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Bifunctional Hydrogen-Bond Donors That Bear a Quinazoline or Benzothiadiazine Skeleton for Asymmetric Organocatalysis

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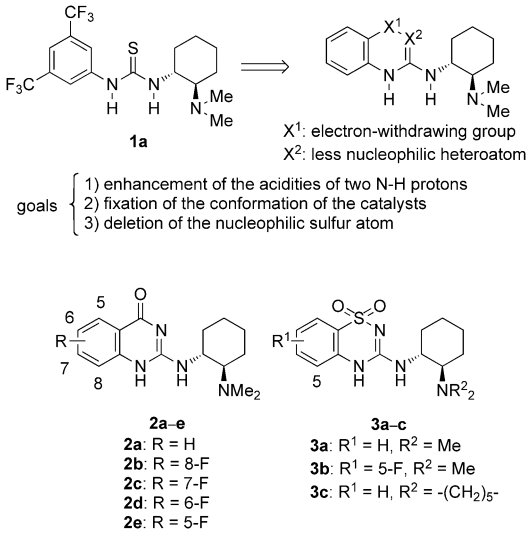
Abstract: Hydrogen-bond (HB)-donor catalysts that bear a 2-aminoquinazolin-4-(1*H*)-one or a 3-aminobenzothiadiazine-1,1-dioxide skeleton have been developed, and it has been shown that these catalyst motifs act similarly to other HB-donor catalysts such as thioureas. The highly enantioselective hydrazination of 1,3-dicarbonyl compounds was realized even at room temperature with up to 96% *ee* for 2-aminoquinazolin-4-(1*H*)-one-type catalysts, which were more effective than the corresponding urea and thiourea catalysts. In addition, benzothiadiazine-1,1-dioxide-type catalysts were shown to promote the isomerization of alkynoates to allenoates with high enantioselectivity. To overcome the problem that the products were obtained as mixtures with the starting alkynoates, we developed the tandem isomerization and cycloaddition of alkynoates for the synthesis of advanced chiral compounds such as bicyclo[2.2.1]heptenes and 3-alkylidene pyrrolidine without a significant loss of enantioselectivity.

Keywords: asymmetric synthesis · hydrogen bonds · isomerization · Michael reaction · organocatalysis

Introduction

Nonmetallic organocatalytic asymmetric reactions are powerful and environmentally friendly strategies for the synthesis of highly valuable chiral building blocks.[1] Hydrogen-bond (HB)-donor catalysts are now considered to be important compounds in organocatalysis.[2] Among them, thioureas have been recognized as some of the most advantageous HB-donating structures due to the suitable positions of two N–H protons.[3] Since we first designed a bifunctional thiourea catalyst (**1a**),[4] we and other groups have used it in various types of asymmetric reactions.[5] Recently, several new classes of HB-donor catalysts have been developed.[6–8] Ellman and co-workers demonstrated that sulfinylurea derivatives, which have more acidic protons than previously used ureas, efficiently promoted the asymmetric aza-Henry reaction of nitroalkanes with *N*-Boc (Boc = *t*-butyloxycarbonyl) imines.[6] The groups of Rawal, Nájera, and Park reported different types of HB-donor catalysts that bear a squaramide or benzimidazole moiety, respectively, and successfully applied these catalysts to several highly enantioselective reactions.[7,8] To further develop more efficient double HB-donor catalysts, we designed new and different types of bifunctional catalysts (Scheme 1). When the HB moiety and aryl group of the original aminothiourea **1a** are bridged with an electron-withdrawing group such as carbonyl or sulfone, both of the N–H protons are predicted to possess lower pK_a values due to the presence of electron-withdrawing groups. In addition, we expected that such ring formation would fix the conformation of the catalysts in a catalytically active form, which would lower the transition-state energy of the substrate–catalyst complex. We also anticipated that removal of the highly nucleophilic sulfur atom in thiourea **1a** would prevent the side reactions that are sometimes problematic in thiourea-catalyzed reactions.[9]



Scheme 1. Concept of the novel scaffolds of the HB donors.

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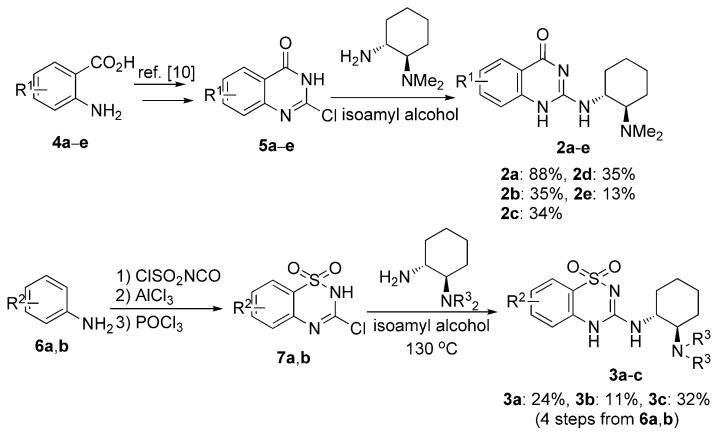
Results and Discussion

Catalysts **2a–e** were prepared from the commercially available anthranilic acids **4a–e** (Scheme 2).

