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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Electrophilic Rearrangements of Chiral Amides: A Traceless Asymmetric α-Allylation

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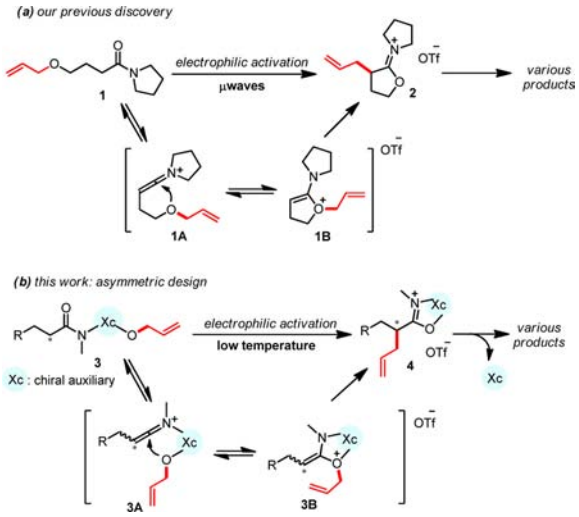
Supporting Information

ABSTRACT: A one-pot protocol for the asymmetric α-allylation reaction is reported relying on a key efficient asymmetric Claisen rearrangement, triggered by electrophilic activation of chiral pseudoephedrine amides. Subsequent reduction or hydrolysis of the resulting iminium ions provides highly enantioenriched α-allylic aldehydes or carboxylic acids in a traceless manner. Compared to traditional alternatives which make use of strongly basic conditions, the work presented herein displays unprecedented functional group tolerance.

As a fundamental tool in synthesis, the Claisen rearrangement has been extensively studied after Ludwig Claisen recognized the [3,3]-sigmatropic rearrangement of allyl vinyl ethers in 1912.[1,2] Asymmetric versions of the parent Claisen rearrangement and its variations[3] have included the use of both stoichiometric and catalytic amounts of chiral promoters,[4] as well as chiral auxiliaries.[5] The catalytic versions commonly rely on preinstalled coordination sites between chiral catalyst and substrate, while difficulties and low step economy in the attachment and removal of chiral auxiliaries have restricted their general adoption among synthetic chemists. In addition, a common limitation is the intolerance of many functional groups to the reaction conditions. More efficient and practical asymmetric Claisen rearrangements, affording products with a broad functional group tolerance, are therefore still desirable.

The natural abundance of several chiral amines and their easy coupling to form chiral amides has resulted in a large body of synthetic work. Evans and Myers (among others) realized that, by deprotonation of these amides with a strong base, chiral nucleophilic anionic ketene aminals (1-azaenolate anions) were formed and added to various electrophiles.[6] This strategy has proven especially successful in stereoselective C−C bond formation and is by now considered to be a textbook synthetic tool.[7] Claisen rearrangements based on the base-mediated enolization of chiral (thio)amides are also known.[5h−k] However, reports on the electrophilic activation of chiral amides for stereoselective transformations are rare.[8] Our group has recently reported a novel Claisen rearrangement of electrophilically activated amides **1**, furnishing α-allylated iminium ethers **2** ripe for further functionalization (Scheme 1a).[9,10] With this reactivity in mind, we were curious whether substitution of pyrrolidine in **1** by chiral amines bearing an O-allyl group **3** would lead to the corresponding rearranged products **4** (Scheme 1b). The new design envisioned the use of chiral 1,2-amino alcohols, several of which are commercially available in enantiopure form. We further reasoned that the intermediates **4** should be amenable to one-pot chemoselective postfunctionalization, tolerating a large variety of functional groups. Herein we report the development of a low-temperature, traceless enantioselective electrophilic α-allylation of amides proceeding through a Claisen rearrangement. This translates to an unusual strategy for asymmetric α-alkylation of amides wherein the alkylating agent is a part of the (traceless) auxiliary moiety.

Scheme 1. Racemic (a) and Enantioselective (b) Approaches for Claisen Rearrangement through Electrophilic Amide Activation

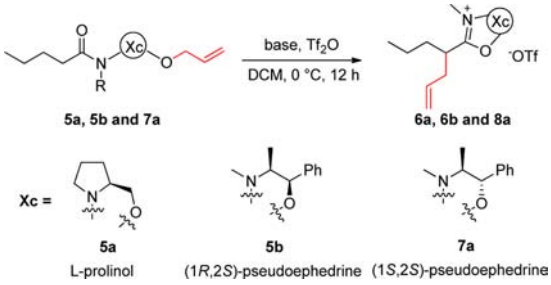


At the outset, we prepared the model substrates **5a**, **5b**, and **7a** starting from prolinol and two diastereomers of pseudoephedrine. All compounds were subjected to treatment with 2,4,6-collidine and Tf_2O.[9d] Although **5a**/**b** deteriorated progressively, the reaction of **7a** (bearing (1*S*,2*S*)-pseudoephedrine as a chiral backbone) gave rise to the desired rearranged iminium ether in low yield.[11] Changing the base to 2-halopyridines was highly beneficial, affording **8a** reproducibly in nearly quantitative NMR yields, and that even at 0 °C (Table 1, entries 4−6). Previous reports have proposed that 2-halopyridines can stabilize iminium ions by formation of the corresponding pyridinium adduct, leading to increased reactivity, and a similar role can be assumed herein.[10b−f,h,i]

