Tandem Palladium and Isothiourea Relay Catalysis: Enantioselective Synthesis of α-Amino Acid Derivatives via Allylic Amination and [2,3]-Sigmatropic Rearrangement

Stéphanie S. M. Spoehrle, Thomas H. West, James E. Taylor, Alexandra M. Z. Slawin, and Andrew D. Smith*

EaStCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews KY16 9ST, U.K.

ABSTRACT: A tandem relay catalytic protocol using both Pd and isothiourea catalysis has been developed for the enantioselective synthesis of α-amino acid derivatives containing two stereogenic centers from readily accessible N,N-disubstituted glycine aryl esters and allylic phosphates. The optimized process uses a bench-stable succinimide-based Pd precatalyst (FurCat) to promote Pd-catalyzed allylic ammonium salt generation from the allylic phosphate and the glycine aryl ester. Subsequent in situ enantioselective [2,3]-sigmatropic rearrangement catalyzed by the isothiourea benzotetramisole forms syn-α-amino acid derivatives with high diastereo- and enantioselectivity. This methodology is most effective using 4-nitrophenylglycine esters and tolerates a variety of substituted cinnamic and styrenyl allylic ethyl phosphates. The use of challenging unsymmetrical N-allyl-N-methylglycine esters is also tolerated under the catalytic relay conditions without compromising stereoselectivity.

1. INTRODUCTION

The functionalization of α-amino acids through enantioselective α-alkylation is an enduring challenge in synthetic chemistry.1 For example, the direct stereoselective transition-metal-catalyzed α-alkylation of amino acid ester derivatives through allylic substitution has received considerable attention.2 In such processes, the use of palladium-based catalysts typically results in formation of the linear substitution product,3,4 whereas catalysts based on either molybdenum,5 ruthenium,6 rhodium,7 or iridium8 can be branched selective (Scheme 1a). In reactions with achiral allylic precursors and prochiral amino acid enolates, product stereochemistry is usually derived from either chiral ligands on the metal center, or from the use of chiral enolate counterions. Alternatively, Snaddon and co-workers reported that chiral ammonium enolates, derived from the reaction of isothiourea catalyst BTM 1 with aryl acetic esters, undergo enantioselective linear α-alkylation with achiral Pd-allyl complexes in a dual-catalytic process (Scheme 1b).9 This methodology uses pentafluorophenyl arylacetic esters as ammonium enolate precursors, demonstrating that an isothiourea/phenoxide-rebound strategy for Lewis base catalyst turnover is compatible with Pd catalysis. Hartwig and co-workers have reported a related enantioselective, stereo-divergent branched allylic substitution of aryl acetic esters using synergistic Ir/isothiourea catalysis.10,11

A conceptually different way of preparing branched α-allyl α-amino acid derivatives has been reported by Tambar and co-workers (Scheme 2a).12 The process uses a Pd-catalyzed linear allylic amination reaction between allylic carbonates 2 and glycine esters 3 to generate quaternary allylic ammonium salts in situ, which undergo stoichiometric Brønsted base-promoted [2,3]-rearrangement to form racemic anti-α-amino acid derivatives 4 with high diastereoselectivity.

However, despite the synthetic potential, the development of enantioselective [2,3]-rearrangements of allylic ammonium ylides for the synthesis of α-amino acid derivatives has remained a significant challenge.13,14 Previous strategies toward such processes have traditionally relied on substrate control and/or the use of chiral auxiliaries.15 Alternatively, Somfai and...
co-workers reported the use of a stoichiometric chiral Lewis acid for the enantioselective synthesis of α-amino amide derivatives. In 2014, we reported the first catalytic enantioselective [2,3]-rearrangement of allylic quaternary ammonium salts 5 using the isothiourea BTM 1 as a Lewis base and co-catalytic hydroxybenzotriazole (HOBt) to form syn-α-amino acid derivatives 6 with excellent stereoselectivity (Scheme 2b). In this process the HOBt additive (i) aids catalyst turnover through interception of a post-[2,3]-rearrangement acylammonium species and (ii) leads to increased diastereoselectivity of the [2,3]-rearrangement products. A recognized challenge encountered by others and ourselves for such [2,3]-rearrangement processes is the problematic synthesis and isolation of the required allylic quaternary ammonium salts. In our case, only limited ammonium salts were amenable to isolation, typically being obtained in moderate yields (ca. 30–90%) from the corresponding allylic amine and 4-nitrophenyl bromoacetate. Although an in situ one-pot salt-formation/[2,3]-rearrangement protocol was developed, the products were formed in moderate overall yields and with reduced enantioselectivity compared with the use of the isolated salts.

Building upon the precedent of Tambar, we questioned the feasibility of merging a Pd-catalyzed allylic amination with an enantioselective isothiourea-catalyzed [2,3]-rearrangement (Scheme 2c). Such a process would allow for the rapid generation of complex enantiomerically enriched α-amino acids bearing two new stereocenters from readily available allylic alcohol derivatives and glycine esters, avoiding the problematic isolation of ammonium salts. To proceed effectively, this relay catalytic system must overcome the inherent challenges associated with combining transition metal and organocatalyzed processes, with all reagents compatible with each independent catalytic cycle. Notably, the inherent substrate bias for [2,3]-rearrangement under the basic Pd-catalyzed conditions developed by Tambar generates anti-α-amino acid derivatives, whereas the isothiourea-catalyzed process forms the opposite syn-diastereoisomer. The proposed relay system must therefore undergo minimal Bronsted base-catalyzed [2,3]-rearrangement protocol was developed, the products were formed in moderate overall yields and with reduced enantioselectivity, it is imperative that any base-promoted [2,3]-rearrangement of the in situ-generated allylic ammonium salt into racemic product is minimized. We hypothesized that the counterion generated from Pd-promoted allylic ammonium salt formation could play a key role in this area. With this in mind, a series of control experiments based upon Tambar’s original report was performed to identify a suitable allylic precursor for the proposed relay catalysis (Table 1). First, N,N-dimethylglycine ethyl ester 8 was reacted with cinnamyl ethyl carbonate in the presence of Pd(dba)₂ (2 mol%) and PPh₃ (4 mol%) using excess Cs₂CO₃ as base (Table 1, entry 1). This gave [2,3]-rearrangement product 12 in good 88% yield and a 65:35 dr in favor of the anti-diastereoisomer, consistent with the literature.

