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Organic Synthesis

α,β-Unsaturated Acyl Cyanides as New Bis-Electrophiles for Enantioselective Organocatalyzed Formal [3+3]Spiroannulation

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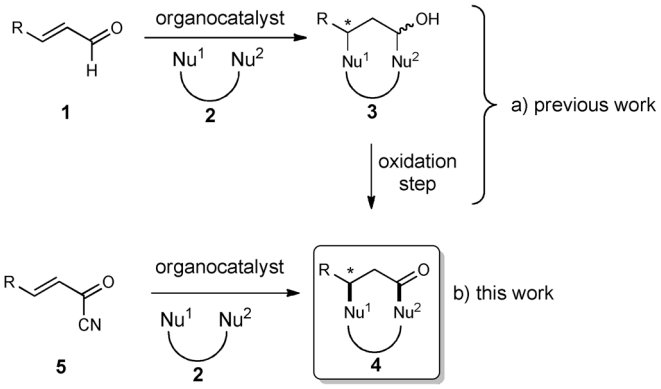
Abstract: α,β-Unsaturated acyl cyanides are key bis-electrophile substrates for successful domino enantioselective organocatalyzed Michael-intramolecular acylation domino sequences. This new reactivity has been applied to the synthesis of enantioenriched azaspiro[4,5]decanone ring systems by a formal [3+3]spiroannulation, constituting a rare example of synthesis of glutarimides in an optically active form.

Enantioselective organocatalysis is a fast-growing area of research in organic chemistry and many elegant synthetic pathways have been developed in their organocatalyzed versions.[1] Among them, enantioselective Michael addition-initiated multiple bond-forming transformations[2] leading to complex structures from simple substrates have received a special enthusiasm becoming a central element in modern organic synthetic chemistry.[3] One of the main requirements is the availability of substrates exhibiting at least two complementary reactive centers in combination with a sharp control of the selectivity of each individual bond-forming event. In this respect, simple enals **1** have been exploited as 1,3-bis-electrophiles with selected 1,3-bis-nucleophiles **2** in Michael acylation organocatalyzed enantioselective formal [3+3]cyclization sequences upon oxidation of the transient cyclic hemiacetals[4] or hemiaminals **3**[5] (Scheme 1a) to afford scaffolds **4**. In sharp contrast, use of the corresponding less reactive unsaturated carboxylic acid derivatives avoiding the oxidation step remains a challenging task and the quest for new unsaturated ester surrogates that could be activated in an organocatalytic transformation is still an active field of research with high synthetic potential.[6]

In this respect, we surmised that acyl cyanides **5** that are unfamiliar Michael acceptors,[7] should also constitute a good acylating agent resulting in a formal [3+3]cyclization process when reacted with a judiciously selected 1,3-dinucleophile (Scheme 1b).



Scheme 1. Organocatalytic strategies for formal [3+3]cyclizations.

Herein, we report our preliminary investigations on the design of a new spirocyclization leading to functionalized azaspiro[4,5]decanones of high synthetic value (Scheme 2). This spirocyclic substructure is found in several natural products, such as meloscandonine[8] and lycoflexine[9] alkaloids, and could therefore be of particular interest in synthetic approaches to these families of natural products. It may also be noted that the corresponding product contains an original spiroimide function,[10] that may confer high synthetic potentialities. To the best of our knowledge, there is no report of direct enantioselective synthesis of glutarimide derivatives,[11] which is an important structural motif found in many natural products.[12] Moreover, the domino sequence involves the dual reactivity of acyl cyanides as new C/C bis-electrophiles allowing a one-pot enantioselective organocatalytic Michael addition-intramolecular acylation with simple β-ketoamides as C/N bis-nucleophiles. The overall cascade forms one C–C and one C–N bond,[13] and produces ring systems bearing two adjacent stereogenic centers including a tetrasubstituted one.[14]