We first synthesized **5a** in three steps from **4a** according to the literature.[10] Next, the condensation of **4a** and (*R*,*R*)-1,2-diaminocyclohexane[11] in isoamyl alcohol at elevated temperature gave the desired 2-aminoquinazolin-4-(1*H*)-



Scheme 2. Synthesis of the novel HB-donor catalysts **2** and **3**.

one-type catalyst **2a** in 88% yield. Catalysts **2b–e** were synthesized from the corresponding benzoic acids **4b–e** by the same method. For the synthesis of benzothiadiazine-1,1-dioxide-type catalyst **3a**, aniline **6a** was converted to **7a** in three steps. The desired product **3a** was obtained by coupling the chloride **7a** with (*R*,*R*)-1,2-diaminocyclohexane in 24% overall yield from **6a**. Benzothiadiazine catalysts **3b** and **3c** were also synthesized in a similar manner.

Single crystals of benzothiadiazine-1,1-dioxide-type catalyst **3c**[26] were obtained and subjected to X-ray crystallography (Figure 1). As in **1a**,[4b] the two N–H protons of **3c** are

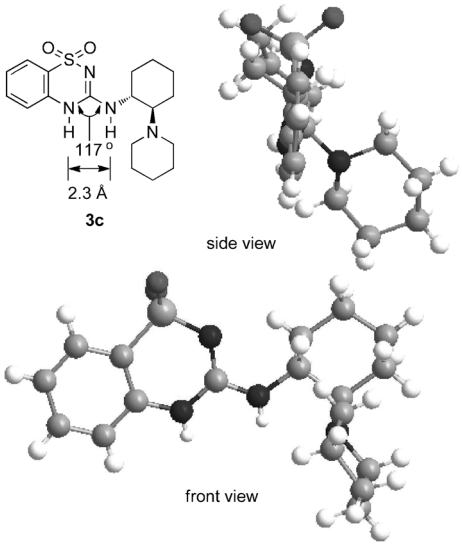


Figure 1. X-ray crystallography of **3c**.

coplanar and positioned *syn* relative to each other. However, the distance between these protons and the dihedral angle of N-C-N are 2.3 Å and 117°, respectively (Figure 1), which are slightly different values from those in **1a** (2.1 Å and 114°, respectively). Unlike in **1a**, the aromatic ring and HB-donor moieties of **3** are coplanar, which suggests that the resonance effect of catalyst **3** should be stronger than that of **1a**. Packing model studies indicated that **3c** formed several inter- and intramolecular hydrogen bonds (Figure 2). One of the two N–H protons coordinates to one of the sulfonyl oxygen atoms of another catalyst molecule, and the other N–H proton interacts with the piperidine nitrogen atom through an intramolecular hydrogen bond. These phenomena are different from those in thiourea **1a**, in which both N–H protons coordinate to the sulfur atom in an intermolecular manner. The results of crystallography suggest that these new HB-donor catalysts **2** and **3** should show catalytic activities different from that of thiourea **1a** in asymmetric reactions.

We anticipated that if these compounds are mixed with Lewis bases, they would form the hydrogen-bonded com-

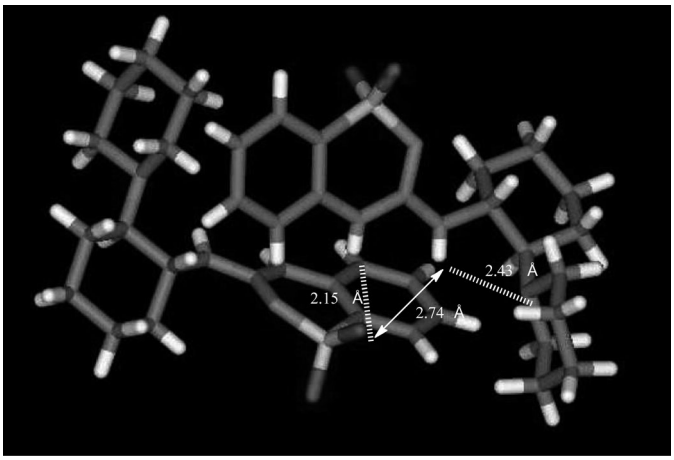
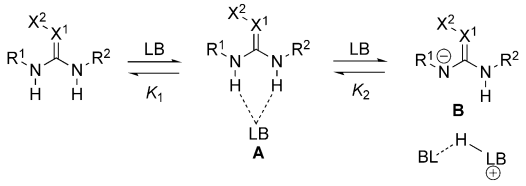


Figure 2. Packing model of **3c**.

plex **A**. In addition, if the Lewis base is strongly basic, an excess amount of Lewis base should abstract the proton from the complex **A** to produce the corresponding anion along with the dimer of the Lewis base (Scheme 3).[12]

We conducted spectrophotometric analyses to identify the HB-donating abilities of catalysts **1–3**.[12,13] In the UV spectrum of **3a** in CH_3CN, the maximum absorption (Abs) was



Scheme 3. Association models of the HB donors and Lewis bases.

observed at 248 nm. When tetrabutylammonium chloride (TBAC) was added to this solution, this signal gradually developed as more TBAC was added, and the maximum wavelength shifted to red (Figure 3A). This tendency disappeared when an excess amount of TBAC was added, and no signal development at other areas was detected over the course of the titration. In addition, two isosbestic points were observed (283 and 267 nm). These results suggest that **3a** forms only an **A**-type complex with TBAC, and the additional reaction to form the anion complex **B** does not occur under these conditions.

