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Chemoselective reactions under solvent-free conditions: lanthanide-catalyzed syntheses of 2-amino-3,1-benzothiazines and 3,4-dihydroquinazoline-2-thiones†

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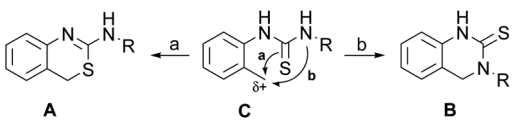
A catalyst-controlled chemoselective reaction of *o*-aminocinnamate and isothiocyanates in the presence of lanthanide complexes under mild and solvent-free conditions was developed. 2-Amino-3,1-benzothiazines were obtained in high yields when the reactions were catalyzed by $Yb(OTf)_3$, whereas those catalyzed by $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ afforded 3,4-dihydroquinazoline-2-thiones in high to excellent yields. The mechanism for the product selectivity and high efficiency of the reaction was proposed.

Introduction

Selective reactions are powerful tools in organic synthesis because they provide chemists with the means to produce different products from the same starting materials, depending on what they are trying to achieve, which not only improves the overall level of synthetic efficiency but also reduces chemical waste and the occurrence of undesired by-products. Catalyst-controlled selective reactions have attracted, and continue to attract, significant levels of attention from synthetic chemists. In a recent review of selectivity in organic synthesis, Bode[1] stated that "there is growing recognition that all classes of selectivity can be exquisitely controlled by the design and choice of the appropriate catalyst". Compared with well-studied catalyst-controlled enantioselective reactions, however, catalyst-controlled chemoselective reactions have received a much lower level of attention.

Lanthanide ions have distinctive characteristics, such as strong Lewis acidity, tuneable ancillary ligation properties, and large ionic radii accompanied with lanthanide contraction. Lanthanide complexes have therefore emerged as efficient catalysts in many useful transformations.[2] Although the subtle combination of these characteristics may lead to divergent reaction pathways with high levels of selectivity when multicenter substrates are used as starting materials, reports concerning the development and application of lanthanide-catalyzed chemoselective reactions have been scarce.

2-Amino-3,1-benzothiazine[3] (Scheme 1, **A**) and 3,4-dihydroquinazoline-2-thione[4] (Scheme 1, **B**) are both useful heterocyclic compounds with a range of biological applications. The majority of the approaches[5] available for the preparation of 2-amino-3,1-benzothiazines are based on the reactions of aromatic amines or thioureas bearing a halomethyl or hydroxymethyl substituent at the *ortho* position of the aromatic ring, with a strong Bronsted acid or noble metal catalyst being required in most cases to facilitate the reaction. Furthermore, these reactions invariably required heating under reflux in organic solvents, as well as complex and sometimes inaccessible substrates, and multistep reaction processes appeared to be essential to obtain satisfactory results. In contrast, 3,4-dihydroquinazoline-2-thiones are generally synthesized according to one of two routes. The first of these routes involves the treatment of 2-aminobenzyl alcohols or 2-aminophenones with isothiocyanates or isothiocyanic esters,[6] and requires the addition of concentrated hydrogen chloride for high yields, whereas the second of these routes involves the condensation of carbon disulfide with aromatic amines bearing an aminomethyl substituent at the *ortho* position of the aromatic ring.[7] Kobayashi *et al.*[8] recently developed an efficient method for the selective preparation of 2-amino-3,1-benzothiazines and 3,4-dihydroquinazoline-2-thiones by the reaction of 3-(2-isothiocyanatophenyl)propanoic acid derivatives with secondary and primary amines, respectively. In this particular case, the structural feature of the substrate (*i.e.*, the amine) effectively dictated the product selectivity.



Scheme 1 Projected synthetic route.

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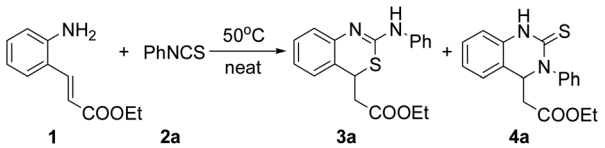
In a recent publication, we described the synthesis of 2-amino-3,1-benzothiazines *via* the ytterbium chloride-catalyzed tandem addition-cyclization reactions of *o*-aminocinnamate with variety of different isothiocyanic esters.[9] The key intermediate in this particular reaction process was identified as a thiourea, which behaves as a nucleophile from its S-terminal to form the target product. Prompted by this result, we envisaged that the thiourea **C** could undergo an intramolecular cyclization reaction, in the presence of suitable metal catalyst, with either the S-terminal or the N-terminal of the thiourea behaving as the nucleophile to selectively form the 2-amino-3,1-benzothiazine **A** or 3,4-dihydroquinazoline-2-thione **B**, respectively (Scheme 1). In a continuation of our previous studies towards the development of lanthanide-catalyzed carbon–nitrogen and carbon–phosphorus bond-forming reactions,[10,11] we became interested in the idea of developing methods utilizing lanthanide complexes as catalysts for constructing these two heterocycles in an efficient, atom-economical, and controllable manner. Herein, we would like to disclose our recent results towards the realization of this idea.