Received: August 27, 2013
Published: September 30, 2013

dx.doi.org/10.1021/ja408856p | J. Am. Chem. Soc. 2013, 135, 14968−14971

Table 1. Exploration and Optimization of the Claisen Rearrangement Step[a]

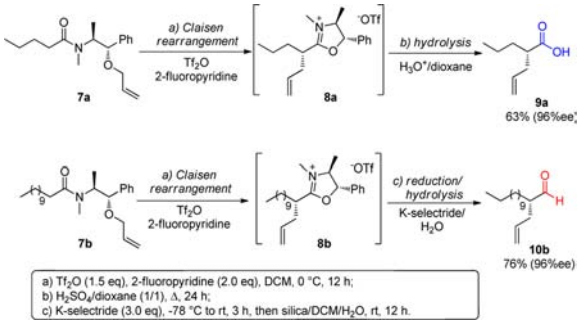


entry	substrate	base (2.0 equiv)	product (yield[b])
1	**5a**	2,4,6-collidine	**6a** (−)[c]
2	**5b**	2,4,6-collidine	**6b** (−)[c]
3	**7a**	2,4,6-collidine	**8a** (16%)
4	**7a**	2-fluoropyridine	**8a** (>95%)

[a]All reactions were performed under argon at 0 °C for 12 h. [b]NMR yield using mesitylene as internal standard. [c]No desired product was observed.

Seeking the *in situ* transformation of **8a** to more useful products, we found out that various alkaline hydrolysis conditions gave rise to decomposition of **8a**.[12] Conversely, acidic hydrolysis afforded carboxylic acid **9a** (Scheme 2).

Scheme 2. Studies on One-Pot Iminium Ether Transformations

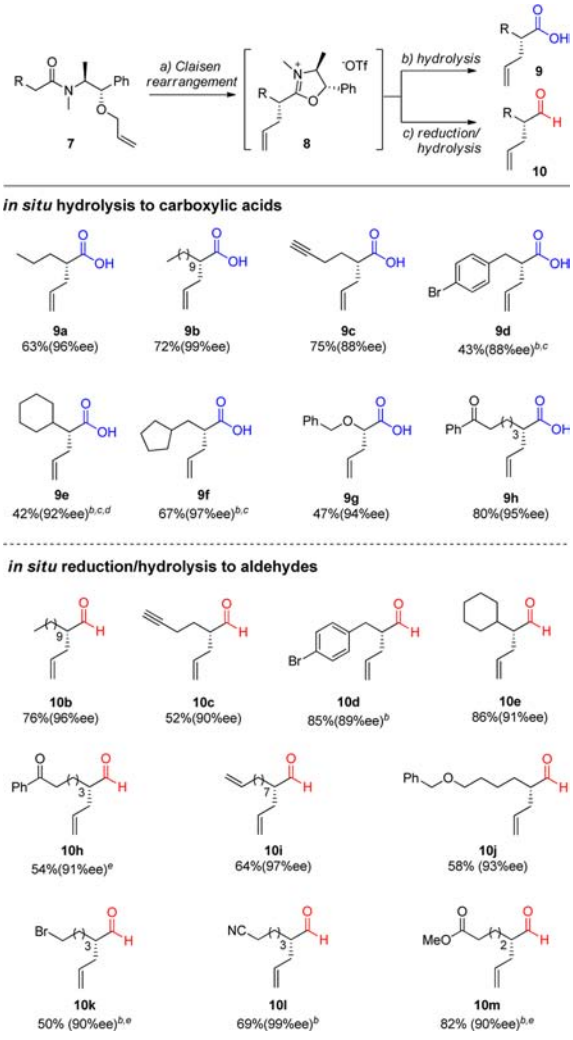


Following optimization,[11] a good yield of carboxylic acid **9a** could be obtained by hydrolysis with aqueous H_2SO_4 (Scheme 2). Moreover, product **9a** was formed in 96% ee in what amounts to a traceless one-pot carboxylic acid α-allylation.[13]

Additionally, reduction of **8a** with K-selectride to form the *N,O*-acetal, followed by hydrolysis, afforded aldehyde **10a** (not shown in Scheme 2).[14] Due to the volatility of **10a**, substrate **7b** was selected for further optimization studies. Using the previously optimized conditions, **7b** was also quantitatively rearranged to **8b** as confirmed by ^{1}H NMR analysis. Reduction of **8b** with K-selectride, followed by hydrolysis with a DCM/silica/water mixture, afforded **10b** in good yield.[11] The enantiopurity of the resulting product **10b** stood equally high at 96% ee.

