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Diarylmethylamine ('Butterfly'-Type Amine) Unit: A Useful Unit for the Modulation of the Catalytic Activity of Aminothiourea Catalysts

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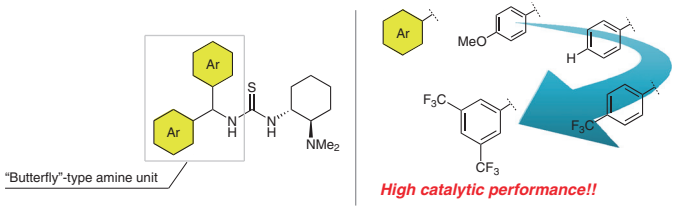


Received: 05.04.2023
Accepted after revision: 23.05.2023
Published online: 27.06.2023 (Version of Record)
DOI: 10.1055/s-0042-1751471; Art ID: ST-2023-04-0143-L

Abstract We investigated the effects of substituents on the aromatic rings in a diarylmethylamine unit (which we have named the 'butterfly'-type amine unit) in an aminothiourea catalyst. Detailed examination of the electronic effects of the aromatic rings revealed that the catalyst having a 3,5-bis(trifluoromethyl)phenyl group was the best, realizing an excellent chemical yield and enantioselectivity in an asymmetric Michael reaction between nitrostyrene and dimethyl malonate. Importantly, its catalytic ability as a chiral catalyst is superior to that of the well-known aminothiourea catalyst, the Takemoto catalyst, and this characteristic was observed in various asymmetric reactions.

Key words thiourea catalysis, asymmetric catalysis, diarylmethylamines, organocatalysis, Michael reaction

The pioneering works of the groups of MacMillan[1] and of List and Barbas[2] have triggered interest in the development of organocatalysts, which has evolved into one of the major topics of research in modern synthetic organic chemistry.[3] Many organocatalysts, such as chiral quaternary ammonium salts (Maruoka catalysts),[4] chiral phosphoric acid catalysts (Akiyama–Terada catalysts),[5,6] chiral cyclic secondary amine catalysts (Hayashi–Jørgensen catalysts),[7] and a chiral aminothiourea catalyst (the Takemoto catalyst)[8,9] have been developed, and their efficiencies have been well showcased in various asymmetric reactions. Among these organocatalysts, the aminothiourea catalyst, which consists of a chiral diamine moiety and a thiourea portion, has received immense attention for two reasons: (1) the ease of modification of the amine moiety, and (2) its high reliability and easy prediction of its asymmetric induction.[10,11] One of the major trends in these catalysts is that an aniline (aromatic amine) moiety is employed as an adjunct to a chiral amine moiety. The aromatic amine moiety is important for the improvement of the hydrogen-bonding ability of the thiourea moiety; however, its rigidity, in other words, its planar structure might be unfavorable for asymmetric induction in some reactions.[12] On the basis of this consideration, we recently focused on the diarylmethylamine unit, namely the so-called 'butterfly'-type amine unit as a potentially good alternative. Because of the presence of one carbon atom between the aromatic rings and the thiourea moiety, a high flexibility and also the construction of a wide reaction field are expected. In addition, the involvement of additional interactions between a substrate and the catalyst, such as a C–H–π/π–π interaction, which is difficult to achieve in the case of an aniline-type catalyst, is also expected.

It is unfortunate that, despite their potential utility, examples of chiral aminothiourea catalysts having a butterfly-type amine unit are quite limited (Figure 1). An early example was reported by Itoh and co-workers in 2010,[13a] who found that a catalyst with a chiral butterfly-type amine unit [a (2-hydroxynaphthyl)(phenyl)methyl group] effectively worked as a chiral unit in the asymmetric acyl-Strecker reaction of dihydroisoquinolines, although the selectivity was moderate (46% ee). In 2017, the group of Li and Cheng reported that the use of a simple (diphenylmethyl)amino-group-substituted catalyst with a chiral 1,2-cyclohexanediamine moiety resulted in moderate enantioselectivity (67% ee) in an asymmetric Michael reaction between nitrostyrene and diethyl malonate.[14] In 2016, Soós and co-workers reported that squaramide catalysts with a butterfly unit [a bis(1-naphthyl)methyl unit] exhibited excellent catalytic performance in a Robinson annulation reaction (91% ee).[15] Surprisingly, however, despite the high potential of the butterfly-type amine unit, no detailed investigation of the substituent effect on the aromatic rings of the amine unit has been conducted. Motivated by these circumstances, we investigated the substituent effect with a focus on the electronic effects of the aromatic rings in butterfly-type cata-