Table 1. Identifying Suitable Allylic Precursors

| entry | X         | Cs₂CO₃ yield (%) | dr*  |
|-------|-----------|------------------|------|
| 1     | C(O)OEt   | 3 equiv          | 88   | 65:35 |
| 2     | C(O)OEt   | 9                 | 76   | 68:32 |
| 3     | C(O)OPh   | 3 equiv          | 0    | N/A   |
| 4     | C(O)OPh   | 10               | 0    | N/A   |
| 5     | P(O)(OEt) | 3 equiv          | 80   | 66:34 |
| 6     | P(O)(OEt) | 11               | 0    | N/A   |

* Determined by 1H NMR analysis of the crude material.

2. RESULTS AND DISCUSSION

2.1. Reaction Optimization. 2.1.1. Identification of a Suitable Allylic Precursor. To achieve high levels of diastereoenantioselectivity during the proposed relay catalysis, it is imperative that any base-promoted [2,3]-rearrangement of the in situ-generated allylic ammonium salt into racemic product is minimized. We hypothesized that the counterion generated from Pd-promoted allylic ammonium salt formation could play a key role in this area. With this in mind, a series of control experiments based upon Tambar’s original report was performed to identify a suitable allylic precursor for the proposed relay catalysis (Table 1). First, N,N-dimethylglycine ethyl ester 8 was reacted with cinnamyl ethyl carbonate in the presence of Pd(dba)₂ (2 mol%) and PPh₃ (4 mol%) using excess Cs₂CO₃ as base (Table 1, entry 1). This gave [2,3]-rearrangement product 12 in good 88% yield and a 65:35 dr in favor of the anti-diastereoisomer, consistent with the literature.
for such base-mediated processes. In the absence of Cs₂CO₃, the reaction still proceeded to give product 12 in 75% yield (Table 1, entry 2). This suggests that the ethyl carbonate and/or ethoxide released during allylic substitution is sufficiently basic to promote the [2,3]-rearrangement step, and that ethyl phosphates are not suitable precursors for a catalytic enantioselective relay process.

Table 2. Optimization of the Enantioselective Relay Process

| entry | [Pd] (mol%) | L (mol%) | yield (%)ab | dr (%) | er (%) |
|-------|-------------|----------|-------------|--------|--------|
| 1     | Pd(dba)₂ (2) | PPh₃   | 20 (5)      | N/A    | N/A    |
| 2     | Pd(dba)₂ (2) | 15      | 20 (11)     | N/D    | N/D    |
| 3     | Pd(dba)₂ (2) | 16      | 20 (13)     | N/D    | N/D    |
| 4     | Pd(κ₃-dba) ClCH₃ (1) | 20       | 47 (95:5)  | 98:2   |        |
| 5     | 17 (1)      | 16      | 20 (70)     | >95:5  | >99:1  |
| 6     | 18 (S)      | –       | 20 (79)     | >95:5  | 99:1   |
| 7     | 18 (S)      | –       | 10 (60)     | 94:6   | 97:3   |
| 8     | 18 (S)      | –       | 5 (56)      | 88:12  | 89:11  |
| 9     | 18 (S)      | –       | –           | N/A    | N/A    |
| 10    | –           | –       | 20 (0)      | N/A    | N/A    |
| 11d   | 18 (S)      | –       | 20 (58)     | 92:8   | 97:3   |
| 12e   | 18 (S)      | –       | 20 (65)     | >95:5  | >99:1  |
| 13f   | 18 (S)      | –       | 20 (60)     | >95:5  | 96:4   |

aYields in parentheses determined by ¹H NMR using L,4-dimethoxybenzene as an internal standard. bDetermined by ¹H NMR analysis of the crude material. cDetermined by HPLC analysis after derivatization into the corresponding benzyl amide. dFree base of 13 and i-Pr₂NH (1.2 equiv) used in place of 13-HCl and i-Pr₂NH (2.2 equiv). eN,N-Dimethyl-3,5-bis-trifluoromethylphenylglycine ester used in place of 13. fCinnamyl trifluoroacetate (2 equiv) used in place of 11.

Next, cinnamyl ethyl phosphate 11 was tested and, as required, only led to product formation in the presence of external base (Table 1, entries 5 and 6), consistent with no phosphate-mediated [2,3]-rearrangement under these conditions.