We then studied the scope of these traceless α-allylation procedures employing substrates **7b**−**m**. Particular emphasis was placed on substrates carrying functional groups that are not tolerated by previously reported methods. Under the optimized conditions, the iminium ethers **8** could typically be formed in very high to quantitative NMR yields (Scheme 3). Following hydrolysis, the desired carboxylic acids **9a**−**h** were isolated in good yields and excellent enantiomeric excess. Worthy of

Scheme 3. One-Pot Asymmetric α-Allylation Accessing Enantioenriched α-Allyl Carboxylic Acids or Aldehydes[a]



[a]Conditions for steps a−c are akin to Scheme 2. [b] Step a was performed at −10 °C. [c] Hydrolysis for 36 h in step b. [d] 23% of lactone **11e** was also isolated.[15] [e] 2.5 equiv of K-selectride was used in step c.

mention is the straightforward access to **9c** (bearing an unprotected terminal alkyne) and **9h** (possessing a free ketone). The lability of those functional groups in the presence of a (strong) base underlines the challenge they pose to other asymmetric allylation procedures. This challenge is neatly illustrated by the preparation of their racemates, as required for HPLC separation (see Supporting Information (SI) for details). The projected use of a classical Ireland−Claisen rearrangement to this end mandated additional protection/deprotection manipulations to finally afford (*rac*)-**9c** in low yield.[11] In the case of (*rac*)-**9h**, the Ireland−Claisen reaction gave only trace amounts of the desired product.

For the stereoselective preparation of α-allyl aldehydes, a broadened set of substrates was employed, since the products are likely to be more synthetically versatile. As oxidation of the aldehydes toward carboxylic acids under mild, nonracemizing, conditions is a straightforward procedure, this approach is complementary to the acidic hydrolysis (*vide supra*). The one-pot telescoped sequence of Claisen rearrangement/reduction/hydrolysis led to aldehydes **10b**−**e** and **10h**−**m** in generally very good yields and very high to excellent enantiomeric

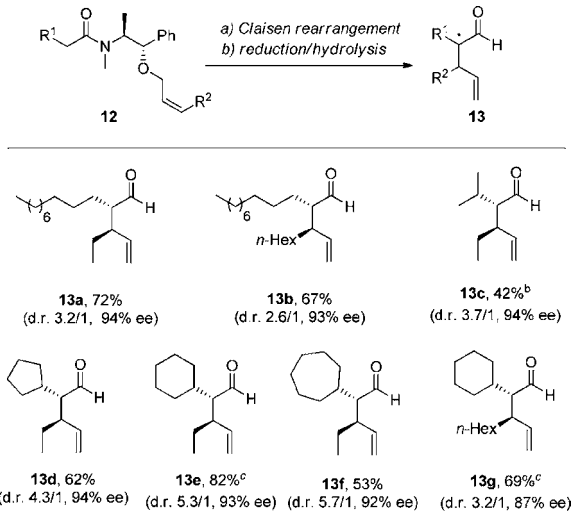
dx.doi.org/10.1021/ja408856p | J. Am. Chem. Soc. 2013, 135, 14968−14971

excesses. In the event, substrates **7k**–**m**, carrying a primary alkyl bromide (**7k**), a nitrile (**7l**), or even a methyl ester (**7m**), posed no compatibility issues to this methodology. Noteworthy is the fact that, in our hands, the preparation of (*rac*)-**10m** eluded all classical protocols and turned out to only be feasible employing the traceless allylation methodology herein reported using "homemade" racemic ephedrine.[11]

As depicted in Scheme 3, moieties such as a terminal alkyne, ketone, alkyl bromide, nitrile, and ester are tolerated using our approach. This broad functional group scope clearly highlights how this synthesis of enantioenriched α-allylated carboxylic acids and aldehydes is complementary to other well-known methodologies.

