JOC The Journal of Organic Chemistry

Article

Modularly Evolved 2-AminoDMAP/Squaramides as Highly Active Bifunctional Organocatalysts in Michael Addition

Cihangir Tanyeli

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo5022597 • Publication Date (Web): 24 Dec 2014

Just Accepted

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Modularly Evolved 2-AminoDMAP/Squaramides as Highly Active Bifunctional Organocatalysts in Michael Addition

Journal:	*The Journal of Organic Chemistry*
Manuscript ID:	jo-2014-022597.R2
Manuscript Type:	Article
Date Submitted by the Author:	12-Dec-2014
Complete List of Authors:	Işık, Murat; Bingöl University, Metallurgical and Materials Science Unver, M. Yagiz; Middle East Technical University, Chemistry Tanyeli, Cihangir; Middle East Technical University, Chemistry

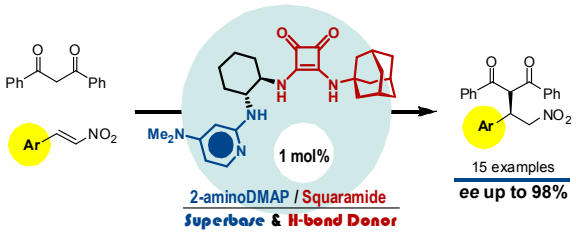
Modularly Evolved 2-AminoDMAP/Squaramides as Highly Active Bifunctional Organocatalysts in Michael Addition

Murat Işık,[†,‡] M. Yagiz Unver,[†] and Cihangir Tanyeli*[,†]

[†]*Department of Chemistry, Middle East Technical University, 06800 Ankara, Turkey and*

[‡]*Department of Metallurgical and Materials Engineering, Bingöl University, 12400 Bingöl, Turkey.*

tanyeli@metu.edu.tr



ABSTRACT

We report a new family of chiral bifunctional acid/base type organocatalysts, 2-aminoDMAP/Squaramides, which are proved to be highly active (1 mol% cat. loading) promoters in conjugate addition of dibenzoylmethane to various *trans*-*β*-nitroalkenes. Steric demand of the catalysts was clearly seen by a set-by-set modulation of the squaramide unit through electronic and steric factors. The synergistic cooperation of 2-aminoDMAP "superbase" and sterically encumbered squaramide (H-bond donor) enabled complete conversion of a range of reactants into corresponding Michael adducts in a couple of hours with exquisite selectivities (up to 98% ee).

INTRODUCTION

Asymmetric organocatalysis offers unique performance advantages over transition metal- and enzyme-based protocols, and thus has encouraged thousands to design a myriad of catalyst examples.[1] Bifunctional acid/base organocatalysis—cooperative activation of substrates—has received considerable attention in this endeavor.[2] *trans*-Cyclohexane-1,2-diamine and chincona alkaloids hold prominent places as "privileged"[3] chiral scaffolds to that end with the majority of efforts focused on exploring novel H-bond donor entities.[4] Integration of novel Brønsted bases into these organic catalysts, on the other hand, can considerably raise their potential and may open new avenues towards "ideal catalysis".[5] Unsuprisingly, this gap has been partially filled by the emerging use of *organic superbase*[6] catalysts, examples of which include amidines (2-aminopyridines[7] and 2-aminoDMAP[8]), guanidines,[9] phosphazenes,[10] and similar molecular architectures.[11] Building upon these precedents, our latest work involved the straightforward preparation of 2-aminoDMAP/Sulfonamides and their application as highly selective bifunctional acid/base type organocatalysts.[8d] Yet, our most notable achievement in that work was the development of a direct, one-step, and selective mono-*N*-pyridylation of *trans*-(*R*,*R*)-cyclohexane-1,2-diamine to build a 2-aminoDMAP—Lewis basic core—unit thereof. Our interest in this *superbasic* module, which was elegantly made use of at first hand by Wulff group[8a] is mainly due to its stronger basicity than the commonly encountered trialkylamine alternatives (Figure 1).

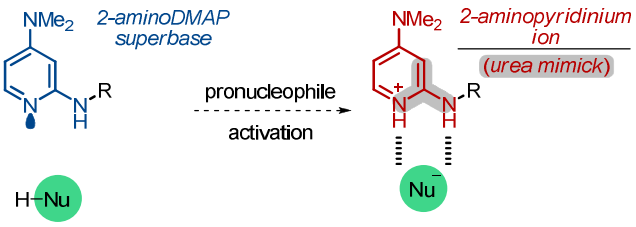


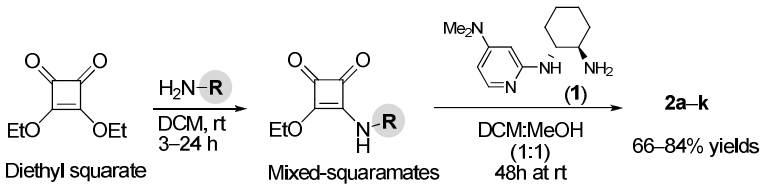
Figure 1. Pronucleophile activation by 2-aminoDMAP superbases

This is in part because a strong base would deprotonate the pronucleophile at an enhanced rate, thereby ensuring rapid conversion of substrates into products, and simultaneously would yield lower catalyst loading as a bonus. The other equally important result of this manipulation would be the stronger and/or tighter binding of the nascent nucleophile with the resulting *2-aminopyridinium ion* (mimicking ureas) through double coordination, which, in turn, is anticipated to result in higher asymmetry induction once chirally well-decorated. Squaramides, on the other hand, display unique performance characteristics as hydrogen-bond donor catalysts in a diverse array of asymmetric reactions and evolve abundantly as described in the highly influential work by Rawal and coworkers.[12] The strong activation of electrophiles by squaramides is attributed at least partly to their double proton donor capacity, rigidity and unique H-bond spacing/angle.[4c] Apart from these appealing features, from a synthetic chemist's perspective, their modular nature coupled with their ease of preparation makes them a favorite among other well-recognized alternatives.[12–14] All these built-in advantages may therefore stimulate the development of more productive catalysts that are also highly stereoselective and time- and cost-effective for sustainable catalysis.[5,15] In this article, we describe a series of 2-aminoDMAP/Squaramides and their modular evolution through electronic and steric fit, which results in a very fruitful interplay of the catalaphores in asymmetric conjugate addition.

RESULTS and DISCUSSION

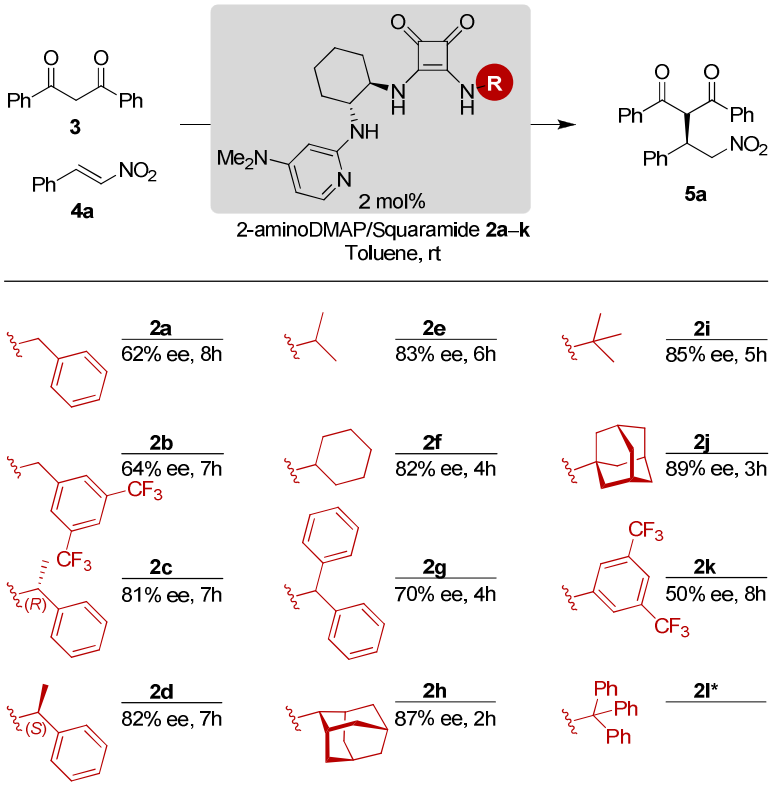
Preparation of the catalysts is very straightforward, as depicted in Scheme 1.