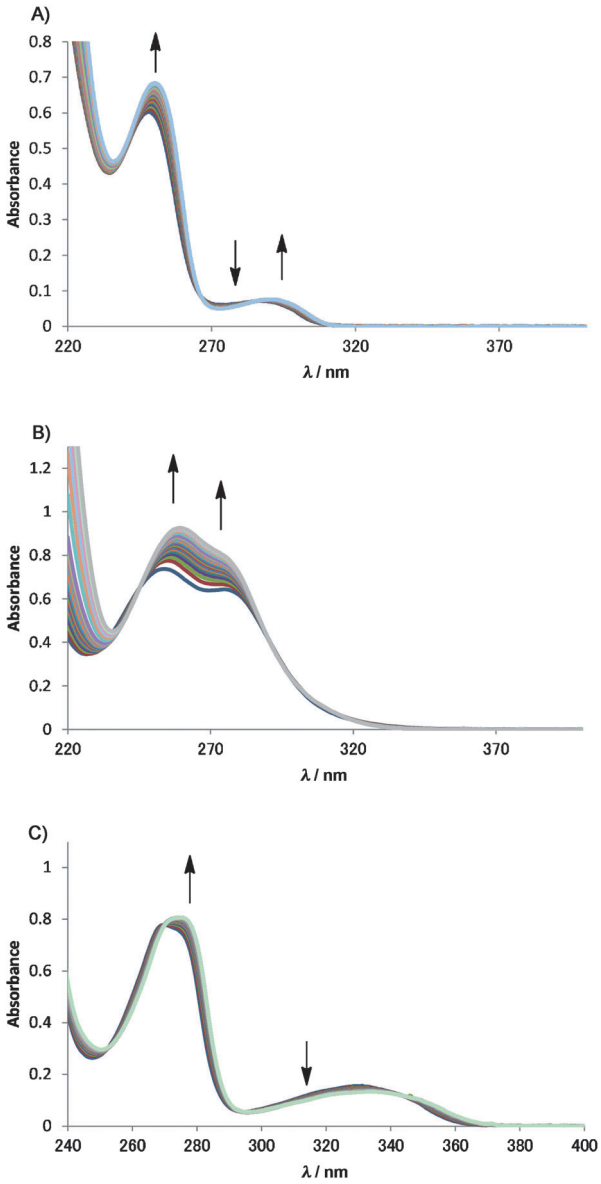


Figure 3. A) Spectrophotometric titration of **3a** (5.40×10^{-5} M) by TBAC in CH_3CN. Arrows show the directions of spectral change at increasing TBAC concentrations (0–5.67 mM). B) Spectrophotometric titration of **1a** (5.40×10^{-5} M) by TBAC in CH_3CN. Arrows show the directions of spectral change at increasing TBAC concentrations (0–13.1 mM). C) Spectrophotometric titration of **2a** (5.40×10^{-5} M) by TBAC in CH_3CN. Arrows show the directions of spectral change at increasing TBAC concentrations (0–19.9 mM).

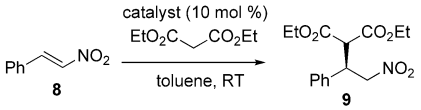
From this measurement we estimated that the association constant K_1^{3a} between free **3a** and the complex of **3a** with TBAC was 1888(±44) by using the following equation in which $\Delta\varepsilon$ is the difference in molar absorptivity between free **3a** and complexed **3a** and T is temperature [Eq. (1)]:[14,15]

$$\mathrm{Abs} = \mathrm{Abs}_0 + 0.5\,\Delta\varepsilon[[\mathrm{RH}]_T + [\mathrm{Cl}^-]_T + 1/K_1 - \{([\mathrm{RH}]_T + [\mathrm{Cl}^-]_T + 1/K_1)^2 - 4\,[\mathrm{RH}]_T[\mathrm{Cl}^-]_T\}^{0.5}] \quad (1)$$

We calculated the association constants K_1^{1a} and K_1^{2a} in the same manner. Both thiourea **1a** and quinazoline **2a** showed similar results, and the association constants K_1^{1a} and K_1^{2a} were estimated to be 1177(±37) and 489(±18), respectively (Figure 3B and C). In summary, the relative abilities of these HB donors to associate with Lewis bases were remarkably different and followed the order **3a** > **1a** > **2a**.

Next, we evaluated the reactivities of novel catalysts **2** and **3** in several asymmetric reactions. First, the Michael addition of β-nitrostyrene **8** and diethyl malonate, which has been widely used for screening the efficacy of asymmetric catalysts,[16] was performed in the presence of our new catalysts (Table 1).

Table 1. Michael addition of **8** and diethyl malonate.[a]



Entry	Catalyst	t [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	24	83	92
2	**2a**	24	70	85
3	**2b**	48	95	76
4	**2c**	48	95	82
5	**2d**	48	95	78
6	**2e**	24	69	84
7	**3a**	24	62	85
8	**3b**	24	65	78

[a] The reactions were conducted with **8** (1.0 equiv), diethylmalonate (2.0 equiv), and catalyst (10 mol %) in toluene at room temperature. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis.

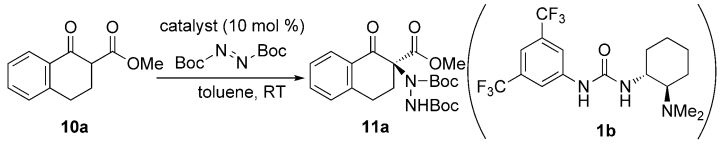
As we reported previously, the reaction of **8** and diethyl malonate catalyzed by thiourea catalyst **1a** provided the desired adduct **9** in 83% yield with 92% *ee* (Table 1, entry 1).[4b] The nonsubstituted quinazoline **2a** gave the same product **9** with slightly lower *ee*, but we also found that the position of the substituent on the aromatic ring affected the stereoselectivity of the reactions. In fact, the 7- and 5-fluoroquinazolines **2c** and **2e** gave enantioselectivities similar to that of **2a**, whereas use of the 8- and 6-substituted catalysts **2b** and **2d** led to diminished stereoselectivities relative to the other catalysts (entries 2–6). The Michael reaction with the stronger HB donors **3a** and **3b** did not improve the *ee*, and the product **9** was obtained in moderate yields and comparable enantioselectivities (entries 7 and 8).

