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Orthogonal Catalysis for an Enantioselective Domino Inverse-Electron Demand Diels–Alder/Substitution Reaction

Sebastian Beeck,[a] Sebastian Ahles,[a] and Hermann A. Wegner*[a, b]

Abstract: An enantioselective domino process for the synthesis of substituted 1,2-dihydronaphthalenes has been developed by the combination of chiral amines and a bidentate Lewis acid in an orthogonal catalysis. This new method is based on an inverse electron-demand Diels–Alder and a subsequent group exchange reaction. An enamine is generated in situ from an aldehyde and a chiral secondary amine catalyst that reacts with phthalazine, activated by the coordination to a bidentate Lewis acid catalyst. The absolute configuration of the product is controlled by chiral information provided by the amine. The formed *ortho*-quinodimethane intermediate is then transformed via a group exchange reaction with thiols. The new method shows a broad scope and tolerates a wide range of functional groups with enantiomeric ratios up to 91:9. All-in-all, this enantioselective synthesis tool provides an easy access to complex 1,2-dihydronaphthalenes starting from readily available phthalazine, aldehydes and thiols in a combinatorial way.

The demand for new efficient chemical processes is constantly increasing, as sustainability,[1] environmental compatibility,[2] selectivity as well as time and cost efficiency have become crucial parameters.[3] Hence, the development of synthetic methods which addresses these requirements is of ever increasing importance.[4] One successful strategy to meet this specifications is to improve the step-economy by performing two or more bond-forming transformations in one single procedure.[5] The obvious advantages compared to a stepwise approach are: use of less solvents and adsorbents and, therefore, a prevention of waste, lower energy consumption, and fewer technical operations. If such a process, in addition, takes place under constant reaction conditions, without adding further reactants or reagents and the individual steps are based on each other, one enters the creative field of domino reactions.[6] Especially Diels–Alder reactions have shown to be effectively incorporated in such domino processes, because they are very valuable transformations themselves and offer various opportunities to be involved in domino processes.[7] A multitude of utilizations of the concept can be found, for example, in a very elegant synthesis of pagodane,[8] via a twofold Diels–Alder event in the synthesis of (–)-chlorothricolide,[9] a cascade of pericyclic reactions of a polyene precursor to form endiandric acids A–G[10] or the in situ generation of an imine dienophile by retro-cycloaddition of an azanorbornene.[11] In the past years we and others investigated domino processes in which phthalazines and enamines undergo an inverse electron-demand Diels–Alder (IEDDA) reactions to provide reactive *ortho*-quinodimethane intermediates.[12] The subsequent domino step depends on the used enamine and the reaction conditions applied. So far, we have reported an IEDDA/elimination,[13] IEDDA/Diels–Alder reaction,[14] IEDDA/group transfer reaction,[15] IEDDA/ring-opening/reduction sequence[16] and IEDDA/photo-induced ring-opening reaction.[17] In all of these reactions, phthalazine is activated by complexation to a (bidentate) Lewis acid. Without catalyst the IEDDA reaction of 1,2-diazenes requires much harsher conditions as, for example, demonstrated in the synthesis of strychnine or vinblastin.[18] In the past years, dimethyl-9,10-diboraanthracene (Me_2–DBA **2**) was established as an efficient Lewis acid catalyst for IEDDA reactions of phthalazines[19] and its ubiquitous potential was illustrated by Burns in the total synthesis of azamerone.[20]

The IEDDA/group transfer reaction published in 2018 produces 1-amino-1,2-dihydronaphthalines, generated in a single step starting from easy available reactants.[15] Based on this work, we envisioned to advance this approach by introducing other functional entities besides amines and also control the absolute stereochemical outcome of this process at the same time. In the previous study we could show, that in fact two amine molecules are involved at different stages of the reaction sequence (Scheme 1): One amine molecule **4** generates the enamine **A** required for the IEDDA reaction and the second one operates as nucleophilic exchange group. The group transfer reaction is mainly regulated by the nucleophilicity of the entering group. Therefore, the usage of suitable alternative

