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Authors: Rundong Zhou and Jan Paradies

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FULL PAPER

Borane catalyzed redox isomerization of 2-amino chalcones: hydride abstraction or hydride migration.

Rundong Zhou, Jan Paradies*

In memory of Klaus Hafner

M.Sc. R. Zhou, Dr. J. Paradies
Chemistry Department
Paderborn University
Warburger Strasse 100, D-33098 Paderborn
E-mail: jan.paradies@uni-paderborn.de
URL: https://chemie.uni-paderborn.de/arbeitskreise/organische-chemie/paradies

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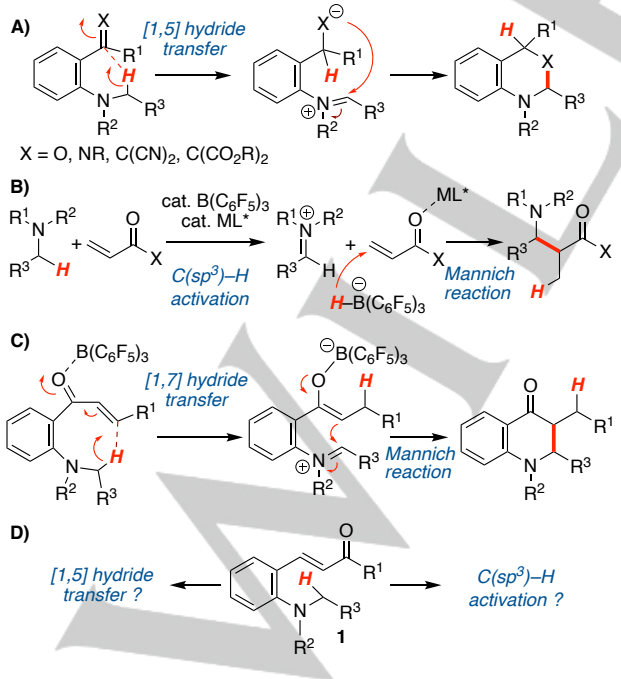
Abstract: The borane catalyzed redox isomerization of 2-amino chalcones is developed. The tetrahydroquinolines are obtained in high yield as a mixture of *cis*/*trans* diastereomers in a ratio of 2:1 to >95:5. The reaction mechanism is investigated by mechanistic, kinetic and computational methods, concluding that the reaction proceeds through concerted [1,5] hydride shift in contrast to borane-mediated C(sp^3)–H hydride abstraction.

Introduction

The organocatalytic C(sp^3)–H bond activation emerged as a versatile tool for the construction of complex organic structures.[1] Particularly, 2-substituted anilines with a strongly activated double bond e.g. malonates, malonitriles, ketones, imines, undergo an intramolecular hydride shift (Scheme 1 A). [1]



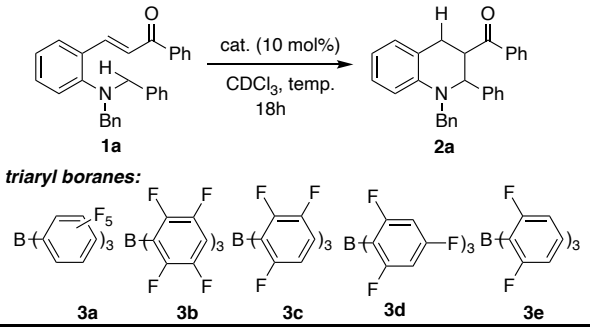
Scheme 1. A) Redox isomerization; B) borane catalyzed Mannich reaction by C(sp^3)–H activation; C) [1,7] endo hydride shift; D) hydride shift or C(sp^3)–H activation.