Results and discussion

To begin with, we tested our idea using the reaction of ethyl *o*-aminocinnamate with phenyl isothiocyanate at 50 °C under solvent-free conditions as a model reaction (Table 1). Our initial efforts revealed that the reaction did not proceed in the absence of catalyst (Table 1, entry 1). When 0.5 mol% of the well-known Lewis acid ytterbium triflate [$Yb(OTf)_3$] was added to the reaction, ethyl 2-(2-(phenylamino)-4*H*-benzo[*d*][1,3]thiazin-4-yl)-acetate **3a** was formed in 50% yield (Table 1, entry 2). Pleasingly, when the catalyst loading was increased to 1 mol%, the reaction proceeded to a greater extent, with the yield increasing dramatically to 98% (Table 1, entry 3). The temperature was also found to have a significant effect on the rate of the reaction. For example, when the reaction carried out at 25 °C, the desired yield could only be obtained when the catalyst loading was increased to 5 mol% and the reaction time was extended to 20 hours (Table 1, entry 4). To assess the influence of the central metal on the catalytic activity of the Lewis acid, a variety of different lanthanide triflates were evaluated in the reaction (Table 1, entries 3 and 5–7). The results revealed that the yield of the reaction decreased progressively as the ionic radius of the Ln(III) increased from the heavy rare earth Yb to the light rare earth La. The triflate complex of Yb, which was the smallest and most Lewis acidic among those tested, gave the best result in the reaction (Table 1, entry 3). The use of $Cu(OTf)_2$ as catalyst in the model reaction was also evaluated (Table 1, entry 8). Interestingly, another compound was isolated as the major product of this particular reaction, and the anticipated product **3a** was isolated only as a minor product in 26% yield. Structure

Table 1 Screening of catalysts for the reaction of ethyl *o*-aminocinnamate and phenyl isothiocyanate[a]



1 2a 3a 4a

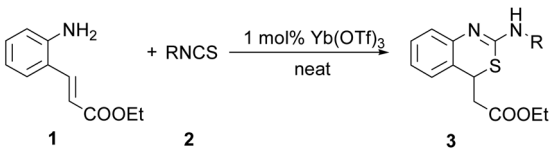
Entry	Catalyst	Loading (mol%)	Time (h)	HPLC yield (%) 3a	4a
1	—		5	Trace	Trace
2	$Yb(OTf)_3$	0.5	4	50	Trace
3	$Yb(OTf)_3$	1	4	98	Trace
4[b]	$Yb(OTf)_3$	5	20	92	Trace
5	$Sm(OTf)_3$	1	4	89	Trace
6	$Nd(OTf)_3$	1	4	85	6
7	$La(OTf)_3$	1	4	84	5
8	$Cu(OTf)_2$	1	4	26	70
9	$Zn(OTf)_2$	1	4	44	42
10	$[(Me_3Si)_2N]_3Yb(\mu\text{-}Cl)Li(THF)_3$	5	5	3	80
11	$[(Me_3Si)_2N]_3Sm(\mu\text{-}Cl)Li(THF)_3$	5	5	4	90
12	$[(Me_3Si)_2N]_3Nd(\mu\text{-}Cl)Li(THF)_3$	5	5	Trace	91
13	$[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$	5	5	Trace	95
14[b]	$[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$	5	13	Trace	97
15	$[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$	2.5	5	Trace	92
16	$[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$	1	5	5	78
17	$[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$	2.5	4	Trace	86
18	$LiN(SiMe_3)_2$	7.5	5	3	73
19[c]	$[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$	2.5	5	Trace	91
20	$La[N(SiMe_3)_2]_3$ + LiCl	2.5	5	23	70

[a] Reactions were performed with 1 mmol of ethyl *o*-aminocinnamate and 1.2 mmol of phenyl isothiocyanate at 50 °C. [b] Reaction conducted at 25 °C. [c] The catalyst in this reaction was formed *in situ*.

elucidation by ^{1}H NMR, ^{13}C NMR and high resolution mass spectroscopy (HRMS) revealed this compound to be ethyl 2-(3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate **4a**. In a separate experiment involving the use of $Zn(OTf)_2$ as the catalyst, compound **4a** was isolated in a 42% yield together with **3a**, which was isolated in 44% yield (Table 1, entry 9). These results indicated that $Ln(OTf)_3$ catalysts are highly efficient catalysts for the selective transformation of the substrates into **3a**, whilst providing only minor traces of **4a**.