[a] S. Beeck, Dr. S. Ahles, Prof. Dr. H. A. Wegner
Justus Liebig University Giessen
Institute of Organic Chemistry
Heinrich-Buff-Ring 17, 35392 Giessen (Germany)
E-mail: Hermann.A.Wegner@org.chemie.uni-giessen.de
[b] Prof. Dr. H. A. Wegner
Justus Liebig University Giessen
Center for Materials Research (LaMa)
Heinrich-Buff-Ring 16, 35392 Giessen (Germany)
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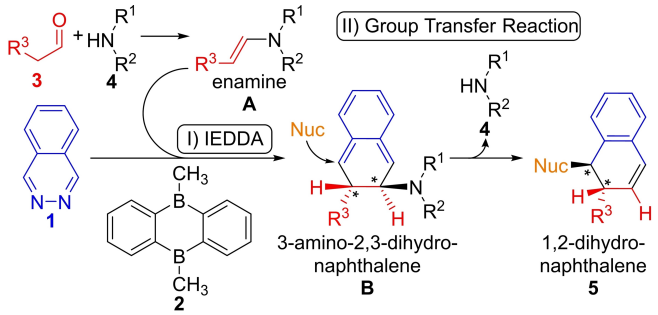
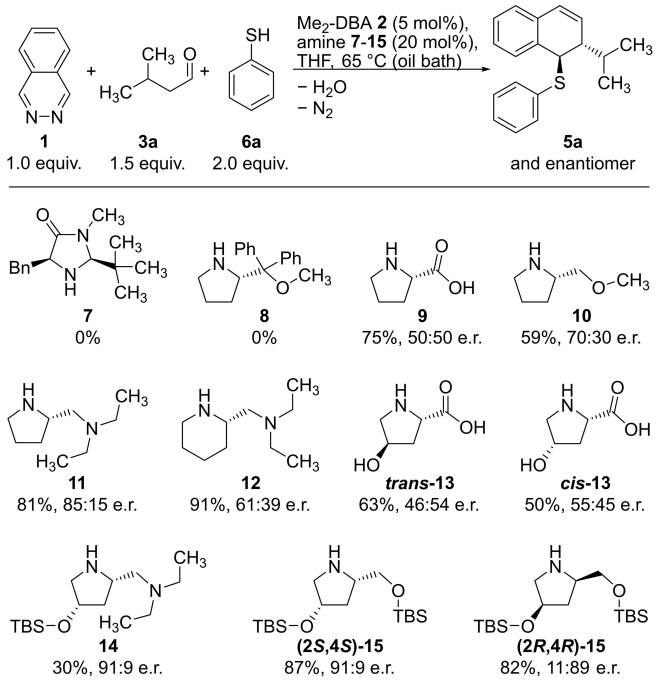


Scheme 1. Overview of the IEDDA/group transfer reaction.

nucleophiles should allow the introduction of other functionalities, by replacing the second amine.

We started our investigations with the search for such a transfer group. Since thiols are better nucleophiles compared to secondary amines it quickly turned out that, for example, thiophenol (Scheme 2, **6a**) is suitable to displace the amine. Two additional aspects of the group transfer sequence were also known from the previous study: It is a concerted process, and the admission of the exchange group is *syn* to the leaving amine. Hence, the absolute configuration of the product **5** is controlled beforehand in the IEDDA step.

Importantly, if an additional, suitable transfer group is present in the reaction mixture, the amine required for the enamine formation is not consumed and hence can be used in catalytic amounts. That opens up the possibility of controlling the stereochemistry with chiral amines, in analogy to many



Scheme 2. Optimization of chiral, secondary amines as co-catalysts. Reaction conditions: phthalazine (**1**, 1.0 mmol, 1.0 equiv.), isovaleraldehyde (**3a**, 1.5 mmol, 1.5 equiv.), thiophenol (**6a**, 2.0 mmol, 2.0 equiv.), dry THF (4.0 mL).

established organocatalyzed reactions.[21] Thus, we tested different chiral, secondary amines to induce enantioselectivity. For this purpose, various amines were applied to the IEDDA/group transfer reaction of phthalazine (**1**), isovaleralde-hyde (**3a**) and thiophenol (**6a**) (Scheme 2). The formation of the desired 1,2-dihydronaphthalene **5a** was monitored by ^{1}H NMR. The product was isolated by silica gel column chromatography and its enantiomeric ratio was determined by chiral HPLC (see details in the Supporting Information).

