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

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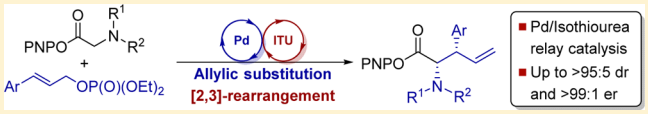
Supporting Information

**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.



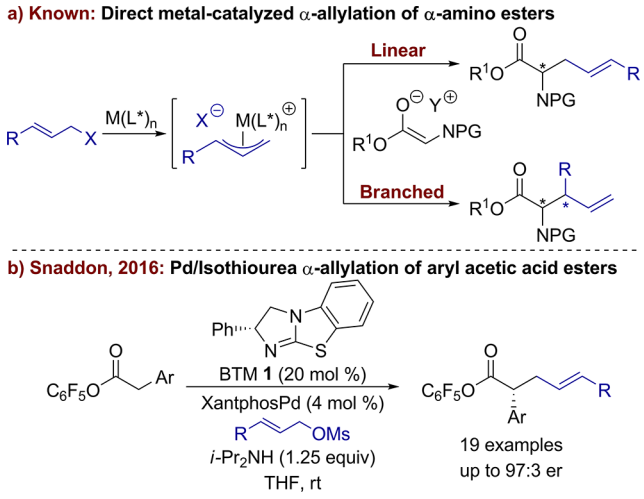

## 1. INTRODUCTION

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 iridium[8] 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-allylation 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, stereodivergent 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

**Scheme 1. Direct α-Allylation of Ester Enolates**

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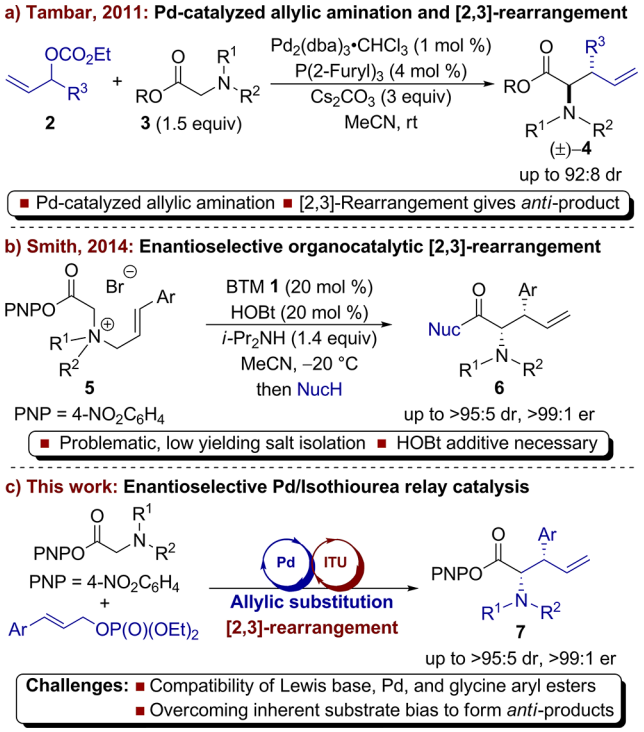
**Scheme 2. Catalytic [2,3]-Rearrangements of Allylic Ammonium Ylides**




co-workers reported the use of a stoichiometric chiral Lewis acid for the enantioselective synthesis of α-amino amide derivatives.[16] 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).[17] 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 diastereo- and enantioselectivity of the [2,3]-rearrangement products.[18] A recognized challenge encountered by ourselves and others[19] for such [2,3]-rearrangement processes is the problematic synthesis and isolation of the required allylic quaternary ammonium salts. In our case,[17] 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.