Scheme 1. Synthesis of 2-aminoDMAP/Squaramides **2a**–**k**.



The synthesis of mixed-squaramates follows one-to-one mixing of diethyl squarate with the desired amine at room temperature in dichloromethane.[12] Subsequently, these mixed-squaramates were coupled to the easily accessible chiral 2-aminoDMAP base (**1**)[8d] by simply stirring them in methanolic dichloromethane for 48 h. All eleven examples of 2-aminoDMAP/Squaramides **2a–k** shown in Scheme 2 were produced by the aforementioned route comprising just two high yielding steps.

Scheme 2. Catalyst tuning on squaramide unit[a–c]

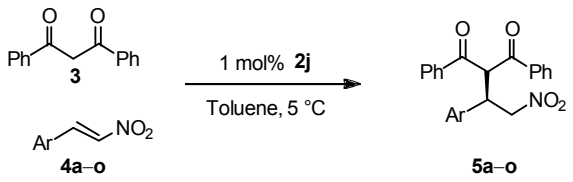


[a]Reactions were carried out in 0.2 M concentration of *trans*-*β*-nitrostyrene (**4a**) with 3 equiv of dibenzoylmethane (**3**). [b]Time for complete conversion. [c]Enantiomers were separated by HPLC using the chiral stationary phase. *All our efforts to synthesize tritylamine bearing mixed-squaramate failed. See experimantal part for a detailed discussion.

Herein, we selected a conjugate addition reaction to test the efficacy of the catalysts. Indeed, Michael addition reactions are typically clean and take place in a clickable manner so that they are the most prominent platform for the evaluation of *de novo* bifunctional organocatalysts to construct carbon–carbon and carbon–heteroatom bonds.[2b,2e,12a] At the outset of the optimization works, reactions were found to proceed best in toluene by employing 2 mol% catalyst loading at room temperature (Scheme 2). The first set of catalysts (**2a–b**) were devised to explore the effect of small acidity differences they had no significant impact on selectivities or reaction times, but were reasonably selective (64% ee; **2b**). To our surprise, the next set (**2c–d**), originally intended to investigate the impact of secondary chirality on the squaramide unit, provided almost equal enantioselection, but with a dramatic positive jump (+20%) in the same sense of chirality induction in each. Considered together, these results suggest two important implications concerning the nature of catalysts: both the same sense of selection (*re*-face attack in both) and the equally higher selectivities obtained by catalysts **2c–d**, (1) indicate that the chirality of the products depends entirely on that of the vicinal diamine scaffold, and (2) nominate the substitution-pattern around the modulated amine as a strong chirality control element. Thereby, catalysts **2e–l** were proposed further to fulfill the steric demand required. Similar stereochemical outcomes obtained by catalysts **2e–f** support the above-mentioned inference as well. Among the squaramides derived from the amines neighboring *sec*-carbon (**2c–h)**, while the distinguished selectivity of the 2-adamantyl amine derived squaramide **2h** (87% ee) can be attributed to its rigid-steric bulk, the noticeable drop in selectivity by means of the benzhydryl derivative **2g** is, however, hard to speculate on. The highest levels of selectivity (up to 89% ee) were achieved by decorating the squaramide unit with *tert*-carbon (3°) bearing amines as can be anticipated by the evolving design. In stark contrast, the only aromatic amine bearing catalyst (**2k**), and probably the most acidic of all, afforded a sluggish reaction with a significant loss of enantioselectivity (50% ee).

Findings presented in scheme 2 clearly demonstrated the superiority of both 2-adamantyl- and 1-adamantyl-unit-incorporating catalysts over the rest. To decide the best, we carried out some additional comparative experiments (1 mol% vs. 2 mol% cat. loadings of **2j** and **2h**) in model reaction of **3** and **4a**. To this end, we first fixed the reaction temperature to 5°C to eliminate its fluctuations. Although reaction times were doubled by doing so, a bit increased-selectivities were obtained (2 mol% **2j**: 89% ee in 3 h, 1 mol% **2j**: 90% ee in 5 h; 2 mol% **2h**: 88% ee in 2 h, 1 mol% **2h**: 89% ee in 4 h). As a result, we selected structurally rigid and sterically congested 1-adamantyl amine bearing squaramide **2j** as the catalyst and decided to use it at 1 mol%. In order to demonstrate the generality of the optimized reaction conditions, various nitroolefins were subjected to this reaction (Table 1).

Table 1. Substrate Scope[a]



entry	Ar	5	time[b] (h)	yield[c] (%)	ee[d] (%)
1		**5a**	5	90	90
2		**5b**	6	70	85
3		**5c**	6	94	90
4		**5d**	4	70	80
5		**5e**	2	85	92
6		**5f**	10	54	86
7		**5g**	3	86	94
8		**5h**	3	74	84
9		**5i**	3	90	87
10		**5j**	3	95	95
11		**5k**	7	75	95

12		**5l**	5	60	83
13		**5m**	4	75	94
14		**5n**	18	68	95
15		**5o**	6	58	98

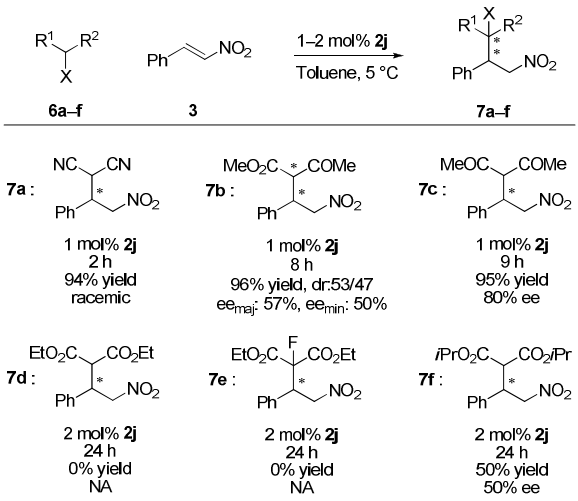
[a]Reactions were carried out in 0.2 M concentration of *trans*-*β*-nitroalkenes **4a–o** with 3 equiv of dibenzoylmethane (**3**). [b]Time for complete conversion. [c]Isolated yields. [d]Enantiomers were separated by HPLC using the chiral stationary phase.

Gratifyingly, most were typically completed in a couple of hours with excellent enantioselectivities and in reasonable yields. The stereoselectivity and chemical yield of conjugate additions (entries 1–15 of Table 1) were apparently insensitive to the substitution pattern around the aromatic ring (*o*-, *m*-, or *p*-) of nitroalkenes, as well as the electronic nature, whether electronically activated (entries 2–6, and 15) or deactivated (entries 7–14). Remarkably, both *o*-fluoro- and *p*-fluoro-aryl substituted substrates (**4j** and **4k**) gave 95% ee. It is notable that all the substrates presented in Table 1 were transformed into highly enantiomerically enriched Michael adducts (enantiomeric ratios >90:10) in highly acceptable reaction times and yields. The absolute configuration of chiral adduct **5i** was assigned as *R* by literature[16] comparison of its specific rotation, and HPLC analysis but those of the rest were assigned, albeit tentatively, in analogy.[18] In other words, asymmetry transfer by means of **2j** was assumed to involve a *re*-face addition of dibenzoylmethane to all prochiral nitroolefins listed in Table 1 (see Figure 2).