Well-established organocatalysts like MacMillan's imidazolidinone **7** or Jørgensen-type pyrrolidine **8**, as well as the chiral alkaloid cytisine or semi-synthetic nornicotine were ineffective in this reaction (Scheme 2, an entire table of examined chiral amines can be found in the Supporting Information). However, applying (*S*)-proline (**9**) to the described benchmark reaction provided the desired thioether **5a** in 75% yield, although as a racemic mixture. Moderate enantioselectivity was obtained when amine **10** was applied (70:30 e.r.). Chiral pyrrolidine **10** is functionalized by a methylene-bridged methoxy group in the 2-position. Based on this framework we varied the substituents on the bridge and in this manner, we improved the yield up to 81% and the enantiomeric ratio to 85:15 using chiral pyrrolidine **11**. We also synthesized and applied the corresponding piperidine **12**, which gave a higher yield of 91%, but a lower enantiomeric ratio of 61:39. Interestingly, an additional OH-group at the pyrrolidine ring also results in slightly enantiomeric enriched **5a** (46:54 and 55:45 e.r.) compared to the parent proline (**9**). *Cis*-configuration represents, at this point, the matched case, positively influencing the asymmetric induction (***trans*-13** vs. ***cis*-13**). The increase in selectivity of the additional OH-groups is small, but it can easily be tuned by introducing bulky substituents, for example by silyl chlorides. A sterically demanding *tert*-butyldimethylsilyl (TBS) group was chosen as modification. The pyrrolidine derivative with a methylene-bridged diethylamine at the 2-position and a TBS ether in the 4-position **14** gave an enantiomeric ratio of 91:9, but a comparable low yield of only 30%. If the amine in the 2-position is changed to another TBS ether **15**, a yield of 87% can be achieved, while maintaining a high enantioselectivity of 91:9 e.r. In addition to its good performance chiral amine **15** can be prepared in a straightforward procedure starting from Boc-protected hydroxyproline ester (3 steps, see Supporting Information) making this secondary amine the preferred choice. Considering, that a TBS-group is very bulky, we assume that the enantioselectivity is mainly controlled by steric effects.

The absolute configuration of the product is of particular interest, especially if it comes to pharmacological uses, as one enantiomer can be effective in the sense of application, while the other is ineffective or even harmful.[22] Vibrational circular dichroism (VCD) is a powerful method to identify the absolute configuration by comparing experimental data and computed spectra.[23] In order to accurately simulate the VCD spectra of both enantiomers, we conducted a conformational analysis using CREST (conformer-rotamer ensemble sampling tool).[24] After that, we optimized the geometries and energies at B3LYP–D3(BJ)/def2tzvpp[25] and selected the relevant conformers on the basis of relative free energies (at 298 K). We

simulated the VCD spectra of the ensemble at B3LYP–D3(BJ)/def2tzvpp and generated a separate Boltzmann-averaged spectrum for both enantiomers. We also synthesized the (2*R*,4*R*)-enantiomer of the amine catalyst **15** and applied it to the benchmark IEDDA reaction (Scheme 2) to obtain product **5a**, enriched with the other enantiomer. The comparison between simulated and measured VCD spectra showed that the simulated spectrum of (1*R*,2*S*)-dihydronaphthaline **(1*R*,2*S*)-5a** is in high agreement with the measured spectrum of the enantiomeric enriched product formed with the (2*S*,4*S*)-enantiomer of catalyst **15** and vice versa (Figure 1, see Supporting Information for the other comparison). In this way, we can unambiguously assign which configuration in the chiral amine **15** leads to which enriched enantiomer in the product **5a**. As expected, it demonstrates that the stereochemistry of this method is only dependent on the chirality of the amine used, as the other enantiomer of amine **15** inverts the enantiomeric ratio in the product to the same extent. It is noted that the (2*S*,4*S*)-enantiomer of pyrrolidine **15** was used in the following substrate screening by default.

First, the substrate scope was evaluated by applying different aldehydes **3a–k** to the IEDDA group transfer reaction (Table 1). Aliphatic aldehydes (entry 1–3, 7 and 9) gave moderate to high yields with high enantioselectivities. It can be noted that larger groups at the aldehyde result in lower yields. However, the sterically more demanding moieties appear to have an amplifying effect on the enantioselectivities (entry 1 vs. entry 3). Aldehydes bearing unsaturated moieties, for instance an alkene (entry 8) or phenyl (entry 4 and 5), gave good yields as well as high enantiomeric ratios. Compound **5e** (entry 5) contains an additional chiral center and was isolated as a mixture of four stereoisomers, which could not be properly separated. If cyclohexane carbaldehyde (**3k**) (entry 11) is used in this reaction, no conversion of phthalazine (**1**) was observed. This substrate would lead to a trifold substituted enamine double bond and the steric demand seems to outweigh the +I-effect on the enamine, which should accelerate the IEDDA reaction.