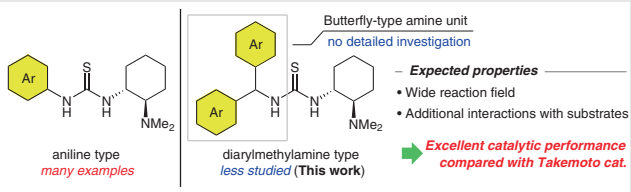
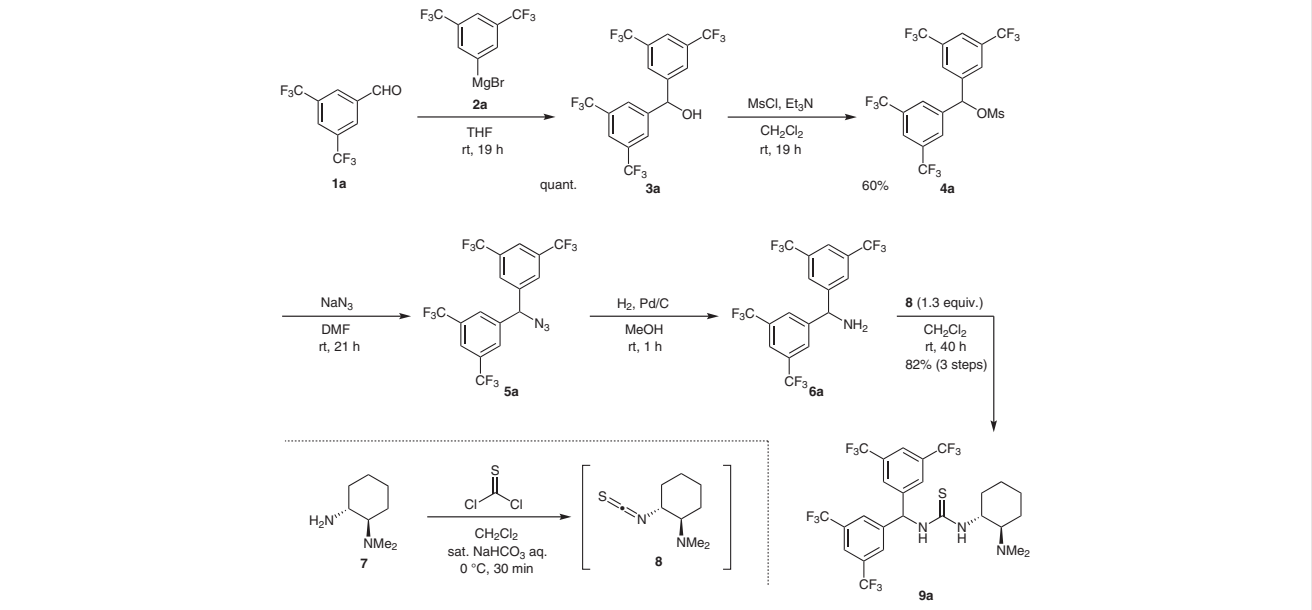