We tested catalytic activity of **2j** also in conjugate addition of malononitrile (**6a**), methyl acetoacetate (**6b**), acetylacetone (**6c**) and several malonates (**6d–f**) to nitrostyrene **4a** under optimized reaction conditions (Scheme 3). Malononitrile gave a fast reaction but yielded a racemic mixture of **7a**, proving the worst nucleophile among all. The highest stereoselectivity

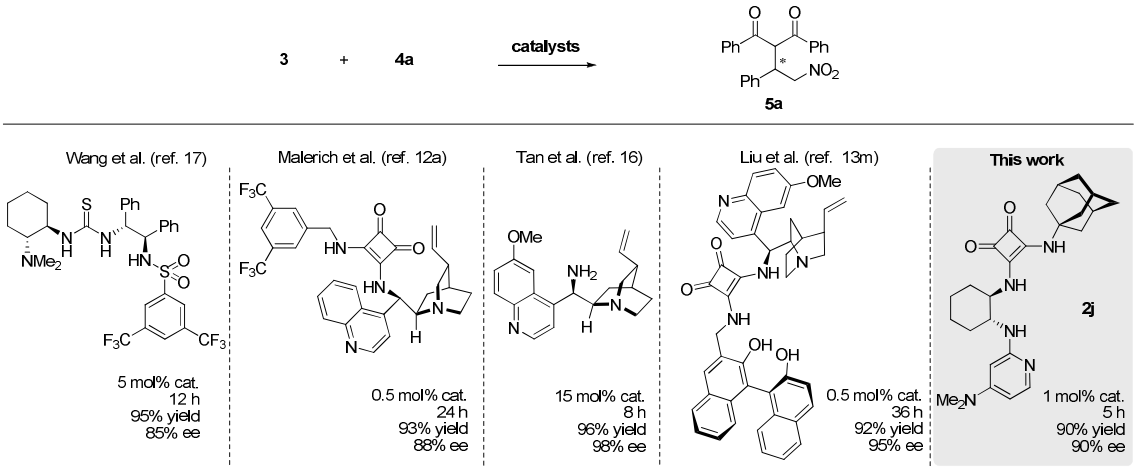
was obtained with acetylacetone, 80% ee with complete conversion in 9 h. Reaction with methyl acetoacetate produced a pair of diastereomers almost in equal ratios (53/47) but with moderate enantioselectivities in reasonable time and yields in each. With malonates **6d–f**, we did not observe any noticeable conversion at 1 mol% catalyst loading, so we raised loadings to 2 mol%, and this time, diisopropyl malonate (**6f**) was the only nucleophile to give reaction, albeit with mild conversion and enantioselectivity (50% ee at 50% yield in 24 h). The slowest reactions of malonate esters, even lack thereof (**6d–e**), can be attributed to the relatively higher p*K*a values of their methylene protons, although the only reaction with diisopropyl malonate remains a mystery.

Scheme 3. Screening of nucleophiles (**3** + **6a–f**)



In a previous report of Michael addition of dibenzoylmethane to nitroalkenes, Tan et al. presented a cinchona alkaloid derived primary amine as the organocatalyst with very impressive selectivities, but the protocol required as much as 15 mol% of the catalyst to complete the reaction within a reasonable time (Scheme 4).[16]

Scheme 4. A literature comparison of **2j** in catalysis of **3** + **4a**



Those authors somewhat circumvented this drawback by recycling their catalyst. Scheme 3 shows a performance comparison of **2j** with its literature precedents in the particular reaction between **3** and **4a**; and fairly exclusive of **2j**, all the others suffer from being either sluggish or in need of high catalyst loadings, although all are almost equally selective and high yielding. In light of this comparative structure–activity analysis, we are convinced that the stronger basic unit of **2j** (2-aminoDMAP) compared to the rest (all-*tert*-amine) is the key factor for the observed rate enhancements. Indeed, our present protocol essentially complements that of Tan et al. with its unique opportunities, such as low catalyst loading (only 1 mol%), faster reactions, and low solvent dependence. The descriptive model displayed in Figure 2 aims to solidify the putative function of each module[18] of 2-aminoDMAP/Squaramide **2j** in this particular asymmetric reaction.

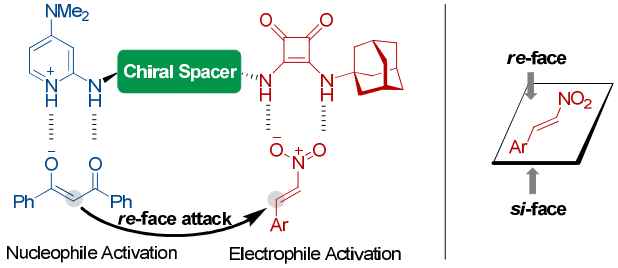


Figure 2. Putative bifunctionality of **2j**

According to this model, upon (partial) deprotonation, dibenzoylmethane may bind doubly to the correspondingly formed 2-aminopyridinium moiety to stabilize the carbanion formed. On the other side, nitroalkene is supposed to be activated through well-oriented double H-bonding by the donor squaramide coordinating point. We think that this two doubly-coordinative activation on each side of the catalyst leads to highly strong binding of the reactants with the catalyst and thereby keeps them in close proximity to the chiral pocket, so that it may partly explain the marked selectivities and fast reactions observed.

CONCLUSION

In summary, the set-by-set modulation driven design herein paved the way for successful organocatalyst generation that costs to develop only a handful of candidates—2-aminoDMAP/Squaramides **2a–k**. While outperforming selectivities (up to 98% ee) of **2j** can be largely ascribable to the rigid-steric bulk (1-adamantyl group) it carries on the squaramide unit, the high activity (1 mol% cat. loading, high yields in short reaction times) of the catalyst apparently emanates mainly from the double coordinative nature of squaramide and 2-aminopyridine fragments, in which the former is thought to activate *trans*-*β*-nitroalkenes and the latter to stabilize the formed *β*-diketonate anion. Enantioselectivity of the catalysts is found to be insensitive to the additional introduction of chiral units through the end caps of squaramides. 2-AminoDMAP superbase-derived catalysts are greatly promising for "ideal catalysis" with their outstanding performances described herein and so are the focus of our current research.

EXPERIMENTAL

In this section, the synthetic procedures and structural characterization of novel compounds (**2a**–**k**, **5f**–**h**, and **5j**–**l**) are reported only. They are listed in order of appearance. For those present in the literature, relevant citations are given where appropriate. Compound 2-aminoDMAP **1**[8d] and mixed-squaramates[12a] were prepared according to published procedures. Structural characterizations of the new compounds were conducted with the instruments and methods given below. Liquid ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 spectrophotometer using $CDCl_3$, or d_6-DMSO as the solvent. Chemical shifts values are reported in ppm taking tetramethylsilane as the internal standard, and J values are given in hertz. Spin multiplicities are reported as follows: s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), m (multiplet). Polarimetric measurements were made by the use of a polarimeter and reported as follows: $[\alpha]_D^T$ (c in g per 100 mL, solvent). Enantiomeric excess (*ee*) values of chiral adducts were detected by a HPLC system using a Daicell AS-H chiral column (0.46 cmØ × 25 cm), AD-H chiral column (0.46 cmØ × 10 cm), OJ-H chiral column (0.46 cmØ × 25 cm), and IA chiral column (0.46 cmØ × 25 cm). HRMS data were acquired on a time of flight (TOF) mass spectrometer. IR spectra of all new compounds were obtained by an IR spectrometer. Flash column chromatography (FCC) was performed by using glass columns with flash grade silica gel (230–400 mesh). Reactions were monitored by thin layer chromatography (TLC) using precoated silica gel plates, visualized by UV light and *p*-anisaldehyde, ninhydrin, and potassium permanganate stains as appropriate. All organic extracts were dehydrated over oven-dried $MgSO_4$ or K_2CO_3 and concentrated by using a rotary evaporator before being subjected to FCC.

General Procedure for the 2-aminoDMAP/Squaramide Catalysts 2a–k.

To a one to one (volume) DCM:MeOH solution (1 mL) of (*R*,*R*)-configurated 2-aminoDMAP **1** (47 mg, 0.2 mmol) was added appropriate mixed-squaramate (0.2 mmol) at rt. The solution was stirred for 48 hours at this temperature. The mixture was directly loaded on to a silica gel column and eluted with DCM:MeOH (90:10) to afford 2-aminoDMAP/Squaramides **2a–k** (66–84% yield) as solid compounds.