2.1.2. Development of Pd/Isothiourea Relay Catalysis.

Having identified easily accessible allylic phosphates as potentially suitable precursors, efforts were focused on developing a catalytic enantioselective relay allylic substitution/[2,3]-rearrangement process (Table 2). Readily accessible N,N-dimethyl 4-nitrophenyl ester hydrochloride salt 13 was chosen as a suitable glycine derivative that would allow for Lewis base incorporation, while the released 4-nitrophenoxide should also be capable of facilitating catalyst turnover. However, initial attempts at reacting 13 and cinnamyl ethyl phosphate 11 with Pd(dba)₂ (2 mol%) and PPh₃ (4 mol%) in the presence of the isothiourea BTM 1 (20 mol%) using i-Pr₂NH as base in MeCN at room temperature led to 5% product formation (Table 2, entry 1). The use of electron-withdrawing heteroaryl phosphines 15 and 16 gave the first sign of the desired reactivity, giving [2,3]-rearrangement product 14 in low conversion by ¹H NMR (Table 2, entries 2 and 3). Altering the source of palladium led to significant improvements in reactivity. Using Pd₂(dba)₂·CHCl₃ (1 mol%) and P(2-furyl), (4 mol%) allowed product 14 to be isolated in 47% yield and 95:5 dr (Table 2, entry 4), while using [Pd(allyl)Cl]₂ 17 (1 mol%) under the same conditions gave 14 in 70% yield as a single diastereoisomer (Table 2, entry 5). In these cases, the syn-configured diastereoisomer is favored and was formed with excellent enantioselectivity (up to >99:1 er), providing proof-of-principle for the desired catalytic relay process. The high stereoselectivity observed is consistent with competitive racemic [2,3]-rearrangement processes having been completely suppressed without recourse to the addition of additives such as HOBt. The use of the defined, bench-stable succinimide-based Pd complex 18 (FurCat, 5 mol%), first developed by Fairlamb and co-workers for use in Stille cross-coupling gave further improvement while simplifying the catalytic system, allowing syn-14 to be isolated in 79% yield as a single diastereoisomer in 99:1 er (Table 2, entry 6). Decreasing the catalyst loading of BTM led to reduced yields and stereoselectivity (Table 2, entries 7 and 8). Control experiments in the absence of either the Pd catalyst 18 or BTM 1 led to no product formation under the otherwise optimal conditions (Table 2, entries 9 and 10). Alternatively the free base of 4-nitrophenol ester 13 and i-Pr₂NH (1.2 equiv) can be used in this protocol, giving syn-14 in reduced 58% yield, 92:8 dr and 97:3 er (Table 2, entry 11). Screening alternative N,N-dimethylglycine aryl esters under the optimized conditions showed that the 3,5-bis-trifluoromethylphenyl ester gave good conversion into the corresponding rearrangement product with high stereoselectivity (Table 2, entry 12). However, use of either 2,4,6-trichlorophenol, 2,3,5,6-tetrafluorophenol, or pentafluorophenol esters resulted in low conversions into the respective products. This contrasts the findings of both Snaddon and Hartwig, who showed that pentafluorophenyl arylacetic esters were optimal in their enantioselective α-alkylation protocols using isothio ureas in combination with either Pd or Ir catalysis, respectively. To further probe the effect of the allylic leaving group a range of alternative cinnamyl alcohol derivatives was also tested under the previously optimized conditions. While both cinnamyl acetate and cinnamyl methyl carbonate gave poor conversion into product 14, use of cinnamyl trifluoroacetate gave 14 in good yield with high stereoselectivity (Table 2, entry 13).

2.2. Scope and Limitations of Pd/Isothiourea Relay Catalysis. 2.2.1. Variation of the Allylic Phosphate. The scope of this process was next assessed through variation of the cinnamyl aryl substituent within the allylic phosphate component (Table 3). Aryl rings bearing electron-withdrawing substituents (4-NO₂ and 4-CF₃) were well tolerated, forming rearranged products 19 and 20 in high yield with excellent stereoselectivity (up to >95:5 dr and 97:3 er). Halogen-substituted aryl rings, including sterically demanding 2-BrC₆H₄ substitution, were also well tolerated, forming 21–23 as single diastereoisomers with high enantioselectivity (up to 99:1 er). The reaction of the allylic phosphate bearing a 4-BrC₆H₄ substituent was also performed on a preparative laboratory scale (3.8 mmol) to give 1.5 g of 22 as a single stereoisomer in
91% yield. The presence of a 3-MeOC₆H₄ substituent led to a slight reduction in diastereoselectivity (91:9 dr), but the major product 24 was still obtained in high 99:1 er. The methodology was also applicable to allylic phosphates bearing oxygenated aryl rings that can be synthesized from the three monolignols, 4-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol, which are the building blocks of lignin biopolymers.30 The relay catalysis allowed amino acid derivatives 25−27 to be isolated in good yields with excellent stereoselectivity (up to >95:5 dr and 99:1 er), demonstrating that complex enantiomerically pure products can be expediently accessed from renewable lignin resources. Alkenyl and heteroaromatic substituents could also be tolerated, forming 28 and 29 in slightly reduced yields but with excellent diastereo- and enantioselectivity. Notably, the yields and stereoselectivity of this relay Pd/isothiourea catalysis generally exceed those obtained from the previously reported isothiourea-catalyzed [2,3]-rearrangement of isolated allylic ammonium salts.17 The reactions of non-aryl-substituted allyl phosphate with 13 under the standard relay conditions gave no [2,3]-rearrangement products, with the major product obtained being the corresponding aryl ether formed from allylic substitution with 4-nitrophenoxide.25

The presence of a 4-nitrophenyl ester within the [2,3]-rearrangement products allows facile derivatization into a range of α-amino acid derivatives through reaction with suitable nucleophiles (Scheme 3). For example, reacting isolated 22 (>95:5 dr, >99:1 er) with either primary or secondary amines gave the corresponding amides 30 and 31 in high yields with no erosion of stereointegrity. Transesterification with methoxide provided α-amino ester 32 in 93% yield as a single diastereoisomer in 97:3 er. The corresponding α-amino acid 33 could be readily obtained as its hydrochloride salt upon hydrolysis, while reduction with LiAlH₄ provided enantiomerically pure amino alcohol 34 in excellent yield.31