We then proceeded to investigate the scope of this $Yb(OTf)_3$ catalyzed transformation by reacting a variety of different isothiocyanates with *o*-aminocinnamate under the optimized conditions (Table 2). It is clear from the table that all of the reactions proceeded smoothly to afford the corresponding 2-amino-3,1-benzothiazines in high yields under solvent-free conditions. The reaction appeared to be generally applicable to aryl isothiocyanates bearing substitutions at the *ortho*-, *meta*- and *para*-positions, with electron deficient and electron rich isothiocyanates being well tolerated under the optimized conditions. In contrast to aryl isothiocyanates, which performed well under the optimized conditions, alkyl isothiocyanates exhibited lower levels of reactivity and required extended reaction time to provide yields comparable to those of aryl isothiocyanates. For example, methyl isothiocyanate only provided a yield similar to those of aryl isothiocyanates when the reaction time was prolonged to 15 hours. The bulkier cyclohexyl isothiocyanate gave a lower yield of 79%, even when the reaction was conducted at 70 °C over an extended reaction time of 48 hours. Overall, however, these results suggested that $Yb(OTf)_3$ was particularly active in catalyzing the addition-cyclization reactions of *o*-aminocinnamate with isothiocyanates to form 2-amino-3,1-benzothiazines.

Table 2 $Yb(OTf)_3$-catalyzed reactions of *o*-aminocinnamate with isothiocyanates[a]



1 2 3

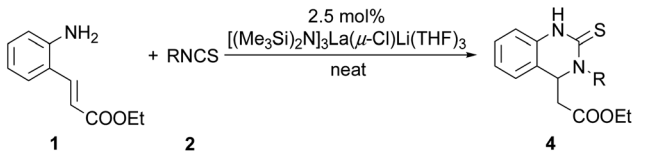
Entry	R	Temp. (°C)	Time (h)	Product	Isolated yield (%)
1	Ph	50	4	**3a**	97
2	*p*-FC_6H_4	50	4	**3b**	98
3	*p*-ClC_6H_4	50	4	**3c**	93
4	*p*-BrC_6H_4	50	4	**3d**	97
5	*p*-$NO_2C_6H_4$	50	4	**3e**	95
6	*p*-MeC_6H_4	50	4	**3f**	98
7	*p*-$MeOC_6H_4$	50	4	**3g**	99
8	*m*-$MeOC_6H_4$	50	4	**3h**	91
9	*m*-ClC_6H_4	50	4	**3i**	90
10	*o*-ClC_6H_4	50	4	**3j**	94
11	*o*-FC_6H_4	50	4	**3k**	96
12	CH_3	50	15	**3l**	95
13	Cyclohexyl	70	48	**3m**	79

[a] Reactions were performed with 1 mmol of ethyl *o*-aminocinnamate and 1.2 mmol of the isothiocyanates.

Although the formation of **4a** was observed in the $Cu(OTf)_2$ and $Zn(OTf)_2$ catalyzed reactions, the product selectivity was not satisfactory. Pleasingly, however, further screening of the lanthanide catalysts revealed that the addition of 5 mol% of the lanthanide amide $[(Me_3Si)_2N]_3Yb(\mu\text{-}Cl)Li(THF)_3$ to the reaction effectively facilitated the selective transformation of the substrates into the corresponding product **4a** at 50 °C under solvent-free conditions (Table 1, entry 10), with only a minor trace of **3a** being formed. Tetracoordinate lanthanide amide complexes of the formula $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$[12,13] are chloride-bridged "ate" complex derived from homoleptic Ln $[N(SiMe_3)_2]_3$, and have been reported as efficient catalysts for a number of useful transformations.[11,14,15] In most cases, their distinctive properties may be rationalized by the cooperation of their Lewis acidity and Bronsted basicity. During the optimization of the reaction conditions, a relationship between the catalytic activity and the size of the metal ion was also observed (Table 1, entries 10–13). The rate of the reaction for the formation of **4a**, however, followed an opposite trend to that observed for **3a**, with lanthanides with a larger ionic radius providing greater reaction rates. Similarly, the temperature had a significant impact on the reactivity. For example, when the reaction was carried out at 25 °C, the desired yield of the product could only be achieved when the reaction time was extended to 13 hours (Table 1, entry 14). When the loading of the catalyst was reduced to 2.5 mol%, a good yield of 92% was still observed (Table 1, entry 15). A further reduction in the catalysts loading to 1 mol%, however, led to a significant reduction in the yield to 78% (Table 1, entry 16). A control reaction was conducted using $LiN(SiMe_3)_2$ (7.5 mol%) as the catalyst and gave **4a** in a yield of 73% (Table 1, entry 18), and effectively highlighted the importance of the lanthanide ion to the catalytic system. It has been reported that $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ can be formed *in situ* by the metathesis reaction of $LnCl_3$ with 3 equiv. of $LiN(SiMe_3)_2$ in THF.[13,14] To develop a greater understanding of the influence of the catalyst structure on the catalytic activity, the model reaction was performed using $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ which was formed *in situ* from the reaction of lanthanum chloride with lithium silylamide as the catalyst (Table 1, entry 19). The result revealed that the *in situ* formed catalyst showed the same level of activity as that of the same catalyst prepared under the standard reaction conditions. However, the use of a 1 : 1 mixture of $La[N(SiMe_3)_2]_3$ and anhydrous LiCl in THF as the catalyst failed to produce the same effect with $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ (Table 1, entry 20). These results indicated that the nature of the combination of $La[N(SiMe_3)_2]_3$ with LiCl in crystalline $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)$-$Li(THF)_3$ may be a key factor in determining its catalytic ability. On the basis of all of these results, the optimized reaction conditions for the selective formation of **4a** were selected as 2.5 mol% $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ at 50 °C for 5 hours.

