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Size-Exclusion Borane Catalyzed Domino 1,3-Allylic/Reductive Ireland-Claisen Rearrangements. Impact of the Electronic and Structural Parameters on the 1,3-Allylic Shift Aptitude

Dániel Fegyverneki, Natália Kolozsvári, Dániel Molnár, Orsolya Egyed, Tamás Holczbauer and Tibor Soós*

Abstract: The reductive Ireland-Claisen rearrangement via borane mediated hydrosilylation is reported. The method employs borane catalyst with a special structural design and affords access to synthetically relevant product with high diastereoselectivity. Depending on electronic and structural parameter, the reaction can be coupled with a 1,3-allylic shift, thus the valence isomer of the Ireland-Claisen product is formed.

Since its discovery in 1912, the Claisen rearrangement has evolved into a powerful synthetic tool for stereoselective carbon–carbon bond formation.[1] Much of its current popularity is due to the subsequent development of a series of new variants to effect this [3,3]-sigmatropic rearrangement in a stereocontrolled manner. Among these variants, the Ireland-Claisen reaction has proven to be the most general method, as this rearrangement requires significantly lower reaction temperature and there exists a unique option to control the silyl ester enolate geometry through the judicious choice of solvent (Scheme 1).[2] Nevertheless, one often-cited drawback of the classical Ireland-Claisen rearrangement is its inherent reliance on the usage of strong bases to provide the requisite silyl ester enolates. As a result, the substrate scope of this rearrangement is bounded as certain functionalities are not tolerated and the silyl ester enolate forming process requires rather low temperature. Consequently, the alternative construction of the requisite silyl ester enolates[3-7] is a particularly promising direction in Ireland-Claisen chemistry.

Thanks to the availability of effective catalysts for reductive silyl ester enolate formation, one-pot 1,4-hydrosilylation of allyl acrylates/[3,3] sigmatropic rearrangement protocols have been developed. First, Morken disclosed a highly diastereoselective rhodium catalyzed reductive Ireland-Claisen rearrangement using Cl_2MeSiH as a stoichiometric reducing agent.[8] Recently, Chiu has advanced further this reductive approach using in situ generated copper hydride catalyst and a less water-sensitive diethoxymethyl-silane reducing agent. Despite the many advances, the reductive Ireland-Claisen rearrangements still lag behind in scope and practicality. As such, the employed metal catalysts have had limited functional group tolerance and the reported protocols have a reliance and dependence on the glove box because of need of rigorous exclusion of water.[9] (Scheme 1.)

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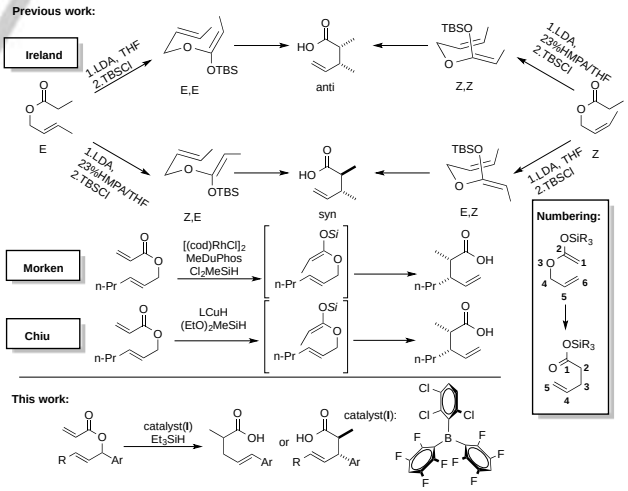
In a dual attempt to further the reductive Ireland-Claisen rearrangement in scope and practicality, we aimed to develop its borane-catalyzed version to amplify substrate scope and significantly upgrade user-friendliness. We assumed that the borane catalyst would promote both the 1,4-hydrosilylation of allyl acrylates and also the rearrangement of the formed silyl ester enolate to afford the appropriate Ireland-Claisen product in a one-pot manner. Additionally, it was expected that utilization of boron-based catalyst would be advantageous as these metal-free catalysts exhibit different chemoselectivity and functional group tolerance [10] than transition metal catalysts in reductive processes. However, the adaptation of borane promoted hydrosilylation for reductive Ireland-Claisen rearrangement was far from being straightforward because of the substrate inhibition and the extreme water sensitivity of the highly oxophilic, hard-type boron catalyst. Nevertheless, based on our previous work in frustrated Lewis pair hydrogenation [11] and hydrosilylation,[12] we conceived that it is possible to tackle these anticipated constrains of a borane catalyzed reductive Ireland-Claisen rearrangement via employing structurally well-designed, so-called size-exclusion boranes. The enhanced steric shielding around the boron Lewis acid center would serves to prevent or retard the complexation ability with Lewis basis (including water and carbonyls' oxygen), while retaining the capacity of cleavage of the silanes and might drive the chemo- and regioselectivity of the hydrosilylation of acrylates.