The hydrazination of 1,3-dicarbonyl compounds with azodicarboxylates is a valuable method for installing an amino

group[17] and for synthesizing optically active quaternary amino compounds, which are often seen in biologically important compounds.[18] We reacted **10a** and *N*,*N*-di-*tert*-butylazodicarboxylate as substrates in the presence of HB-donor catalysts (Table 2).

In this reaction, use of the thiourea **1a** gave the product **11a** in poor yield (22%) (Table 2, entry 1). This low yield can be explained by the strong Lewis basicity of the sulfur atom of thiourea. Under these conditions, the sulfur moiety reacted with azodicarboxylate to completely lose its catalyst activity. To avoid this problem, we had previously used the corresponding urea catalyst **1b** instead of **1a** (entry 2).[9] With our new catalysts, the reaction proceeded smoothly in the presence of the catalyst **2a** to give the product in high yield and excellent enantioselectivity even at room temperature (entry 3), which is a major advantage over the low-temperature conditions required for catalyst **1b**. In contrast, whereas **3a** exhibited a similar reactivity, the product was obtained with lower enantioselectivity (entry 4). After further screening, we found that the 8-fluoro-substituted quinazoline **2b** was the best catalyst in terms of catalytic activity and enantioselectivity (entries 5–8).

Table 2. Hydrazination of **10a** and *tert*-butyl azodicarboxylate.[a]



Entry	Catalyst	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	20	22	83
2[d]	**1b**	5	99	87
3	**2a**	3	93	96
4	**3a**	3	82	84
5	**2b**	5	quant	96
6	**2c**	3	98	95
7	**2d**	5	99	95
8	**2e**	3	93	92

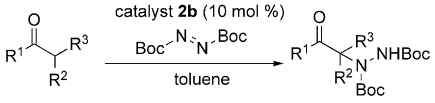
[a] Unless otherwise noted, the reactions were conducted with **10a** (1.1 equiv), di-*tert*-butyl diazodicarboxylate (1.0 equiv), and the catalysts (10 mol%) in toluene at room temperature. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] The reaction was performed at −40°C.

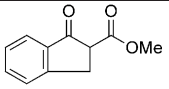
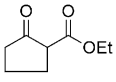
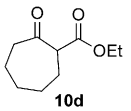
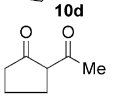
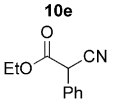
Next, we screened the scope of the 1,3-dicarbonyl compounds (Table 3). We first examined the five-membered cyclic compound **10b** as a nucleophile. When the reaction of **10b** was performed in the presence of urea catalyst **1b**, bulky *tert*-butyl ester was required as the substrate to achieve high enantioselectivity (90% *ee*).[9] With the quinazoline catalyst **2b**, even sterically less-hindered methyl ester **10b** could be used and the desired aminated compound **11b** was produced in 94% yield and 91% *ee* (Table 3, entry 1). Monocyclic compound **10c**, which is so reactive that the reaction should be performed at −78°C to maintain high stereoselectivity in **1b**-catalyzed amination,[9] furnished the adduct **11c** in high *ee* even at room temperature (entry 2). Although the 7-membered **10d** was less reactive, a prolonged reaction time led to a good chemical yield with a reasonable *ee* value (entry 3). Under the previous conditions, the reactive substrates such as 1,3-diketone **10e** and α-cyanoester **10f** led to only moderate stereoselectivities (80 and 73% *ee*, respectively).[9] However, both **10e** and **10f** reacted smoothly in the presence of **2b** to give **11e** and **11f** in high enantioselectivity (94 and 88% *ee*, respectively), which were significantly better than the results with the urea catalyst (entries 4 and 5). We suppose that the high enantioselectivities and broad substrate scopes in this reaction are due to the mild association activities of the quinazoline catalyst **2** relative to benzothiadiazine **3** described in the previous section.

To further examine the catalytic potential of these new catalysts, we explored the asymmetric isomerization of alkynoates **12** to allenoates **13**. In 2000, Shioiri and co-workers reported that chiral phase-transfer catalysts effectively promoted this isomerization, but the enantioselectivities of the obtained allenes were moderate.[19] Recently, Tan et al. succeeded in the highly enantioselective isomerization of alkynyl esters by using chiral guanidines.[20] However, the reaction has to be performed with *tert*-butyl esters at low temperature to achieve high enantioselectivity.

We initiated our investigation by studying the reaction of *tert*-butyl alkynoates **12a** and chiral HB-donors in toluene (Table 4). Although no isomerized product

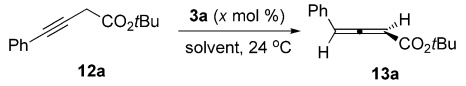
Table 3. Hydrazination of **10** and *tert*-butyl azodicarboxylate by using **2b**.[a]



Entry	Compound	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	 **10b**	−78	5	94	91
2	 **10c**	RT	4	99	84
3	 **10d**	RT	78	86	81
4	 **10e**	−78	16	87	94
5	 **10f**	−78	3	quant	88

[a] The reactions were conducted with **10** (1.1 equiv) di-*tert*-butyl diazodicarboxylate (1.0 equiv), and the catalysts (10 mol%) in toluene. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis.