The [1,5] hydride migration reaction has been intensively investigated[2] and challenged scientists to develop more sophisticated annulation cascades through sequential [1,*n*] hydride migration processes of up to *n* = 6 or even n = 7.[3] Such redox isomerization can be efficiently catalyzed by magnesium,[4] platinum,[5] rare earth element[6] complexes or by Brønsted acids e.g. phosphoric acid[7] derivatives. Also boron derived Lewis acids were employed in redox isomerizations although with limited success.[3e,8]. The Wasa group demonstrated that the strong Lewis acidic borane $B(C_6F_5)_3$ [3e, 9] is capable to transfer a hydride from an amine to a Michael-system by dual activation and can be exploited for intermolecular C–C bond formation (Scheme 1 B).[10] The mechanistic picture of the activation of both the carbonyl group and the C(sp^3)–H bond was supported by kinetic experiments. The reaction order in borane was determined to close to two, sustaining the role of the borane as Lewis acid and as hydride shuttle reagent.[11] However, borohydride species were not detected by NMR spectroscopy.[12] Recently we investigated if such process can be utilized for an intramolecular reaction in order to construct dihydro quinoline-4-one scaffolds (Scheme 1 C).[8b] We found that the hydride abstraction from the borane coordinated substrate is 5-15 kcal/mol higher in energy that the corresponding [1,7] endo hydride shift, which renders this reaction pathway unfavorable. The reaction order in borane of close to one corroborated the concerted hydride shift as operative mechanism. The discrepancy in reaction mechanism of the inter- and the intramolecular reaction was attributed to the reduced electron density of the nitrogen atom affected by the electron-withdrawing carbonyl group. Thus, positioning the carbonyl group in a remote location, as in **1**, may trigger a change in reaction mechanism in favor to the two-step hydride abstraction/Michael-addition sequence.

Results and Discussion

In order to explore this reaction, we first investigated the reactivity of **1a** in the presence of 10 mol% of different Lewis acids, including the triaryl boranes **3a-e,**[13] featuring graduated Lewis acidity and $Yb(OTf)_3$ as common hydride shift catalyst (Table 1).

Table 1. Redoxneutral isomerization of **1a** to tetrahydroquinoline **2a.**



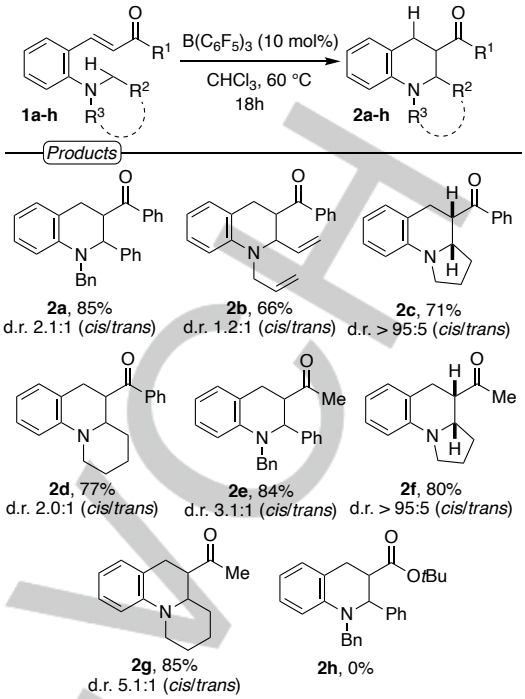
entry	cat.	temp. [°C]	yield [%][a]	d.r.[b] (*cis*/*trans*)
1	**3a**	24	<1	n.d.
2	**3a**	60	>95	2.2:1
3	**3b**	60	33	1:1.5
4	**3c**	60	7	n.d.
5	**3d**	60	8	n.d.
6	**3e**	60	6	n.d.
7	$Yb(OTf)_3$	60	17	>95:1
8	$Yb(OTf)_3$	90	91	>95:1

[a] yields were determined by ^{1}H NMR spectroscopy using hexamethylbenzene as internal standard. [b] determined from crude reaction mixture; [b] determined by ^{1}H NMR of the crude reaction mixture.