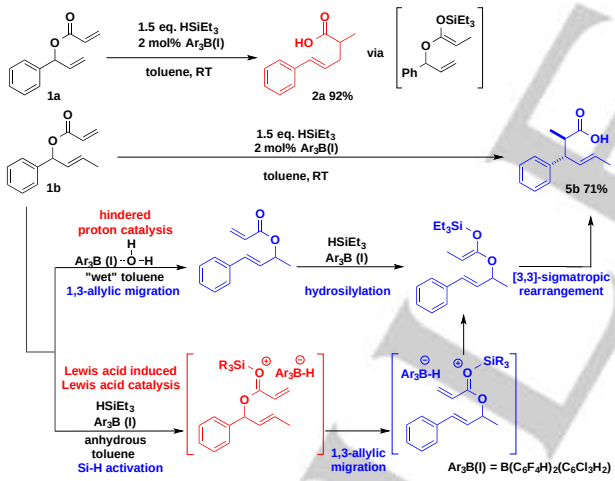


Scheme 1. Prior art and numbering of Ireland-Claisen rearrangements via silyl ester enolates.

On the basis of the precedent in size-exclusion FLP hydrogenation and hydrosilylation reactions, we attempted a borane mediated reductive Ireland-Claisen rearrangement using bulky borane **I**. Gratifyingly, the model substrate 4-phenylallylic acrylate (**1a**) underwent the proposed catalytic transformation with stoichiometric Et_3SiH. Further evaluation of a variety of

borane catalysts and experimental conditions (concentration, catalyst load) led to the identification of optimal reaction condition for the two-step tandem process. A subsequent survey of reaction solvent found toluene to be superior to ethereal type solvents, and most importantly, even technical grade solvent could be used. As catalyst **I** proved to be air and moisture stable, we performed all synthetic manipulation, as well as all others reported in this study, at laboratory bench without the reliance and dependence on inert techniques. Although the presence of water did not mitigate the reaction, our preliminary results also indicated that a small excess of silane was needed to reach full conversion in the hydrosilylation step.[13]

Next, we conducted an experiment to probe the diastereoselectivity of the cascade reaction. However, when a methyl substituent was introduced into position 6, the product was not the expected Ireland-Claisen product (Scheme 2). Further structural information derived from NMR spectroscopy and X-ray crystallography indicated the formation of a formal valence isomer with *syn* diastereoselectivity. As it is known that allylic esters can rearrange in the presence of Lewis and Brønsted acids[14], we assumed that a 1,3-allylic shift preceded the sigmatropic rearrangement.[15] Nevertheless, the *syn* diastereoselectivity of the rearrangement revealed that the hydrosilylation step prefers a Z-selective silyl enol ether formation which selectivity is in agreement with our previous observation in related borane mediated 1,4-hydrosilylation of unsaturated ketones.[12]