Table 4. Isomerization of **12a** using chiral HB-donor catalysts.[a]



12a **13a**

Entry	Catalyst	*x*	Solvent	Yield [%][b]	**12a**:**13a**[c]	*ee* of **13a** [%][d]
1	none	–	toluene	100	100:0	–
2	**1a**	10	toluene	87	32:68	87
3	**2a**	10	toluene	100	34:66	80
4	**3a**	10	toluene	93	32:68	90
5	**3b**	10	toluene	100	30:70	83
6	**3a**	10	CH_2Cl_2	100	34:66	76
7	**3a**	10	THF	100	33:67	91
8	**3a**	5	THF	100	34:66	96
9	**3a**	2	THF	98	36:64	98

[a] The reactions were conducted with **12a** (1.0 equiv) and catalyst (*x* mol %) in several solvents at room temperature. [b] Combined yield of **12a** and **13a** after purification by column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis.

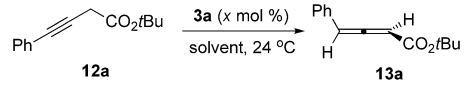
was obtained in the absence of the catalysts (Table 4, entry 1), isomerization occurred in the presence of 10 mol % of thiourea catalyst **1a**, and the desired allene **13a** was obtained as an inseparable mixture with the starting alkyne **12a** (entry 2). The enantioselectivity of **13a** was found to be 87 % *ee*. The new quinazoline-type catalyst **2a** gave a slightly diminished stereoselectivity relative to thiourea catalyst **1a** (entry 3). However, when we used the benzothiadiazine-type catalyst **3a**, we observed an increased enantioselectivity (entry 4). These results imply that the high recognition activities of HB donors were desirable for the achievement of high enantioselectivities in contrast to the hydrazination reaction in the previous section. Unfortunately, the 5-fluoro-substituted catalyst **3b** gave inferior results compared to **3a** (entry 5). In a subsequent solvent-screening, we found that THF was a suitable solvent (entries 6 and 7). We then tried to decrease the catalyst loading and found that only 2 mol % of catalyst **3a** was sufficient for the reaction to proceed smoothly (entries 8 and 9). The absolute configuration of **13a** was determined to be *S* by the Lowe–Brewster rule.[21]

We monitored the progress of the isomerization by using ^{1}H NMR spectroscopy and HPLC analysis at several time points (Table 5). Surprisingly, the reaction in dichloromethane was completed within 3 h, and the enantioselectivities gradually diminished with time (Table 5, entry 1). In THF, the reaction proceeded more slowly than in dichloromethane, and there was no decrease in stereoselectivities in this time-course study (entry 2). Next, we examined the effect of catalyst loading in a similar way and found that an increase in the catalyst loading caused high reactivity at the expense of enantioselectivity (entries 3 and 4). In summary, the reaction should be performed with a low amount of the catalyst and for just enough time for the reaction to progress to completion.

With the optimized conditions in hand (2 mol % of **3a** for 24 h at room temperature), we next explored the scope of the substrates (Table 6).

Substrates **12b–d** with electron-donating or electron-withdrawing groups at the *para* position of the phenyl rings

Table 5. Time-course analysis of the isomerization of alkynoate.[a]

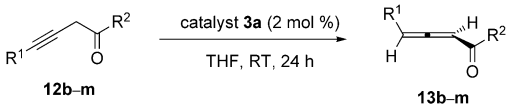


12a **13a**

Entry	*x*	Solvent	3 h	6 h	12 h	24 h
1	5	CH_2Cl_2	63:37 (96)	64:36 (93)	64:36 (90)	66:34 (83)
2	5	THF	37:63 (94)	54:46 (96)	64:36 (95)	62:38 (92)
3	10	THF	49:51 (97)	63:37 (94)	63:37 (92)	67:33 (87)
4	2	THF	18:82 (97)	32:68 (98)	49:51 (97)	61:39 (96)

[a] The reactions were conducted with **12a** (1.0 equiv) and **3a** (*x* mol %) in several solvents at room temperature. The values show the ratio of **13a**/**12a**; *ee* values of **13a** in brackets.

Table 6. Substrate scope of isomerization.[a]



12b–m **13b–m**

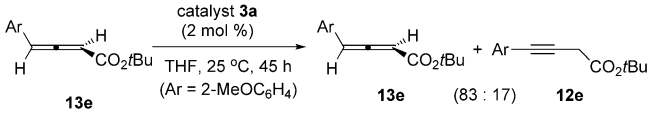
Entry	R^1	R^2	**13**	Yield [%][b]	**12**/**13**[c]	*ee* of **13** [%][d]
1	4-$MeOC_6H_4$	O*t*Bu (**12b**)	**13b**	100	47:53	97
2	4-MeC_6H_4	O*t*Bu (**12c**)	**13c**	98	39:61	95
3	4-ClC_6H_4	O*t*Bu (**12d**)	**13d**	100	30:70	95
4	2-$MeOC_6H_4$	O*t*Bu (**12e**)	**13e**	91	23:77	96
5[e]	2-ClC_6H_4	O*t*Bu (**12f**)	**13f**	100	49:51	91
6	3-MeC_6H_4	O*t*Bu (**12g**)	**13g**	100	36:64	98
7	2-$CHOC_6H_4CH_2$	O*t*Bu (**12h**)	**13h**	96	77:23	95
8	$BnOC(CH_3)_2$	O*t*Bu (**12i**)	**13i**	100	40:60	98
9	$HOC(CH_3)_2$	O*t*Bu (**12j**)	**13j**	99	23:77	97
10	C_6H_5	OEt (**12k**)	**13k**	96	33:67	97
11	C_6H_5	NMe_2 (**12l**)	**13l**	100	38:62	96
12	C_6H_5	$N(CH_2)_4$ (**12m**)	**13m**	100	38:62	94

[a] Unless otherwise noted, the reactions were conducted with **12** (1.0 equiv) and **3a** (2 mol %) in THF at room temperature for 24 h. [b] Combined yield of **13** and **12** after purification with column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] The reaction was performed for 12 h.

