Tetrahedron Letters 49 (2008) 5527–5530

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Catalytic enantioselective electrophilic α-hydrazination of β-ketoesters using bifunctional organocatalysts

Sun Hee Jung, Dae Young Kim *

Department of Chemistry, Soonchunhyang University, Asan, Chungnam 336-745, Republic of Korea

ARTICLE INFO

Article history:
Received 19 June 2008
Accepted 8 July 2008
Available online 11 July 2008

Keywords:
Bifunctional organocatalysts
Hydrazination
Asymmetric reactions
β-Ketoesters

ABSTRACT

The catalytic enantioselective electrophilic α-hydrazination promoted by chiral bifunctional organocatalysts is described. Treatment of β-ketoesters with azodicarboxylates as electrophilic amination reagents under mild reaction conditions afforded the corresponding α-amino β-ketoesters with excellent enantiomeric excesses (93–99% ee).

Amino acids constitute one of the most important families of natural products and are used as pharmaceuticals, agrochemicals, and fundamental synthetic building blocks for preparation of an assortment of biologically valuable molecules.[1] The development of stereoselective synthetic methods for the preparation of natural and non-natural α-amino acid derivatives has attracted considerable attention over the past decades.[2] The most popular methods for the catalytic asymmetric synthesis of α-amino acids are C–C bond formation and include the catalytic hydrogenation of α-dehydroamino acids,[3] alkylation of a *tert*-butyl glycinate-benzophenone Schiff base[4] using phase-transfer catalysts, and addition to imines using Strecker[5] and Mannich reactions[6] with chiral Lewis acids or organocatalysts.

The catalytic enantioselective electrophilic amination of carbonyl compounds represents an efficient and the simplest procedures to generate stereogenic carbon center attached to a nitrogen atom.[7] Recently, several groups presented the direct enantioselective amination of 1,3-dicarbonyl compounds catalyzed by chiral Lewis acids,[8] cinchona alkaloid,[9a] chiral urea,[9b] and chiral guanidines[9c] as organocatalysts. Bifunctional organocatalysts possessing a combination of thiourea and amine groups have been developed for activation of both electrophilic and nucleophilic components. They have emerged as powerful tools for the enantioselective formation of carbon–carbon bond and carbon–heteroatom bonds.[10] Nonetheless, substrate dependence still remains an important issue in asymmetric reactions using bifunctional organocatalysts. Therefore, the development of highly efficient chiral amine–thiourea catalysts, which show high enantioselectively for a broad scope of substrates, is still in great demand.

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[11] we report the catalytic enantioselective amination of ester derivatives promoted by chiral palladium complexes.[8f,11f] To the best of our knowledge, there are no example of the electrophilic α-hydrazination of β-ketoesters using thiourea-based organocatalysts. In this Letter, we wish to report the direct α-amination of β-ketoesters **1** catalyzed by using chiral amine–thiourea bifunctional organocatalysts with azodicarboxylates **2** as the electrophilic nitrogen source.

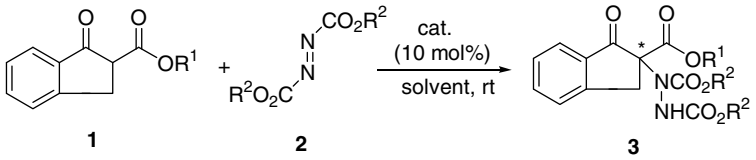
We envision that the assembly of a structurally well-defined chiral 1,2-diamine and binaphthyl scaffold with a thiourea motif could constitute a new class of bifunctional organocatalyst. The rigid binaphthyl structure can serve as an efficient stereocontrolling element. The new bifunctional organocatalysts **IV**–**VII** were synthesized according to the reported procedure from the reaction of 3,5-bis(trifluoromethyl)phenyl iso(thio)cyanate with chiral 1,2-diamines containing (*R*)-binaphthyl moiety.[12,13]

A survey of some reaction parameters was performed, and some representative results are presented in Table 1. Our investigation began with the catalytic enantioselective electrophilic amination of indanone carboxylate **1a** with *tert*-butyl azodicarboxylates **2** as the electrophilic aminating reagent in toluene at room temperature in the presence of 10 mol % of catalysts. We surveyed chiral thioureas containing a tertiary amine as catalysts (Fig. 1). High yields with moderate enantioselectivities (15–67% ee) were observed for structurally variable bifunctional catalysts (entries 1–7). Under the standard reaction conditions, catalyst **V** exhibited

