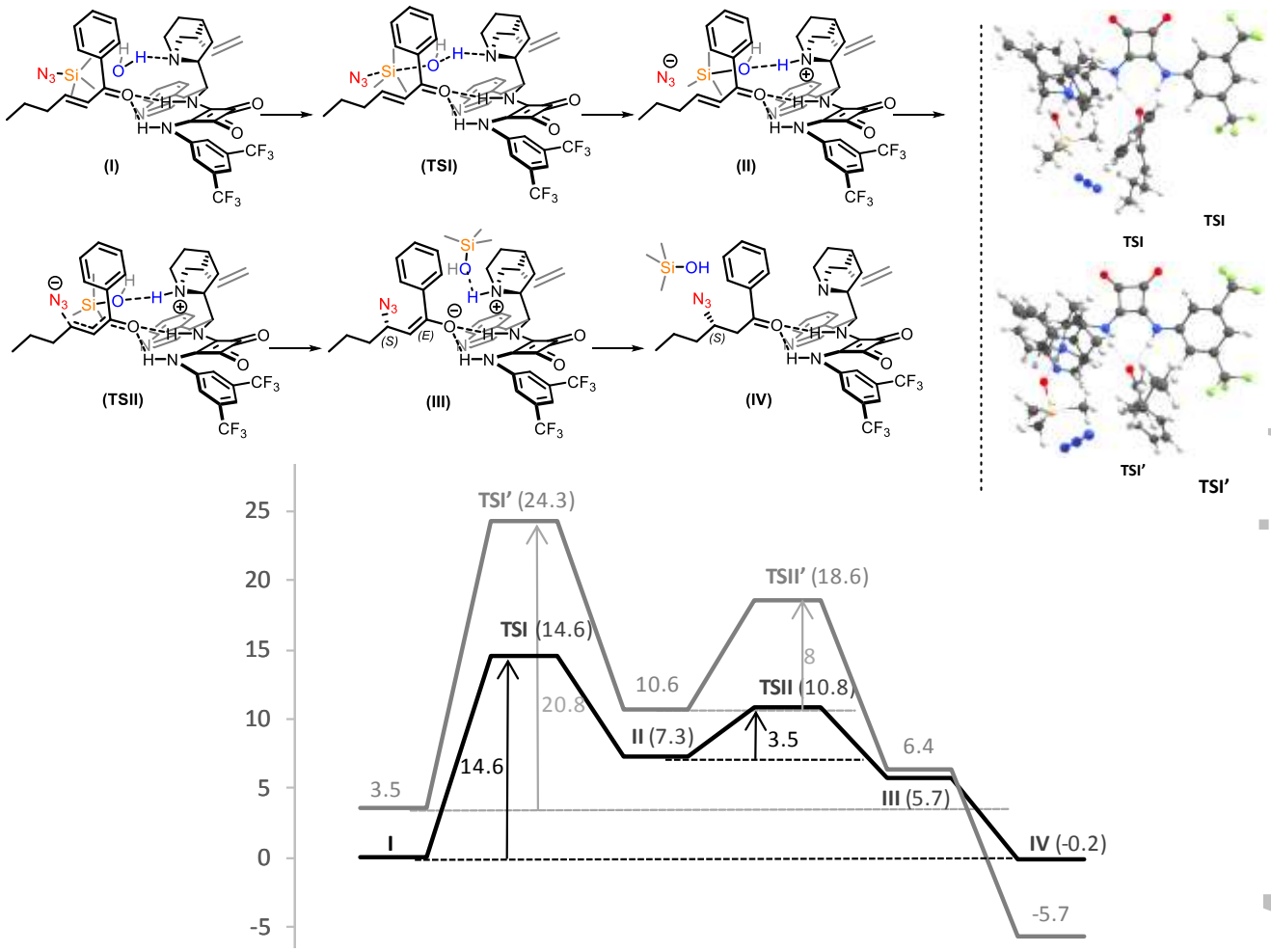

Figure 1. DFT M062x/6-3111G** reaction energy (ΔG in Kcal/mol) profile in the addition of $TMSN_3$ to **1a**.

Thus, after a catalytic run, even if water is not explicitly added to the system, two new silylated species were observed in the reaction mixture by means of 2D-HMBC{^{1}H,^{29}Si} (Scheme 3, eq. iii), that showed signals clearly identified as trimethyl silanol (^{29}Si-NMR shift 15.82 ppm) and its corresponding siloxane (^{29}Si-NMR shift 6.57 ppm) (Scheme 3, eq. iii.). Therefore, water – even at low concentrations – seems to play a crucial role in the reaction. To further support such feature, subsequent experiments in the presence of an excess of water resulted in an increase of the reaction kinetics and, as a result, a decrease in the enantioselectivity (Scheme 3, eq. i). This observation suggests that the activation of reagent **1a** proceeds *via* hydrolysis. A positive KIE value (see Supporting Information) when monitoring the reaction in presence of H_2O or D_2O confirms that water is involved in the rate determining step. Previous observations described in the literature[19] suggest the spontaneous reaction of $TMSN_3$ with water, generating HN_3 in solution. In contrast, under our reaction conditions, water itself is not capable of activating $TMSN_3$ in the absence of the catalyst (Scheme 3, eq. ii), which is in accordance with the high enantiocontrol achieved in the organocatalyzed conjugate azidation of enones.

