An Isothiourea-catalyzed Asymmetric [2,3]-Rearrangement of Allylic Ammonium Ylides

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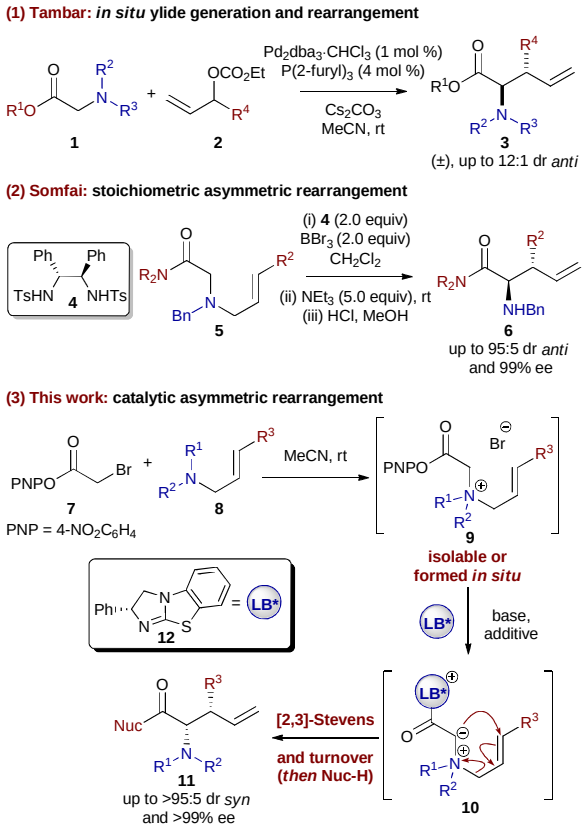
Supporting Information Placeholder

ABSTRACT: Benzotetramisole promotes the catalytic asymmetric [2,3]-rearrangement of allylic quaternary ammonium salts (either isolated or prepared *in situ* from *p*-nitrophenyl bromoacetate and the corresponding allylic amine), generating *syn*-α-amino acid derivatives with excellent diastereo- and enantioselectivity (up to >95:5 dr; up to >99% ee).

The [2,3]-rearrangement[1] of glycine-derived allylic ammonium ylides is widely recognized as a versatile process for the synthesis of stereodefined unnatural α-amino acid derivatives containing multiple stereocentres.[2] Current limitations of this processes include the difficulty associated with the generation and isolation of the reactive ammonium salts,[3] alongside the development of catalytic asymmetric methods for inducing enantiocontrol.[4] Recent work by Tambar and Sohelie has elegantly utilized Pd-catalyzed allylic substitution to facilitate tandem ammonium ylide generation and [2,3]-rearrangement, generating racemic *anti*-configured products **3** with high diastereoselectivity (Scheme 1, eq 1).[5] While asymmetric [2,3]-rearrangements of allylic ammoniums can be induced by chiral auxiliary control as demonstrated by Sweeney and co-workers,[4a] Somfai *et al.* have applied stoichiometric asymmetric Lewis acids to promote the enantioselective rearrangement of allylic amines **5** (Scheme 2, eq 2).[4b,6] Within the last fifteen years, advances in asymmetric organocatalysis[7] have been applied to asymmetric [3,3]-sigmatropic rearrangements.[8] However, organocatalytic [2,3]-sigmatropic rearrangements are an underexplored concept, with the secondary amine catalyzed [2,3]-Wittig rearrangement developed by Gaunt *et al.* representing the current state-of-the-art within this area.[9] Given our interest in Lewis base promoted organocatalytic processes,[10] in this manuscript we show that sub-stoichiometric isothioureas[11] promote the asymmetric [2,3]-rearrangement of ylides **10** derived from isolable or *in situ* generated allylic ammonium salts **9**, forming stereodefined α-amino acid derivatives **11** with excellent *syn*-diastereocontrol and enantiocontrol (up to >95:5 dr and 99% ee) (Scheme 1, eq 3).