* Corresponding author. Tel.: +82 41 530 1244; fax: +82 41 530 1247.
E-mail address: dyoung@sch.ac.kr (D. Y. Kim).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.07.041

Table 1
Optimization of the reaction conditions



1 2 3

Entry	**1**, R^1	**2**, R^2	Cat.	Solvent	Time (h)	Yield[a] (%)	ee[b] (%)
1	**1a**, Me	**2a**, *t*-Bu	**I**	Toluene	0.5	**3a**, 95	40
2	**1a**, Me	**2a**, *t*-Bu	**II**	Toluene	0.3	**3a**, 94	15
3	**1a**, Me	**2a**, *t*-Bu	**III**	Toluene	0.5	**3a**, 92	50
4	**1a**, Me	**2a**, *t*-Bu	**IV**	Toluene	0.5	**3a**, 91	51
5	**1a**, Me	**2a**, *t*-Bu	**V**	Toluene	0.3	**3a**, 96	67
6	**1a**, Me	**2a**, *t*-Bu	**VI**	Toluene	0.5	**3a**, 90	55
7	**1a**, Me	**2a**, *t*-Bu	**VII**	Toluene	1	**3a**, 85	−51
8	**1a**, Me	**2b**, *i*-Pr	**V**	Toluene	0.3	**3ab**, 95	55
9	**1a**, Me	**2c**, Et	**V**	Toluene	0.3	**3ac**, 94	17
10	**1a**, Me	**2a**, *t*-Bu	**V**	CH_2Cl_2	2	**3a**, 90	57
11	**1a**, Me	**2a**, *t*-Bu	**V**	THF	2	**3a**, 93	57
12	**1a**, Me	**2a**, *t*-Bu	**V**	Acetone	24	**3a**, 90	53
13	**1a**, Me	**2a**, *t*-Bu	**V**	*t*-BuOH	2	**3a**, 91	39
14	**1b**, Et	**2a**, *t*-Bu	**V**	Toluene	0.3	**3b**, 95	40
15	**1c**, Bn	**2a**, *t*-Bu	**V**	Toluene	0.3	**3c**, 93	33
16	**1d**, *t*-Bu	**2a**, *t*-Bu	**V**	Toluene	4	**3d**, 94	90
17[c]	**1d**, *t*-Bu	**2a**, *t*-Bu	**V**	Toluene	11	**3d**, 93	99

[a] Yield of isolated product.
[b] Enantiopurity of **3** was determined by HPLC analysis using Chiralpak AD-H column.
[c] Reaction was carried out at −70 °C.

better enantioselectivity (67% ee, entry 5), where catalyst **III** afforded product **3** in lower enantioselectivity (50% ee, entry 3). These results represent that increasing the sterical demand of the catalyst increases the selectivity. Compared with catalyst **V**, diastereomeric catalyst **VII** gave desired product **3** in lower enantioselectivity with the reversal absolute configuration as that of major enantiomer (−51% ee, entry 7). It suggest that chirality of (*R*)-binaphthyl moiety and (1*S*,2*S*)-diaminocyclohexane unit in catalyst **V** is matched in this reaction. Varying the structure of the azodicarboxylates had an impact on asymmetric induction (entries 5, 8, and 9). The best results have been obtained with *tert*-butyl ester of azodicarboxylates. Concerning the solvent (entries 5, 10–13), there is a little influence on the stereochemical outcome of the process but a significant impact on the reaction time. The nature of ester group of β-ketoesters has a significant impact on the selectivity (entries 5, 14–16). When employing synthetically attractive, but sterically hindered, *tert*-butyl ester of indanone carboxylate **1d**, the corresponding aminated adduct **3d** was isolated with high enantioselectivity of 90% ee (entry 16). Finally, we conducted the amination at low temperature in order to improve the enantioselectivity. The enantioselectivity was elevated at −70 °C in the reaction catalyzed by organocatalyst **V**, and up to 99% ee was obtained in good isolated yield (93%) after 11 h (entry 17).