could be converted to the corresponding allenes **13b–d** in high enantioselectivities (Table 6, entries 1–3). In addition, the positions of the substituents on the phenyl rings did not influence the stereoselectivities of the isomerization, and all of the substrates **12e–g** achieved good to high *ee* values (entries 4–6). As with the aromatic substrates, alkyl alkynoates **12h–j** underwent the desired reaction smoothly with excellent selectivity with only 2 mol % of the catalyst (entries 7–9). We next examined substrates other than *tert*-butyl esters and found that, in contrast to Tan and co-workers' report, the considerably less bulky ethyl ester **12k** was well tolerated and the enantioselectivity was still excellent (entry 10). Although the reactions of alkynyl amides **12l** and **12m** gave somewhat lower conversion compared to alkynyl esters, the stereoselectivities remained at high levels (entries 11 and 12). To the best of our knowledge, these are the first examples of the highly enantioselective isomerization of alkynyl amides to the corresponding allenes.

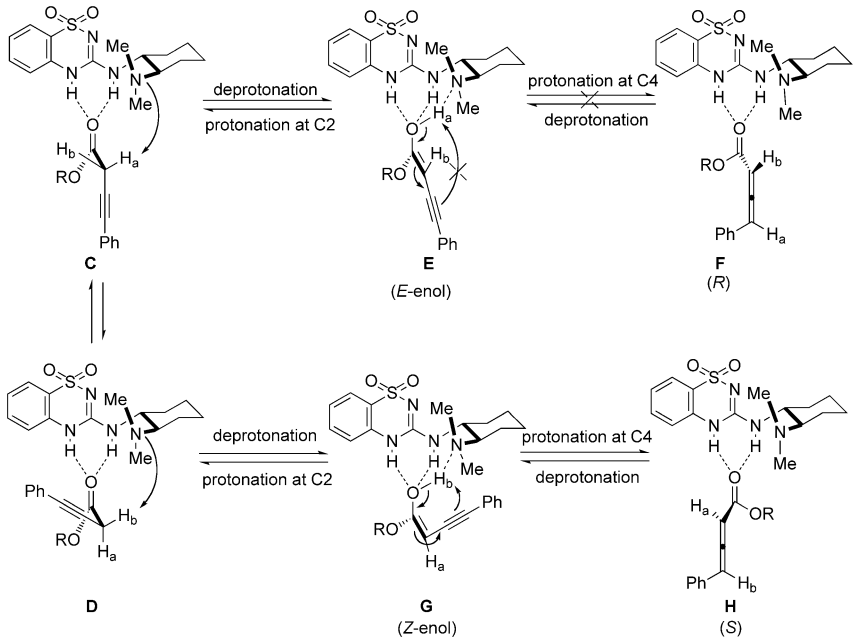
Among the allenoates that we prepared, **13e** and **13j** were isolable from the corresponding alkynoates **12e** and

12j. When the isolated allene **13e** was treated with catalyst **3a** for a longer time (45 h), the corresponding alkynoate **12e** was produced slowly and obtained as a minor product along with **13e** (Scheme 4). This result confirms that the isomerization of **12** or **13** in the presence of **3a** is reversible.



Scheme 4. Isomerization of allenoate to alkynoate.

A plausible reaction mechanism of this enantioselective isomerization is shown in Scheme 5. This mechanism is consistent with the results of the isomerization of the allenoate to alkynoate and the absolute configuration of the resulting allenoate.



Scheme 5. Plausible mechanism of the enantioselective isomerization of the alkynoates.

At the point of the abstraction of the α proton of the alkynoate, two possibilities can be considered. If the catalyst predominantly abstracts the H_a proton of conformer **C**, allenoate **F** with an *R* configuration would be formed through the *E*-enol **E**. On the other hand, if the same reaction occurs from **D**, the absolute configuration of the allenoate **H** should be *S* through the *Z*-enol **G**. All of these pathways should be reversible to explain the observed conversion of the allenoate to the corresponding alkynoate in the presence of the HB donor. If we compare these two pathways, the proton-migration step from **G** to **H** is expected to be more favorable than that from **E** to **F**, and this could explain the stereoselectivity of this isomerization. This selectivity agrees with the experimental results. Further studies that use a computational analysis to reveal the reaction mechanism are currently underway.

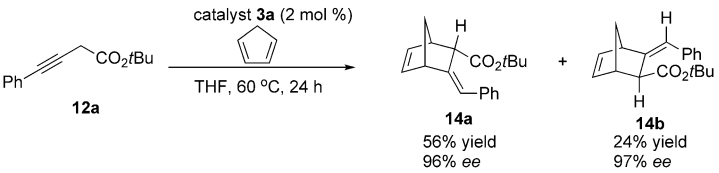
To improve the conversion of the desired allenoates, we attempted the tandem isomerization and cycloaddition of the obtained **13e** with a proper diene or 1,3-dipole.[22] We considered that if the generated allenes would be trapped by the coexisting reagents, the equilibrium of the isomerization may be shifted to the generation of allenes and complex cyclic compounds would be obtained in high enantioselectivities and in one pot.

Indeed, when cyclopentadiene was present during the isomerization of **12a**, a subsequent Diels–Alder reaction of the resulting allene and cyclopentadiene occurred[23] to give the corresponding cycloadduct **14a** in good yield and high *ee*, even at elevated temperature, together with the minor product **14b** (Scheme 6).