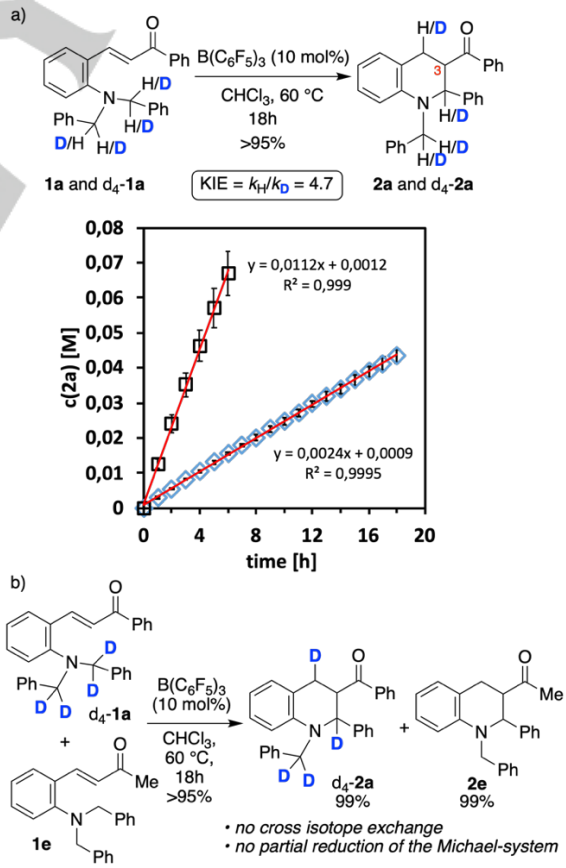
We found that reaction required slight heating to 60 °C in the presence of the strong Lewis acid $B(C_6F_5)_3$ (**3a**) for completion within 18h (Table 1, entries 1 and 2). The reaction became significantly less efficient with triaryl borane catalysts having reduced Lewis acidity as a result of their reduced fluorine content (entries 3-6). This finding already indicates that the formation of **2a** is most likely the result of Lewis acid activation of the Michael-system. Boranes with less Lewis acidity than **3a** have so far not been reported to initiate the C(sp^3)–H bond activation. Furthermore, this is supported by the observation that $Yb(OTf)_3$ is able to trigger the redox neutral isomerization of **1a** to **2a** in quantitative yield, though elevated temperatures of 90 °C were required.

Next, we investigated the impact of the substituents at the amine and ketone on the diastereoselectivity (Scheme 2). Generally, the tetrahydroquinolines were obtained in 66% to 85% yield. The diastereoselectivity was less affected by the carbonyl substituent, e. g. when **1a** and **1e** is compared, but rather dominated by the amine substituents. The hexahydro-1*H*-pyrido[1,2-*a*]quinoline derivatives **2d** and **2g** were obtained with slightly enhanced d.r. of 2:1 to 5:1. However, the corresponding hexahydropyrrolo[1,2-a]quinoline derivatives **2c** and **2f** were obtained an excellent d.r. of > 95:5. The *tert*butyl ester underwent cleavage of the ester group, which inhibited the redox isomerization.

In order to shed light into the reaction mechanism, we conducted mechanistic and kinetic experiments. The primary kinetic isotope effect was determined to 4.7 which is in good agreement with the C–H bond breaking being the rate determining step (Scheme 3a).



Scheme 2. Examples for the redox-neutral borane-catalyzed isomerization of chalcone derivatives.



Scheme 3. a) Kinetic isotope effect data in the borane-catalyzed redox-isomerization of **1a** and d_4-**1a** (both reactions run at 0.1 M). ☐ data for **1a**; ◇ data for d_4-**1a**; each data point reflects the average of three individual experiments; error bars correspond to standard deviation; b) cross isotope experiment.

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The incorporation of deuterium in 3-position was not observed, which suggest that the observed diastereoselectivity results from the differences in transition state energies and not from prototopic reactions. This was further confirmed by control experiments in which nor isomerizations were induced by extended heating in the presence of **3a** or base (see Supporting Information) neither cross isotope exchange using the labelled d_4-**1a** and **1e** (Scheme 3b). However, the primary KIE does not exclude the hydride abstraction mechanism from the list of potential hydride transfer mechanisms. According to Wasa's mechanism for the intermolecular hydride transfer two borane molecules are involved in the rate determining step. In order to examine this, we determined the reaction rates with catalyst loadings of 10 mol%, 20 mol% and 30 mol% (see Figure 1).