Figure 1 Butterfly-type aminothiourea catalysts

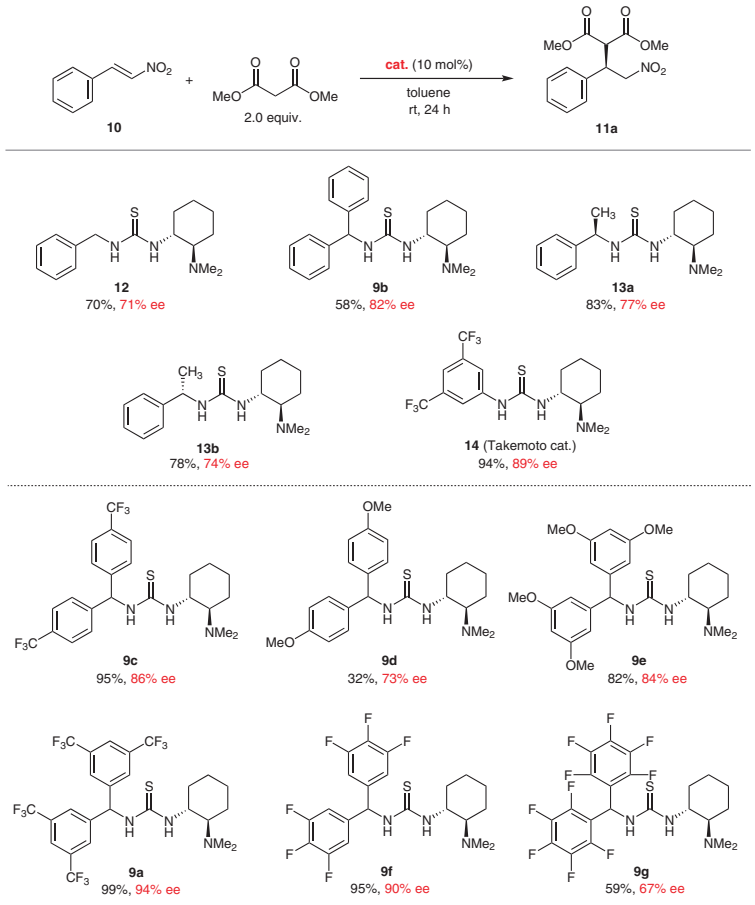
lysts, and we found that a 3,5-bis(trifluoromethyl)phenyl-group-substituted catalyst exhibited superior catalytic performance compared with the well-known Takemoto catalyst in some asymmetric reactions.

The preparation of the catalyst **9a**, containing a 3,5-bis(trifluoromethyl)phenyl group, is shown as a representative example in Scheme 1. The coupling reaction between aldehyde **1a** and the Grignard reagent **2a**, prepared from commercially available 1-bromo-3,5-bis(trifluoromethyl)benzene, followed by mesylation of the resulting alcohol group, gave mesylate **4a** in a good chemical yield (60% for the two steps). (Diarylmethyl)amine **6a**, which was synthesized from **4a** by a two-step azidation/reduction sequence, reacted with the known isothiocyanate **8**[16] to afford **9a** in a good chemical yield (82% for the three steps).

By following this procedure, a series of catalysts **9b–g** having various electronic natures of the aromatic rings were synthesized and their performance as catalysts was evaluated in the asymmetric Michael reaction between nitrostyrene **10** and dimethyl malonate as a model reaction (Scheme 2). In the case of the benzylic-type catalyst **12**, product **11a** was obtained in 70% chemical yield with 71% ee. The enantioselectivity increased to 82% ee when the simplest butterfly-type catalyst **9b** was employed. The use of catalysts **13a** and **13b**, derived from (*R*)- and (*S*)-1-phenylethylamine, respectively,[17] resulted in lower enantioselectivities of the product (77% ee and 74% ee, respectively) than the use of **9b**. Although the selectivity toward the product obtained with **9b** was lower than that obtained with the Takemoto catalyst **14** (82% ee vs 89% ee), the high potential of the butterfly-type catalyst prompted us to perform a detailed examination of the electronic effects of the aromatic rings on the catalytic activity. An excellent chemical yield (95%) and a high selectivity (86% ee) were realized when catalyst **9c** with a 4-(trifluoromethyl)phenyl group was employed, whereas the use of 4-methoxyphenyl-group-substituted catalyst **9d** resulted in a low chemical yield (32%) and a moderate enantioselectivity (73% ee). Catalyst **9e** with a 3,5-dimethoxyphenyl group exhibited a good catalytic performance (82% yield and 84% ee). Gratifyingly, both the chemical yield and the enantioselectivity were improved to excellent levels (99% yield, 94% ee) when catalyst **9a** with a 3,5-bis(trifluoromethyl)phenyl group was employed. It is worth emphasizing that both the chemical yield and the enantioselectivity were superior to those obtained when the Takemoto catalyst **14** was used. Stimulated by these results, we concentrated on the catalysts with highly electron-deficient aromatic rings (fluoroaromatic rings) and we obtained unexpected results. A satisfactory chemical yield (95%) and a high selectivity (90% ee) were achieved in the case of catalyst **9f** with a 3,4,5-trifluorophenyl group. In sharp contrast, catalyst **9g** with a penta-



Scheme 1 Synthesis of the butterfly-type aminothiourea catalyst **9a**



Scheme 2 Evaluation of the catalytic performance of butterfly-type catalysts

fluorophenyl group afforded adduct **11a** in 59% yield with 67% ee, the lowest among the butterfly-type catalysts examined.