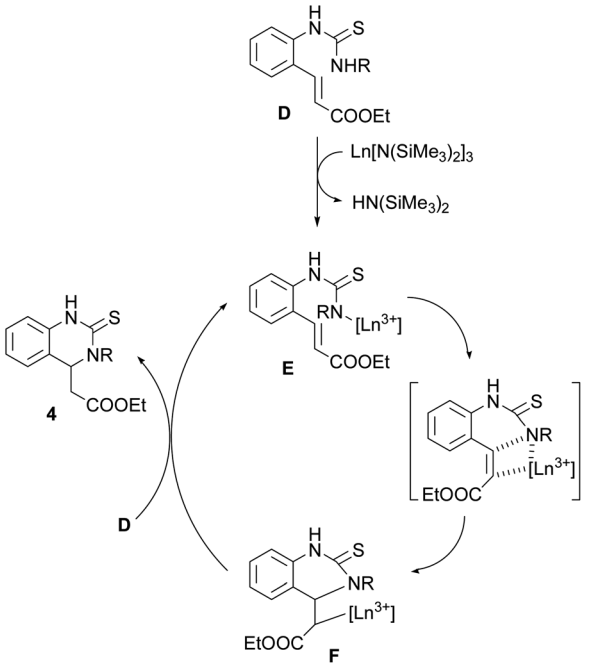
With the optimized conditions in hand, the scope of the $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ catalyzed reaction of *o*-aminocinnamate was evaluated using a variety of different isothiocyanates (Table 3). The results suggest that $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ was highly active in catalyzing the addition-cyclization reactions of *o*-aminocinnamate with isothiocyanates to form

Table 3 $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ catalyzed reactions of *o*-aminocinnamate with isothiocyanates[a]



Entry	R	Temp. (°C)	Time (h)	Product	Isolated yield (%)
1	Ph	50	5	**4a**	91
2	*p*-FC_6H_4	50	5	**4b**	95
3	*p*-ClC_6H_4	50	5	**4c**	91
4	*p*-BrC_6H_4	50	5	**4d**	89
5	*p*-$NO_2C_6H_4$	50	5	**4e**	98
6	*p*-MeC_6H_4	50	5	**4f**	89
7	*p*-$MeOC_6H_4$	50	5	**4g**	87
8	*m*-$MeOC_6H_4$	50	5	**4h**	96
9	*m*-ClC_6H_4	50	5	**4i**	90
10	*o*-ClC_6H_4	50	5	**4j**	96
11	*o*-FC_6H_4	50	5	**4k**	86
12	CH_3	50	20	**4l**	97
13	Cyclohexyl	70	72	**4m**	89

[a] Reactions were performed with 1 mmol of ethyl *o*-aminocinnamate and 1.2 mmol of the isothiocyanates.

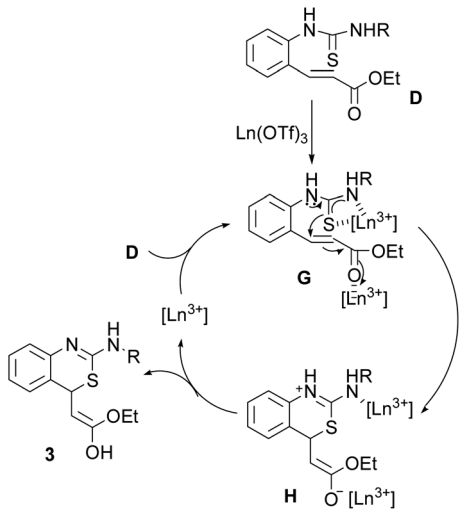


Scheme 2 Proposed mechanism for the $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ catalyzed reaction.