Data for 2a. The use of 3-(benzylamino)-4-ethoxycyclobut-3-ene-1,2-dione (46 mg, 0.2 mmol) gave compound **2a** as pale yellow amorphous solid (60 mg, 72% yield). Mp = 142.5 – 159.6 °C (decomp.). $[\alpha]_D^{31}$ = –145.1 (*c* 0.25, CH_2Cl_2). ^{1}H NMR (400 MHz, d6-DMSO) δ 1.05 – 1.45 (m, 4H), 1.70 (bs, 2H), 1.95 – 2.18 (m, 2H), 2.83 (s, 6H), 3.58 – 3.88 (m, 2H), 4.65 (bs, 2H), 5.56 (s, 1H), 5.88 (bs, 1H), 5.95 (d, *J* = 6.2 Hz, 1H), 7.20 – 7.35 (m, 5H), 7.58 (bs, 1H). Two protons could not be located. ^{13}C NMR (101 MHz, d_6-DMSO) δ 23.6, 24.8, 31.5, 33.0, 46.0, 52.9, 54.2, 56.58, 87.9, 98.3, 126.6, 126.7, 127.9, 138.1, 145.8, 154.7, 158.3, 166.7, 166.9, 181.4, 181.9. HRMS (ESI) calcd for $C_{24}H_{30}N_5O_2$ $[M + H]^+$ 420.2400, found 420.2412.

Data for 2b. The use of 3-(3,5-bis(trifluoromethyl)benzylamino)-4-ethoxycyclobut-3-ene-1,2-dione (73 mg, 0.2 mmol) gave compound **2b** as pale yellow amorphous solid (91 mg, 82% yield). Mp = 162.2 – 173.0 °C. $[\alpha]_D^{31}$ = –141.7 (c 0.25, CH_2Cl_2). ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.09 – 1.55 (m, 4H), 1.71 (bs, 2H), 1.91 – 2.15 (m, 2H), 2.85 (s, 6H), 3.61 – 3.91 (m, 2H), 4.85 (bs, 2H), 5.59 (s, 1H), 5.81 – 6.06 (m, 2H), 7.60 (d, *J* = 4.4 Hz, 1H), 8.06 (s, 3H). Two protons could not be located. ^{13}C NMR (101 MHz, d_6-DMSO) δ 24.3, 25.4, 32.2, 33.8, 45.7, 53.5, 58.0, 62.0, 88.7, 98.8, 121.1, 123.2 (q, *J* = 272.85), 128.5, 130.4 (q, *J* = 32.78), 142.4, 146.7, 155.3, 159.2, 167.2, 168.0, 182.1, 182.9. HRMS (ESI) calcd for $C_{26}H_{26}N_5O_2F_6$ $[M – H]^–$ 554.1991, found 554.1978. IR (neat) 2935, 2860, 1796, 1605, 1526, 1378, 1276, 1168, 1126, 982.

Data for 2c. The use of (*R*)-3-ethoxy-4-(1-phenylethylamino)cyclobut-3-ene-1,2-dione (49 mg, 0.2 mmol) gave compound **2c** as colorless amorphous solid (59 mg, 68% yield). Mp = 185.0 – 190.0 °C (decomp.). $[\alpha]_D^{31}$ = –33.4 (*c* 0.25, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 – 1.40 (m, 5H), 1.45 (d, *J* = 6.7 Hz, 3H), 1.55 – 1.70 (m, 2H), 1.86 – 1.95(m, 1H), 1.99 – 2.09 (m, 1H), 2.86 (s, 6H), 3.57 – 3.75 (m, 2H), 5.08 (bs, 1H), 5.44 (d, *J* = 1.8 Hz, 1H), 5.89 (dd, *J* = 2.3, 6.4Hz, 1H), 7.13 – 7.33 (m, 5H), 7.48 (d, *J* = 6.4 Hz, 1H). Two protons could not be located. ^{13}C NMR (101 MHz, d_6-DMSO) δ 23.0, 24.4, 25.4, 32.2, 33.6, 52.5, 53.7, 57.7, 61.7, 88.6, 98.9, 126.0, 127.3, 128.6, 143.4, 146.6, 155.4, 159.1, 166.7, 167.7, 181.7, 182.5. HRMS (ESI) calcd for $C_{25}H_{32}N_5O_2$ $[M + H]^+$ 434.2556, found 434.2547. IR (neat) 3158, 2930, 1796, 1640, 1549, 1447, 1375, 1159, 1121, 981, 758, 695.

Data for 2d. The use of (*S*)-3-ethoxy-4-(1-phenylethylamino)cyclobut-3-ene-1,2-dione (49 mg, 0.2 mmol) gave compound **2d** as colorless amorphous solid (61 mg, 70% yield). Mp = 194.0 – 203.0 °C. $[\alpha]_D^{31}$ = –103.6 (*c* 0.25, CH_2Cl_2). ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.10 – 1.41 (m, 4H), 1.47 (d, *J* = 6.4 Hz, 3H), 1.60 – 1.76 (s, 2H), 1.90 – 2.10 (m, 2H), 2.83 (s, 6H), 3.59 – 381 (m, 2H), 5.12 (bs, 1H), 5.54 (s, 1H), 5.85 – 6.02 (m, 2H), 7.21 – 7.39 (m, 5H), 7.52 (bs, 1H), 7.57 (d, *J* = 5.6 Hz, 1H), 7.82 (bs, 1H). ^{13}C NMR (101 MHz, d_6-DMSO) δ 23.1, 24.3, 32.1, 33.7, 38.9, 39.1, 39.3, 39.5, 39.7, 39.9, 40.1, 48.6, 52.5, 53.6, 57.6, 88.5, 99.0, 125.9, 127.2, 128.6, 143.5, 146.7, 155.6, 158.8, 166.8, 167.5, 181.7, 182.5. IR (neat) 3152, 2932, 2836, 1796, 1603, 1541, 1446, 1374, 1290, 1160, 757, 696.

Data for 2e. The use of 3-ethoxy-4-(*iso*-propylamino)cyclobut-3-ene-1,2-dione (37 mg, 0.2 mmol) gave compound **2e** as colorless amorphous solid (59 mg, 80% yield). Mp = 206.6 – 227.4 °C (decomp.). $[\alpha]_D^{31}$ = –7.1 (*c* 0.25, DMSO). ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.17 (d, *J* = 6.3 Hz, 6H), 1.26 – 1.55 (m, 4H), 1.74 (bs, 2H), 1.95 – 2.18 (m, 2H), 2.90 (s, 6H), 3.0 – 3.75 (m, 1H), 3.77 – 3.92 (m, 1H), 4.04 (bs, 1H), 5.59 (bs, 1H), 5.92 (bs, 1H), 6.04 (dd, *J* =

2.0, 6.1 Hz, 1H), 7.44 (bs, 2H), 7.65 (d, *J* = 6.2 Hz, 1H). ^{13}C NMR (101 MHz, d_6-DMSO) δ 23.6, 23.8, 30.4, 32.2, 33.6, 34.3, 45.4, 53.7, 56.65, 88.5, 98.9, 146.2, 155.4, 158.9, 167.0, 167.5, 181.7, 182.2. HRMS (ESI) calcd for $C_{20}H_{30}N_5O_2$ $[M + H]^+$ 372.2400, found 372.2399. IR (neat) 3367, 3208, 2930, 2858, 1795, 1602, 1403, 1386, 1155, 800.