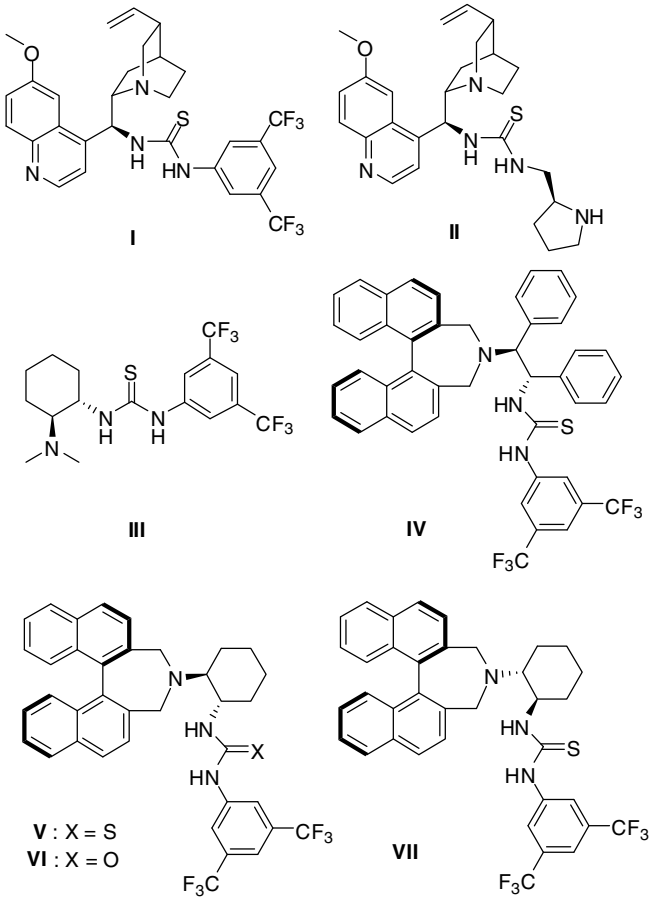
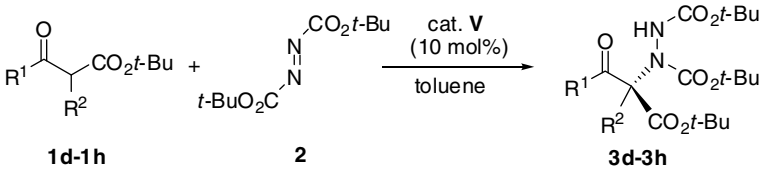


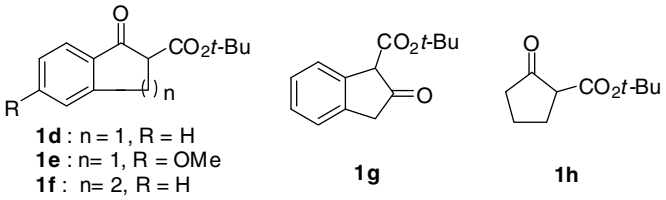
Figure 1. Structures of various chiral thiourea-tertiary amine catalysts.

To examine the generality of the catalytic enantioselective amination of β-ketoesters **3** by using new bifunctional organocatalyst **V**, we studied the amination of various β-ketoesters **1**.[14] As it can be seen by the results summarized in Table 2, the corresponding α-aminated β-ketoesters **3** were obtained in high to excellent yields and excellent enantioselectivities. The cyclic β-ketoesters **1d**–**h**, with cyclic aromatic ketones **1d**–**g** and cyclic aliphatic ketone **1h**, reacted with *tert*-butyl azodicarboxylates **2** to give the corresponding α-aminated β-ketoesters **3d**–**h** in 85–95% yields and 93–99% ee. In the contrast to the cyclic β-ketoesters, unfortunately, the reaction of acyclic β-ketoesters with azodicarboxylate proceeded slowly even at room temperature to give the α-aminated products in low enantioselectivity (Scheme 1).