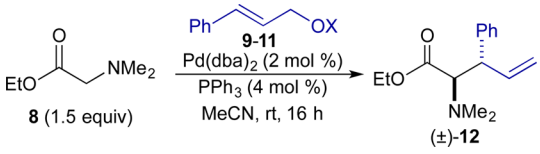
Building upon the precedent of Tambar, we questioned the feasibility of merging a Pd-catalyzed allylic amination with an enantioselective isothiourea-catalyzed [2,3]-rearrangement (Scheme 2c). Such a process would allow for the rapid generation of complex enantiomerically enriched α-amino acids **7** 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,[20,21] with all reactants 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 **4**,[12] whereas the isothiourea-catalyzed process forms the opposite *syn*-diastereoisomer **6**. The proposed relay system must therefore undergo minimal Brønsted base-catalyzed [2,3]-rearrangement (*anti*-selective) to allow the desired products from the tandem isothiourea-catalyzed pathway to be formed with high *syn*-diastereoselectivity. The desired process must also be tolerant of glycine derivatives bearing labile phenol esters that are required both for initiation of the Lewis base-catalyzed process and to generate the phenoxide necessary to facilitate catalyst turnover.[22] The nucleophilic isothiourea catalyst[23] and generated phenoxide must also not interfere with, or inhibit, the Pd-catalyzed allylic substitution process.[24]

In this context, this manuscript documents the merger of transition metal and Lewis base catalysis for an unprecedented tandem relay catalytic allylic amination followed by enantioselective [2,3]-rearrangement. The methodology uses a bench-stable succinimide-based Pd precatalyst (FurCat) to promote allylic substitution and an isothiourea catalyst to perform the enantioselective [2,3]-rearrangement, forming functionalized α-amino acid derivatives in good yields with high stereoselectivity. The scope and limitations of this new process have been fully explored, including the use of unsymmetrical *N*,*N*-disubstituted glycine esters. The utility of the products has been demonstrated through various derivatizations, while crossover and control experiments are used to probe the mechanism of the allylic amination step.

## 2. RESULTS AND DISCUSSION

**2.1. Reaction Optimization.** *2.1.1. Identification of a Suitable Allylic Precursor.* To achieve high levels of diastereo- and enantioselectivity 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[12] 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 **9** in the presence of $Pd(dba)_2$ (2 mol%) and $PPh_3$ (4 mol%) using excess $Cs_2CO_3$ 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 | $Cs_2CO_3$ | yield (%) | dr[a] |
|---|---|---|---|---|
| 1 | C(O)OEt (**9**) | 3 equiv | 88 | 65:35 |
| 2 | C(O)OEt (**9**) | – | 75 | 68:32 |
| 3 | C(O)OPh (**10**) | 3 equiv | 0 | N/A |
| 4 | C(O)OPh (**10**) | – | 0 | N/A |
| 5 | $P(O)(OEt)_2$ (**11**) | 3 equiv | 80 | 66:34 |
| 6 | $P(O)(OEt)_2$ (**11**) | – | 0 | N/A |

[a]Determined by $^1$H NMR analysis of the crude material.



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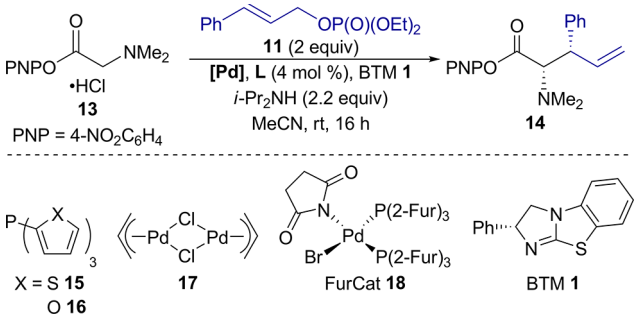
for such base-mediated processes.[12] In the absence of $Cs_2CO_3$ the reaction still proceeded to give product **12** in 75% yield (Table 1, entry 2). This suggests that the ethyl carbonate and/or ethoxide released during allylic substitution is sufficiently basic to promote the [2,3]-rearrangement step, and that ethyl carbonates are not suitable precursors for a catalytic enantioselective relay process. To reduce the basicity of the released counterion, cinnamyl phenyl carbonate **10** was investigated; however, this did not lead to product formation in either the presence or absence of external base with the starting materials mostly returned in both cases (Table 1, entries 3 and 4).[25] 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[25] 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 $PPh_3$ (4 mol%) in the presence of the isothiourea BTM **1** (20 mol%) using *i*-$Pr_2NH$ 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,[26] 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 $Pd_2(dba)_3{\cdot}CHCl_3$ (1 mol%) and P(2-furyl)$_3$ (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),[27] 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.[17,18] 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[28] 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 **1** 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-nitrophenyl ester **13** and *i*-$Pr_2NH$ (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).[29] 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-trichlorophenyl, 2,3,5,6-tetrafluorophenyl, or pentafluorophenyl esters resulted in low conversions into the respective products.[25] This contrasts the findings of both Snaddon[9] and Hartwig,[10] who showed that pentafluorophenyl arylacetic esters were optimal in their enantioselective α-allylation protocols using isothioureas 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**,[25] use of cinnamyl trifluoroacetate gave **14** in good yield with high stereoselectivity (Table 2, entry 13).