Taking all the experimental evidence presented above as starting point, we carried out a series of DFT calculations at the M06-2X/6311G** level[20] in order to define a plausible mechanism (Figure 1). First, with the aim of determining the most feasible initial species, we calculated an initial complex that includes a water molecule, $TMSN_3$, enone **1a** and the catalyst. Enone **1a** interacts with the squaramide moiety through two practically equal H···O=C hydrogen bonds (O···H = 1.88-1.99 Å), while the water molecule does it with the tertiary nitrogen atom of the quinuclidine moiety of the cinchona fragment (N···H = 1.90-1.94 Å). Thus, $TMSN_3$ is allocated between the water and the enone molecules, favouring the overall reaction. In the initial structure, a hydrogen bond interaction is found between the water molecule and the amine group (N···H = 1.90-1.94 Å). Further evolution of this system implies at first, a proton transfer from the water molecule to the nitrogen atom of the quinuclidine moiety followed by a nucleophilic attack of the resulting hydroxide to the silicon atom that results in the N-Si bond cleavage (**II**). Exhaustive exploration of the potential energy surface indicates that these

processes take place in an asynchronous concerted manner, and only a transition state (**TSI**) has been found that connects species **I** to species **II**. **TSI**, which is depicted in Figure 1, could be described as a pentacoordinated $N_3\cdots Si(OH)(CH_3)_3$ silicon species, found in the pro-*R* and pro-*S* dispositions. This transition state results from the cleavage of an O-H bond of the water molecule, which is compensated by the formation of a N-H bond (N···H = 1.07-1.06 Å) and Si-O bond (Si-O = 1.78-1.77 Å), and is concomitant to the elongation of Si-N bond to 2.45-2.47 Å. On this overall process, any minimum can be observed, and therefore it can be described as an uphill path up to **TSI** that costs 16.0 kcal/mol (pro-*R*) and 14.6 kcal/mol (pro-*S*). This is the greatest kinetic barrier found in the reaction profile, indicating that the proton transfer is involved in the rate determining step (in good agreement with experimental kinetic data). Further evolution of **TSI** leads to the rupture of the Si−N bond to produce the silanol byproduct and generating the nucleophile (N_3^-). The latter species is enclosed within the chiral pocket of the pre-organized system, reacting then with the enone **1a**. Thus, such pre-organization of the two fragments directs the geometry of the system to specifically generate the new C−N bond: this nucleophilic attack proceeds though a low kinetic barrier (3.5-8.0 kcal/mol) to generate the slightly endothermic enolate intermediate **III**. Final proton transfer leads to the thermodynamically stable ketone **IV** (-0.2 and -5.1 kcal/mol).

Conclusion

In conclusion, we have described a highly enantioselective organocatalyzed 1,4 addition of an azido group to *α,β*-unsaturated ketones. This system avoids the use or pre-formation of dangerous and highly explosive hydrazoic acid; $TMSN_3$ is used as nucleophile in the absence of carboxylic acid as additive. In addition, the mechanistic investigations and DFT calculations carried out show how the organocatalyst is able to activate the organosilyl species directly through a molecule of water, allowing the asymmetric synthesis of challenging and versatile *β*-azido ketones.

Experimental Section

General procedure for the Azidation of *α,β* Unsaturated Ketones

To a solution of the catalyst **2g** (9 mg, 0.015 mmol, 0.15 equiv.) in hexane (1.2 mL), the corresponding enone (0.1 mmol, 1 equiv.) was added. The reaction was cooled to 4 °C. Then, the azidotrimethylsilane (0.075 mmol, 10.5 µL, 0.75 equiv.) and hexafluorobenzene (1.2 mL) were sequentially added. H_2O content was 0.0035 mmol (0.5 equiv.). The reaction was stirred for 48 hours at 4 °C. Then, the solvents were evaporated under reduced pressure (high vacuum line) and the crude was purified on a Biotage Isolera Prime using SNAP Cartridge KP-SIL 10g charged with Geduran® Si 60 or IATROBEADs® 6RS-8060 (see each case).

(*S*)-3-Azido-1-phenylhexan-1-one (3a). Following the general procedure, enone **1a** (17 µL, 0.1 mmol) and $TMSN_3$ (10.5 µL, 0.075 mmol) gave the product **3a** as a colorless oil (14.3 mg, 66% yield). Purification was performed on a Biotage Isolera Prime using SNAP Cartridge KP-SIL 10g charged with Geduran® Si 60. Eluent: hexane: dichloromethane; 12%, 3 CV; 12% - 19%; 6 CV; 19%, 5 CV; 19% - 27%, 2.7 CV; 24%, 4.2 CV. TLC in hexane: dichloromethane; 1:1; $R_{f\ product}$= 0.34 and $R_{f\ enone}$ = 0.31. $[\alpha]^{20}_D$= -43 (*c* 0.02, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 – 7.93 (m, 2H), 7.63 – 7.55 (m, 1H), 7.48 (ddt, *J* = 8.3, 6.6, 1.2 Hz, 2H), 4.18 – 4.01 (m, 1H), 3.25 (dd, *J* = 17.2, 8.0 Hz, 1H), 3.04 (dd, *J* = 17.2, 4.8 Hz, 1H), 1.68 – 1.50 (m, 2H), 0.98 (t, *J* = 7.1 Hz, 3H). ^{13}C-NMR (76 MHz, $CDCl_3$) δ 197.5, 136.9, 133.6, 128.9, 128.3, 58.6, 43.5, 37.0, 19.5, 13.9. HRMS (ESI): calculated for $C_{12}H_{16}N_3O^+$ $[M+H]^+$: 218.1288; found 218.1290. The enantiomeric ratio was determined by SFC using a Chiralpak IC column [CO_2/MeOH 98:2 in 10 min, flow rate 3.0 mL/min], τ_{major} = 5.38 min, τ_{minor} = 5.04 min (e.r. = 97:3).

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FULL PAPER

Enantioselective Conjugate Azidation of α,β-Unsaturated Ketones under Bifunctional Organocatalysis by Direct Activation of $TMSN_3$

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