3,4-dihydroquinazoline-2-thiones in high to excellent yields. An electronic effect was observed: the activity of isothiocyanates with the aryl at 4-position bearing electron-withdrawing groups was higher than that of those bearing electron-donating groups (Table 3, entries 2–7). In a similar manner to the preceding $Yb(OTf)_3$ catalyzed reaction for the synthesis of 2-amino-3,1-benzothiazines, the $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ catalyzed reaction for the synthesis of 3,4-dihydroquinazoline-2-thiones also encountered some difficulties when alkyl isothiocyanates were used as substrates. For example, a prolonged time of 20 hours was necessary for the reaction with methyl isothiocyanate to reach the desired yield (Table 3, entry 12).

The ability to exert such a high level of product selectivity by changing the catalyst suggested that very different mechanisms were in operation for the two different processes, which compelled us to conduct a mechanistic analysis to develop some insight into the origin of this unusual selectivity. We were already aware that the reaction started with the rapid condensation of the aromatic amino group of the aniline to the isothiocyanate to form thiourea **D** as an intermediate, which could be detected and isolated during the course of reaction. It was then proposed (Scheme 2) that the use of $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ as a catalyst would lead to the rapid deprotonation of the thiourea and result in the generation of an amine–ligated amido complex **E**, which would most probably be the catalytically active species, with concomitant liberation of $(Me_3Si)_2NH$. This proposal was based on the unique properties of $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ and the consideration that thiourea would be sufficiently acidic to be irreversibly metallated by $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$. The unsaturated C–C bond of the *o*-aminocinnamate would then insert into the Ln–N bond,[16] followed by the subsequent protonolysis of the resulting Ln–C bond to form 3,4-dihydroquinazoline-2-thione **4** and regenerate **E**.

From another perspective, the results obtained from $Ln(OTf)_3$-catalyzed reaction can be explained (Scheme 3) according to the hard-soft acid–base (HSAB) theory.[17] At the same time of activating the unsaturated ester as a Lewis acid, lanthanide can coordinate to the thiourea and delocalize the S═C–NH moiety. Based on the HSAB theory, nitrogen, which is more electronegative and non-pololarizable than sulfur, is harder than sulfur. It can therefore be considered that N is the hard end of the thiourea **D**, whereas S is the soft end. Following the principles of the HSAB theory, the S-terminal of thiourea



Scheme 3 Proposed mechanism for the $Ln(OTf)_3$ catalyzed reaction.

would be more prone to reacting as a nucleophile to attack the carbon atom, which is soft as well. Thus, cyclization takes place *via* an intramolecular thia-Michael addition leading to intermediate **H**, which would then be converted to 2-amino-3,1-benzothiazine **3** upon work-up.

Conclusions

We have successfully developed a catalyst-controlled chemoselective reaction for the construction of 2-amino-3,1-benzothiazines and 3,4-dihydroquinazoline-2-thiones from *o*-aminocinnamate and isothiocyanates in the presence of lanthanide complexes as catalysts under mild and solvent-free conditions. 2-Amino-3,1-benzothiazines were obtained in high yields when the reactions were catalyzed by $Yb(OTf)_3$, whereas 3,4-dihydroquinazoline-2-thiones were obtained in high to excellent yields when the reaction was catalyzed by $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$. This product selectivity induced by the lanthanide complexes provided efficient, atom-economical, and practical approaches to the production of the corresponding heterocycles. Mechanistic studies towards developing a greater understanding of the catalytic selectivity, as well as studies aimed at identifying further applications for the observed selectivity are currently underway in our laboratories.

Experimental section

General information

All manipulations were conducted under an atmosphere of dry Ar with flame-dried glassware. $Ln(OTf)_3$[18] and $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$[13,14] were synthesized according to the literature method. ^1H and ^{13}C NMR spectra were obtained on Varian INOVA-400 and System-300 spectrometers using tetramethylsilane (TMS) as an internal reference. HRMS data were obtained on a Micromass GCT instrument. IR spectra were obtained on a Nicolet FT-IR 1000 spectrophotometer.

Typical procedure for the $Yb(OTf)_3$-catalyzed reactions of *o*-aminocinnamate and isothiocyanates

A mixture of ethyl *o*-aminocinnamate (191 mg, 1 mmol), isothiocyanate (1.2 mmol) and ytterbium triflate (6.2 mg, 0.01 mmol) was stirred at 50 °C for 4 hours. Water was added, and the mixture was extracted with EtOAc. The combined organic layers were dried with anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by chromatography on silica gel [eluent–EtOAc/petroleum ether (60–90 °C) 1 : 10] to afford the desired 2-amino-4*H*-3,1-benzothiazine.