**Table 2. Optimization of the Enantioselective Relay Process**




| entry | [Pd] (mol%) | L | 1 (mol%) | yield (%)[a] | dr[b] | er[c] |
|---|---|---|---|---|---|---|
| 1 | $Pd(dba)_2$ (2) | $PPh_3$ | 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 | $Pd_2(dba)_3{\cdot}CHCl_3$ (1) | **16** | 20 | 47 | 95:5 | 98:2 |
| 5 | **17** (1) | **16** | 20 | 70 | >95:5 | >99:1 |
| 6 | **18** (5) | – | 20 | 79 | >95:5 | 99:1 |
| 7 | **18** (5) | – | 10 | 60 | 94:6 | 97:3 |
| 8 | **18** (5) | – | 5 | 56 | 88:12 | 89:11 |
| 9 | **18** (5) | – | – | 0 | N/A | N/A |
| 10 | – | – | 20 | 0 | N/A | N/A |
| 11[d] | **18** (5) | – | 20 | 58 | 92:8 | 97:3 |
| 12[e] | **18** (5) | – | 20 | 65 | >95:5 | >99:1 |
| 13[f] | **18** (5) | – | 20 | 60 | >95:5 | 96:4 |

[a]Yields in parentheses determined by $^1H$ NMR using 1,4-dinitrobenzene as an internal standard. [b]Determined by $^1H$ NMR analysis of the crude material. [c]Determined by HPLC analysis after derivatization into the corresponding benzyl amide. [d]Free base of **13** and *i*-$Pr_2NH$ (1.2 equiv) used in place of **13**·HCl and *i*-$Pr_2NH$ (2.2 equiv). [e]*N*,*N*-Dimethyl-3,5-bis-trifluoromethylphenylglycine ester used in place of **13**. [f]Cinnamyl trifluoroacetate (2 equiv) used in place of **11**.

**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 cinnamic aryl substituent within the allylic phosphate component (Table 3). Aryl rings bearing electron-withdrawing substituents (4-$NO_2$ and 4-$CF_3$) 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-$BrC_6H_4$ 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-$BrC_6H_4$ substituent was also performed on a preparative laboratory scale (3.8 mmol) to give 1.5 g of **22** as a single stereoisomer in


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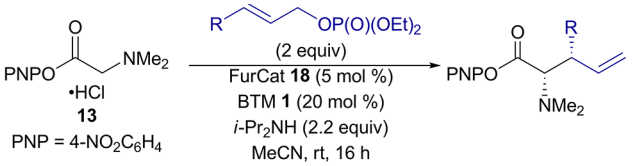
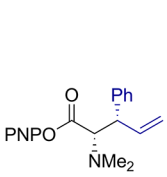
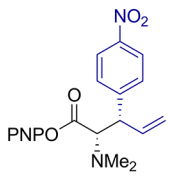
**Table 3. Scope of Allylic Ethyl Phosphates**[a,b,c]