Based on our experience in enantioselective domino transformations,[15] we started our investigations using β-ketoamide **6a** as the bis-nucleophilic partner, which was reacted with cinnamoyl cyanide (**5a**) under hydrogen-bonding catalysis (Table 1).[16] Hence, when the reaction was conducted in toluene at 0 °C with Takemoto's thiourea catalyst **I**,[17,18] we were pleased to find that the domino-Michael-intramolecular nucleophilic substitution was efficient and the spiroimide **7a** was produced in 90% yield albeit in low stereoselectivity (Table 1, entry 1). We have identified the crucial role of the amide

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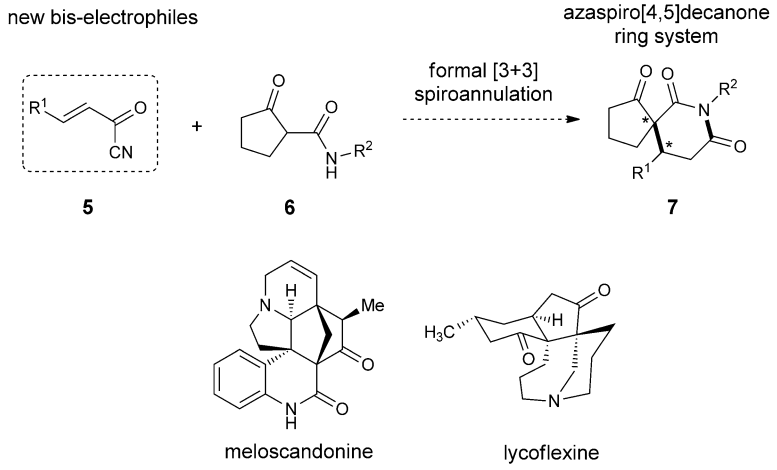
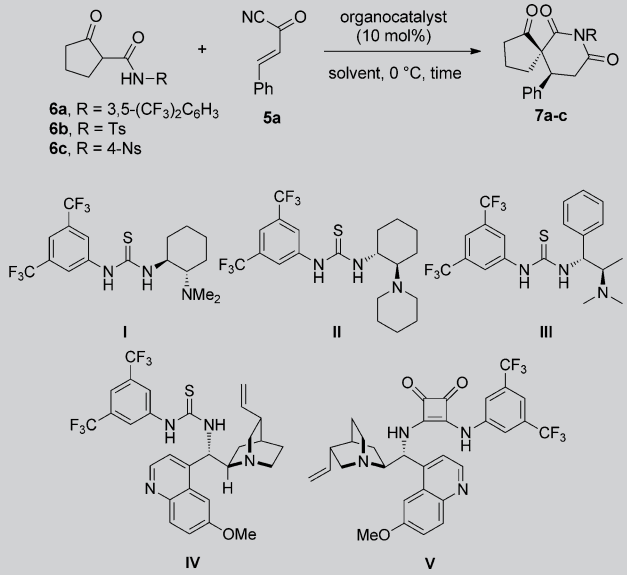
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201303613. It contains experimental procedures, complete characterization for all new compounds, VCD analysis, X-ray diffraction analysis, chiral HPLC analysis, and ^{1}H and ^{13}C NMR spectra.



Scheme 2. New approach to the azaspiro[4,5]decanone ring system.