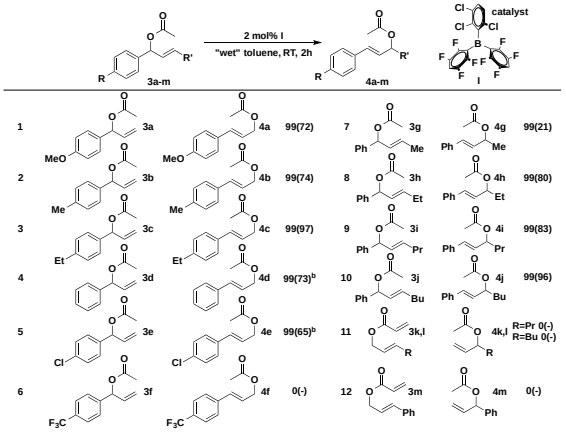


Scheme 2. Hydrosilylation/ Ireland-Claisen tandem reactions and proposed reaction pathways forming classical and formal valence isomer products.

Subsequent studies revealed that the borane **I** itself was incapable to promote the 1,3-allylic shift because of the confined space around the Lewis acidic center. However, as our observations[13] suggest, the allylic transposition (Scheme 2) could proceed via either a Lewis acid induced Lewis acid promotion (hydride abstraction from $HSiEt_3$ with borane **I**)[16] or hidden proton catalysis[17] (protonation by trace amount of borane **I**-water adduct[11,18]). Finally, it was established that the enhanced steric hindrance around the borane **I** was a critical factor in this reductive Ireland-Claisen reaction. The sterically less demanding $B(C_6F_5)_3$ **II**,[19] which is the archetypical borane of frustrated Lewis pair chemistry, failed to deliver any products under the same reaction condition and gave only a multicomponent mixture.[13]

As seemingly slight structural modification would change the 1,3 allylic shift aptitude (**1a** vs **1b**), we became interested to determine how electronic and structural parameters affect the 1,3-allylic transposition (Table 1). As hidden Brønsted catalyst proved to be an efficient promoter in this rearrangement, we deliberately generated the Brønsted acid catalyst using borane **I** in technical grade, "wet" toluene solvent. Examining the impact of the electronic effects on reactivity of **1a** acetyl analogs showed that the electron-donating substituents in *para* position on the aromatic ring lowered the activation barrier and full conversion to the thermodynamically more stable styrene derivatives was observed within one hour at room temperature (Table 1, entries 1–3). However, similar to what we have observed before, there was no allylic rearrangement without activating group at room temperature, but the process did take place at elevated the temperature and elongated reaction time (Table 1, entry 4). Introducing electron-withdrawing substituents resulted also decreased reactivity, there was no reaction in case of trifluoromethyl substituent even under forcing reaction condition (Table 1, entries 5, 6). Introducing substituents into position 5 facilitated the rearrangement, smooth transformation occurred at room temperature. (Table 1, entries 7–10). However, acetates of primary allylic alcohols did not rearrange even at elevated temperature showing that an electron rich aromatic substituent at position 4 is a requisite for this transformation (Table 1, entries 11,12). To determine whether the allylic rearrangement was the result of an inter- or an intramolecular process, a crossover experiment was performed.[13] As no crossover products formation was detected, the allylic rearrangement seems to follow an intramolecular mechanism.

Table 1. Hidden Brønsted acid mediated 1,3-allylic rearrangement of allylic acetates using borane **I** in "wet" toluene.



[a]Reaction conditions: in a capped vial, acetate (1.0 mmol), borane **I** (0.02 mmol) in 8 mL of "wet" toluene was stirred at RT for 2h. Conversions were determined by ^{1}H-NMR [b] reaction was conducted at 60°C for 16h.