Data for 2f. The use of 3-(cyclohexylamino)-4-ethoxycyclobut-3-ene-1,2-dione (45 mg, 0.2 mmol) compound **2f** as colorless amorphous solid (62 mg, 76% yield). Mp = 144.0 – 152.8 °C. $[\alpha]_D^{31}$ = –66.4 (*c* 0.25, CH_2Cl_2). ^{1}H NMR (400 MHz, d_6-DMSO) δ 0.99 – 1.37 (m, 10H), 1.39 – 1.50 (m, 1H), 1.50 – 1.66 (m, 4H), 1.66 – 1.83 (m, 2H), 1.83 – 2.06 (m, 2H), 2.78 (s, 6H), 3.61 (bs, 1H), 3.65 – 3.80 (m, 1H), 5.45 (bs, 1H), 5.75 (d, *J* = 8.0 Hz, 1H), 5.91 (dd, *J* = 2.1, 6.2 Hz, 1H), 7.33 (bs, 2H), 7.52 (d, *J* = 6.2 Hz, 1H). ^{13}C NMR (101 MHz, d_6-DMSO) δ 23.9, 24.3, 24.8, 32.2, 33.5, 33.7, 51.8, 53.8, 54.9, 57.5, 88.4, 98.9, 146.1, 155.4, 158.8, 167.0, 167.6, 181.6, 182.2. HRMS (ESI) calcd for $C_{23}H_{34}N_5O_2$ $[M + H]^+$ 412.2713, found 412.2718. IR (neat) 3153, 2928, 2854, 1795, 1648, 1525, 1455, 1367, 1159, 981.

Data for 2g. The use of 3-(benzhydrylamino)-4-ethoxycyclobut-3-ene-1,2-dione (61 mg, 0.2 mmol) gave compound **2g** as colorless amorphous solid (70 mg, 71% yield). Mp = 182.3 – 187.5°C (decomp.). $[\alpha]_D^{31}$ = –111.4 (*c* 0.25, CH_2Cl_2). ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.11 – 1.56 (m, 4H), 1.62 – 1.81 (m, 2H), 1.94 – 2.16 (m, 2H), 2.85 (s, 6H), 3.65 – 3.78 (m, 1H), 3.79 – 3.93 (m, 1H), 5.58 (s, 1H), 5.88 (bs, 1H), 5.96 (d, *J* = 4.8 Hz, 1H), 6.36 (bs, 1H), 7.12 – 7.44 (m, 10H), 7.54 (bs, 1H), 7.64 (d, *J* = 5.1 Hz, 1H), 8.28 (bs, 1H). ^{13}C NMR (101 MHz, d_6-DMSO) δ 24.4, 32.3, 33.8, 38.7, 53.6, 57.9, 60.2, 88.7, 98.9, 127.0, 128.6, 141.9, 142.0, 146.8, 155.3, 159.2, 166.52, 167.8, 181.7, 182.9. HRMS (ESI) calcd for $C_{30}H_{34}N_5O_2$ $[M + H]^+$ 496.2713, found 496.2676. IR (neat) 3150, 2929, 2855, 1797, 1644, 1525, 1262, 986, 695.

Data for 2h. The use of 3-(2-adamantylamino)-4-ethoxycyclobut-3-ene-1,2-dione (55 mg, 0.2 mmol) gave compound **2h** as pale yellow amorphous solid (64 mg, 69% yield). Mp = 160.1 – 174.0 °C. $[\alpha]_D^{31}$ = –50.9 (*c* 0.25, DMSO). ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.09 – 1.69 (m, 6H), 1.69 – 2.02 (m, 14H), 2.02 –2.23 (m, 2H), 2.91 (s, 6H), 3.78 (s, 1H), 3.93 (bs, 1H), 4.12 (bs, 1H), 5.57 (bs, 1H), 5.74 (bs, 1H), 6.01 (bs, 1H), 7.42 – 7.64 (m, 2H), 7.69 (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, d_6-DMSO) δ 23.0, 23.1, 24.0, 24.9, 25.2, 28.8, 28.9, 31.0, 31.3, 31.4, 32.3, 34.9, 35.0, 35.4, 52.4, 55.6, 56.3, 60.6, 87.3, 97.4, 145.6, 153.8, 158.0, 165.5, 166.3, 180.2, 181.2. HRMS (ESI) calcd for $C_{27}H_{38}N_5O_2$ $[M + H]^+$ 464.3026, found 464.3020. IR (neat) 2904, 2852, 1663, 1581, 1517, 1365, 1292, 1101, 980.

Data for 2i. The use of 3-(*tert*-butylamino)-4-ethoxycyclobut-3-ene-1,2-dione (39 mg, 0.2 mmol) gave compound **2i** as pale yellow amorphous solid (56 mg, 73% yield). Mp = 250.4 – 254.3 °C. $[\alpha]_D^{31}$ = +59.2 (*c* 0.25, DMSO). ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.01 – 1.50 (m, 4H), 1.22 (s, 9H), 1.54 – 1.72 (m, 2H), 1.86 – 2.04 (m, 2H), 2.78 (s, 6H), 3.55 – 3.78 (m, 2H), 5.45 (d, *J* = 1.8 Hz, 1H), 5.79 (d, *J* = 8.5 Hz, 1H), 5.92 (dd, *J* = 2.1, 6.2 Hz, 1H), 7.49 (bs, 2H), 7.52 (d, *J* = 6.2 Hz, 1H). ^{13}C NMR (100.6 MHz, d_6-DMSO) δ 24.3, 30.1, 32.1, 33.4, 52.0, 53.9, 57.6, 88.3, 98.9, 145.6, 155.4, 158.4, 167.6, 168.3, 180.4, 182.3. HRMS (ESI) calcd for $C_{21}H_{32}N_5O_2$ $[M + H]^+$ 386.2556, found 386.2572. IR (neat) 2928, 2855, 1791, 1668, 1520, 1446, 1358, 1300, 1163, 979.

Data for 2j. The use of 3-(1-adamantylamino)-4-ethoxycyclobut-3-ene-1,2-dione (55 mg, 0.2 mmol) gave compound **2j** as colorless amorphous solid (61 mg, 66% yield). Mp = 254.7 – 259.0 °C. $[\alpha]_D^{26}$ = –37.7 (*c* 0.25, DMSO). ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.01 – 1.45 (m, 10H), 1.46 – 1.56 (m, 1H), 1.57 – 1.87 (m, 6H), 1.90 – 2.10 (m, 2H), 2.85 (s, 6H), 3.59 – 3.87 (m, 4H), 5.52 (s, 1H), 5.85 (d, *J* = 7.6 Hz, 1H), 5.99 (dd, *J* = 2.0, 6.2 Hz, 1H), 7.41 (bs, 2H), 7.59 (d, *J* = 6.2 Hz, 1H). Two protons could not be located. ^{13}C NMR (101 MHz, d_6-

DMSO) δ 23.8, 24.3, 24.8, 32.2, 33.5, 33.7, 51.8, 53.8, 54.8, 57.6, 88.4, 98.9, 146.0, 155.4, 158.7, 167.0, 167.5, 181.6, 182.2. HRMS (ESI) calcd for $C_{27}H_{38}N_5O_2$ $[M + H]^+$ 464.3026, found 464.3023. IR (neat) 3321, 3233, 2905, 2855, 1785, 1655, 1519, 1490, 1379, 1307, 1071, 945.

Data for 2k. The use of 3-(3,5-bis(trifluoromethyl)phenylamino)-4-ethoxycyclobut-3-ene-1,2-dione (71 mg, 0.2 mmol) gave compound **2k** as pale yellow amorphous solid (91 mg, 84% yield). Mp = 196.7 – 204.0 °C (decomp.). $[\alpha]_D^{31}$ = –325.2 (*c* 0.25, CH_2Cl_2). ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.14 – 1.57 (m, 4H), 1.66 – 1.81 (m, 2H), 1.92 – 2.03 (m, 1H), 2.04 – 2.15 (m, 1H), 2.74 (s, 6H), 3.69 – 3.81 (m, 1H), 3.82 – 3.96 (m, 1H), 5.53 (s, 1H), 5.75 (d, *J* = 4.9 Hz, 1H), 5.88 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 6.0 Hz, 1H), 7.63 (s, 1H), 7.93 (s, 2H). Two protons could not be located. ^{13}C NMR (101 MHz, d_6-DMSO) δ 24.3, 24.5, 32.1, 33.4, 53.6, 59.6, 88.8, 98.7, 114.3, 117.7, 123.13 (q, *J* = 272.96 Hz), 131.25 (q, *J* = 32.2 Hz), 141.2, 146.7, 155.16, 159.4, 162.3, 169.9, 180.3, 184.7. HRMS (ESI) calcd for $C_{25}H_{26}N_5O_2F_6$ $[M + H]^+$ 542.1991, found 542.2019. IR (neat) 3322, 2936, 2860, 1792, 1696, 1604, 1529, 1448, 1378, 1276, 1125, 850.