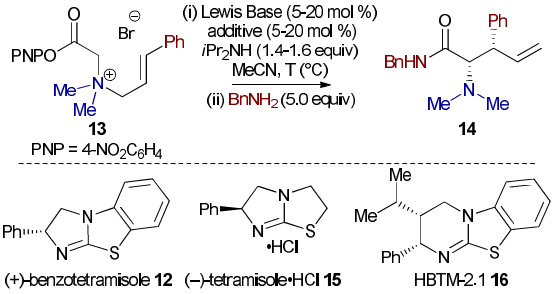
Scheme 1: [2,3]-Rearrangements of Allylic Ammonium Ylides



Proof of concept studies focused upon asymmetric isothiourea-promoted [2,3]-rearrangement of pre-formed allylic ammonium salt **13** bearing an activated *p*-nitrophenyl ester (Table 1).[12,13] Treatment of ammonium salt **13** with (−)-tetramisole·HCl **15** (20 mol%) and *i*Pr$_2$NH at rt led to [2,3]-Stevens rearrangement, with subsequent nucleophilic quench with benzylamine giving amide **14** in 89:11 dr and promising 81% ee (entry 1).[14] Further optimization showed that addition of HOBt (20 mol%) as a co-catalyst led to improved diastereo- and enantiocontrol (entry 2).[15] Alternative organic bases

such as iPr$_2$NEt or NEt$_3$ could also be used without affecting the dr or ee, although *N*-methylmorpholine gave reduced diastereocontrol.[16] Lowering the reaction temperature to −20 °C gave increased product ee, whilst catalyst variation showed that (+)-benzotetramisole (BTM) was optimal, giving **14** in 76% yield, >95:5 dr and 99% ee (entries 3-7). The additive HOBt is essential to achieve excellent stereocontrol when using BTM at −20 °C (entries 5 and 6), whilst reduced catalyst loadings gave lower, but still acceptable, asymmetric induction (entries 9-10).