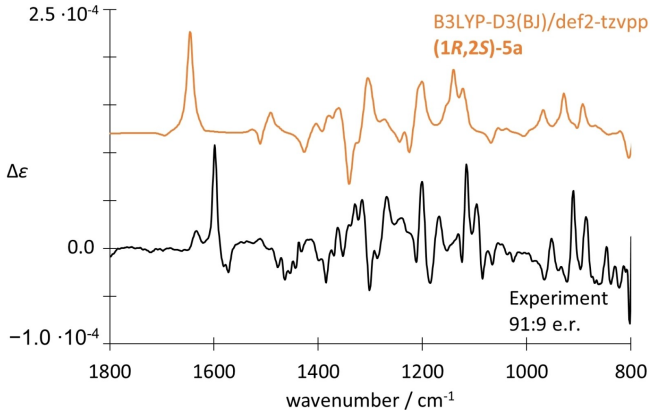
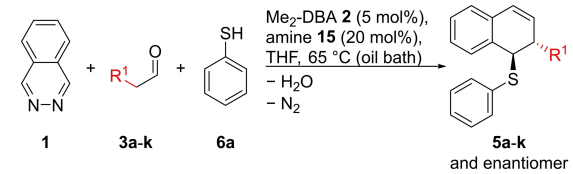
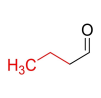
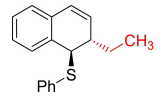
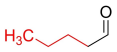
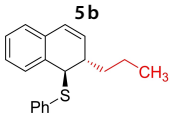
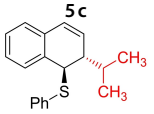
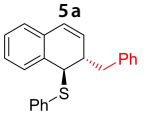
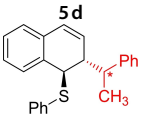
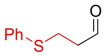
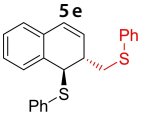
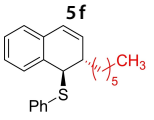
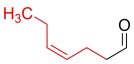
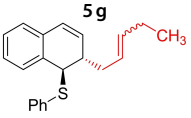
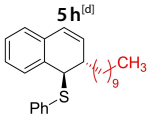
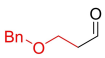
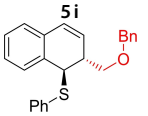
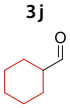
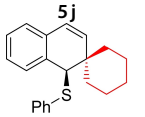


Figure 1. Assignment of absolute configuration of **5a** by VCD: Experimental (black, 91:9 e.r.) and computed (B3LYP-D3(BJ)/def2–tzvpp, gas phase, Boltzmann-averaged, orange) VCD-spectra of **(1*R*,2*S*)-5a**.

Table 1. Scope of aldehydes in the enantioselective IEDDA/group transfer reaction.



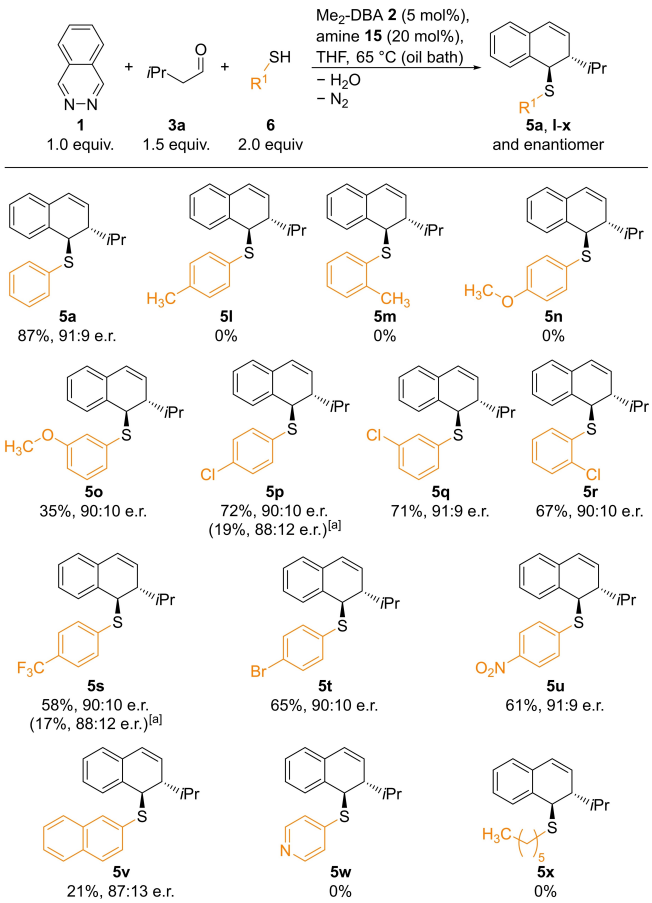
Entry	Aldehyde	Product	Yield[a] e.r.
1	 **3b**	 **5b**	91 % 85:15
2	 **3c**	 **5c**	90 % 87:13
3	 **3a**[b]	 **5a**	87 % 91:9
4	 **3d**	 **5d**	87 % 85:15
5	 **3e**	 **5e**	78 % 1:1.13 d.r.[c]
6	 **3f**	 **5f**	78 % 81:19
7	 **3g**	 **5g**	76 % 86:14
8	 **3h**	 **5h**[d]	65 % 83:17
9	 **3i**	 **5i**	59 % 84:16
10	 **3j**	 **5j**	0 %
11	 **3k**	 **5k**	0 %