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

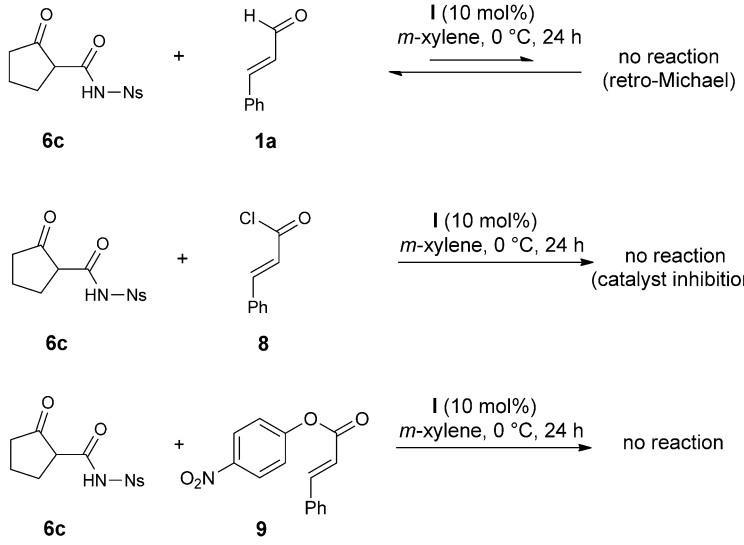


Entry	Cat.	Solvent	T [°C]	6	Product	Yield [%][b]	d.r.[c]	e.r. [%][d,e]
1	**I**	toluene	0	**6a**	**7a**	90	67:33	75:25
2	**I**	toluene	0	**6b**	**7b**	83	83:17	90:10
3	**I**	toluene	0	**6c**	**7c**	87	75:25	96:4
4	**II**	toluene	0	**6c**	**7c**	<10	n.d.	n.d.
5	**III**	toluene	0	**6c**	**7c**	35	80:20	9:91
6	**IV**	toluene	0	**6c**	**7c**	61	75:25	96:4
7	**V**	toluene	0	**6c**	**7c**	41	83:17	33:67
8	**I**	toluene	−10	**6c**	**7c**	73	87:13	92:8
9	**I**	EtOAc	0	**6c**	**7c**	89	88:22	87:13
10	**I**	CH_3CN	0	**6c**	**7c**	61	89:12	79:21
11	**I**	CH_2Cl_2	0	**6c**	**7c**	83	80:20	87:13
12	**I**	Et_2O	0	**6c**	**7c**	87	80:20	92:8
13	**I**	*m*-xylene	0	**6c**	**7c**	92	87:13	98:2

[a] Reaction conditions: ketoamide **6** (1.0 equiv) and catalyst (**I**–**V**; 10 mol%) were dissolved in the solvent and stirred at 0 °C for 15 min. Then, the α,β-unsaturated acyl cyanide **5a** (2.0 equiv) was added and the mixture was stirred for 40 h at 0 °C. [b] Yield of isolated major diastereomer after flash chromatography. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction product. [d] Determined by HPLC analysis on chiral stationary phase. [e] Values are for the major diastereomer.

proton of ketoamides in earlier studies on enantioselective Michael additions, and we clearly observed that increasing its acidity resulted in increased enantioselectivities.[5a] Consequently, more electron-withdrawing substituents on the nitrogen atom of ketoamides **6** were screened (entries 2–4). As expected, lowering the pK_a of the amide proton had a beneficial impact on stereoselectivities and this was particularly the case for enantioselectivities (entries 2 and 3). When ketoamide **6c** (R = 4-nosyl) was employed we observed the formation of **7c** in good yield (83%) and with an excellent enantiomeric ratio of 96:4 for its major diastereomer (in this case diastereomeric ratio (d.r.) = 3:1). Other organocatalysts were investigated and catalyst **II** bearing a piperidine ring instead of the dimetylamine moiety of **I** was not efficient and the product **7c** was obtained in less than 10% yield (entry 4). Catalyst **III** allowed the formation of the desired product **7c** with equivalent stereoselectivity albeit a lower yield was obtained (35%, entry 5). Chiral cinchona alkaloid-derived thiourea catalysts **IV**[19] and **V**[20] were used in the present transformation but were not as efficient as the Takemoto catalyst **I** especially in term of yields (entries 6 and 7). The temperature was then lowered to −10 °C (entry 8) and we observed similar stereoselectivity and a slight decrease in the yield that could be due to lower solubility of the starting materials. The use of more polar solvents such as ethyl acetate, acetonitrile, or dichloromethane resulted in lower enantioselectivities (entries 9–11) with similar yields. When the reaction was conducted in diethyl ether (entry 12) the yield as well as the stereoselectivity were comparable to the ones obtained in toluene (entry 3). When the reaction was conducted in *m*-xylene a slight increase in the diastereoselectivity was observed (6:1, entry 13) and these last reaction conditions were chosen for subsequent substrate scope evaluations.