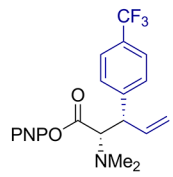


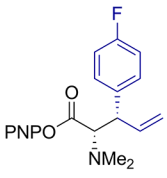

**14** 79%
>95:5 dr, 99:1 er



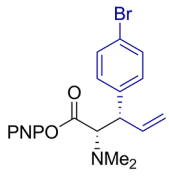

**19** 89%
>95:5 dr, 96:4 er



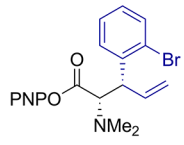

**20** 83%
95:5 dr, 97:3 er



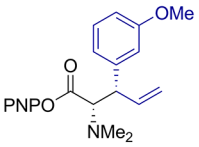

**21** 80%
>95:5 dr, 99:1 er



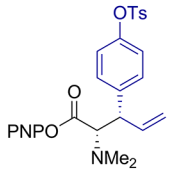

**22** 83%
>95:5 dr, 99:1 er
(91%, >95:5 dr, >99:1 er)[d]



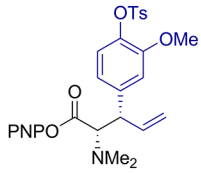

**23** 67%
95:5 dr, 97:3 er



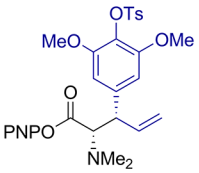

**24** 79%
91:9 dr, 99:1 er



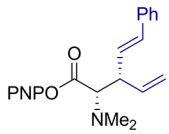

**25** 88%
>95:5 dr, 97:3 er



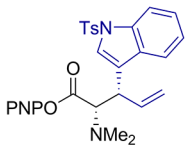

**26** 82%
>95:5 dr, 98:2 er




**27** 68%
>95:5 dr, 99:1 er




**28** 61%
>95:5 dr, >99:1 er



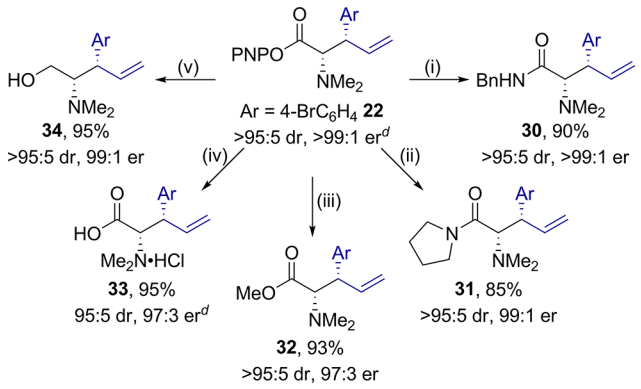

**29** 63%
>95:5 dr, 98:2 er

[a]Reactions performed on a 0.5 mmol scale. [b]dr determined by $^1$H NMR analysis of the crude material. [c]er determined by HPLC analysis after derivatization into the corresponding benzyl amide. [d]Reaction performed on a 3.8 mmol scale.

91% yield. The presence of a 3-MeOC$_6$H$_4$ 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 $\alpha$-amino acid derivatives through reaction with suitable nucleophiles (Scheme 3). For example, reacting isolated **22**

**Scheme 3. Product Derivatizations**[a,b,c]




[a]Reaction conditions: (i) BnNH$_2$ (5.0 equiv), CH$_2$Cl$_2$, rt, 16 h; (ii) pyrrolidine (5.0 equiv), CH$_2$Cl$_2$, rt, 16 h; (iii) NaOMe (1.5 equiv), MeOH, 0 °C to rt, 1 h; (iv) H$_2$O/HCl, 110 °C, 16 h; (v) LiAlH$_4$ (1.5 equiv), THF, 0 °C to rt, 1 h. [b]dr determined by $^1$H NMR analysis of the crude material. [c]er determined by HPLC analysis. [d]er determined after derivatization into the corresponding benzyl amide.