A synthetically important trait of Claisen (and other sigmatropic) rearrangements is the potential ability to install two adjacent chiral centers from precursors bearing terminally substituted allyl moieties.[2] We were thus eager to explore such substrates, and Scheme 4 depicts our results. Varying the olefin

Scheme 4. Diastereo- and Enantioselective Traceless α-Allylations[a]

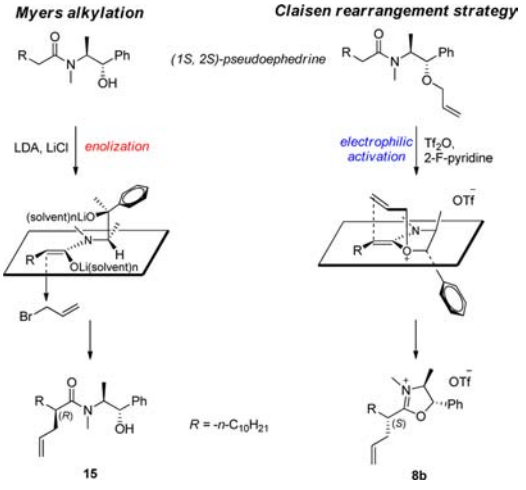


[a]Conditions for steps a–b are akin to Scheme 2; 2-iodopyridine was used instead of 2-fluoropyridine; d.r. values were determined by crude ^{1}H NMR analysis; ee values refer to the major diastereoisomer. [b] The volatility of product **13c** accounts for losses in yield. [c] Step a was conducted at −10 °C.

substituent from ethyl to *n*-hexyl afforded products in moderate to good yields and equally respectable diastereomeric ratios (**13a**–**g**).[16,17] The use of α-branched amide starting materials led to improved diastereoselectivities (cf. **13c**–**f**).

A mechanistic and stereochemical comparison of the base-mediated asymmetric alkylation procedure reported by Myers,[6b] also employing pseudoephedrine as the source of chirality, and our traceless allylation is shown in Scheme 5. In the Myers alkylation it is assumed that the fully deprotonated pseudoephedrine backbone shields one enolate face, allowing the electrophile approach to proceed from the opposite face and leading to product **15**. As our "alkylating agent" (the allyl group) is embedded in the auxiliary, it transpires that the use of the same enantiomer of pseudoephedrine leads, in the method reported herein, to the opposite enantiomeric series of products than the Myers alkylation.[6b] This was verified in practice, and the products **15** and **8b** obtained (and their derivatives) were indeed of opposite absolute configuration at the α-center.[11] In

Scheme 5. Comparative Analysis of Asymmetric Induction in the Myers Alkylation and the Claisen Rearrangement Reported Herein



addition, we determined the absolute configuration at the iminium ether stage by X-ray crystallography of **8d**·BF_4 (Figure 1).

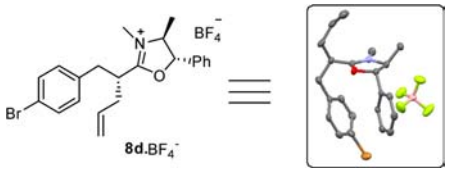


Figure 1. Single-crystal X-ray determination of the absolute configuration of the iminium ether intermediate.

In summary, a novel traceless asymmetric α-allylation triggered by an electrophilic Claisen rearrangement of chiral amides is reported. The intermediate chiral iminium ether intermediates can be directly converted into highly enantioenriched α-allyl carboxylic acids or aldehydes. The substrate scope of this transformation is unusually broad, as it tolerates a variety of common functional groups otherwise incompatible with base-mediated procedures. The intrinsic modularity suggested by the embedding of the desired alkylating agent into the chiral auxiliary combined with its traceless nature should render this a broadly useful synthetic strategy.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are greatly indebted to the Max-Planck Society and the Max-Planck-Institut für Kohlenforschung for generous funding of our research programs. This work was funded by the Fonds

der Chemischen Industrie (Sachkostenzuschuss to N.M.) and the Deutsche Forschungsgemeinschaft (Grant MA 4861/1-2). Invaluable assistance from our HPLC (Ms. D. Klütt) and X-ray (Dr. R. Goddard) departments is acknowledged.

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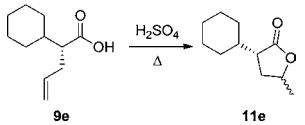
(15) Lactone **11e** was formed by the acid promoted lactonization of product **9e**. Under the optimized conditions, analogous side reactions of products **9a−d** and **9f−h** were suppressed.



9e **11e**

(16) Use of the corresponding *E*-olefin isomers led to eroded diastereoselection. See SI for details.

(17) The use of *Z*-olefins affords the depicted *syn*-**13a−g** as the major products. The observed chemical shifts for the olefinic protons in the ^{1}H NMR spectra of **13a−g**, compared to previously reported spectral data, confirm this. See: (a) Miller, S. P.; Morken, J. P. *Org. Lett.* **2002**, *4*, 2743−2745. (b) Aris, V.; Brown, J. M.; Golding, B. T. *J. Chem. Soc., Perkin Trans. 2* **1974**, 700−704.