Reaction conditions: phthalazine (**1**, 1.0 mmol, 1.0 equiv.), aldehyde **3a–k** (2.0 mmol, 2.0 equiv.), thiophenol (**6a**, 1.1 mmol, 1.1 equiv.), dry THF (4.0 mL). [a] Indicated yields are after purification by column chromatography. E.r.s were determined by chiral HPLC. [b] Alternative reaction conditions: 1.5 equiv. isovaleraldehyde (**3a**) and 2.0 equiv. thiophenol (**5a**). [c] D.r. determined by ^{1}H NMR. [d] Product **5h** was isolated as a mixture of *cis-trans*-isomers.

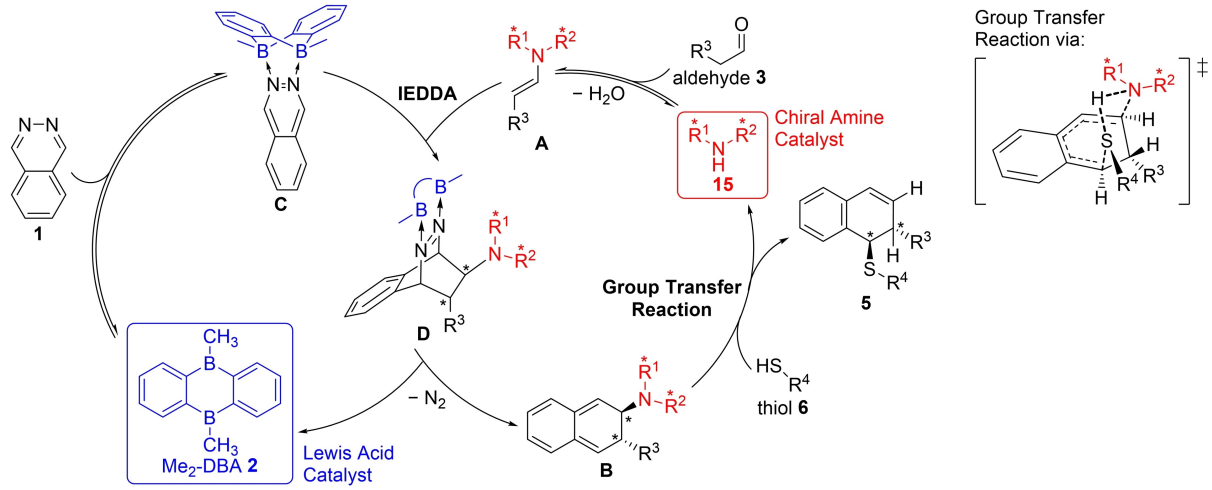
Next, we extended the substrate scope of the method by using different thiols **6** (Scheme 3). As previously described, a yield of 87% (91:9 e.r.) is achieved with unsubstituted thiophenol (**6a**). Electron-rich *para*-substituted thiophenols did not yield the desired thioether-substituted products. This is the case for both, substituents with +I-effect (**5l** and **5m**) as well as +M-effect (**5n**). However, *meta*-substituted 3-methoxythiophenol provides the desired product **5o** in a yield of 35%. Aliphatic thiols are represented in the substrate scope by 1-hexanethiol and also did not give the expected product **5x**. A possible reason is, that aliphatic moieties also offer a +I-effect. In contrast, electron-deficient substrates provided moderate yields (**5p–u**). There is only a small difference, if the substituent is in *ortho*-, *meta*- or *para*-position to the thiol group (**5p–r**). The electron-deficient, heterocyclic 4-mercaptopyridine gave no product **5w**, probably due to the competing nucleophilicity of the nitrogen atom. The enlargement of the aromatic system at the thiophenol significantly reduces the yield to 21% (**5v**). If the ratio of isovaleralde-hyde (**3a**) to thiophenol **6** is increased from 1.5:2.0 to 2.0:1.1, which was in same cases beneficial for specific aldehydes, the yields were lower (**5p** and **5s**).