(>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 $\alpha$-amino ester **32** in 93% yield as a single diastereoisomer in 97:3 er. The corresponding $\alpha$-amino acid **33** could be readily obtained as its hydrochloride salt upon hydrolysis, while reduction with LiAlH$_4$ 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 stereoisomer. 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.


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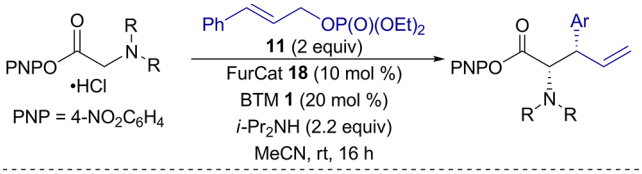
**Table 4. Use of Symmetrical *N,N*-Dialkylglycine Esters**[a,b,c]

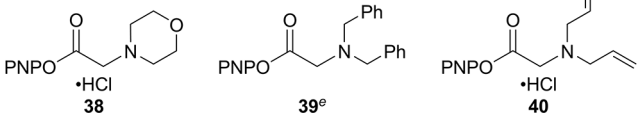



**35** 75%[d]
95:5 dr, 99:1 er

**36** 42%
88:12 dr, 99:1 er

**37** 47%
80:20 dr, 98:2 er

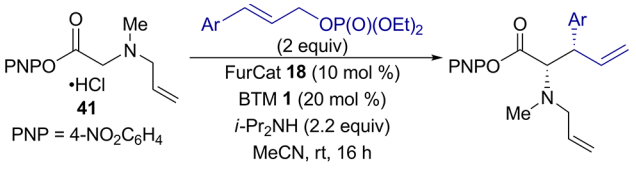
***Unreactive N,N-dialkyl substituents:***

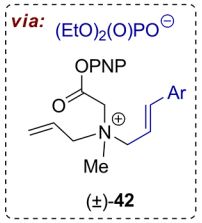


**38** **39**[e] **40**

[a]Reactions performed on a 0.5 mmol scale. [b]dr determined by $^1$H NMR analysis of the crude material. [c]er determined by HPLC analysis after derivatization into the corresponding benzyl amide. [d]Reaction performed using 5 mol% FurCat **18**. [e]Reaction performed using *i*-$Pr_2NH$ (1.2 equiv).

**Table 5. Use of Unsymmetrical *N,N*-Dialkylglycine Esters**[a]




**43** 40%
95:5 dr,[b] 99:1 er[c]

**44** 63%
93:7 dr,[b] 95:5 er[c]

**45** 64%
95:5 dr,[b] 97:3 er[c]

**46** 38%
>95:5 dr,[d] 99:1 er[c]

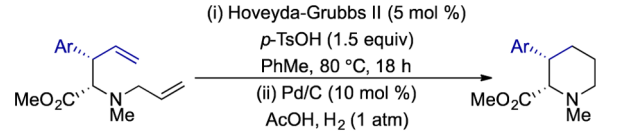
**47** 32%
94:6 dr,[d] 98:2 er[c]

[a]Reactions performed on a 0.5 mmol scale. [b]dr determined by $^1$H NMR analysis of the crude material. [c]er determined by HPLC analysis after derivatization into the corresponding benzyl amide. [d]dr of isolated material.

Previous studies found that isolated allylic quaternary ammonium salts bearing *N,N*-diallyl substituents undergo isothiourea-catalyzed [2,3]-rearrangement,[32] 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).[33] Such a substrate is particularly challenging as the proposed Pd-catalyzed allylic substitution would lead to an intermediate ammonium salt **42** containing a stereogenic nitrogen atom, 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 carbonate.[12a] 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-$NO_2C_6H_4$ and 4-$CF_3C_6H_4$) 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**.[34]

The presence of the *N*-allyl substituent within the products allowed for further derivatization of **45** into a stereodefined piperidine (Scheme 4). Facile methanolysis of **45** generated *N*-allyl-*N*-methyl amino ester **48**, which undergoes catalytic ring-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 4. Product Derivatization**[a,b]




Ar = 4-$CF_3C_6H_4$ **48**
>95:5 dr, 98:2 er

**49** 89% (2 steps)
>95:5 dr, 97:3 er

[a]dr determined by $^1$H NMR analysis of the crude material. [b]er determined by HPLC analysis.