Table 1: Optimization of Reaction Conditions

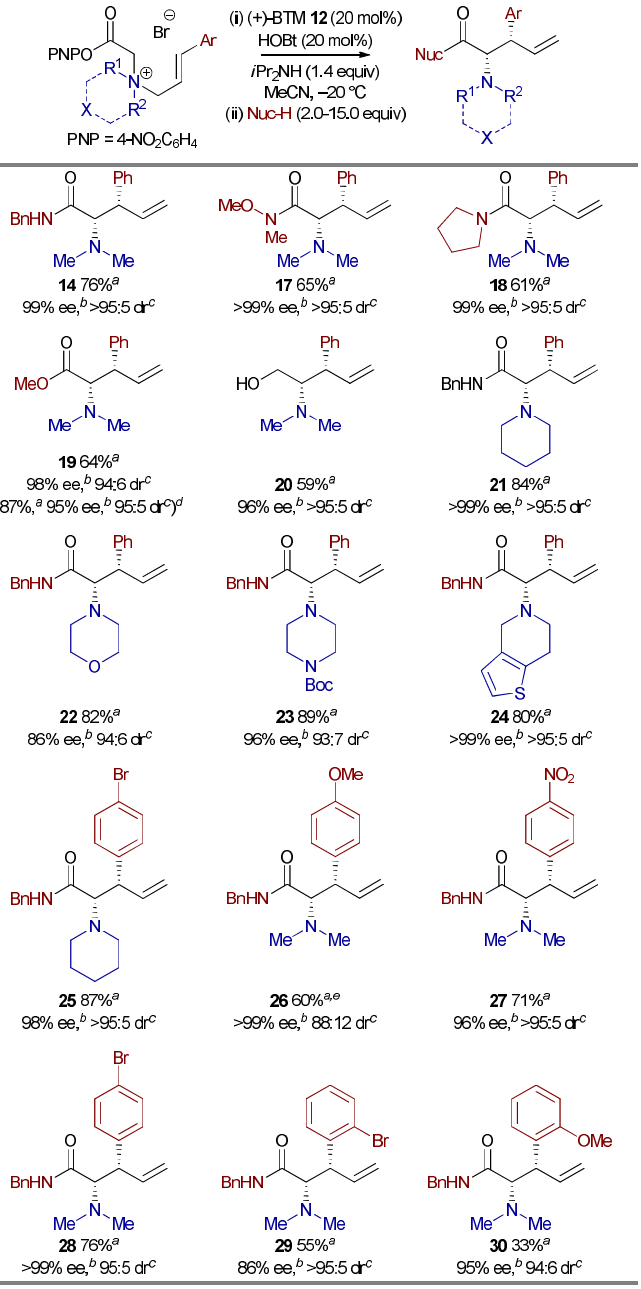


Entry	LB[a]	additive[a]	T (°C)	Yield (%)[b,c]	dr[d]	ee[e]
1	**15**	--	rt	(83)[c]	89:11	81 (*ent*)
2	**15**	HOBt	rt	68	93:7	84 (*ent*)
3	**15**	HOBt	0 to rt	88	92:8	89 (*ent*)
4	**12**	HOBt	−20	65	91:9	93 (*ent*)
5	**12**	--	−20	61	92:8	95
6	**12**	**HOBt**	**−20**	**76**	**>95:5**	**99**
7	**16**	HOBt	−20	(33)[c]	62:38	ND
8	**12**	HOAt	−20	49	90:10	98
9	**12**[f]	HOBt[f]	−20	62	88:12	96
10	**12**[g]	HOBt[g]	−20	41[h]	79:21	92

Reactions performed on 0.24 mmol scale [a]20 mol% unless stated. [b]Isolated yield after chromatographic purification of >95:5 dr. [c]Yield in parentheses determined by ^{1}H NMR in comparison to internal standard (4-nitrotoluene). [d]Determined by ^{1}H NMR analysis of crude material. [e]Determined by Chiral HPLC analysis. [f]10 mol%. [g]5 mol%. [h]Isolated as a 84:16 mixture of diastereomers.

With an optimized protocol identified, the scope of this process was initially examined through sequential variation of the nucleophile (Table 2). Using ammonium salt **13**, *N*,*O*-dimethylhydroxylamine, pyrrolidine, methoxide, or LiAlH$_4$ could be used to generate functionalized amino carbonyl and alcohol compounds **17-20** in good yields, high dr and ee. This process is readily scalable, with 1.95 g of amino ester **19** (86% yield, 95:5 dr, 95% ee) generated from 9.6 mmol of salt **13**. Various *N*-substituents encompassing simple and functionalized piperidines, morpholine and *N*-Boc-piperazine motifs are readily accommodated, giving functionalized amino amides (**21-25**) in excellent yield (80-89%), dr and ee (up to >95:5 dr and >99% ee). Variation of the allylic *C*(3)-aryl substituent within the salt showed that both electron-donating and withdrawing 4-substituents are well tolerated (**26-28**). 2-Substitution of the aryl ring can also be incorporated, albeit in only modest isolated yields but high dr and ee (**29** and **30**).

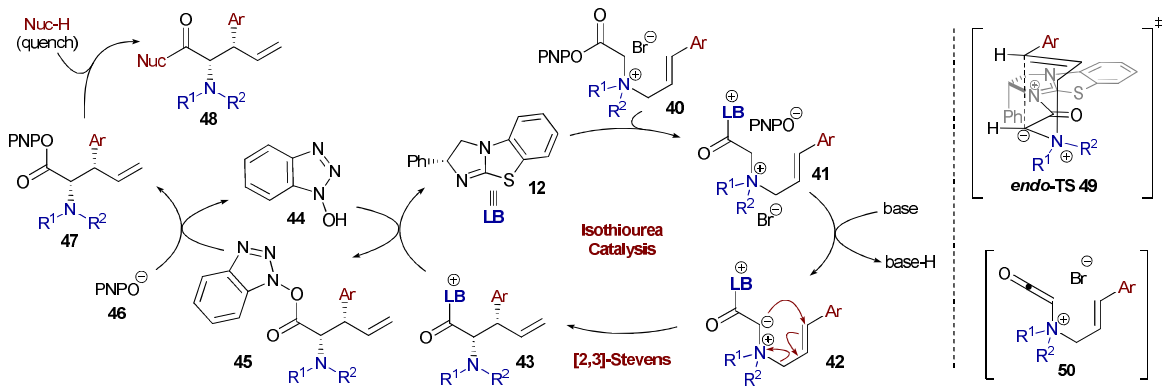
Table 2: Scope of Isolable Ammonium Salts