To demonstrate the specificity of acyl cyanides, the reaction was conducted by using other potential bis-electrophiles. Hence, replacing **5a** by cinnamaldehyde (**1a**), under identical reaction conditions (Scheme 3), proved unproductive, possibly due to retro-Michael addition. Therefore, the use of acyl cyanides **5** answers to a limitation in permitting the introduction of a substituent alpha to the quaternary carbon in the final spirocyclic structure **7**, which was not possible using the corresponding enals.[5a] Similarly, the corresponding cinnamoyl chloride **8** did not react under these reaction conditions possibly due to catalyst inhibition.[21] In addition, the reaction was also conducted using 4-nitrophenyl cinnamate (**9**),[22] which could in theory behave as an efficient bis-electropile for this transformation but here also, no reaction occurred. These experiments show the specificity of unsaturated acyl cyanides for this trans-



Scheme 3. Control experiments with other potential bis-electrophiles.

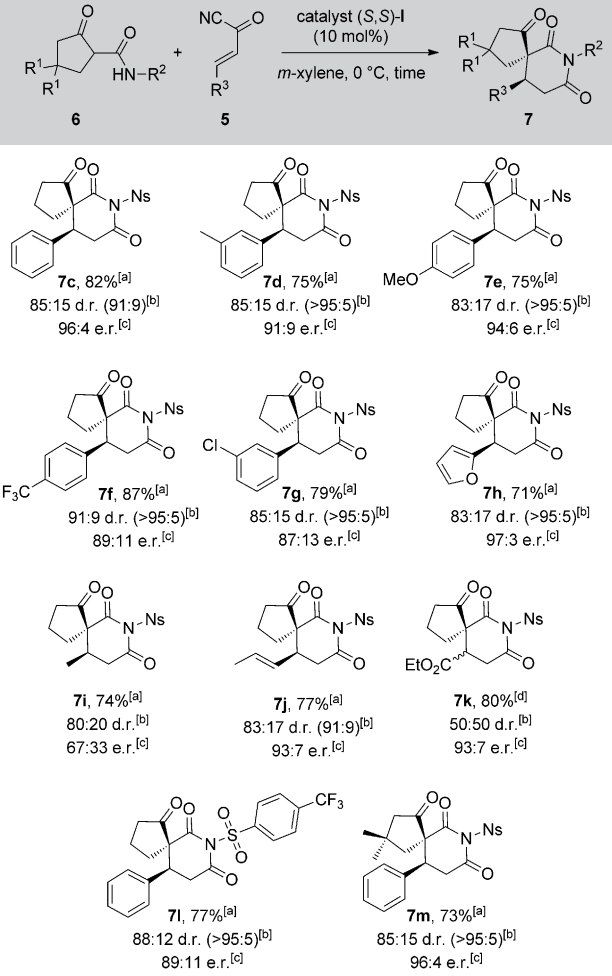
formation and for an efficient access to the azaspiro-[4,5]decanone ring system.