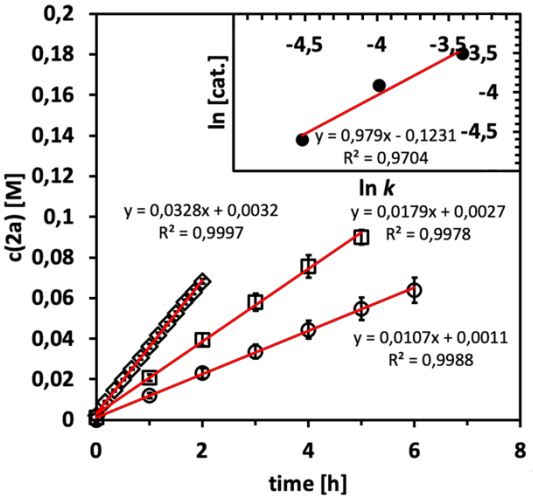
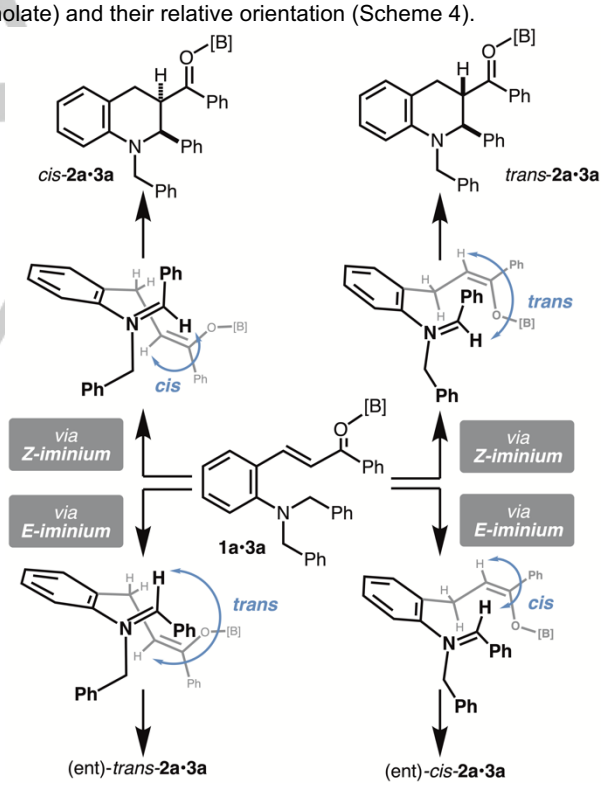


Figure 1. Determination of reaction rates at different catalyst loadings (O 10 mol%, □ 20 mol%, ◇ 30 mol%) and determination of reaction order in borane (inset); each data point reflects the average of three independent experiments; error bars correspond to standard deviation of the three individual experiments.

The reaction order in borane was determined to 0.98 which indicates that one borane molecule is incorporated in the rate determining step. This kinetic picture clearly rules out that the reaction proceeds through hydride abstraction and transfer to a borane-activated Michael-system. This is also in agreement with our computational studies using density functional theory (DFT) on the dispersion corrected (D3BJ) PW6B95/def2-QZVPP//PBEh-3c/def2-mSVP[14] level of theory with CPCM solvent correction[15] for dichloromethane as implemented in the ORCA software package.[16] All molecules were preoptimized with the tight-binding method xTB-GFN2.[17] Transition states were either found by potential energy scans on the tight-binding level along the reaction coordinate or by the growing string method[18] prior to final geometry optimization on DFT level. The connectivity of transition states to minimum energy structures were verified by the intrinsic reaction coordinate (IRC) method. The kinetic experiments revealed a reaction order of one in catalyst. Therefore, we investigated scenarios in which only one **3a** molecule interacts with **1a** as model substrate in its lowest energy conformation as identified by Grimme's CREST method.[19] One reasonable reaction is the abstraction of one of the hydride atoms from the free 2-amino chalcone by **3a** in order to generate an iminium borohydride salt, which would be in agreement with our kinetic data. All four benzylic hydrogen atoms of the dibenzyl amino moiety were considered to participate in this process (see Supporting Information for details). The barriers for the intermolecular hydride abstraction by $B(C_6F_5)_3$ were calculated to 27.8 kcal•mol^{-1} to 37.9 kcal•mol^{-1}. A most unlikely mechanism and not supported by our kinetic data is the Lewis acid activation of the Michael-system in combination with borane-induced hydride abstraction (a reaction second order in borane) in analogy to Wasa's mechanism.[10] The activation barrier is by 15-22 kcal•mol^{-1} higher in energy compared to the Lewis acid induced hydride migration (13.9 kcal•mol^{-1}) and renders this mechanism as kinetically highly unfavorable (see Supporting Information). The energies for the hydride abstraction by $B(C_6F_5)_3$ are significantly higher than the computed energies of 13.9 to 21.1 kcal•mol^{-1} for the concerted hydride shift mechanism (compare Figure 2). Furthermore, this mechanism is supported by the detection of oxygen-coordinated tetragonal boron species by ^{11}B NMR (δ = 0.7 ppm) and the absence of any resonance accounting for a borohydride species. Having established that the reaction proceeds most likely through Lewis acid induced [1,5] hydride migration, we investigated the stereochemical features in more detail. The diastereselectivity in the product is established by double stereodifferentiation of the two double bonds (iminium and enolate) and their relative orientation (Scheme 4).