**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,[18] control experiments were performed to probe the Pd-catalyzed allylic substitution step within this relay methodology.[12,35] 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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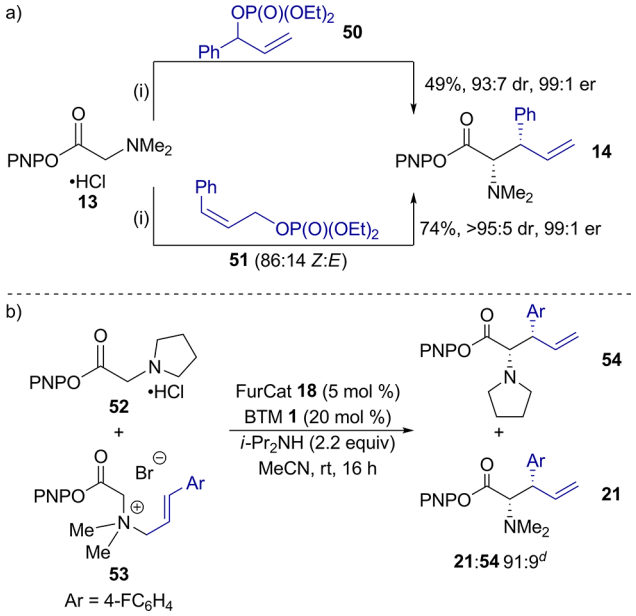
**Scheme 5. Mechanistic Control Experiments**[a,b,c]