We next focused on testing our methodology by varying the nature of the α,β-unsaturated acyl cyanide **5** using optimized reaction conditions (Table 2). Both electron-enriched as well as electron-impoverished aryl-substituted acyl cyanides **5** are suitable substrates for this transformation (**7c**–**g**) even if slightly better enantioselectivities were noticed when an electron-donating group was present on the phenyl ring (**7d** and **7e**, 91:9 and 94:6 enantiomeric ratio (e.r.), respectively). The use of furane-substituted acyl cyanide **5f** (R^3 = 2-furyl) allowed the formation of the desired spirocyclic product **7h** in good yield and very good stereoselectivity. The reaction was also possible with alkyl-substituted acyl cyanide **5g** (R^3 = Me) with good yield (74%) though stereoselectivity was moderate in product **7i** (80:20 d.r., 67:33 e.r.). The introduction of an alkenyl moiety in the final structure **7j** was successfully achieved using α,β-unsaturated acyl cyanides **5h** (R = CH=CHCH$_3$) and the reaction outcome was comparable to the use of aryl-substituted acyl cyanides. Interestingly, an ester moiety could also be introduced increasing the molecular complexity and functional-group density and diversity in the final spirocyclic structure **7k**. Even if no diastereoselectivity was observed, the enantioselectivity and the yield were very good (80% yield, 50:50 d.r., 93:7 e.r.). Unfortunately, the use of acryloyl cyanide (**5i**, R^3 = H) was not successful, and the starting ketoamide **6c** was recovered. This highlights the complementarity of the present methodology with our previous results in which the synthesis of **7n** (R^1 = H, R^2 = Ts, R^3 = H) is possible by a two-step procedure.[5a] Finally, concerning the starting β-ketoamide **6**, the use of another activating group on the amide (**6d**, R^1 = H, R^2 = SO$_2$-C$_6$H$_4$-CF$_3$) as well as substitution of the cyclopentanone ring (**6e**, R^1 = Me, R^2 = Ns) were possible and the corresponding spiroimides **7l** and **7m** were obtained in good yields and very good stereoselectivities.

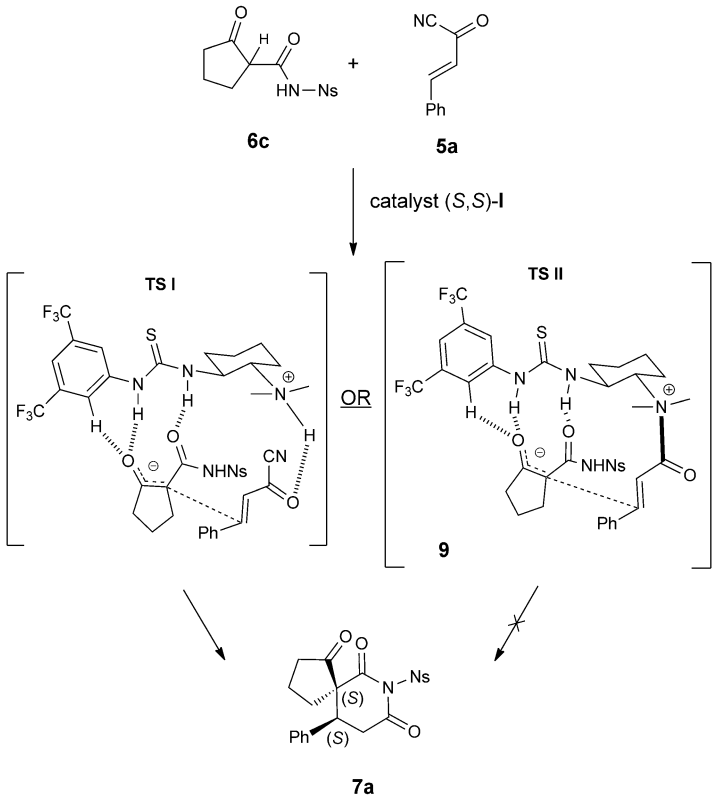
While the relative configuration of the two stereogenic centers was unambiguously determined by X-ray diffraction analysis, a reasonable proposal for the assignment of the absolute configuration could be obtained by VCD analysis of compound **7c**, which indicated a (*S*,*S*) relationship (see the Supporting Information for details).[23]

Two possible activation modes could in theory explain the observed stereochemical outcome (Scheme 4). Based on our previous studies regarding the enantioselective Michael addition of β-ketoamides to α,β-unsaturated carbonyl compounds,[5a] the enolate of the ketoamide **6c** is coordinated to the thiourea moiety in a perpendicular fashion in

Table 2. Reaction scope of the formal azaspiro[4,5]annulation.