Efforts for the synthesis of precursor of 2l.

The standard procedure failed when the amine was tritylamine even after 48 hour of stirring.[12a] Triethyl amine was added as a base in one equivalent next to activate the primary amine, but no trace of product formation was observed. Then, we tried nucleophile catalysis as well to promote the reaction using DMAP (10 mol%) in 1,2-dichloroethane, but no conversion was observed even at reflux. We tried Lewis acid catalysis ($Sc(OTf)_3$, $Zn(OTf)_2$) too, but fate did not change again.[19,20] We reasoned that the unreactivity of tritylamine could

be attributable to three phenyl rings, which might impose high steric bulkiness thereby strongly shielding the lone pair electrons on the amine.

General Procedure for Asymmetric Michael Additions

To a toluene solution (1.0 mL) of *trans-β*-nitroalkenes **4a–o** (0.20 mmol) was added 2-aminoDMAP/Squaramide **2j** (0.002 mmol, 0.98 mg or 0.004 mmol, 1.96 mg) and dibenzoylmethane **3** or active methylene compounds **6a–f** (134 mg, 0.6 mmol) at 5 °C. Stirring was continued till the consumption of limiting reagent (monitored by TLC). Thereafter, the reaction mixture was directly subjected to flash column chromatography using 1:10 EtOAc:*n*-hexanes as the eluent to afford the conjugate addition products **5a–o**.

Data for 5a. The use of (*E)*-nitrovinylbenzene **4a** (0.2 mmol) gave chiral adduct **5a** in 92% yield in 5 hours. Spectroscopic data were reported previously.[16] HPLC (AS-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 33.8 min, t_{minor} = 24.6 min, 90% ee; $[\alpha]_D^{20}$ = –6.5 (*c* 0.25, CH_2Cl_2).

Data for 5b. The use of (*E*)-1-methoxy-2-(2-nitrovinyl)benzene **4b** (0.2 mmol) gave chiral adduct **5b** in 70% yield in 6 hours. Spectroscopic data were reported previously.[16] HPLC (AS-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 20.4 min, t_{minor} = 16.6 min, 85% ee; $[\alpha]_D^{20}$ = –35.7 (*c* 1.00, CH_2Cl_2).

Data for 5c. The use of (*E*)-1-methoxy-3-(2-nitrovinyl)benzene **4c** (0.2 mmol) gave chiral adduct **5c** in 94% yield in 6 hours. Spectroscopic data were reported previously.[16] HPLC (AS-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 49.6 min, t_{minor} = 64.8 min, 90% ee; $[\alpha]_D^{19}$ = –16.2 (*c* 1.00, CH_2Cl_2).

Data for 5d. The use of (*E*)-1-methoxy-4-(2-nitrovinyl)benzene **4d** (0.2 mmol) gave chiral adduct **5d** in 70% yield in 6 hours. Spectroscopic data were reported previously.[16] HPLC (AS-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 49.7 min, t_{minor} = 35.7 min, 80% ee; $[\alpha]_D^{24}$ = –17.9 (*c* 1.00, CH_2Cl_2).

Data for 5e. The use of (*E*)-1-methyl-4-(2-nitrovinyl)benzene **4e** (0.2 mmol) gave chiral adduct **5e** in 85% yield in 2 hours. Spectroscopic data were reported previously.[16] HPLC (AS-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 30.6 min, t_{minor} = 23.0 min, 92% ee; $[\alpha]_D^{24}$ = –13.0 (*c* 1.00, CH_2Cl_2).

Data for 5f. The use of (*E*)-1-(benzyloxy)-4-(2-nitrovinyl)benzene **4f** (0.2 mmol) gave chiral adduct **5f** in 54% yield in 10 hours. HPLC (AS-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 59.1 min, t_{minor} = 47.9 min, 86% ee; $[\alpha]_D^{20}$ = –22.0 (*c* 0.25, CH_2Cl_2). Mp = 156 – 159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (dd, *J* = 14.2, 7.6 Hz, 1H), 4.75 – 4.97 (m, 4H), 5.73 (d, *J* = 8.1 Hz, 1H), 6.69 – 6.76 (m, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 7.20 – 7.36 (m, 9H), 7.38 – 7.51 (m, 2H), 7.70 (d, *J* = 7.4 Hz, 2H), 7.80 (d, *J* = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 42.4, 59.1, 68.9, 114.2, 126.4, 127.0, 127.55, 127.58, 127.76, 127.80, 127.9, 128.4, 132.7, 133.0, 134.8, 135.2, 134.9, 135.7, 157.5, 192.7, 193.3. HRMS calcd for $C_{30}H_{25}NO_5$, m/z 479.1733, found 479.1760. IR (neat) 2965, 2960, 1691,1595, 1546, 1513, 1448, 1286, 1117, 1039, 821, 733, 689 cm^{-1}.

Data for 5g. The use of (*E*)-1-chloro-2-(2-nitrovinyl)benzene **4g** (0.2 mmol) gave chiral adduct **5g** in 86% yield in 3 hours. HPLC (AS-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 24.6 min, t_{minor} = 23.1 min, 94% ee; $[\alpha]_D^{20}$ = +31.5 (*c* 0.25, CH_2Cl_2). Mp = 110 – 115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 – 5.21 (m, 3H), 5.99 (d, *J* = 6.5 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 7.03 – 7.08 (m, 1H), 7.17 – 7.12 (m, 1H), 7.25 – 7.35 (m, 5H),

7.46 (t, *J* = 7.2 Hz, 2H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.82 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 39.2, 56.1, 74.2, 126.2, 127.61, 127.66, 127.88, 127.92, 128.3, 128.6, 129.4, 132.8, 132.9, 133.1, 133.2, 134.6, 135.2, 192.3, 193.5. HRMS calcd for $C_{23}H_{18}ClNO_4$, m/z 407.0924, found 407.094. IR (neat) 2921, 2850, 1686, 1549, 1447, 1376, 1258, 1179, 756, 684 cm^{-1}.

Data for 5h. The use of (*E*)-1-chloro-3-(2-nitrovinyl)benzene **4h** (0.2 mmol) gave chiral adduct **5h** in 74% yield in 2.5 hours. HPLC (AS-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 43.9 min, t_{minor} = 24.7 min, 84% ee; $[\alpha]_D^{19}$ = +25.0 (*c* 1.00, CH_2Cl_2). Mp = 86 – 88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (td, *J* = 8.2, 5.4 Hz, 1H), 4.80 – 4.98 (m, 2H), 5.74 (d, *J* = 8.2 Hz, 1H), 7.00 – 7.07 (m, 3H), 7.15 (s, 1H), 7.24 – 7.36 (m, 4H), 7.39 – 7.51 (m, 2H), 7.67 – 7.74 (m, 2H), 7.76 – 7.83 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 42.6, 58.4, 75.9, 125.6, 127.4, 127.5, 127.6, 127.7, 127.9, 128.0, 129.2, 132.9, 133.2, 133.7, 134.6, 134.9, 137.8, 192.4, 192.9, HRMS calcd for $C_{23}H_{18}ClNO_4$, m/z 407.0921, found 407.0941. IR (neat) 2820, 1689, 1656, 1593, 1544, 1446, 1379, 1255, 958, 683 cm^{-1}.

Data for 5i. The use of (*E*)-1-chloro-4-(2-nitrovinyl)benzene **4i** (0.2 mmol) gave chiral adduct **5i** in 90% yield in 3 hours. Spectroscopic data were reported previously.[16] HPLC (AS-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 33.8 min, t_{minor} = 24.6 min, 89% ee; $[\alpha]_D^{19}$ = –6.5 (*c* 0.25, CH_2Cl_2).