[a]Isolated yield after chromatographic purification of >95:5 dr. [b]Determined by Chiral HPLC analysis. [c]Determined by ^{1}H NMR analysis of crude material. [d]Performed on 9.6 mmol scale. [e]Isolated in 93:7 dr.

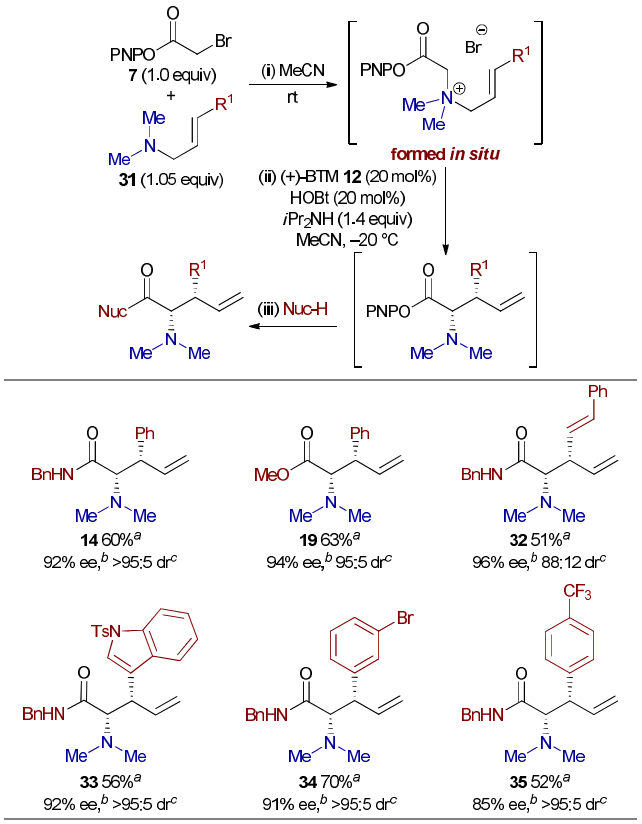
Further studies into the scope of the reaction were limited by the difficulty in the formation and isolation of certain ammonium salts. This was circumvented through the development of a one-pot protocol composed of *in situ* formation of the ammonium salt, followed by direct [2,3]-rearrangement under isothiourea catalysis (Table 3). As a direct comparison, treatment of *p*-nitrophenyl bromoacetate **7** with excess amine **31** (R^1 = phenyl) followed by rearrangement under standard conditions, gave both **14** and **19** in excellent yield, ee and dr with benzylamine and NaOMe as nucleophilic quenches. Pleasingly, this one-pot process allows the incorporation of

Scheme 3: Mechanistic and Stereochemical Proposal



styryl, heteroaryl and alternative aryl functional groups (**32-35**), for which isolation of the corresponding ammonium salts proved difficult in our hands.

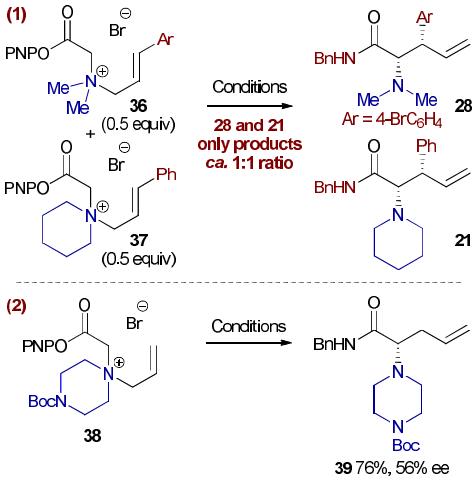
Table 3: *In Situ* Generated Ammonium Salts



[a] Isolated yield after chromatographic purification of >95:5 dr; [b] Determined by Chiral HPLC analysis; [c] Determined by ^{1}H NMR analysis of crude material.