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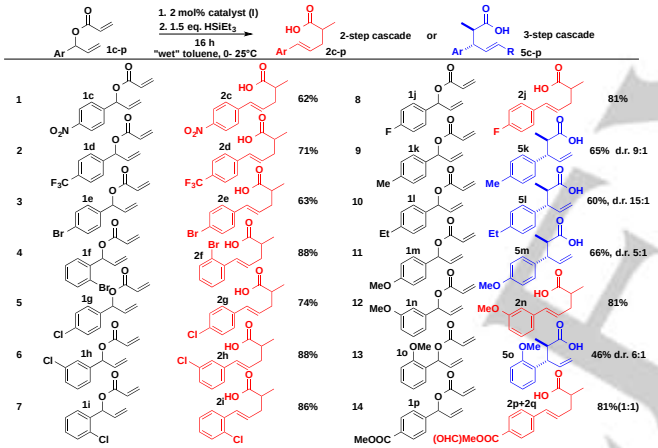
Given the effects of substituents on the 1,3-allylic migration, we aimed to interweave this reactivity with the hydrosilylation/Ireland-Claisen rearrangement reaction cascade by the judicious choice of substituent on the aromatic ring (Table 2). Compounds with electron-withdrawing substituents did not give the preceding 1,3-rearrangement and resulted in the classical 2-step cascade products respectively (Table 2, entries 1–8). These experiments also indicated that the reactions were not affected by the position of the substituent (Table 2, entries 5–7). As expected, the presence of electron-donating substituents on the phenyl ring facilitated the allylic rearrangement, resulting in the formation of formal valence isomer products via 3-step reaction cascade. In case of alkyl group at para position, the desired 3-step cascade compounds were obtained with high diastereoselectivity (Table 2, entries 9,10). As the geometry of the allylic double bond in the starting material was *trans*, the diastereomeric ratio of the [3,3]-sigmatropic rearrangement step was determined by the geometrical selectivity of the hydrosilylation step on the newly formed enolate double bond.

Table 2. Domino 1,3-Allylic/reductive Ireland-Claisen rearrangements of 4-aryl allylic acrylates.

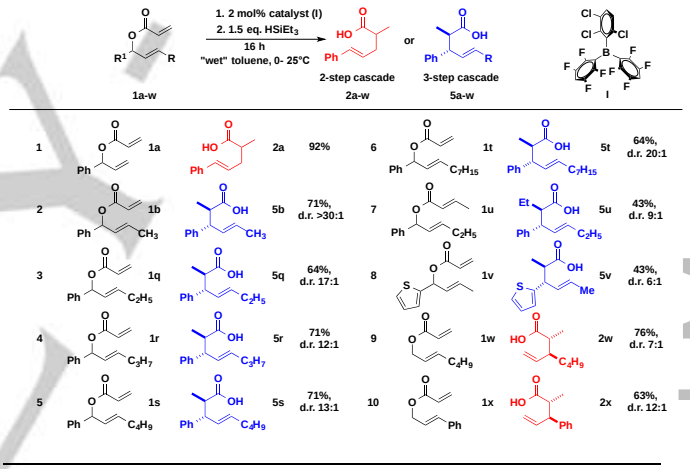


Reaction conditions: in a septum-capped vial, acrylate (1.0 mmol), **I** (0.02 mmol) in 8 mL of "wet" toluene were stirred for 1 hour at RT, then Et_3SiH (1.5 mmol) was added at 0°C. [(a)] Diastereomeric ratio was determinded by ^{1}H-NMR. [(b)] 1:1 mixture of products.

The effect of the methoxy group was also systematically investigated (Table 2, entries 11–13). The substituent exerted its electron-donating effect in *ortho* and *para* positions, resulting in the formation of the 2,3-disubstituted unsaturated **5m**,**o** carboxylic acid derivatives. However, at *meta* position, methoxy group showed electron-withdrawing effect that could be foreseen from the σ Hammett-constants and afforded **2n** in a two-step hydrosilylation/Ireland-Claisen rearrangement cascade process. Introducing an ester group resulted in more complex transformation. As 0.5 equivalent excess of silane reagent was used, 50% of the **2p** product was reduced to **2q** 4-formyl compound (Table 2, entry 14).