The substrate scope of the asymmetric Michael reaction was then evaluated (Figure 2). Various Michael adducts **11b–d** possessing an electron-donating group (OMe) or an electron-withdrawing group (F or Br), and naphthyl-type adduct **11e** were obtained in excellent enantioselectivities (≥91% ee) when catalyst **9a** was employed. These enantioselectivities were higher than those obtained with the catalyst **14**.

Examination of the above-mentioned catalysts offered helpful hints on the transition-state model of the present catalytic system. The clear correlation between the electronic nature of the aromatic groups and the enantioselectivity suggests the involvement of some interactions, such as a π–π/C–H–π interaction, between the aromatic groups in the catalyst and the substrate. The presence of an internal hydrogen-bonding interaction between the sulfur atom of the thiourea moiety and the hydrogen at the 2-position of the aromatic group, which is proposed for the Takemoto catalyst and the Schreiner catalyst,[18] is implied by considering the low enantioselectivity, even when using the highly electron-deficient catalyst **9g**, which does not have hydrogen atoms at appropriate positions. On the basis of these considerations and the precedent of aminothiourea cata-

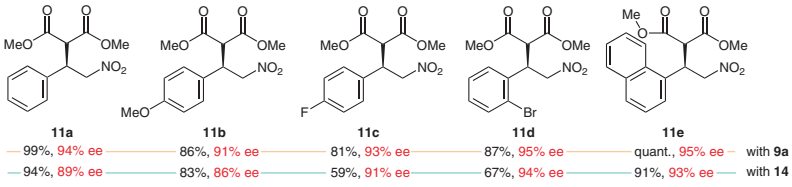


Figure 2 Substrate scope of the asymmetric Michael reaction

lysts,[19] we propose the transition-state model for the present reaction shown in Figure 2. In the same manner as the Takemoto catalyst, a hydrogen-bonding interaction between the nitrostyrene moiety and the conjugated acid of the dimethylamino portion of the catalyst, and two hydrogen-bonding interactions between the two hydrogens of the thiourea moiety and the conjugated base of malonate are involved. The above-mentioned hydrogen-bonding interaction between the sulfur atom of the thiourea moiety and the hydrogen at the 2-position of the aromatic group fixes the position of one of the aromatic rings, that is, it fixes the position of the other aromatic ring to the β-face, which is responsible for some interactions with the nitrostyrene moiety. These interactions give rise to the superior performance of **9a** compared with the Takemoto catalyst in terms of enantioselectivity. This proposed transition state explains the slightly lower enantioselectivity of **13b** than **13a**, as shown in Figure 2. Whereas a small hydrogen atom was located on the β-face in the case of **13a**, a methyl group, which can cause a steric repulsion with a substrate, occupied the same position when **13b** was employed and, consequently, a lower enantioselectivity was observed.

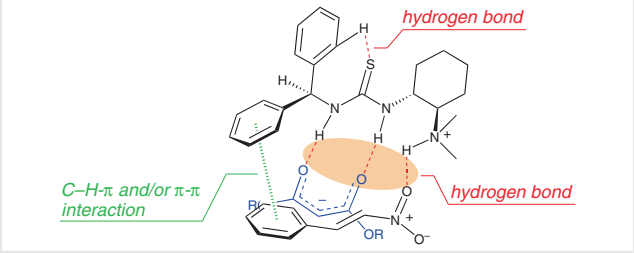
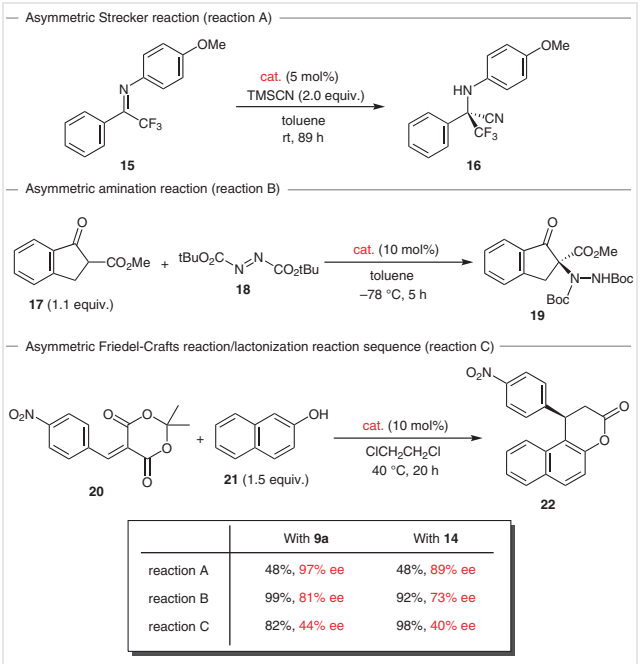