Crossover studies with **36** and **37** (Scheme 2, eq 1) indicate that the allylic transfer process is intramolecular, consistent with the expected [2,3]-sigmatropic rearrangement.[16] Further mechanistic investigations showed that epimerization or racemization is not observed upon retreatment of the major diastereoisomer to the reaction conditions. Probing of the substrate scope showed that reduced enantioselectivity (56% ee) is observed with an *N*-allyl rather than a *N*-cinnamyl unit (**39**, Scheme 2, eq 2), indicating that an aryl or vinyl unit is a structural requirement for high enantioselectivity in this process.[17]

Scheme 2: Mechanistically Significant Examples



Conditions: (i) **12** (20 mol %), HOBt (20 mol %), iPr$_2$NH (1.4 equiv), MeCN, −20 °C; (ii) BnNH$_2$ (5.0 equiv).

While a Brønsted base-catalyzed mechanism cannot be ruled out at present, the following mechanistic possibilities and catalytic cycle for this transformation are proposed (Scheme 3). Dicationic acyl ammonium ion **41**[18] can be formed through direct *N*-acylation of (+)-BTM (**12**) with **40**, with deprotonation of **41** with a suitable base forming ylide **42**. Alternatively, **42** may arise from the addition of **12** to ketene **50**, formed by formal elimination of *p*-nitrophenol from **40**.[19] [2,3]-rearrangement of **42** gives acyl ammonium **43** that can either be intercepted by *p*-nitrophenoxide (**46**) or alternatively with HOBt (**44**) as a nucleophilic co-catalyst to give **47**, in a second catalytic cycle as previously described by Rovis.[15] The observed *syn*-diastereoselectivity[20] may arise from the rearrangement occurring preferentially through an *endo*-type pre-transition state assembly **49**. In this array, the carbonyl oxygen preferentially lies *syn* to the S atom within the isothiouronium ion, allowing a stabilizing n_o to $\sigma^*_{C\text{-}S}$ interaction[21] or electrostatic stabilization. The stereodirecting *C*(2)-phenyl unit within

BTM adopts a pseudoaxial position to minimize 1,2-steric interactions. A π-cation interaction between the allylic *C*(3)-aryl or styryl substituent and the acyl ammonium ion, previously suggested in other asymmetric isothiourea catalyzed processes,[21d,22] is proposed as key for high stereocontrol.

In summary, we have developed the first catalytic asymmetric [2,3]-rearrangement of allylic ammonium ylides. Isothiourea (+)-BTM **12** promotes the rearrangement of *p*-nitrophenyl ester ammonium salts, producing *syn*-configured α-amino acid derivatives with excellent stereocontrol (up to >95:5 *dr* and >99% *ee*). Further investigations into the mechanism of this process and applications of this reaction are currently being pursued in our laboratory.

ASSOCIATED CONTENT

Supporting Information: Complete experimental procedures including: X-ray structural data for **29**, spectral and HPLC data for all novel compounds. 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 interests.

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(13) The *t*-butyl analogue of **13** was found to be inactive under the catalytic reaction conditions

(14) The rearranged *p*-nitrophenyl ester could be isolated, albeit in modest yield, see SI for details.

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(16) See SI for a full optimization table and crossover experiments.

(17) Further investigation showed that the (*Z*)-cinnamyl isomer of **13** gave preferentially the *syn*-diastereoisomer but in reduced ee (dr 87:13, 64% ee), see SI for further information.

(18) Dicationic amidines are well characterized, see: Corr, M. J.; Gibson, K. F.; Kennedy, A. R.; Murphy J. A. *J. Am. Chem. Soc*. **2009**, *131*, 9174-9175.

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