Scheme 4. Conceptional origin of diastereoselectivity in the redox isomerization of **1a** ([B] = $B(C_6F_5)_3$).

The complexation and activation of the chalcone **1a** occurs from its *s-cis* conformation as most stable conformer. Subsequent

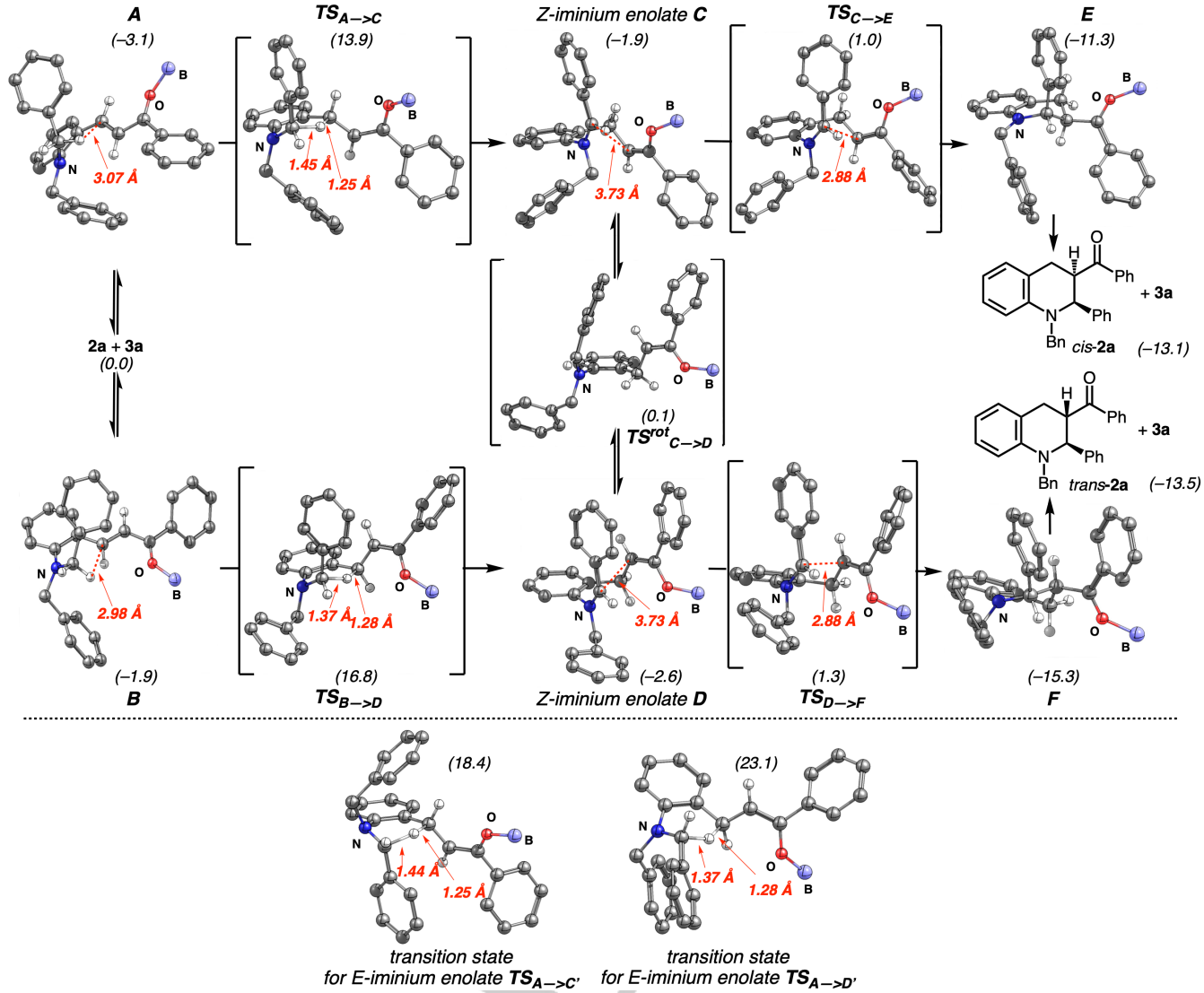


Figure 2. Details of the computational studies for the conversion of **1a** to *cis*/*trans*-**2a** *via* the *Z*-enolate intermediate (top); transition state structures and energies for the *E*-iminium enolates **C'** and **D'** (bottom). Values in parentheses correspond to free energies of ground state and transition states in kcal•mol^{-1} (± 3 kcal•mol^{-1}). Selected hydrogen atoms and C_6F_3 fragments were omitted for clarity. Representations generated by ChemCraft.[20]