2.2.2. Variation of the Glycine Ester N-Substituents. Next, variation of the N-substituents within the glycine ester was investigated in the Pd/isothiourea relay catalysis (Table 4). Cyclic N-pyrrolidinyl substitution was tolerated under the previously optimized conditions, forming 35 in 75% yield as a single stereoisoemer in 97:3 er. However, increasing the ring size to either N-piperidinyl or N-azepanyl resulted in lower yields (33% for 36 and 38% for 37) and reduced diastereoselectivity (75:25 dr and 73:27 dr, respectively) under the standard reaction conditions. Increasing the Pd catalyst loading to 10 mol% gave products 36 and 37 in improved yields, and although these reactions again proceeded with lower diastereoselectivity (88:12 and 80:20 dr, respectively), the enantioselectivity of the major syn-diastereoisomer remained high (>98:2 er). Limitations of the relay process include the use of N-morpholinylglycine ester 38, which was unreactive under both the standard reaction conditions and with an increased 10 mol% loading of FurCat 18. The use of glycine esters bearing symmetrical N,N-dialkyl substituents such as N,N-dibenzylglycine ester 39 and N,N-diallylglycine ester 40 was also unsuccessful, with unreacted starting materials returned in both cases.

| Table 3. Scope of Allylic Ethyl Phosphates<sup>a,b,c</sup> |
|---------------------------------|
| Reaction performed on a 0.5 mmol scale. | 
| dr determined by <sup>1</sup>H NMR analysis of the crude material. | 
| er determined by HPLC analysis after derivatization into the corresponding benzyl amide. | 

<sup>a</sup>Reaction conditions: (i) BnNH₂ (5.0 equiv), CH₂Cl₂, rt, 16 h; (ii) pyrrolidine (5.0 equiv), CH₂Cl₂, rt, 16 h; (iii) NaOMe (1.5 equiv), MeOH, 0 °C to rt, 1 h; (iv) H₂O/HCl, 110 °C, 16 h; (v) LiAlH₄ (1.5 equiv), THF, 0 °C to rt, 1 h. <sup>b</sup>dr determined by <sup>1</sup>H NMR analysis of the crude material. <sup>c</sup>er determined by HPLC analysis. <sup>d</sup>er determined after derivatization into the corresponding benzyl amide.

<sup>a</sup>Reactions performed on a 0.5 mmol scale. <sup>b</sup>dr determined by <sup>1</sup>H NMR analysis of the crude material. <sup>c</sup>er determined by HPLC analysis after derivatization into the corresponding benzyl amide.

The yields and stereoselectivity of this relay Pd/isothiourea catalysis generally exceed those obtained from the previously reported isothiourea-catalyzed [2,3]-rearrangement of isolated allylic ammonium salts. The reactions of non-aryl-substituted allyl phosphate with 13 under the standard relay conditions gave no [2,3]-rearrangement products, with the major product obtained being the corresponding aryl ether formed from allylic substitution with 4-nitrophenoxide.

The presence of a 4-nitrophenyl ester within the [2,3]-rearrangement products allows facile derivatization into a range of α-amino acid derivatives through reaction with suitable nucleophiles (Scheme 3). For example, reacting isolated 22 (>95:5 dr, >99:1 er) with either primary or secondary amines gave the corresponding amides 30 and 31 in high yields with no erosion of stereointegrity. Transesterification with methoxide provided α-amino ester 32 in 93% yield as a single diastereoisomer in 97:3 er. The corresponding α-amino acid 33 could be readily obtained as its hydrochloride salt upon hydrolysis, while reduction with LiAlH₄ provided enantiomerically pure amino alcohol 34 in excellent yield.31

2.2.2. Variation of the Glycine Ester N-Substituents. Next, variation of the N-substituents within the glycine ester was investigated in the Pd/isothiourea relay catalysis (Table 4). Cyclic N-pyrrolidinyl substitution was tolerated under the previously optimized conditions, forming 35 in 75% yield as a single stereoisoemer in 97:3 er. However, increasing the ring size to either N-piperidinyl or N-azepanyl resulted in lower yields (33% for 36 and 38% for 37) and reduced diastereoselectivity (75:25 dr and 73:27 dr, respectively) under the standard reaction conditions. Increasing the Pd catalyst loading to 10 mol% gave products 36 and 37 in improved yields, and although these reactions again proceeded with lower diastereoselectivity (88:12 and 80:20 dr, respectively), the enantioselectivity of the major syn-diastereoisomer remained high (>98:2 er). Limitations of the relay process include the use of N-morpholinylglycine ester 38, which was unreactive under both the standard reaction conditions and with an increased 10 mol% loading of FurCat 18. The use of glycine esters bearing symmetrical N,N-dialkyl substituents such as N,N-dibenzylglycine ester 39 and N,N-diallylglycine ester 40 was also unsuccessful, with unreacted starting materials returned in both cases.
Previous studies found that isolated allylic quaternary ammonium salts bearing N,N-diallyl substituents undergo isothiourea-catalyzed [2,3]-rearrangement, so therefore it is likely that this represents a limitation within the Pd-catalyzed allylic substitution step in the relay procedure using 40. The use of unsymmetrical N-allyl-N-methylglycine ester 41 was then studied in the Pd/isothiourea relay catalysis (Table 5). Such a substrate is particularly challenging as the proposed Pd-catalyzed allylic substitution step would lead to an intermediate allylic ammonium salt, which may impact upon the stereoselectivity of the subsequent [2,3]-rearrangement. Furthermore, there is the potential for rearrangement via either the N-cinnamyl or N-allyl substituent in this case. Initial investigations found that the Pd/isothiourea relay [2,3]-rearrangement of 41 required 10 mol% of Pd precatalyst 18 for good conversion into product. Exclusive [2,3]-rearrangement through the N-cinnamyl substituent gave α-amino ester 43 in 40% yield with excellent stereoselectivity (95:5 dr, 99:1 er). The high chemoselectivity of this process is in contrast to the observations of Tambar and co-workers, who reported an 80:20 mixture of N-cinnamyl versus N-allyl rearrangement for the base-promoted reaction of an ammonium salt generated from N-allyl-N-methylglycine tert-butyl ester and cinnamyl carbamate. The relay reaction of 41 was further explored through variation of the allylic ethyl phosphate. The use of allylic phosphates bearing electron-withdrawing aryl substituents (4-NO2C6H4 and 4-CF3C6H4) led to improved reactivity, forming products 44 and 45 in higher yields (63% and 64%, respectively), while maintaining excellent stereoselectivity. Conversely, the presence of oxygenated aryl substituents led to decreased yields of 46 and 47, although stereoselectivity remained high. The relative and absolute configurations of the products from this series were confirmed by X-ray crystallographic analysis of the benzyl amide of 47.