Although the reason for the observed enantioselectivity is still unclear, we believe that a carbonyl group of the azodicarboxylate is activated by a thiourea moiety through hydrogen bonding, and

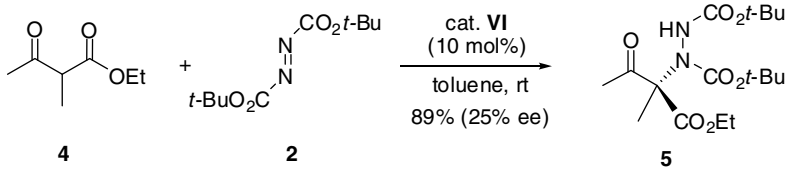
Table 2
Catalytic enantioselective amination of β-ketoesters





Entry	1	Temp. (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	**1d**	−70	11	**3d**, 93	99
2	**1d**	−30	10	**3d**, 94	95
3	**1e**	−30	7	**3e**, 95	97
4	**1f**	−70	10 d	**3f**, 85	93
5	**1g**	−30	3	**3g**, 92	93
6	**1h**	−30	36	**3h**, 93	97 (*R*)[c]

[a] Yield of isolated product.
[b] Enantiopurity of **3** was determined by HPLC analysis using Chiralpak AD-H (for **3d**, **3f**, **3g**, **3h**) and (*S,S*)-Whelk-O1 (for **3e**) columns.
[c] Absolute configuration was determined by comparison of the optical rotation and the HPLC retention time of the corresponding ester with literature value.[8g]



Scheme 1.

β-ketoester is activated by the basic nitrogen atom in tertiary amine (Fig. 2). These interactions control the stereochemical outcome of the reaction and accelerate the reaction rate.

In conclusion, we have developed a highly efficient catalytic enantioselective α-amination of cyclic β-ketoesters using new bifunctional organocatalyst **V**. The desired α-aminated products were obtained in good to high yields, and excellent enantioselectivities (93–99% ee) were observed. We believe that this method provides an efficient route for the preparation of chiral α-amino acid derivatives, and the availability of these compounds should facilitate medicinal chemical studies in various fields. Further study of these new bifunctional organocatalysts in asymmetric reactions is being under investigation.

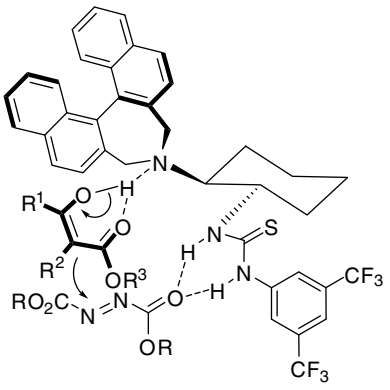


Figure 2. Proposed stereochemical model.

Acknowledgment

This research was supported by Korea Research Foundation Grant funded by the Korean Government (MOEHRD, Basic Research Promotion Fund) (KRF-2006-521-C00099).

References and notes

1. (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989; (b) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789; (c) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.. In *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vols. 1–3.
2. Reviews on synthesis of α-amino acids, see: (a) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539; (b) Arend, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 2873; (c) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342; (d) Najera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584.
3. (a) Okuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 1–110; (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.
4. (a) Corey, E. J.; Now, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414; (b) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595; For review, see: (c) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.
5. See, for example: (a) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279; (b) Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibassaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650; (c) Corey, E. J.; Grogan, M. J.

Org. Lett. **1999**, *1*, 157; (d) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762.