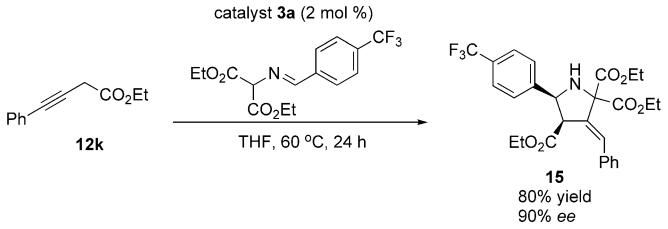
Furthermore, azomethine ylide proved to be useful for the tandem reaction. Using this method, we synthesized the synthetically useful 3-alkylidene pyrrolidine **15** as a single product in a one-pot process from the corresponding alkynoate **12k** without a significant loss of enantioselectivity (Scheme 7).[24,25]

Conclusion

In summary, we have shown that the newly designed 2-aminoquinazolin-4-(1*H*)-one **2** and 3-amino-4*H*-benzo[*e*]-[1,2,4]thiadiazine-1,1-dioxide **3** are novel, active, and selective bifunctional HB-donor catalysts. The association activities of these HB donors with the Lewis bases differ from each other, and the optimal catalysts were different depending on the reaction examined. Catalysts **2**, which possessed mild association activities, showed good results in the hydrazination. In contrast, with **3**, which possess high activities for the association with the Lewis base, we achieved the highly enantioselective isomerization of alkynoates to allenoates and showed that it could be used in a tandem reaction for



Scheme 6. Tandem isomerization: Diels–Alder reaction.



Scheme 7. Tandem isomerization: [3+2] cycloaddition.

the synthesis of more advanced compounds. Mechanistic studies regarding these novel catalysts are currently underway.

Experimental Section

Typical procedure for the synthesis of the quinazoline catalyst: Compound **5a** (393 mg, 2.18 mmol) was added to a mixture of N^1,N^1-dimethylcyclohexanediamine (282 mg, 1.98 mmol) and triethylamine (0.3 mL, 2.14 mmol) in isoamylalcohol (4.0 mL) and stirred at 130 °C for 13 h. Then, the reaction mixture was extracted with $CHCl_3$ three times. The extract was dried over K_2CO_3 and purified by silica gel column chromatography (EtOAc/MeOH/triethylamine 97:0:3 to 80:15:5) to afford quinazoline **2a** (yellow amorphous, 537 mg, 88 %). $[\alpha]_D^{25} = -30$ ($c = 0.93$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 8.10$ (dd, $J^1 = 7.9$ Hz, $J^2 = 1.4$ Hz, 1H), 7.52 (ddd, $J^1 = J^2 = 7.9$ Hz, $J^3 = 1.4$ Hz, 1H), 7.22 (d, $J = 7.9$ Hz, 1H), 7.12 (dd, $J^1 = J^2 = 7.9$ Hz, 1H), 3.69–3.57 (m, 1H), 2.52 (ddd, $J^1 = J^2 = 10.3$ Hz, $J^3 = 2.9$ Hz, 1H), 2.45–2.32 (m, 1H), 2.36 (s, 6H), 1.96–1.87 (m, 1H), 1.87–1.69 (m, 2H), 1.52–1.16 ppm (m, 4H); ^{13}C NMR ($(CD_3)_2CO$, 126 MHz) $\delta = 165.5$, 153.3, 150.7, 134.6, 127.1, 124.1, 122.5, 118.7, 67.5, 53.0, 40.4, 33.7, 25.8, 25.4, 22.7 ppm; IR (KBr) $\tilde{\nu} = 3254$, 1679, 1606 cm^{-1}; LRMS (FAB$^+$): m/z: 287 [M+H$^+$] (100); HRMS (FAB$^+$): m/z: calcd for $[C_{16}H_{23}N_4O]^+$: 287.1872; found: 287.1881.

Typical procedure for the synthesis of the benzothiadiazine catalyst: $ClSO_2NCO$ (1.17 mL, 13.4 mmol) was added to a solution of **6a** (1.04 g, 11.2 mmol) was added at −40 °C and stirred at room temperature. After 30 min, $AlCl_3$ (2.00 g, 15.0 mmol) was added and stirred at 110 °C for 30 min. Then the reaction mixture was poured into ice water, and the resulting brown precipitate was washed with water. This crude product was used without further purification. 2,6-Lutidine (0.507 mL, 4.35 mmol) was added to a mixture of the crude solids and $POCl_3$ (5.10 mL, 54.4 mmol) at room temperature and stirred at 110 °C for 12 h. Then the reaction mixture was cooled to 0 °C, quenched with water, and the resulting brown precipitate was washed with water. This crude product was used without further purification. N^1,N^1-dimethylcyclohexanediamine (498 mg, 3.50 mmol) and triethylamine (0.488 mL, 3.50 mmol) were added to a solution of the crude solids in isoamylalcohol (15 mL) and stirred at 130 °C for 24 h. Then the reaction mixture was evaporated in vacuo, extracted with $CHCl_3$ three times, dried over Na_2SO_4, and evaporated in vacuo. The resulting residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/30 % NH_3 (aq) = 85:15:1) to afford benzothiadiazine **3a** (white solid, 866 mg, 24 % from **6a**). M.p. 222–223 °C (hexane/ethyl acetate); $[\alpha]_D^{25} = +32.6$ ($c = 0.97$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta =$ 7.88 (d, $J = 7.80$ Hz, 1H), 7.42 (dd, $J^1 = J^2 = 7.80$ Hz, 1H), 7.22 (dd, $J^1 = J^2 = 7.80$ Hz, 1H), 6.91 (d, $J = 7.80$ Hz, 1H), 6.19–4.96 (br, 1H), 3.60–3.40 (m, 1H), 2.48–2.19 (m, 1H), 2.34 (s, 6H), 1.96–1.85 (m, 1H), 1.85–1.77 (m, 1H), 1.77–1.64 (m, 1H), 1.33–1.06 ppm (m, 4H); ^{13}C NMR ($CDCl_3$, 126 MHz) $\delta = 151.8$, 136.1, 132.5, 124.0, 123.6, 122.1, 116.7, 67.0, 52.5, 40.2, 32.9, 24.6, 24.4, 22.1 ppm; IR (ATR) $\tilde{\nu} = 3292$, 1626, 1583, 1500, 1257, 1153 cm^{-1}; LRMS (FAB$^+$): m/z: 323 [M+H$^+$] (100); HRMS (FAB$^+$): m/z: calcd for $[C_{15}H_{23}N_4O_2S]^+$: 323.1536; found: 323.1544.