The presence of the N-allyl substituent within the products allowed for further derivatization of 45 into a stereodefined closing metathesis in the presence of Hoveyda–Grubbs II (5 mol%) followed by Pd/C-catalyzed hydrogenation to form substituted piperidine 49 in 89% yield (over two steps) as a single diastereoisomer in 97:3 er.

2.3. Mechanistic Control Experiments. The relay protocol is thought to proceed via a Pd-catalyzed allylic substitution of an allylic phosphate with a glycine ester to form an intermediate allylic ammonium salt, which undergoes an enantioselective isothiourea-catalyzed [2,3]-rearrangement to give the observed α-amino ester products. Having previously reported detailed investigations into the mechanism of the isothiourea-catalyzed [2,3]-rearrangement of isolated allylic ammonium salts, control experiments were performed to probe the Pd-catalyzed allylic substitution step within this relay methodology. The reaction of branched cinnamyl phosphate 50 with glycine ester 13 under the standard reaction conditions gave rearranged product 14 (Scheme 5a), albeit in slightly reduced yield (49%) and lower diastereoselectivity.

### Table 4. Use of Symmetrical N,N-Dialkylglycine Esters

| R | Ar | Ph | N | Me | Ar | Ph | N | Me |
|---|---|---|---|---|---|---|---|---|
| PNP | 4-NO2C6H4 | OP(O)(OEt)2 | FurCat 18 | (10 mol%) | N,N,N,N-tetrakis(2-methoxyphenyl)phosphoramide | (2 equiv) | MeCN, rt, 16 h | PNP | 4-NO2C6H4 | OP(O)(OEt)2 | FurCat 18 | (10 mol%) | N,N,N,N-tetrakis(2-methoxyphenyl)phosphoramide | (2 equiv) | MeCN, rt, 16 h |
| 35 | 75% | 95:5 dr, 99:1 er | 36 | 42% | 88:12 dr, 99:1 er | 37 | 47% | 80:20 dr, 98:2 er |

Unreactive N,N-dialkyl substituents:

- [Scheme 4. Product Derivatization](#)

Reactions performed on a 0.5 mmol scale. Relative and absolute configurations of the products from this series were confirmed by X-ray crystallographic analysis of the benzyl amide of 47.

The presence of the N-allyl substituent within the products allowed for further derivatization of 45 into a stereodefined closing metathesis in the presence of Hoveyda–Grubbs II (5 mol%) followed by Pd/C-catalyzed hydrogenation to form substituted piperidine 49 in 89% yield (over two steps) as a single diastereoisomer in 97:3 er.

### Table 5. Use of Unsymmetrical N,N-Dialkylglycine Esters

| R | Ar | Ph | N | Me | Ar | Ph | N | Me |
|---|---|---|---|---|---|---|---|---|
| PNP | 4-NO2C6H4 | OP(O)(OEt)2 | FurCat 18 | (10 mol%) | N,N,N,N-tetrakis(2-methoxyphenyl)phosphoramide | (2 equiv) | MeCN, rt, 16 h | PNP | 4-NO2C6H4 | OP(O)(OEt)2 | FurCat 18 | (10 mol%) | N,N,N,N-tetrakis(2-methoxyphenyl)phosphoramide | (2 equiv) | MeCN, rt, 16 h |
| 43 | 40% | 95:5 dr, 99:1 er | 44 | 63% | 93:7 dr, 95:5 er |
| 45 | 64% | 95:5 dr, 97:3 er | 46 | 38% | >95:5 dr, 99:1 er |
| 47 | 32% | 94:6 dr, 98:2 er |

Reactions performed on a 0.5 mmol scale. Relative and absolute configurations of the products from this series were confirmed by X-ray crystallographic analysis of the benzyl amide of 47.