6. See, for example: (a) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc* **2002**, *154*, 5640; (b) Ferassis, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J.; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67; (c) Cordova, A.; Watanabe, S. I.; Tanaka, F.; Notz, W.; Barbas, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1842; (d) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1866; (e) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827; (f) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 112964; (g) Juhl, K.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995.
7. For reviews on asymmetric α-amination reactions, see: (a) Genet, J.-P.; Creck, C.; Lavergne, D. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000. Chapter 3; (b) Greck, C.; Drouillat, B.; Thomassigng, C. *Eur. J. Org. Chem.* **2004**, 1377; (c) Erdik, E. *Tetrahedron* **2004**, *60*, 8742; (d) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292.
8. (a) Juhl, K.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 2420; (b) Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1367; (c) Ma, S.; Jiao, N.; Zheng, Z.; Ma, Z.; Lu, Z.; Ye, L.; Deng, Y.; Chen, G. *Org. Lett.* **2004**, *6*, 2193; (d) Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, 2115; (e) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137; (f) Kang, Y. K.; Kim, D. Y. *Tetrahedron Lett.* **2006**, *47*, 4565; (g) Comelles, J.; Pericas, A.; Moreno-Manas, M.; Vallribera, A.; Drudis-Sole, G.; Lledos, A.; Parella, T.; Roglans, A.; Garcia-Grands, S.; Roces-Fernandez, L. *J. Org. Chem.* **2007**, *72*, 2077; (h) Mashiko, T.; Hara, K.; Tanaka, D.; Fujiwara, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 11342; (i) Hasegawa, Y.; Watanabe, M.; Gridnev, I. D.; Ikariya, T. *J. Am. Chem. Soc.* **2008**, *130*, 2158.
9. (a) Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, 2115; (b) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137; (c) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044.
10. For selected recent reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (b) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418; (c) Tylor, M. S.; Jacobson, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520; (d) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909; (e) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299; (f) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999; (g) Yu, X.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516.
11. (a) Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545; (b) Kim, D. Y.; Choi, Y. J.; Park, H. Y.; Joung, C. U.; Koh, K. O.; Mang, J. Y.; Jung, K.-Y. *Synth. Commun.* **2003**, *33*, 435; (c) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897; (d) Park, E. J.; Kim, H. R.; Joung, C. W.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2004**, *25*, 1451; (e) Kim, D. Y.; Huh, S. C. *Bull. Korean Chem. Soc.* **2004**, *25*, 347; (f) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309; (g) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett.* **2005**, *46*, 3115; (h) Kim, S. M.; Kang, Y. K.; Lee, K.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2006**, *27*, 423; (i) Kang, Y. K.; Cho, M. J.; Kim, S. M.; Kim, D. Y. *Synlett* **2007**, 1135; (j) Cho, M. J.; Kang, Y. K.; Lee, N. R.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2191; (k) Kim, S. M.; Kang, Y. K.; Cho, M. J.; Mang, J. Y.; Kim, D. Y. *Bull. Korean Chem. Soc.* **2007**, *28*, 2435.
12. (a) Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6978; (b) Arai, T.; Watanabe, M.; Yanagisawa, A. *Org. Lett.* **2007**, *9*, 3595.
13. *Typical procedure for the preparation of ogranocatalyst* **V**: To a stirred solution of *N*-(1*S*,2*S*)-2-[(*R*)-3,5-dihydro-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepin-4-yl]cyclohexanamine (785 mg, 2 mmol)[12] in dry THF (10 mL) was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (542 mg, 2 mmol). After the reaction mixture was stirred for 48 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5/1) gave the desired thiourea **V** (862 mg, 65%) as yellow solid. Mp = 151–152 °C; $[\alpha]_D^{21}$ −349 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.77 (m, 4H), 7.62–7.38 (m, 5H), 7.35–7.15 (m, 6H), 6.72–6.15 (br s, 1H), 4.16–3.66 (m, 3H), 3.65–3.40 (m, 2H), 2.73–2.53 (m, 1H), 2.48–2.12 (br s, 1H), 2.09–1.88 (m, 1H), 1.87–1.67 (m, 3H), 1.66–1.45 (m, 1H), 1.44–1.21 (m, 2H), 1.20–1.04 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.0, 135.09, 133.15, 132.19, 131.15, 130.89, 129.05, 128.33, 127.48, 127.34, 126.09, 125.89, 125.46, 123.07, 120.05, 117.58, 69.46, 52.30, 33.34, 28.54, 25.54, 25.35; ESI-HRMS: *m*/*z* calcd for $C_{37}H_{32}F_6N_3S$ $[M+H]^+$: 664.2221; found: 664.2212.
14. *General procedure for the α-hydrazination of β-ketoesters* **1**: A mixture of β-ketoester **1** (0.2 mmol) and catalyst **V** (13.24 mg, 0.02 mmol) in toluene (0.4 mL) was stirred at room temperature for 10 min and then was cooled to −70 °C (or −30 °C). A solution of *tert*-butyl azodicarboxylate (46.05 mg, 0.4 mmol) in toluene (0.3 mL) was added dropwise over a period of 5 min. The reaction mixture was stirred for indicated time in Table 2. After completion of the reaction, the resulting solution was allowed to warm to room temperature, concentrated in vacuo and the obtained residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to give the α-aminated products **3**.