Data for 5j. The use of (*E*)-1-fluoro-2-(2-nitrovinyl)benzene **4j** (0.2 mmol) gave chiral adduct **5j** in 95% yield in 3 hours. HPLC (OJ-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 53.9 min, t_{minor} = 80.4 min, 95% ee; $[\alpha]_D^{19}$ = –49.1 (*c* 1.00, CH_2Cl_2). Mp = 88 – 91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.87 – 4.70 (m, 2H), 5.02 (dd, *J* = 13.2, 10.2 Hz, 1H), 5.92 (d, *J* = 8.6 Hz, 1H), 6.82 – 6.91 (m, 2H), 7.01 – 7.09 (m, 1H), 7.16 (dt, *J* = 7.6,

1.7 Hz, 1H), 7.24 – 7.36 (m, 4H), 7.39 – 7.50 (m, 2H), 7.75 – 7.80 (m, 2H), 7.80 – 7.85 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 39.9, 57.5, 75.9, 115.9 (d, J = 22.1 Hz), 123.5 (d, J = 13.0 Hz), 124.66, 124.69, 128.58, 128.68, 128.90, 129.1, 130.01, 130.09, 131.3 (d, J = 4.1 Hz), 134.1 (d, J = 17.6 Hz), 135.9 (d, J = 41.7 Hz), 161.1 (d, J = 245.3 Hz), 193.4, 193.8. HRMS calcd for $C_{23}H_{18}FNO_4$, m/z 391.1220, found 391.1247. IR (neat) 2950, 2945, 1685, 1593, 1555, 1469, 1448, 1258, 1204, 682 cm^{-1}.

Data for 5k. The use of (*E*)-1-fluoro-4-(2-nitrovinyl)benzene **4k** (0.2 mmol) gave chiral adduct **5k** in 75% yield in 7 hours. HPLC (AS-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 34.1 min, t_{minor} = 23.3 min, 95% ee; $[\alpha]_D^{20}$ = –9.1 (*c* 0.25, CH_2Cl_2). Mp = 115 – 119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (td, J = 8.3, 5.3 Hz, 1H), 4.78 – 4.93 (m, 2H), 5.73 (d, J = 8.3 Hz, 1H), 6.76 – 6.86 (m, , 2H), 7.26 – 7.36 (m, 4H), 7.40 – 7.51 (m, 2H), 7.10–7.16 (m, 2H), 7.68–7.73 (m, 2H), 7.78–7.85 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 42.4, 58.9, 76.5, 114.8, 115.0, 126.2, 127.56, 127.68, 127.75, 127.88, 128.0, 129.0, 129.1, 131.46 (d, J = 4.0 Hz), 133.1 (d, J = 27.3 Hz), 134.96 (d, J = 30.6 Hz), 161.3 (d, J = 247.7 Hz), 192.5, 193.0. HRMS calcd for $C_{23}H_{18}FNO_4$, $[M - H]^+$ 390.1220, found 390.1239. IR (neat) 2954, 2950, 1690, 2595, 1551, 1509, 1447, 1377, 1258, 970,820, 687 cm^{-1}.

Data for 5l. The use of (*E*)-1-bromo-3-(2-nitrovinyl)benzene **4l** (0.2 mmol) gave chiral adduct **5l** in 60% yield in 5 hours. HPLC (AS-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 46.8 min, t_{minor} = 26.4 min, 83% ee; $[\alpha]_D^{24}$ = –14.6 (*c* 1.00, CH_2Cl_2). Mp = 102 – 105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51 (td, J = 8.2, 5.2 Hz, 1H), 4.80 – 4.98 (m, 2H), 5.72 (d, J = 8.0 Hz, 1H), 6.99 (t, J = 7.8 Hz, 1H), 7.09 (d, J = 7.7 Hz, 1H), 7.21 (d, J = 7.9 Hz, 1H), 7.26 – 7.38 (m, 5H), 7.43 – 7.53 (m, 2H), 7.72 (d, J = 7.5 Hz, 2H), 7.80 (d, J = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 42.6, 58.3, 75.9, 121.9, 126.1, , 127.6, 127.7, 127.9, 128.1, 129.4, 130.3, 130.4, 132.9, 133.2, 134.6, 134.9, 138.0, 192.3, 192.9. HRMS

calcd for $C_{23}H_{18}BrNO_4$, m/z 451.0419, found 451.0443. IR (neat) 2960, 1686, 1539, 1256, 1189, 1176, 958, 799, 771, 711, 666 cm^{-1}.

Data for 5m. The use of (*E*)-1-bromo-4-(2-nitrovinyl)benzene **4m** (0.2 mmol) gave chiral adduct **5m** in 75% yield in 4 hours.Spectroscopic data were reported previously.[16] HPLC (AS-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 37.0 min, t_{minor} = 26.7 min, 94% ee; $[\alpha]_D^{24}$ = –16.2 (*c* 1.00, CH_2Cl_2).

Data for 5n. The use of (*E*)-1-nitro-2-(2-nitrovinyl)benzene **4n** (0.2 mmol) gave chiral adduct **5n** in 68% yield in 18 hours. Spectroscopic data were reported previously.[16] HPLC (AS-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 32.6 min, t_{minor} = 27.2 min, 95% ee; $[\alpha]_D^{24}$ = –93.2 (*c* 1.00, CH_2Cl_2).

Data for 5o. The use of (*E*)-2-(2-nitrovinyl)furan **4o** (0.2 mmol) gave chiral adduct **5o** in 58% yield in 6 hours. Spectroscopic data were reported previously.[16] HPLC (AD-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 254 nm): t_{major} = 38.4 min, t_{minor} = 48.5 min, 98% ee; $[\alpha]_D^{19}$ = –29.5 (*c* 1.00, CH_2Cl_2).

Data for 7a. The use of malononitrile **6a** (0.2 mmol) gave racemic adduct **7a** in 94% yield in 2 hours.

Data for 7b. The use of methyl acetoacetate **6b** (0.2 mmol) gave diastereomers of chiral adduct **7b** in 96% yield in 8 hours. Spectroscopic data were reported previously.[21] HPLC (AD-H, 95:5 *n*-hexane:isopropyl alcohol, 1 mL/min, 210 nm): t_{major1} = 24.6 min, t_{minor1} = 16.7 min, 50% ee; t_{major2} = 23.2 min, t_{minor2} = 30.1 min, 57% ee.

Data for 7c. The use of acetylacetone **6c** (0.2 mmol) gave chiral adduct **7c** in 95% yield in 9 hours. Spectroscopic data were reported previously.[21] HPLC (AD-H, 85:15 *n*-hexane:isopropyl alcohol, 1 mL/min, 220 nm): t_{major} = 12.2 min, t_{minor} = 9.3 min, 80% ee;. $[\alpha]_D^{20}$ = –104.6 (*c* 0.50, CH_2Cl_2).

Data for 7f. The use of diisopropyl malonate **6f** (0.2 mmol) gave chiral adduct **7f** in 50% yield in 24 hours. Spectroscopic data were reported previously.[22] HPLC (AD-H, 80:20 *n*-hexane:isopropyl alcohol, 1 mL/min, 210 nm): t_{major} = 8.6 min, t_{minor} = 21.0 min, 50% ee. $[\alpha]_D^{20}$ = –27.0 (*c* 1.00, CH_2Cl_2).

ACKNOWLEDGEMENT

We thank to Dilşad Susam very much for conducting some experiments. We are grateful to TÜBİTAK for supporting this study (113Z156).

SUPPORTING INFORMATION

Copies of ^{1}H NMR and ^{13}C NMR spectra, and chiral HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES

1) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis.* Wiley VCH: Weinheim, 2005. (b) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed*. **2008**, *47*, 4638. (c) Macmillan, D. W. C. *Nature* **2008**, *455*, 304. (d) List, B.; Yang, J. W. *Science* **2006**, *313*, 1584.