The presence of the N-allyl substituent within the products allowed for further derivatization of 45 into a stereodefined closing metathesis in the presence of Hoveyda–Grubbs II (5 mol%) followed by Pd/C-catalyzed hydrogenation to form substituted piperidine 49 in 89% yield (over two steps) as a single diastereoisomer in 97:3 er.
Scheme 5. Mechanistic Control Experiments\textsuperscript{a,b,c}

Reaction conditions: (i) allylic phosphate (2 equiv), FurCat 18 (5 mol\%), BTM 1 (20 mol\%), i-Pr\textsubscript{2}NH (2.2 equiv), MeCN, rt, 16 h. \textsuperscript{a}dr determined by \textsuperscript{1}H NMR analysis of the crude material. \textsuperscript{b}er determined by HPLC analysis after derivatization into the corresponding benzyl amide. \textsuperscript{c}Product ratio determined by \textsuperscript{19}F{\textsuperscript{1}H} NMR analysis. (93:7 dr, 99:1 er) compared with the use of linear cinnamyl phosphate 11 (79\%, >95:5 dr, 99:1 er).\textsuperscript{34,36} This suggests that the proposed Pd-\textit{π}-allyl intermediate preferentially reacts at the least sterically hindered terminal position to give the required ammonium salt for [2,3]-rearrangement.\textsuperscript{3,37} Reacting (Z)-cinnamyl phosphate 51 (86:14 Z:Z) with glycine ester 13 under the relay conditions led to the formation of the same proposed Pd-ammonium salt for [2,3]-rearrangement.\textsuperscript{3,37} Further analysis of the \textsuperscript{1}H NMR spectrum of the crude material showed that the Z/E ratio of the unreacted allylic phosphate 51 had not changed, while a control experiment reacting (Z)-51 with only FurCat 18 also showed no isomerization into (E)-11. This demonstrates that isomerization of (Z)-51 is unlikely to occur prior to the initial oxidative addition.

Next, a 50:50 mixture of isolated allylic ammonium salt 53 and N-\textit{pyrrolidinylglycine} ester 52 was reacted under the relay catalysis conditions (Scheme 5b). The major product obtained was from the expected [2,3]-rearrangement of 53 into 21; however, small amounts of crossover rearrangement product 54 were also observed (91:9 21:54). In the absence of FurCat 18, no crossover product 54 was obtained, suggesting that 53 is a suitable substrate for Pd-\textit{π}-allyl complex formation and that allylic ammonium salt formation is at least partially reversible under the reaction conditions.

The proposed overall relay catalytic cycle for the reaction of cinnamyl phosphate 11 with glycine ester 13 is depicted in Scheme 6. The active Pd catalyst is generated in situ from \textit{Py}

Scheme 6. Proposed Relay Catalytic Mechanism
preferred due to a π-cation interaction between the cinnamyl substituent and the isothioureia core. The presence of this favorable interaction may account for the selective rearrangement through the N-cinnamyl substituent over the unsubstituted N-allyl terminus in the reaction of unsymmetrical N,N-dialkylglycine esters.

3. CONCLUSIONS

In conclusion, a tandem Pd/isothioureia relay catalysis has been developed for the synthesis of functionalized α-amino acid derivatives from readily available glycine ester derivatives and allylic phosphates. The process is thought to proceed via Pd-catalyzed allylic ammonium salt formation followed by an isothioureia-catalyzed enantioselective [2,3]-rearrangement reaction to form the α-amino acid products with high levels of stereoselectivity. The methodology works for a range of substrates, including unsymmetrical N-allyl-N-methylglycine derivatives that would contain a stereogenic nitrogen atom in the intermediate ammonium salt. The α-amino acid products undergo a series of derivatization reactions to further demonstrate the synthetic utility of this process. Ongoing studies within this laboratory are aimed at developing further catalytic, enantioselective rearrangement processes.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05619.

Experimental procedures, characterization data, NMR spectra, and HPLC chromatograms (PDF)

X-ray crystallographic data for the corresponding benzylic amide of 47 (CIF)

AUTHOR INFORMATION

Corresponding Author
*ads10@st-andrews.ac.uk

ORCID

James E. Taylor: 0000-0002-0254-5536
Andrew D. Smith: 0000-0002-2104-7313

Notes
The authors declare no competing financial interest.
The research data underpinning this publication can be found at http://dx.doi.org/10.17630/1cf1b3d5-3882-49a4-b859-d24129c022bc.

ACKNOWLEDGMENTS

We thank Prof. Ian Fairlamb and Dr. Thomas Ronson (University of York) for helpful discussions regarding the preparation and use of FurCat 18. The research leading to these results (S.S.M.S) has received funding from the European Union (Marie Curie ITN “SubiCat” PITN-GA-2013-607044) and the ERC under the European Union’s Seventh Framework Programme (FP7/2007-2013)/ERC grant agreement no. 279850 (T.H.W., J.E.T.). A.D.S. thanks the Royal Society for a Wolfson Research Merit Award. We also thank the EPSRC UK National Mass Spectrometry Facility at Swansea University.

REFERENCES

(1) Najera, C.; Sansano, J. M. Chem. Rev. 2007, 107, 4584–4671.

(2) For selected reviews on stereoselective transition-metal-catalyzed allylic substitution, see: (a) Trost, B. M.; Van Vranken, D. L. Chem. Rev. 1996, 96, 395–422. (b) Miyabe, H.; Takemoto, Y. Synlett 2005, 2005, 1641–1655. (c) Oliver, S.; Evans, P. A. Synthesis 2013, 45, 3179–3198.

(3) For reviews on selectivity in Pd-catalyzed allylic substitution, see: (a) Frost, C. G.; Howarth, J.; Williams, J. M. J. Tetrahedron: Asymmetry 1992, 3, 1089–1122. (b) Poli, G.; Prestat, G.; Liron, F.; Kammerer-Pentier, C. Top. Organomet. Chem. 2011, 38, 1–63.