Ethyl 2-(2-(phenylamino)-4*H*-benzo[*d*][1,3]thiazin-4-yl)-acetate (3a).[9] Following the typical procedure above, compound **3a** (316 mg, 97%) was obtained as a white solid. The spectral data were in agreement with reported literature values: ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 2H), 7.36–7.27 (m, 3H), 7.22–7.16 (m, 2H), 7.09 (t, J = 7.2 Hz, 2H), 6.71 (br s, 1H), 4.51 (dd, J = 8.8, 6.4 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 2.83 (dd, J = 16.0, 8.8 Hz, 1H), 2.75 (dd, J = 16.0, 6.4 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H).

Typical procedure for the $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$-catalyzed reactions of *o*-aminocinnamate and isothiocyanates

A mixture of ethyl *o*-aminocinnamate (191 mg, 1 mmol), isothiocyanate (1.2 mmol) and $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ (22 mg, 0.025 mmol) was stirred at 50 °C for 5 hours. Water was added, and the mixture was extracted with EtOAc. The combined organic layers were dried with anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by chromatography on silica gel [eluent–EtOAc/petroleum ether (60–90 °C) 1 : 10] to afford the desired 3,4-dihydroquinazoline-2-thione.

Ethyl 2-(3-phenyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)-acetate (4a). Following the typical procedure above, compound **4a** (297 mg, 91%) was obtained as a white solid: mp 154–155 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.51–7.40 (m, 5H), 7.29–7.24 (m, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 5.26 (dd, J = 8.1, 4.8 Hz, 1H), 4.06–3.95 (m, 2H), 2.93 (dd, J = 15.0, 4.8 Hz, 1H), 2.85 (dd, J = 15.0, 8.4 Hz, 1H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 169.7, 143.9, 134.6, 129.6, 129.3, 128.8, 128.5, 126.0, 124.0, 120.8, 114.2, 61.20, 61.0, 40.0, 14.1; IR ν_{max}/cm^{-1} 3332, 2980, 1730, 1594, 1514, 765; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_2S$ 327.1162, found 327.1164.

Ethyl 2-(3-(4-fluorophenyl)-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (4b). Following the typical procedure above, compound **4b** (327 mg, 95%) was obtained as a white solid: mp 147–149 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.42–7.14 (m, 6H), 7.07 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 5.23 (dd, J = 7.8, 5.1 Hz, 1H), 4.07–3.96 (m, 2H), 2.90 (dd, J = 15.0, 5.1 Hz, 1H), 2.82 (dd, J = 15.0, 8.1 Hz, 1H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 169.5, 162.0 ($^1J_{CF}$ = 247 Hz), 139.7, 134.4, 130.6 ($^3J_{CF}$ = 8 Hz), 129.3, 125.8, 124.0, 120.6, 116.5 ($^2J_{CF}$ = 22 Hz), 114.2, 61.2, 61.0, 40.0, 14.1; IR ν_{max}/cm^{-1} 3322, 2981, 1716, 1603, 1509, 1463, 1373, 1219, 837, 764; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{18}FN_2O_2S$ 345.1068, found 345.1070.

Ethyl 2-(3-(4-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (4c). Following the typical procedure above, compound **4c** (328 mg, 91%) was obtained as a white solid: mp 135–136 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.46–7.26 (m, 6H), 7.16 (d, J = 7.2 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 5.23 (dd, J = 7.8, 4.8 Hz, 1H), 4.07–3.97 (m, 2H), 2.89 (dd, J = 15.0, 4.8 Hz, 1H), 2.82 (dd, J = 15.0, 7.8 Hz, 1H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 169.5, 142.2, 134.4, 134.2, 130.2, 129.8, 129.4, 125.9, 124.1, 120.6, 114.2, 61.2, 60.9, 40.0, 14.1; IR ν_{max}/cm^{-1} 3342, 2977, 1716, 1618, 1493, 1462, 1374, 1092, 829, 754; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{18}ClN_2O_2S$ 361.0772, found 361.0770.