2) For a clear presentation of this highly emerging field see: (a) Wang, Y.; Deng, L. In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; 3rd ed.; Wiley VCH: Newyork, 2010, 59-94. For some seminal works see: (b) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417. (c) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (d) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157. (e) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

3) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

4) (a) Doyle, G.; Jacobsen, E. N. *Chem. Rev.* **2007**, ***107***, 5713. (b) Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jap.* **2008**, *81*, 785. (c) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem.—Eur. J.* **2011**, *17*, 6890. (d) Narayanaperumal, S.; Rivera, D. G.; Silva, R. C.; Paixão, M. W. *ChemCatChem* **2013**, *5*, 2756.

5) (a) Gladysz, J. A. *Pure Appl. Chem.* **2001**, *73*, 1319. (b) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632.

6) Ishikawa, T. *Superbases for Organic Synthesis,* Wiley: New York, 2009.

7) (a) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. (b) Singh, A.; Yoder, R. A; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466. (c) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866. (d) Dobish, M. C.; Johnston, J. N. *Org. Lett.* **2010**, *12*, 5744. (e) Davis, T. A.; Wilt, J. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2010**, *132*, 2880. (f) Davis, T. A.; Johnston, J. N. *Chem. Sci.* **2011**, *2*, 1076. (g) Dobish, M. C.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 6068. (h) Davis, T. A.; Danneman, M. W.; Johnston, J. N. *Chem. Commun.* **2012**, *48*, 5578. (i) Shen, B.; Makley, D. M.; Johnston, J. N. *Nature* **2010**, *465*, 1027. (j) Davis, T. A.; Vilgelm, A. E., Richmond, A.; Johnston, J. N. *J. Org. Chem.* **2013**, *78*, 10605.

8) (a) Rabalakos, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 13524. (b) Wang, J.; Feringa, B. L. *Science* **2011**, *331*, 1429. (c) Yazıcıoğlu, E. Y.; Tanyeli, C. *Tetrahedron: Asymmetry* **2012**, *23*, 1694. (d) Isik, M.; Tanyeli, C. *J. Org. Chem*. **2013**, *78*, 1604.

9) (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910. (b) Ref. 2(d) herein. (c) Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. *Chem. Commun*. **2001**, 245. (d) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454. (e) Yu, Z.; Liu, X.; Zhou, L.; Lin, L.; Feng, X. *Angew. Chem. Int. Ed.* **2009**, *48*, 5195. (f) Sohtome, Y.; Shin, B.; Horitsugi, N.; Takagi, R.; Noguchi, K.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 7299. (g) Sohtome, Y.; Tanaka, S.; Takada, K.; Yamaguchi, T.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 9254. (h) Chen, X.; Dong, S.; Qiao, Z.; Zhu, Y.; Xie, M.; Lin, L.; Liu, X.; Feng, X. *Chem.—Eur. J.* **2011**, *17*, 2583.

10) For a review see: (a) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, 737. Selected examples: (b) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392. (c) Uraguchi, D.; Yoshioka, K.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2012**, *134*, 19370. (d) Corbett, M. T.; Uraguchi, D.; Ooi, T.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 4685. (e) Takeda, T.; Terada, M. *J. Am. Chem. Soc.* **2013**, *135*, 15306.

11) (a) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc*. **2012**, *134*, 5552. (b) Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc*. **2013**, *135*, 11799. (c) Núñez, M. G.; Farley, A. J. M.; Dixon, D. J. *J. Am. Chem. Soc*. **2013**, *135*, 16348.

12) (a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416. (b) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028. (c) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem., Int. Ed*. **2010**, *49*, 153. (d) Qian, Y.; Ma, G.; Lv, A.; Zhu, H.-L.; Zhao, J.; Rawal, V. H. *Chem. Commun.* **2010**,

46, 3004. (e) Yang, K. S.; Nibbs, A. E.; Türkmen, Y. E.; Rawal, V. H. *J. Am. Chem. Soc.* **2013**, *135*, 16050.

13) Recent examples of Squaramides by other groups: (a) Dai, L.; Wang, S.-X.; Chen, F.-E. *Adv. Synth. Catal*. **2010**, *352*, 2137. (b) W. Yang, D. -M. Du, *Org. Lett.* **2010**, *12*, 5450. (c) Ling, J.-B.; Su, Y.; Zhu, H.-L.; Wang, G.-Y.; Xu, P.-F. *Org. Lett.* **2012**, *14*, 1090. (d) Wang, X.; Yao, W.; Yao, Z.; Ma, C. *J. Org. Chem.* **2012**, *77*, 2959. (e) Yang, W.; Du, D.-M. *Chem. Commun.* **2011**, *47*, 12706. (f) Yang, W.; Du, D.-M. *Adv. Syn. Catal.* **2011**, *353*, 1241. (g) Xu, D. Q.; Wang, Y.-F.; Zhang, W.; Luo, S.-P.; Zhong, A.-G.; Xia, A.-B.; Xu, Z.-Y. *Chem. —Eur. J.* **2010**, *16*, 4177. (h) Wang, Y.-F.; Zhang, W.; Luo, S.-P.; Zhang, G.-C.; Xia, A.-B.; Xu, X.-S.; Xu, D.-Q. *Eur. J. Org. Chem*. **2010**, 4981. (i) Bae, H. Y.; Some, S.; Lee, J. H.; Kim, J.-Y.; Song, M. J.; Lee, S.; Zhang, Y. J.; Song, C. E. *Adv. Synth. Catal*. **2011**, *353*, 3196. (j) Min, C.; Han, X.; Liao, Z. Q.; Wu, X. F.; Zhou, H.-B.; Dong, C. *Adv. Synth. Catal*. **2011**, *353*, 2715. (k) Pansare, S. V.; Paul, E. K. *Chem. Commun*. **2011**, *47*, 1027. (l) Wu, X. F.; Min, C.; Nyamzundui, E.; Zhou, H.-B.; Dong, C. *Tetrahedron: Asymmetry* **2011**, *22*, 1640. (m) Liu, B.; Han, X.; Dong, Z.; Lv, H.; Zhou, H.-B.; Dong, C. *Tetrahedron: Asymmetry* **2013**, *24*, 1276. (n) Zhao, M.-X.; Ji, F.-H.; Wei, D.-K.; Shi, M. *Tetrahedron* **2013**,*69*, 10763. (o) Kasaplar, P.; Riente, P.; Hartmann, C.; Pericàs, M. A. *Adv. Synth. Catal*. **2012**, *354*, 2905. (p) Kasaplar, P.; Rodríguez-Escrich, P.; Pericàs, M. A. *Org. Lett.* **2013**, *15*, 3498. (q) Yang, W.; Yang, Y.; Du, D.-M. *Org. Lett.* **2013**, *15*, 1190. (r) Loh, C. C. J.; Hack, D.; Enders, D. *Chem. Commun.* **2013**, *49*, 10230. (s) Zhao, M.-X.; Bi, H.-L.; Zhou, H.; Yang, H.; Shi, M. *J. Org. Chem*. **2013**, *78*, 9377.

14) For reviews on squaramides, see ref. 4c of this work, and Storer, R. I.; Aciro, C. Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330.

15) For a review on low catalyst loading, see: Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev.* **2012**, *41*, 2406.

16) Tan, B.; Zhang, X.; Chua, P. J.; Zhong, G. *Chem. Commun.* **2009**, 779.

17) Wang, C.-J.; Zhang, Z.-H.; Dong, X.-Q.; Wu, X.-J. *Chem. Commun*. **2008**, 1431.

18) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc*. **2005**, *127*, 119.

19) Rostami, A.; Colin, A.; Li, X. Y.; Chudzinski, M. G.; Lough, A. J.; Taylor, M. S. *J. Org. Chem*. **2010**, *75*, 3983.

20) Rostami, A.; Wei, C. J.; Guérin, G.; Taylor, M. S. *Angew. Chem., Int. Ed*. **2011**, *50*, 2059.

21) Peng, F.-Z; Shao, Z.-H; Fan, B.-M; Song, H.; Li, G.-P; Zhang, H.-B *J. Org. Chem*. **2008**, 5202.

22) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc*. **2007**, *129*, 11583.