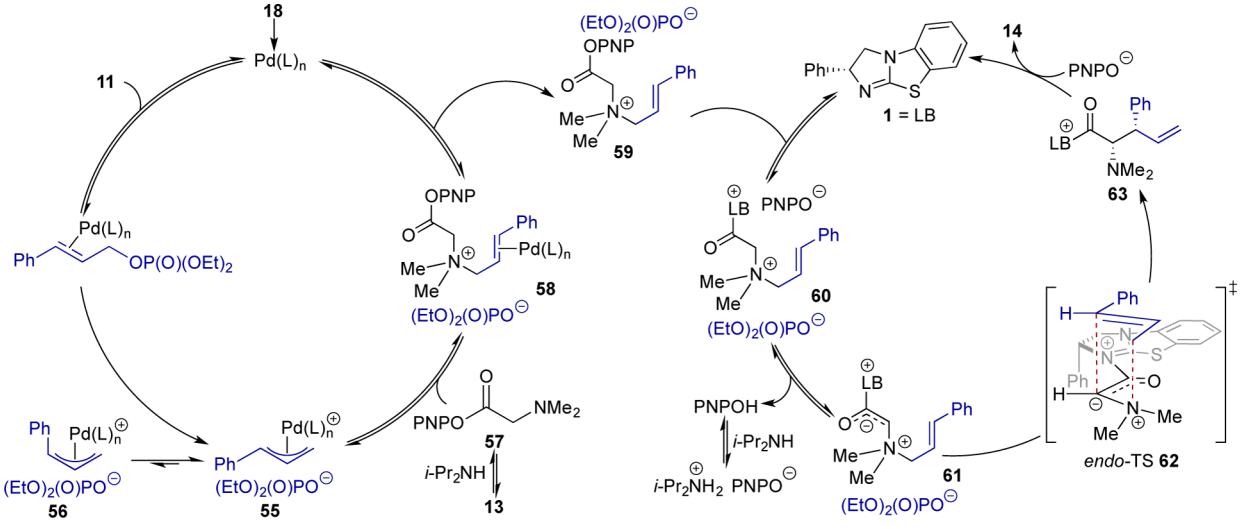

[a]Reaction conditions: (i) allylic phosphate (2 equiv), FurCat **18** (5 mol%), BTM **1** (20 mol%), *i*-$Pr_2NH$ (2.2 equiv), MeCN, rt, 16 h. [b]dr determined by $^1H$ NMR analysis of the crude material. [c]er determined by HPLC analysis after derivatization into the corresponding benzyl amide. [d]Product ratio determined by $^{19}F\{^1H\}$ NMR analysis.

(93:7 dr, 99:1 er) compared with the use of linear cinnamyl phosphate **11** (79%, >95:5 dr, 99:1 er).[36] This suggests that the proposed Pd-$\pi$-allyl intermediate preferentially reacts at the least sterically hindered terminal position to give the required ammonium salt for [2,3]-rearrangement.[3,37] Reacting (*Z*)-cinnamyl phosphate **51** (86:14 *Z*:*E*) with glycine ester **13** under the relay conditions led to the formation of the same *syn*-diastereoisomer of **14** (>95:5 dr and 99:1 er) in 74% yield (Scheme 5a), which is comparable to the result obtained starting from (*E*)-**11**. As (*Z*)-cinnamylammonium salts formed in situ are only poorly reactive in the isothiourea-catalyzed [2,3]-rearrangement,[17a] this suggests that $\eta^3$-Pd-$\pi$-allyl complex **56** formed from (*Z*)-**51** undergoes $\pi-\sigma-\pi$ isomerization into the more favorable $\eta^3$-Pd-$\pi$-allyl complex **55** prior to ammonium salt formation and [2,3]-rearrangement.[38] Further analysis of the $^1H$ 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*-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-$\pi$-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 FurCat **18**,[28] although the specific ligands associated with the Pd species and its oxidation state have not been determined. Coordination, followed by oxidative addition into allylic phosphate **11**, generates $\eta^3$-Pd-$\pi$-allyl complex **55**. Nucleophilic attack of free-base glycine ester **57** reversibly generates coordinated ammonium salt **58**, which can dissociate to form the key allylic ammonium salt **59** that links the two tandem catalytic cycles. Acylation of the isothiourea BTM **1** with **59** forms dication **60**,[39] with subsequent deprotonation into ammonium ylide **61** using 4-nitrophenoxide ($PNPO^-$). Stereoselective [2,3]-sigmatropic rearrangement affords acylammonium **63**, which reacts with $PNPO^-$ to affect isothiourea turnover and release product **14**. The observed diastereo- and enantioselectivity can be rationalized by the [2,3]-rearrangement proceeding via *endo*-TS **62**.[18] Ammonium ylide **61** is thought to have significant enolate character, favoring a (*Z*)-conformation that is further stabilized by a nonbonding 1,5-S···O interaction resulting from $n_O$ to $\sigma^*_{C-S}$ overlap between the carbonyl and the isothiourea sulfur atom.[40−42] Rearrangement occurs on the face opposite to the stereodirecting phenyl substituent on the catalyst, with an *endo*-conformation

**Scheme 6. Proposed Relay Catalytic Mechanism**



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preferred due to a $\pi$-cation interaction between the cinnamyl substituent and the isothiourea 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/isothiourea relay catalysis has been developed for the synthesis of functionalized $\alpha$-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 isothiourea-catalyzed enantioselective [2,3]-rearrangement reaction to form the $\alpha$-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 $\alpha$-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 benzyl amide of **47** (CIF)

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### Notes

The authors declare no competing financial interest.

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(32) BTM-catalyzed [2,3]-rearrangement of isolated *N*,*N*-diallylammonium salts gives chemoselective 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 Schaaf, 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 $\alpha$-amino esters, see: (a) Bower, J. F.; 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.
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(40) An alternative mechanism in which BTM **1** acts as a Brønsted 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.
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