Typical procedure for enantioselective Michael addition of malonate to nitroolefin: A mixture of *trans*-β-nitrostylene **8** (34.3 mg, 0.23 mmol), diethyl malonate (2.0 equiv, 0.065 mL), and thiourea catalyst **1a** (10 mol %, 9.5 mg) in toluene (0.4 mL) was stirred at room temperature for 24 h. Without any other manipulation, the reaction mixture was purified by silica gel column chromatography with hexane/EtOAc (95:5→9:1→4:1) to afford desired product **9** (59.2 mg, 83 %). ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 7.34$–7.23 (m, 5H), 4.95–4.83 (m, 2H), 4.27–4.18 (m, 3H), 4.01 (q, $J =$ 7.08 Hz), 3.82 (d, $J = 9.28$ Hz), 1.26 (t, $J = 7.08$ Hz), 1.05 ppm (t, $J =$ 7.08 Hz); HPLC: Chiralcel AD-H, hexane/EtOH 9:1, 1 mL min^{-1}, 254 nm, retention times: 11.7 min (major), 15.5 min (minor).

Typical procedure for enantioselective amination reaction: Compound **11a** (46.7 mg, 1.1 equiv) and quinazoline-4-one catalyst **2b** (6.2 mg, 10 mol %) were added to a stirred solution of di-*tert*-butylazodicarboxylate (47.8 mg, 0.21 mmol) in toluene (2.0 mL) at room temperature. After 5 h, the reaction mixture was purified by silica gel column chromatography with hexane/EtOAc (9:1→1:1) to afford desired **11a** (83.5 mg, 97 %) as a white solid. ^{1}H NMR ($CDCl_3$, 500 MHz) $\delta = 7.89$–7.70 (br, 1H), 7.49–7.29 (br, 1H), 7.25–7.01 (br, 2H), 6.31 (brs, 1H), 3.72 (s, 3H), 3.50–3.08 (br, 1H), 3.08–2.75 (br, 1H), 2.74–2.43 (br, 1H), 1.38–0.79 ppm (m, 18H); HPLC: Chiralcel OD-H, hexane/isopropanol = 95:5, 0.5 mL min^{-1}, 254 nm, retention times: 15.5 min (major), 18.2 min (minor).

Typical procedures for preparation of alkynyl esters: *tert*-Butyl diazoacetate (855 mg, 6.01 mmol) was added slowly to a mixture of phenylacetylene (614 mg, 6.01 mmol), MeCN (5.0 mL), and CuI (619 mg, 3.25 mmol) at room temperature and stirred at the same temperature for 13 h under an argon atmosphere. The reaction mixture was concentrated in vacuo and purified by silica gel column chromatography with hexane/chloroform = 7:3 to afford desired product as yellow oil (910 mg, 70 % with corresponding allenoate **13a** as inseparable minor product (5 %)). The allenoate **13a** could be removed by a known procedure.[19] *tert*-Butyl-4-phenylbut-3-ynoate (**12a**): yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 7.47$–7.40 (m, 2H), 7.32–7.21 (m, 3H), 3.41 (s, 2H), 1.49 ppm (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 167.4$, 131.7, 128.2, 128.1, 123.2, 83.3, 81.9, 81.8, 27.9, 27.8 ppm; HPLC: Chiralpak IC, hexane/isopropanol 98:2, 0.5 mL min^{-1}, 254 nm, retention time: 12.6 min.

Typical procedure for enantioselective isomerization of alkynyl esters or amides to allenes: A solution of *tert*-butylalkynoate (**12a**; 67.0 mg, 0.32 mmol) and benzothiadiazine catalyst **3a** (2.1 mg, 0.0065 mmol) in THF (3.0 mL) was stirred at 25 °C for 24 h. The resulting mixture was directly purified by silica gel column chromatography to afford a mixture of corresponding allenoate **13a** and alkynoate **12a** (69.2 mg, 98 %, **13a**/**12a** 64:36). The ratio of allenoate/alkynoate was determined by the integration values of ^{1}H NMR spectroscopy. The absolute configuration of allenes were determined by the Lowe–Brewster rule.[20] (*S*)-*tert*-Butyl-4-phenylbuta-2,3-dienoate (**13a**): Yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 7.37$–7.19 (m, 5H), 6.54 (d, $J = 6.4$ Hz, 1H), 5.92 (d, $J = 6.4$ Hz, 1H), 1.48 ppm (s, 9H); HPLC: Chiralpak IC, hexane/isopropanol = 98:2, 0.5 mL min^{-1}, 254 nm, retention times: 10.8 min (major), 13.6 min (minor), 98 % *ee*.

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[25] The stereochemistries of **17a**,**b** and **18** were determined by NOESY. See the Supporting Information for details.

[26] CCDC-821385 contains the supplementary crystallographic data for **3c**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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