Ethyl 2-(3-(4-bromophenyl)-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (4d). Following the typical procedure above, compound **4d** (360 mg, 89%) was obtained as a white solid: mp 146–147 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.59 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.24 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 7.2 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 5.23 (dd, J = 7.5, 5.1 Hz, 1H), 4.06–3.95 (m, 2H), 2.88 (dd, J = 14.7, 4.8 Hz, 1H), 2.81 (dd, J = 14.7, 7.5 Hz, 1H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 169.5, 142.7,

134.3, 132.7, 130.5, 129.3, 125.8, 124.0, 122.3, 120.6, 114.3, 61.2, 60.8, 40.0, 14.1; IR ν_{max}/cm^{-1} 3323, 2978, 1716, 1618, 1491, 1461, 1375, 1069, 826, 752; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{18}BrN_2O_2S$ 405.0267, found 405.0269.

Ethyl 2-(3-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (4e). Following the typical procedure above, compound **4e** (364 mg, 98%) was obtained as a yellow solid: mp 155–156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.33 (d, J = 8.7 Hz, 2H), 7.67 (d, J = 8.7 Hz, 2H), 7.28 (t, J = 6.9 Hz, 1H), 7.18 (d, J = 6.9 Hz, 1H), 7.10 (t, J = 7.2 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 5.33 (dd, J = 7.5, 4.8 Hz, 1H), 4.08–3.97 (m, 2H), 2.90 (dd, J = 15.3, 5.1 Hz, 1H), 2.83 (dd, J = 15.5, 7.8 Hz, 1H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 169.3, 149.2, 146.9, 134.1, 129.9, 129.6, 125.9, 124.8, 124.5, 120.6, 114.4, 61.4, 60.7, 40.1, 14.1; IR ν_{max}/cm^{-1} 3296, 3068, 2993, 1708, 1607, 1526, 1373, 1350, 862, 758; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{18}N_3O_4S$ 372.1013, found 372.1014.

Ethyl 2-(2-thioxo-3-(*p*-tolyl)-1,2,3,4-tetrahydroquinazolin-4-yl)-acetate (4f). Following the typical procedure above, compound **4f** (303 mg, 89%) was obtained as a white solid: mp 157–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.30–7.26 (m, 5H), 7.16 (d, J = 7.2 Hz, 1H), 7.08–7.05 (m, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.23 (dd, J = 8.4, 4.8 Hz, 1H), 4.05–3.96 (m, 2H), 2.92 (dd, J = 15.2, 4.8 Hz, 1H), 2.84 (dd, J = 15.2, 8.4 Hz, 1H), 2.40 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177. 2, 169.7, 141.3, 138.4, 134.6, 130.2, 129.3, 128.4, 126.0, 123.8, 120.8, 114.1, 61.1, 61.0, 39.9, 21.4, 14.1; IR ν_{max}/cm^{-1} 3335, 3120, 2927, 1716, 1615, 1506, 1463, 1373, 821, 763; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{21}N_2O_2S$ 341.1318, found 341.1322.

Ethyl 2-(3-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (4g). Following the typical procedure above, compound **4g** (310 mg, 87%) was obtained as a white solid: mp 145–145.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.23 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 7.05–6.96 (m, 4H), 5.21 (dd, J = 7.5, 4.8 Hz, 1H), 4.02–3.99 (m, 2H), 3.84 (s, 3H), 2.91 (dd, J = 15.0, 5.1 Hz, 1H), 2.83 (dd, J = 15.0, 8.4 Hz, 1H), 1.13 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 169.7, 159.1, 136.6, 134.3, 129.8, 129.2, 125.9, 123.8, 120.8, 114.7, 114.1, 61.2, 61.1, 55.6, 39.9, 14.1; IR ν_{max}/cm^{-1} 3180, 3020, 1743, 1604, 1507, 1444, 1378, 1246, 1024, 836, 751; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{21}N_2O_3S$ 357.1267, found 357.1266.

Ethyl 2-(3-(3-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (4h). Following the typical procedure above, compound **4h** (342 mg, 96%) was obtained as a white solid: mp 117–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.04–7.00 (m, 3H), 6.97–6.93 (m, 2H), 5.25 (dd, J = 8.0, 4.8 Hz, 1H), 4.04–3.95 (m, 2H), 3.82 (s, 3H), 2.93 (dd, J = 15.2, 4.8 Hz, 1H), 2.85 (dd, J = 14.8, 8.4 Hz, 1H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 169.5, 160.2, 144.7, 134.5, 130.0, 129.1, 125.7, 123.7, 120.9, 120.6, 114.5, 114.2, 113.9, 61.0, 60.8, 55.4, 40.0, 14.0; IR ν_{max}/cm^{-1} 3122, 3202, 2939, 1730, 1608, 1497, 1441, 1047, 857, 785, 750, 692; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{21}N_2O_3S$ 357.1267, found 357.1267.