Figure 3 Proposed transition-state model

The superior catalytic performance of **9a** compared with the Takemoto catalyst was not limited to the asymmetric Michael reaction, as shown in Scheme 3. In the asymmetric Strecker reaction of trifluoromethyl ketimine **15**,[20] the asymmetric amination of the β-keto ester **17**,[21] and the asymmetric Friedel–Crafts reaction/lactonization reaction sequence of the benzylidene Meldrum's acid **20** with 2-naphthol (**21**),[22] our catalyst **9a** exhibited a good performance, and the corresponding adducts were obtained with higher enantioselectivities than those obtained when the Takemoto catalyst was used.

In summary, we have evaluated the electronic effects of the aromatic rings in the diarylmethylamine unit, namely, the butterfly-type amine unit, on the performance of aminothiourea catalysts.[23] Among the aromatic rings examined, the 3,5-bis(trifluoromethyl)phenyl group was the best; an excellent enantioselectivity was realized in the asymmetric Michael reaction between nitrostyrene and dimethyl malonate. It is worth noting that its asymmetry-inducing ability was superior to that of the well-known aminothiourea catalyst, the Takemoto catalyst, and this characteristic was observed in various asymmetric reactions. These catalysts could provide a trump card for the improvement of enantioselectivity in aminothiourea-catalyzed asymmetric reactions. The development of novel asymmetric reactions with these catalysts is underway in our laboratory.



	With **9a**	With **14**
reaction A	48%, 97% ee	48%, 89% ee
reaction B	99%, 81% ee	92%, 73% ee
reaction C	82%, 44% ee	98%, 40% ee

Scheme 3 Examination of the catalytic performance of **9a** in other asymmetric reactions

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

This work was partially supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0042-1751471.

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(23) ***N*-{Bis[3,5-bis(trifluoromethyl)phenyl]methyl}-*N*′-[(1*R*,2*R*)-2-(dimethylamino)cyclohexyl]thiourea (9a): Typical Procedure**

To a solution of the commercially available aldehyde **1a** (767 mg, 3.17 mmol) in THF (12.3 mL) at 0 °C was added [3,5-bis(trifluoromethyl)phenyl]magnesium bromide (**2a**), prepared from Mg (110.7 mg, 4.61 mmol) and 1-bromo-3,5-bis(trifluoromethyl)benzene (0.640 mL, 3.78 mmol). The mixture was stirred for 19 h at r.t., then the reaction was quenched by adding sat. aq NH_4Cl. The crude product was extracted with EtOAc (×3), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography [silica gel, hexane–EtOAc (4:1)] to give alcohol **3a** as a white solid; yield: 1.44 g (quant); mp 92–94 °C.

IR (KBr): 3338, 3105, 2918, 2849, 1626, 1466, 1363, 1319, 1278, 1131, 937 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.86 (s, 6 H), 6.07 (br s, 1 H), 2.71 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.5, 151.3 (q, $J_{C–F}$ = 33.3 Hz), 126.6, 123.0 (q, $J_{C–F}$ = 270 Hz), 122.5 (m), 74.1. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –62.6. Anal. Calcd for $C_{17}H_8F_{12}O$: C, 44.76; H, 1.77. Found: C, 44.98; H, 1.96.