Next, the effect of substitution at position 6 was examined (for numbering see Scheme 1). As expected, allylic acetates with alkyl chain were readily converted in the 1,3-allylic rearrangement/hydrosilylation/Ireland-Claisen rearrangement cascade to unsaturated carboxylic acid products with *syn* diastereoselectivity (Table 3, entries 2–6). Expanding the scope of the unsaturated acid part also allowed transforming crotylate esters with the method albeit yields were lower (Table 3, entry 7). To perform our reaction cascade in the presence of heteroaryl rings seemed to be challenging due to their possible coordination to Lewis acid catalyst **I**. To our delight, the reaction went smoothly in the presence of thiophene ring (Table 3, entry 8). Substituents at position 6 (for numbering see Scheme 1) afforded the diastereoselective formation of the 2,3-disubstituted products without allylic rearrangement, therefore allowed to obtain products that are not accessible from substrate with substitution at position 4 (Table 3, entries 9,10).

Table 3. Domino 1,3-allylic/reductive Ireland-Claisen rearrangements of 6-substituted allylic acrylates.



Reaction conditions: in a septum-capped vial, acrylate (1.0 mmol), **I** (0.02 mmol) in 8 mL of "wet" toluene were stirred for 1 hour at RT, then Et_3SiH (1.5 mmol) was added at 0°C. [(a)] Diastereomeric ratio was determinded by ^{1}H-NMR.

In summary, a metal-free, one-pot reductive Ireland-Claisen rearrangement has been developed. With the applied air and moisture tolerant borane Lewis acid **I** a two or three-step tandem reaction cascade can be processed to form the Claisen products with good yields and high diastereoselectivity. As the *syn* diastereomer product proved to be the major product of the reaction, the 1,4-hydrosilylation step should form the Z-enolate respectively, which preference is the opposite of the metal catalyzed alternatives. The utilization of designer boron Lewis acid **I** represent not only a metal-free alternative but alleviated various restrictions of previous rearrangements, thus, the synthetic manipulations can be performed at the laboratory bench without the reliance and dependence on glove box and there was no need for purification of the solvent and reagents. Since the method requires mild reaction conditions, it establishes a practical alternative over the traditional Ireland-Claisen methods.

Experimental Section

General procedure of tandem reactions

In a 20 mL septum-capped vial equipped with a magnetic stirring bar, starting ester (1.0 mmol) and **I** (10 mg, 0.02 mmol, 2.0 mol%) was dissolved in 8 mL of technical grade, "wet" toluene. The reaction was stirred for 1 hour (this step is not required for the 2-step cascade). Then the mixture was cooled to 0°C with an ice/water bath. Et_3SiH (176 mg, 1.5 mmol, 1.5 equiv.) was added dropwise via syringe. The reaction was left to warm to room temperature and stirred overnight. After completion, TBAF (2 equiv.) was added and the reaction was stirred for 15 minutes. Then 8 mL 10% HCl solution was added and the mixture was stirred for 15 minutes. The phases were separated and the water phase was extracted with 2x5 mL of toluene. The organic phases were collected and dried on Na_2SO_4. Solvent was evaporated, and crude product was purified with flash chromatography (eluent: hexanes/EtOAc/acetic acid: 100/10/1) to obtain the desired carboxylic acid.

Acknowledgements

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Keywords: sigmatropic rearrangement • boranes • silanes • Ireland-Claisen • diastereoselectivity

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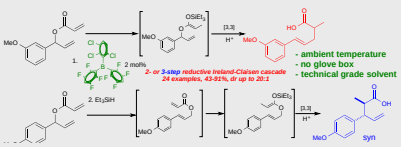

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Page No. – Page No.

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