(4) For selected examples, see: (a) Genet, J. P.; Fierroud, D.; Juge, S.; Montes, J. R. Tetrahedron Lett. 1986, 27, 4573–4576. (b) Trost, B. M.; Ariza, X. Angew. Chem., Int. Ed. Engl. 1997, 36, 2635–2637.

(5) Kuwano, R.; Ito, Y. J. Am. Chem. Soc. 1999, 121, 3236–3237.

(6) Trost, B. M.; Ariza, X. J. Am. Chem. Soc. 1999, 121, 10272–10277.

(7) Kazmaier, U.; Zampé, F. L. Angew. Chem., Int. Ed. 2000, 39, 802–804.

(8) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. Org. Lett. 2001, 3, 3329–3331.

(9) Kazmaier, U.; Stolz, D. Angew. Chem., Int. Ed. 2006, 45, 3072–3075.

(10) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. Chem. Rev. 2013, 113, 5141–5177.

(11) For selected examples, see: (a) Song, J.; Zhang, Z.-J.; Gong, L.-Z. Angew. Chem., Int. Ed. 2017, 56, S212–S216. (b) Lu, X.; Ge, L.; Cheng, C.; Chen, J.; Cao, W.; Wu, X. Chem. - Eur. J. 2017, 23, 7686–7693.

(12) Soheili, A.; Tambar, U. K. J. Am. Chem. Soc. 2011, 133, 12956–12959.

(13) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. Chem. Rev. 1997, 97, 2341–2372. (b) Nitrogen, Oxygen, and Sulfur Ylide Chemistry: A Practical Approach in Chemistry; Clark, J. S., Ed.; Oxford University Press: New York, 2002; pp 1–308. (c) Sweeney, J. B. Chem. Soc. Rev. 2009, 38, 1027–1038. (d) Bao, H.; Tambar, U. K. 2,3-Rearrangements of Ammonium Zwitterions, in Molecular Rearrangements in Organic Synthesis; Rojas, C. M., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, 2015; pp 459–496.

(14) For a review on catalytic stereoselective [2,3]-rearrangements, see: West, T. H.; Speoehle, S. S. M.; Kasten, K.; Taylor, J. E.; Smith, A. D. ACS Catal. 2015, 5, 7446–7479.

(15) Workman, J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. J. Am. Chem. Soc. 2005, 127, 1066–1067.

(16) Bld, J.; Brandt, P.; Somfai, P. J. Org. Chem. 2004, 69, 3043–3049.

(17) Workman, J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. J. Am. Chem. Soc. 2005, 127, 1066–1067.

(18) Bld, J.; Panknin, O.; Somfai, P. J. Am. Chem. Soc. 2005, 127, 9352–9353. (c) Bld, J.; Panknin, O.; Tuzina, P.; Somfai, P. J. Org. Chem. 2007, 72, 1294–1300.

(19) Workman, J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. J. Am. Chem. Soc. 2005, 127, 1066–1067.

(20) Bld, J.; Brandt, P.; Somfai, P. J. Org. Chem. 2004, 69, 3043–3049.

(21) Workman, J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. J. Am. Chem. Soc. 2005, 127, 1066–1067.