Ethyl 2-(3-(3-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (4i). Following the typical procedure above, compound **4i** (324 mg, 90%) was obtained as a white solid: mp 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.43–7.26 (m, 5H), 7.16 (d, J = 7.6 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 5.24 (dd, J = 8.0, 5.2 Hz, 1H), 4.06–3.97 (m, 2H), 2.90 (dd, J = 15.2, 4.8, 1H), 2.82 (dd, J = 15.2, 8.0, 1H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 169.5, 144.8, 134.9, 134.4, 130.4, 129.4, 129.2, 128.7, 127.3, 125.9, 124.1, 120.7, 114.3, 61.3, 60.9, 40.0, 14.1; IR ν_{max}/cm^{-1} 3319, 2979, 1718, 1617, 1373, 1094, 856, 788, 758, 686; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{18}ClN_2O_2S$ 361.0772, found 361.0773.

Ethyl 2-(3-(2-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (4j). Following the typical procedure above, compound **4j** (346 mg, 96%) was obtained as a white solid: mp 200–201 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.64–7.62 (m, 1H), 7.55–7.53 (m, 1H), 7.40–7.25 (m, 3H), 7.17 (d, J = 7.6 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.16 (dd, J = 7.2, 5.6 Hz, 1H), 4.06–3.97 (m, 2H), 2.90 (dd, J = 14.8, 5.2 Hz, 1H), 2.85 (dd, J = 15.2, 7.6 Hz, 1H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 169.6, 140.5, 134.3, 133.2, 131.6, 130.9, 129.9, 129.2, 127.3, 126.0, 124.1, 120.7, 114.3, 61.2, 59.4, 40.2, 14.1; IR ν_{max}/cm^{-1} 3315, 2926, 1730, 1618, 1480, 1373, 1219, 753; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{18}ClN_2O_2S$ 361.0772, found 361.0777.

Ethyl 2-(3-(2-fluorophenyl)-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (4k). Following the typical procedure above, compound **4k** (296 mg, 86%) was obtained as a white solid: mp 164–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.40–7.23 (m, 5H), 7.15 (d, J = 7.6 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.20 (m, 1H), 4.05–3.96 (m, 2H), 3.02–2.92 (m, 1H), 2.83 (dd, J = 15.6, 8.4 Hz, 1H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 169.6 (J = 31 Hz), 156.7 ($^1J_{CF}$ = 212 Hz), 134.2 ($^3J_{CF}$ = 13 Hz), 133.0, 130.5 ($^3J_{CF}$ = 14 Hz), 130.1, 129.1, 125.6, 123.9 ($^2J_{CF}$ = 17 Hz), 120.8, 120.3, 117.0 ($^2J_{CF}$ = 20 Hz), 114.3, 61.0, 59.7, 40.3, 13.9; IR ν_{max}/cm^{-1} 3321, 2898, 1724, 1602, 1518, 1464, 1175, 762; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{18}FN_2O_2S$ 345.1068, found 345.1060.

Ethyl 2-(3-methyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)-acetate (4l). Following the typical procedure above, compound **4l** (257 mg, 97%) was obtained as a white solid: mp 77–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 7.2 Hz, 1H), 7.01 (t, J = 7.2 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 5.03 (dd, J = 7.2, 5.6 Hz, 1H), 4.11 (q, J = 7.2 Hz, 2H), 3.52 (s, 3H), 2.81 (dd, J = 15.2, 4.8 Hz, 1H), 2.65 (dd, J = 15.2, 8.0 Hz, 1H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 170.1, 134.3, 129.1, 125.6, 123.7, 120.5, 113.7, 61.2, 59.1, 40.7, 39.3, 14.1; IR ν_{max}/cm^{-1} 3192, 2978, 1720, 1602, 1367, 1203, 748; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{17}N_2O_2S$ 265.1005, found 265.1000.

Ethyl 2-(3-cyclohexyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-yl)acetate (4m). Following the typical procedure above, compound **4m** (295 mg, 89%) was obtained as a white solid: mp 76–78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.28–7.15 (m, 2H), 7.04–6.93 (m, 2H), 5.27–5.19 (m, 1H), 5.09 (dd, J = 10.5,

3.0 Hz, 1H), 4.09–3.99 (m, 2H), 2.79 (dd, $J = 15.6$, 10.8 Hz, 1H), 2.55 (dd, $J = 15.6$, 3.0 Hz, 1H), 2.19–1.22 (m, 10H), 1.15 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 170.1, 134.6, 128.9, 125.4, 123.6, 122.0, 113.8, 60.9, 60.8, 51.3, 40.4, 31.3, 30.7, 25.8, 25.7, 25.3, 14.1; IR ν_{max}/cm^{-1} 3370, 2929, 1740, 1608, 1498, 1371, 1032, 935, 760; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{25}N_2O_2S$ 333.1631, found 333.1628.

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