[a] Isolated yield of the major diastereomer. [b] Determined by ^{1}H NMR spectroscopy of the crude reaction product. In brackets is the d.r. of the isolated product. [c] Values are for the major diastereomer. [d] Isolated yield of the 1:1 mixture of the two diastereomers (not separable by flash chromatography).



Scheme 4. Possible transition states for the dual activation

both **TSI** and **TSII** exposing the *Re* face of the enolate to the electrophile **5a**. In **TSI**, an activation of the α,β-unsaturated acyl cyanide **5a** through hydrogen-bonding with the ammonium part of the organocatalyst **I** is proposed. In **TSII**, the catalyst could form a covalent bond with **5a** by nucleophilic displacement of the cyanide ion.[24]

In both cases, the nucleophile would react on the *Re* face of the electrophile explaining the stereoselectivity. As a proof of possible formation of **9**, a proton NMR experiment of a 1:1 mixture of catalyst **I** and **5a** in deuterated acetonitrile clearly showed the formation of acyl ammonium **9** by creation of a covalent bond between **I** and **5a** (Figure 1), explaining the important shifts of the ^{1}H NMR proton signals. These shifts are particularly significant for vinylic protons H_a and H_b in **5a** as well as H_c, H_d and protons of the dimethylamine moiety of catalysts **I**. In intermediate **9**, all these protons are close to the acyl ammonium moiety and are the more prompt to suffer important shifts. Moreover, its formation was followed by HRMS (electrospray ionization in positive mode, see Supporting Information). Gratifyingly, we clearly observed the expected signal at *m/z*: 544.1856 corresponding to the acyl ammonium **9** ($[C_{26}H_{28}F_6N_3OS]^+$). More importantly, when we ran similar NMR spectroscopic experiments in deuterated benzene, which displays