Et_3N (0.900 mL, 6.46 mmol) and MsCl (0.300 mL, 3.88 mmol) were successively added to a solution of alcohol **3a** (1.44 g, 3.15 mmol) in CH_2Cl_2 (31.7 mL) at 0 °C, and the mixture was stirred for 19 h at r.t. The crude products were concentrated in vacuo, and the residue was purified by column chromatography [silica gel, hexane–EtOAc (4:1)] to give mesylate **4a** as a white solid; yield: 1.02 g (60%); mp 105–108 °C.

IR (KBr): 3584, 3063, 2913, 2846, 1626, 1466, 1378, 1340, 1280, 1173, 1131, 958 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.95 (s, 2 H), 7.82 (s, 4 H), 6.85 (s, 1 H), 3.04 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.6, 132.9 (q, $J_{C–F}$ = 33.9 Hz), 127.3 (m), 123.6 (m), 122.7 (q, $J_{C–F}$ = 271.3 Hz), 79.5, 39.4. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –62.8. Anal. Calcd for $C_{18}H_{10}F_{12}O_3S$: C, 40.46; H, 1.89. Found: C, 40.72; H, 1.64.

NaN_3 (68.2 mg, 1.05 mmol) was added to a solution of mesylate **4a** (485 mg, 0.91 mmol) in DMF (0.962 mL) at r.t., and the mixture was stirred for 14 h at r.t. The reaction was quenched by adding H_2O, and the crude products were extracted with EtOAc (×3). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography [silica gel, hexane–EtOAc (4:1)] to give azide **5a**; yield: 403 mg. At this stage, some impurities, which were hard to separate, were present and, consequently, this material was used for the next reaction without further purification.

To a solution of **5a** in MeOH (8.5 mL) was added 10% Pd/C (43.8 mg) at r.t., and the mixture was stirred under H_2 (1 atm) at r.t. for 1 h. The mixture was then filtered through a Celite pad and

concentrated in vacuo to give amine **6a** (382 mg) as a yellow oil. This material was used in a subsequent reaction with isothiocyanate **8** without further purification.>

Thiophosgene (0.198 mL, 2.60 mmol) was added to a solution of [(1*R*,2*R*)-2-aminocyclohexyl]dimethylamine (**7**; 339.8 mg, 2.39 mmol) in CH_2Cl_2 (13.4 mL) and sat. aq $NaHCO_3$ (13.4 mL) at 0 °C, and the mixture was stirred at 0 °C for 0.5 h. The crude products were extracted with CH_2Cl_2 (×3), and the combined organic extracts were washed with sat. aq $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo to give isothiocyanate **8** (261.2 mg), which was used in the next reaction without further purification.

To a solution of amine **6a** in CH_2Cl_2 (6.01 mL) was added a solution of isothiocyanate **8** in CH_2Cl_2 (2.62 mL) at r.t., and the mixture was stirred for 40.5 h at r.t. The crude products were concentrated in vacuo, and the residue was purified by column chromatography [silica gel, CH_2Cl_2–MeOH (20:1)] to give thiourea **9a** as a yellow amorphous solid; yield: 475 mg (82% from **4a**); $[\alpha]_D^{25}$ +36.6 (*c* 1.00, $CHCl_3$).

IR (neat): 3219, 3055, 2941, 2866, 1556, 1467, 1375, 1279, 1173, 1132 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (s, 2 H), 7.83 (s, 1 H), 7.82 (s, 1 H), 7.73 (s, 2 H), 7.02 (d, *J* = 8.0 Hz, 1 H), 4.38 (br s, 1 H), 3.17 (br s, 1 H), 2.59 (br s, 6 H), 2.40–2.32 (m, 1 H), 2.07–1.94 (m, 2 H), 1.85–1.78 (m, 1 H), 1.46–1.12 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.9, 143.2, 142.7, 132.6 (q, J_{C-F} = 33.4 Hz), 132.2 (q, J_{C-F} = 33.4 Hz), 128.2, 127.9, 124.5 (q, J_{C-F} = 270.8 Hz), 124.3 (q, J_{C-F} = 270.8 Hz), 67.3, 60.7, 55.1, 39.1, 32.8, 29.7, 24.4, 24.1, 22.7. ^{19}F NMR (283 MHz, $CDCl_3$): δ = –62.6 (s, 6 F), –62.8 (s, 6 F). Anal. Calcd for $C_{26}H_{25}F_{12}N_3S$: C, 48.83; H, 3.94; N, 6.57. Found: C, 48.68; H, 4.05; N, 6.36.