intramolecular hydride shift generates the corresponding transient iminium enolate with exclusive *cis* enolate configuration. However, the hydride shift may generate both *E*- and *Z*-iminium moieties, leading to the *cis*- and *trans*-isomers of **2a**.

Detailed computational studies support the exergonic formation of two **1a**•B(C_6F_5)$_3$ adducts (–3.1 kcal•mol^{-1} and –1.9 kcal•mol^{-1}), one conformer with the O–[B] group pointing away from the NBn_2 group and one pointing towards the NBn_2 group, the latter being 1.2 kcal•mol^{-1} less stable compared to the first conformer (Figure 2). Nonetheless, the small energy difference and the comparable low exergonicity of the complexation suggests that the two adducts are in equilibrium (Figure 2). The intramolecular hydride shift proceeds through transfer of one of the inner-lying hydrogen atoms to the activated Michael-position leading to the two *Z*-iminium enolate intermediates **C** and **D** (Figure 2) with comparable reaction barriers of 17.0 kcal•mol^{-1} and 18.1 kcal•mol^{-1}. In contrast, the formation of the corresponding *E*-iminium enolates **C'** and **D'** Figure 2 bottom) is kinetically less favorable by a barrier of 21.5 kcal•mol^{-1} and 25.0 kcal•mol^{-1}. The exergonically formed *Z*-iminium enolates **C** and **D** (–1.9 kcal•mol^{-1} and –2.6 kcal•mol^{-1}) are converted into the *cis*- and *trans*-products as B(C_6F_5)$_3$ adducts over small barriers of 2.9 kcal•mol^{-1} and 3.9 kcal•mol^{-1} respectively. Although the rotation around a C–C bond in order to interconvert **C** into **D** through the **TS$^{rot}_{C→D}$** has a very low barrier of 2.8 kcal•mol^{-1} and 2.1 kcal•mol^{-1}, such movement requires extensive atomic redistribution so that the direct conversion of **C** → **E** and **D** → **F** over comparable energy barriers is most likely to occur. This picture is corroborated by the transient nature of the iminium enolates **C** and **D**, which were not detected by ^{1}H NMR spectroscopy. The small difference in free energies of the hydride migration barrier in **TS$_{A→C}$** and **TS$_{B→D}$** is reflected by the slight preference for *cis*-**2a** in the catalytic experiments.

Conclusion

In summary, we have shown that $B(C_6F_5)_3$ is a viable catalyst for the redox isomerization of 2-amino chalcones. The tetrahydroquinoline derivatives are formed in high yield. In particular, the pyrrolo derivative *cis*-**2f** was obtained as single diastereomer. Mechanistic, kinetic and computational experiments support that the redox isomerization proceeds through Lewis acid induced hydride shift in contrast to hydride abstraction by the borane.

Experimental Section

Exemplary procedure for the redox isomerization of **1a**.

In a glovebox, a vial was charged with the α,β-unsaturated ketone **1a** (0.25 mmol, 1.00 equiv.) and $B(C_6F_5)_3$ (**3a**) (10 mol%, 0.025 mmol, 12.8 mg, 0.010 equiv.). The mixture was dissolved in abs. $CHCl_3$ (2.50 mL). The vial was heated to 60 °C for 18 h. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (10 ml) and poured into water (10 mL). The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure. After purification by column chromatography (silica, mixtures of cyclohexane and ethyl acetate (50:1) the product was obtained as yellow solid in 85% yield as diastereomeric mixture with a ratio of *cis*/*trans* 2.1:1.