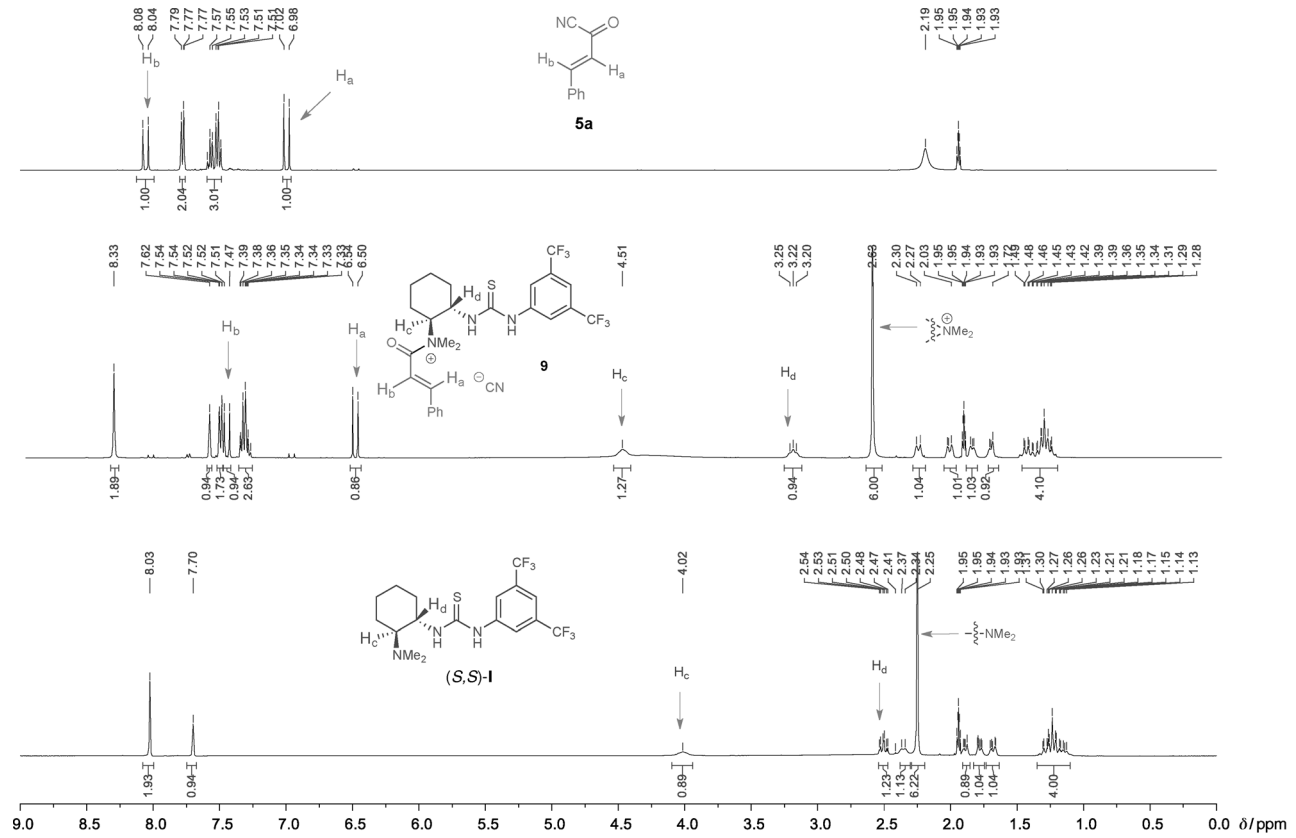


Figure 1. ^{1}H NMR of **5a** (top), **I** (bottom), and the mixture of **5a** and **I** (middle) in CD_3CN.

similar properties to the solvent of the reaction (*m*-xylene), no chemical shift was observed (see the Supporting Information), which indicates that the formation of **9** is not probable in non-polar solvents. These investigations led us to conclude that the reaction was presumably going through **TSI** even if we cannot completely rule out **TSII** and additional experiments and theoretical calculations are underway to shed light on this intriguing mechanism.

In conclusion, we have demonstrated the possible use of α,β-unsaturated acyl cyanides as efficient bis-electrophiles in enantioselective organocatalyzed formal [3+3]spiroannulations leading to synthetically valuable azaspiro[4,5]decanones. Moreover, this method constitutes the first direct access to chiral functionalized glutarimides in an optically active form. We are now working to gain further insight into the present reaction as well as extending the reactivity of this simple α,β-unsaturated ester surrogate towards other bis-nucleophiles.

Experimental Section

General procedure for the enantioselective formal [3+3]spiroannulation

The freshly sublimated acyl cyanide **5** (0.4 mmol, 2 equiv) was added in one portion to a solution of ketoamide **6** (0.2 mmol, 1.0 equiv) and the thiourea catalyst **I** (0.02 mmol, 0.1 equiv) in *m*-xylene (0.06 M, 3.3 mL) at 0 °C. The reaction mixture was stirred 40 h at 0 °C and then diluted with a mixture of ethyl acetate and petroleum ether (1:1, 10 mL) and filtrated on a short plug of silica gel. Purification by flash column chromatography (silica gel, petroleum ether/EtOAc) afforded the pure product.

Typical procedure for the enantioselective formal [3+3]spiroannulation (on 2 mmol scale)

The freshly sublimated acyl cyanide **5** (628 mg, 4 mmol, 2.0 equiv) was added in one portion to a solution of ketoamide **6c** (624 mg, 2 mmol, 1.0 equiv) and the thiourea catalyst **I** (82 mg, 0.2 mmol, 0.1 equiv) in *m*-xylene (0.06 M, 33 mL) at 0 °C. The reaction mixture was stirred for 40 h at 0 °C and then diluted with a mixture of ethyl acetate and petroleum ether (1:1, 100 mL) and filtrated on a short plug of silica gel. Purification by flash column chromatography (silica gel, petroleum ether/EtOAc) afforded the pure product **7c** as a white solid (645 mg, 73 %, 10:1 d.r., 96:4 e.r.).

Acknowledgements

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Keywords: domino reactions · enantioselectivity · glutarimides · organocatalysis · spiroannulation

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