(22) Workman, J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. J. Am. Chem. Soc. 2005, 127, 1066–1067.
L.; Taylor, P. J. Chem. Soc., Perkin Trans. 1 1998, 2817–2822.
(c) Gawley, R. E.; Moon, K. Org. Lett. 2007, 9, 3093–3096.
(20) For selected reviews on tandem catalytic reactions, see:
(a) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. Chem.
Res. 2005, 105, 1001–1020. (b) Chapman, C. J.; Frost, C. G. Synthesis
2007, 2007, 1–21. (c) Zhou, J. Chem. - Asian J. 2010, 5, 422–434.
(d) Pellissier, H. Tetrahedron 2013, 69, 7171–7210. (e) Lohr, T. L.;
Marks, T. J. Nat. Chem. 2015, 7, 477–482.
(21) For reviews on merging transition metal catalysis and
organocatalysis, see: (a) Shao, Z.; Zhang, H. Chem. Soc. Rev.
2009, 38, 2745–2755. (b) Du, Z.; Shao, Z. Chem. Soc. Rev. 2013, 42,
1337–1378. (c) Afewerki, S.; Córdova, A. Chem. Rev. 2016, 116, 13512–
13570.
(22) For a seminal example of 4-nitrophenoxy rebound in NHC
activation, see: Wakanaka, Y.; Phillips, E. M.; Scheidt, K. A. J. Am.
Chem. Soc. 2009, 131, 18028–18029.
(23) For reviews on isothiourea catalysis, see: (a) Taylor, J. E.;
Bull, S. D.; Williams, J. M. J. Chem. Soc. Rev. 2012, 41, 2109–2121.
(b) Merad, J.; Pons, J.-M.; Chuzel, O.; Bressy, C. Eur. J. Org. Chem.
2016, 2016, 5589–5610.
(24) For selected reviews on allylic amination, see: (a) Johannsen,
M.; Jørgensen, K. A. Chem. Rev. 1998, 98, 1689–1708. (b) Muzart,
J. Eur. J. Org. Chem. 2007, 2007, 3077–3089. (c) Marvin, C. C. In
Comprehensive Organic Synthesis II; Knochel, P., Molander, G. A., Eds.;
Elsevier: Amsterdam, 2014; pp 34–99. (d) Grange, R. L.; Clizbe, E. A.;
Evans, P. A. Synthesis 2016, 48, 2911–2968.
(25) See the Supporting Information for more details.
(26) Andersen, N. G.; Keay, B. A. Chem. Rev. 2001, 101, 997–1030.
(27) The relative and absolute configurations of 14 were assigned by
comparison of 1H NMR and HPLC traces of the corresponding
benzylamide with those of previously synthesized products.
(28) Ronson, T. O.; Carney, J. R.; Withwood, A. C.; Taylor, R. J. K.;
Fairlamb, I. J. S. Chem. Commun. 2015, 51, 3466–3469.
(29) N,N-Dimethyl-4-nitrophenyl ester 13 is most conveniently
prepared, stored, and used as its HCl salt. However, free base 13 can
also be used, requiring only 1.2 equiv of i-Pr_2NH to give product 14 in
58% yield, 92:8 dr, and 97:3 er.
(30) (a) Zakzeski, J.; Bruijininx, P. C. A.; Jongerius, A. L.;
Weckhuysen, B. M. Chem. Rev. 2010, 110, 3552–3599. (b) Lancefield,
C. S.; Ojo, O. S.; Tran, F.; Westwood, N. J. Angew. Chem., Int. Ed.
2015, 54, 258–262.
(31) Attempted epimerization of syn-32 (>95:5 dr) with KOt-Bu in
THF at 60 °C gave a 50:50 mixture of syn- and anti-diastereoisomers
(both 97:3 er). Retreatment of the anti-diastereoisomer (>95:5 dr) with
KOt-Bu in THF at 60 °C also gave a 50:50 mixture of syn- and
anti-diastereoisomers. This suggests that the β-stereocenter does not
fluence the facial selectivity of protonation and that the observed
preference for the anti-diastereoisomer in Bronsted base-catalyzed
processes is a consequence of the geometry adopted in the [2,3]-
rearrangement transition state.
(32) BTM-catalyzed [2,3]-rearrangement of isolated N,N-diallyl-
ammonium salts gives cheomoselective rearrangement through the
cinnamyl substituent. See ref 17b.
(33) The use of an unsymmetrical N-Me-N-Bn glycine ester was
unsuccessful under the previously optimized conditions.
(34) The absolute configuration of the corresponding benzyl amide
of 47 was confirmed by X-ray crystallographic analysis. CCDC
1549468 contains the supplementary crystallographic data for this
paper. These data can be obtained free of charge from The Cambridge
Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/
cif.
(35) For examples of intramolecular allylic substitution with tertiary
amines to form quaternary ammonium salts, see: (a) Grellier, M.;
Pfeffer, M.; van Koten, G. Tetrahedron Lett. 1994, 35, 2877–2880.
(b) van der Schaar, P. A.; Sutter, J.-P.; Grellier, M.; van Mier, G. P. M.;
Spek, A. L.; van Koten, G.; Pfeffer, M. J. Am. Chem. Soc. 1994, 116,
5134–5144. (c) Chengebroyen, J.; Linke, M.; Robitzer, M.; Sirlin,
C.; Pfeffer, M. J. Organomet. Chem. 2003, 687, 313–321.
(36) Branched cinnamyl phosphate 50 slowly isomerizes into linear
cinnamyl phosphate 11 upon standing. However, no isomerization of
unreacted 50 was observed under the reaction conditions. See the
Supporting Information for details.
(37) For examples of Pd-catalyzed allylic amination with α-amino
esters, see: (a) Bower, J. E.; Jumnah, R.; Williams, A. C.; Williams, J.
M. J. J. Chem. Soc., Perkin Trans. 1 1997, 1411–1420. (b) Humphries,
M. E.; Clark, B. P.; Williams, J. M. J. Tetrahedron: Asymmetry 1998, 9,
749–751. (c) Humphries, M. E.; Clark, B. P.; Regini, S.; Acemoglu,
L.; Williams, J. M. J. Chirality 2003, 15, 190–195.
(38) (a) Hayashi, T.; Yamamoto, A.; Hagiwara, T. J. Org. Chem.
1986, 51, 723–727. (b) Solin, N.; Szabó, K. J. Organometallics 2001, 20,
5464–5471.
(39) Alternative pathways in which BTM 1 reacts with either glycine
ester 57 or intermediate 58 cannot be ruled out. It is also assumed that
the reaction does not proceed via direct α-allylation of the amonium
eolate derived from BTM 1 and 57 given the observed branched
selectivity.
(40) An alternative mechanism in which BTM 1 acts as a Bronsted
base catalyst is ruled out based upon previous mechanistic studies. See
ref 18.
(41) For examples of S–O interactions as controlling elements in
isothiourea catalysis, see: (a) Birman, V. B.; Li, X.; Han, Z. Org. Lett.
2007, 9, 37–40. (b) Liu, P.; Yang, X.; Birman, V. B.; Houk, K. N. Org.
Lett. 2012, 14, 3288–3291. (c) Abbasov, M. E.; Hudson, B. M.;
Tantillo, D. J.; Romo, D. J. Am. Chem. Soc. 2014, 136, 4492–4495.
(d) Robinson, E. R. T.; Walden, D. M.; Fallan, C.; Greenhalgh, M. D.;
Cheong, P. H.-Y.; Smith, A. D. Chem. Sci. 2016, 7, 6919–6927.
(42) For discussions regarding the origin of S–O interactions, see:
(a) Reid, R. C.; Yau, M.-K.; Singh, R.; Lim, J.; Fairlie, D. P. J. Am.
Chem. Soc. 2014, 136, 11914–11917. (b) Beno, B. R.; Yeung, K.-S.;
Bartberger, M. D.; Pennington, L. D.; Meanwell, N. A. J. Med. Chem.
2015, 58, 4383–4438. (c) Zhang, X.; Gong, Z.; Li, J.; Lu, T. J. Chem.
Inf. Model. 2015, 55, 2138–2153.