^{1}H-NMR (700 MHz, 298 K, $CDCl_3$) *cis* diastereomer δ = 7.80-7.76 (m, 2H, H_{Ar}), 7.49 (m, 1H, H_{Ar}), 7.41-7.36 (m, 3H, H_{Ar}), 7.34-7.31 (m, 1H, H_{Ar}), 7.27-7.14 (m, 8H, H_{Ar}), 7.07 (m, 1H, H_{Ar}), 7.01 (m, 1H, H_{Ar}), 6.68-6.65 (m, 2H, H_{Ar}), 4.98 (d, $^3J_{HH}$ = 5.9 Hz, 1H, NC*H*Ph), 4.63 (d, $^2J_{HH}$ = 16.8 Hz, 1H, NCH_2), 4.14 (d, $^2J_{HH}$ = 16.8 Hz, 1H, NCH_2), 3.98-3.94 (m, 1H, C(=O)C*H*), 3.06 (dd, $^2J_{HH}$ = 15.5 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, C(=O)CHCH_2), 2.97 (dd, $^2J_{HH}$ = 15.5 Hz, $^3J_{HH}$ = 4.8 Hz, 1H, C(=O)CHCH_2); *trans* diastereomer δ = 7.88-7.84 (m, 2H, H_{Ar}), 7.58 (m, 1H, H_{Ar}), 7.47-7.43 (m, 2H, H_{Ar}), 7.34-7.31 (m, 1H, H_{Ar}), 7.27-7.14 (m, 8H, H_{Ar}), 7.12 (m, 1H, H_{Ar}), 6.77-6.74 (m, 2H, H_{Ar}), 6.72 (m, 1H, H_{Ar}), 6.70-6.68 (m, 1H, H_{Ar}), 5.04 (d, $^3J_{HH}$ = 4.3 Hz, 1H, NC*H*Ph), 4.75 (d, $^2J_{HH}$ = 17.2 Hz, 1H, NCH_2), 4.22 (dt, $^3J_{HH}$ = 13.1 Hz, 4.0 Hz, 1H, C(=O)C*H*), 4.16 (d, $^2J_{HH}$ = 17.2 Hz, 1H, NCH_2), 3.25-3.18 (m, 1H, C(=O)CHCH_2), 2.80-2.74 (m, 1H, C(=O)CHCH_2).
^{13}C-NMR (176 MHz, 298 K, $CDCl_3$) *cis* diastereomer δ = 200.5 (C_q), 145.4 (C_q), 142.9 (C_q), 138.5 (C_q), 136.5 (C_q), 133.4 (CH), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.5(CH), 128.4 (CH), 127.8(CH), 127.4 (CH), 127.1 (CH), 126.9 (CH), 122.1 (C_q), 117.0 (CH), 112.2 (CH), 63.5 (CH), 53.1 (NCH_2), 49.0 (CH), 29.4 (C(=O)CHCH_2); *trans* diastereomer δ = 199.1 (C_q), 144.9 (C_q), 139.1 (C_q), 138.7 (C_q), 136.9 (C_q), 133.1 (CH), 129.9 (CH), 129.2 (CH), 129.1 (CH), 128.3(CH), 128.1 (CH), 127.9(CH), 127.7 (CH), 127.4 (CH), 126.7 (CH), 120.7 (C_q), 116.6 (CH), 112.5 (CH), 63.3 (CH), 53.1 (NCH_2), 45.8 (CH), 25.2 (C(=O)CHCH_2).
HRMS (ESI) exact mass for $[MH]^+$($C_{29}H_{26}NO$): calc m/z 404.2014, found 404.1988

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Keywords: Redox isomerization • Tert-amino effect • Nitrogen heterocycle • Boranes • Hydride shift

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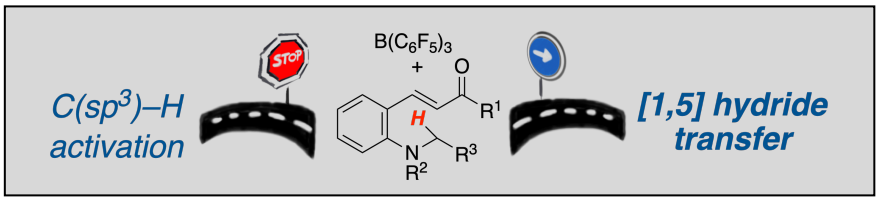

The borane catalyzed redox isomerization of 2-amino chalocones is developed. Mechanistic investigations by kinetic, isotopic labelling and competition experiments as well as computational studies corroborate the concerted [1,5] hydride shift as operative mechanism. The redox isomerization products are obtained in high yield and with up to > 95:5 diastereoselectivity.