Regardless of the applied thiophenol, the e.r.s remain the same of at about 90:10. If the thiol is not suitable to react as an exchange group, the amine is eliminated from the 3-amino-2,3-dihydronaphthalene intermediate, and the isopropyl substituted naphthalene was isolated (see Supporting Information).

Based on previous studies on the bidentate Lewis acid catalyzed IEDDA reactions of phthalazines[26] as well as organocatalysis[27] we propose an orthogonal,[28] bicyclic mechanism (Scheme 4). One cycle is centered around the bidentate complexation of phthalazine (**1**) to Me_2-DBA **2**. In the resulting complex **C** the $LUMO_{phthalazine}$ is lowered and thus the phthalazine is activated for the crucial cycloaddition step. In parallel, the second cycle describes the generation of the enamine **A**. It results from a condensation reaction of an aldehyde and the chiral secondary amine catalyst. Then, phthalazine complex **C** and enamine **A** undergo the central IEDDA reaction resulting in complex **D**. Because the (*E*)-isomer of enamine **A** is exclusively formed, the amine group (–NR^1R^2) and R^4 are oriented *trans* to



Scheme 3. Scope of thiols in the enantioselective IEDDA/group transfer reaction. Reaction conditions: phthalazine (**1**, 1.0 mmol, 1.0 equiv.), isovaleraldehyde (**3a**, 1.5 mmol, 1.5 equiv.), thiol (2.0 mmol, 2.0 equiv.), dry THF (4.0 mL). [a] Alternative reaction conditions: 2.0 equiv. isovaleraldehyde (**3a**) and 1.1 equiv. thiophenol. Given yields are after purification by column chromatography. E.r.s were determined by chiral HPLC.



Scheme 4. Mechanistic proposal of the enantioselective IEDDA/group transfer reaction.

each other in IEDDA product **D**. This explains the relative configuration at the newly generated stereogenic centers. Furthermore, the preferred alignment of enamine **A** to complex **C** in the transition state of the IEDDA reaction is mainly influenced by bulky, chiral groups on enamine **A**. These chiral elements originate from the secondary amine catalyst controlling the absolute configuration in IEDDA product **D**. After dissociation of the Lewis acid catalyst **2** and elimination of N_2 *ortho*-quinodimethane intermediate **B** is formed, where the group transfer reaction takes place: The attack of the thiol at C1 and the simultaneously release of the amine catalyst at C3 re-establishes aromaticity and leads to the 1-thio-substituted 1,2-dihydronaphthalene product **5**. Following our mechanistic proposal, the thiol enters the reaction cascade in the group exchange reaction after the IEDDA reaction resulted in the 3-amino-2,3-dihydronaphthalene intermediate **B**. In this mechanism the stereochemical outcome of the reaction is solely determined in the preliminary IEDDA step, which is in accordance with the observation, that the influence of different thiols on the enantiomeric ratio is negligible (Scheme 3). It completely depends on the chirality of the applied chiral amine catalyst.

In summary, we successfully combined the concept of bidentate Lewis acid activation of phthalazine with the asymmetric features of organocatalysis to launch a new enantioselective IEDDA/group transfer domino process. It is a *trans*-selective approach, in which the absolute stereochemistry is controlled by a new chiral amine catalyst developed for the requirements of the process (e.r.s up to 91:9). Well-established catalysts did not provide the desired product. Its simple preparation makes it a promising candidate to be applied also in other organocatalyzed methods. Simple and readily available substances, like phthalazine, aldehydes and thiophenoles were used and gave preparative access to new thioether substituted *trans*-1,2-dihydronaphthalenes. This so far unexplored compound class bears high potential for drug development, as sulfur-containing compounds represent a large portion of FDA (U.S. Food and Drug Administration) approved drugs and they conform to Lipinski's rule of five.[29]

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: bidentate Lewis acids · dihydronaphthalenes · domino processes · inverse electron-demand Diels–Alder reaction · organocatalysis

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