Enantioselective Coupling of Nitroesters and Alkynes

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Abstract: By using Rh-H catalysis, we couple *α*-nitroesters and alkynes to prepare α-amino acid surrogates. This atom-economical strategy generates two contiguous stereocenters, with high enantio- and diastereocontrol. In this transformation, the alkyne undergoes isomerization to generate a Rh(III)-*π*-allyl electrophile, which is trapped by an *α*-nitroester nucleophile. A subsequent reduction with In powder transforms the allylic *α*-nitroesters to the corresponding *α*,*α*-disubstituted *α*-amino esters.

By designing and synthesizing *α*-amino acids (*α*-AAs), chemists have expanded the genetic code, shed light on protein function, and invented medicines.[1-3] The *α*,*α*-disubstituted *α*-AAs and related analogs attract interest due to their metabolic stability, unique conformations, and potent bioactivity (Figure 1).[4] Enantioenriched *α*,*α*-disubstituted *α*-AAs are targeted by various strategies, including phase-transfer catalysis, organocatalysis, and transition-metal catalysis.[5] Despite an interest in these motifs, methods for the enantio- and diastereoselective preparation of *α*,*α*-disubstituted *α*-AAs bearing contiguous stereocenters remain sought after;[6] emerging reports feature pre-functionalized allylic partners (e.g., allylic carbonates). The direct addition of an amino acid surrogate to a π-system represents an attractive approach to *α*,*α*-disubstituted *α*-AAs. Towards this end, Zi and coworkers exploited synergistic Pd/Cu catalysis for the stereodivergent coupling of aldimine esters and 1,3-dienes.[7] In a complementary approach, we propose using a Rh-hydride (Rh-H) catalyst to couple *α*-nitrocarbonyls and alkynes to generate the corresponding *α*-AA surrogates. This atom-economical[8] coupling exploits two simple functional groups and provides rapid access to analogs for the building blocks of life.[9]

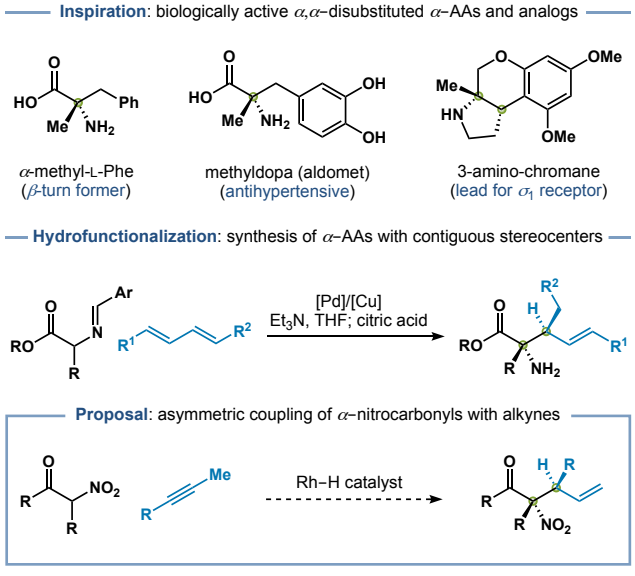


Figure 1. Enantioselective preparation of *α*-AAs and analogs.

On the basis of literature precedent,[10] we envisioned a tandem catalytic cycle for the asymmetric coupling of *α*-nitrocarbonyls **1** and alkynes **2** to yield *α*-AA surrogates **3** (Figure 2). Wolf and Werner discovered that Rh-H complexes isomerize alkynes (**2**) via an allene intermediate (**4**) to form Rh-*π*-allyl species **IV**.[11] By using this isomerization, the Breit laboratory achieved asymmetric and catalytic couplings of alkynes with a wide-range of heteroatom nucleophiles to afford branched allylic products.[12] In comparison, the analogous coupling of alkynes with carbon nucleophiles remains more limited, with only three asymmetric variants.[13] Of these three reports, only two afford products that contain vicinal stereocenters. We showed that aldehydes couple to alkynes with high enantio- and diastereoselectivity when using a chiral Rh-H catalyst in synergy with a chiral amine co-catalyst.[13a] Xing and coworkers expanded this approach for the coupling of ketones with alkynes, but the use of an achiral amine co-catalyst furnishes the branched products with little to no diastereocontrol.[13c]

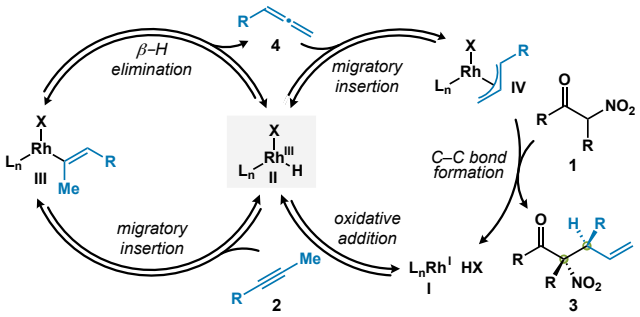
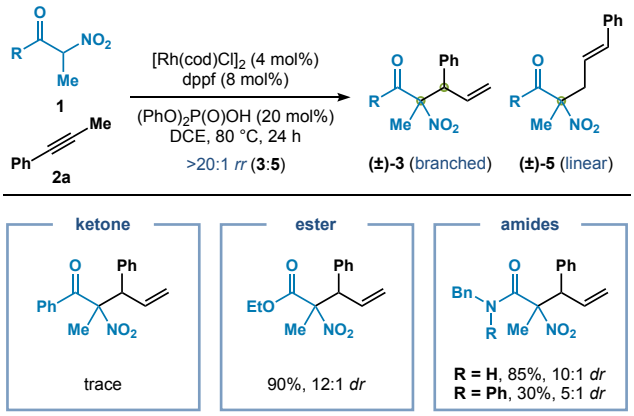


Figure 2. Proposed mechanism for Rh-catalyzed allylation.

In related studies, we and others have shown that 1,3-dicarbonyls can couple to alkynes to generate branched allylic carbonyl motifs.[14] Promising reactivity and regioselectivity has been achieved. However, obtaining high levels of enantio- and diastereoselectivity has been challenging. It occurred to us that *α*-nitrocarbonyls display comparable chelation aptitude[15] and acidity (pK_a = ca. 8)[16] to 1,3-dicarbonyls. Thus, we imagined *α*-nitrocarbonyls would be suitable nucleophiles for trapping Rh-*π*-allyl species **IV**. With this design in mind, we set out to couple *α*-nitrocarbonyls and alkynes with enantio- and diastereocontrol.

In initial studies, we discovered that various *α*-nitrocarbonyls add to the commercially available alkyne **2a** (Table 1). Using a combination of $[Rh(cod)Cl]_2$, dppf, and diphenyl phosphate, we observe allylic *α*-nitroketone, *α*-nitroester, and *α*-nitroamide products as single regioisomers (>20:1 *rr*) with moderate to high diastereoselectivity (5:1–12:1 *dr*). In accordance with previous reports, there is a preference for the branched regioisomer, which bears two contiguous stereocenters.[10a-d,12-14] Our findings complement an enantioselective Pd-catalyzed *α*-nitroester allylation reported by Ooi and coworkers.[17] In Ooi's study, the use of allylic carbonates affords linear regioisomers with one stereocenter.

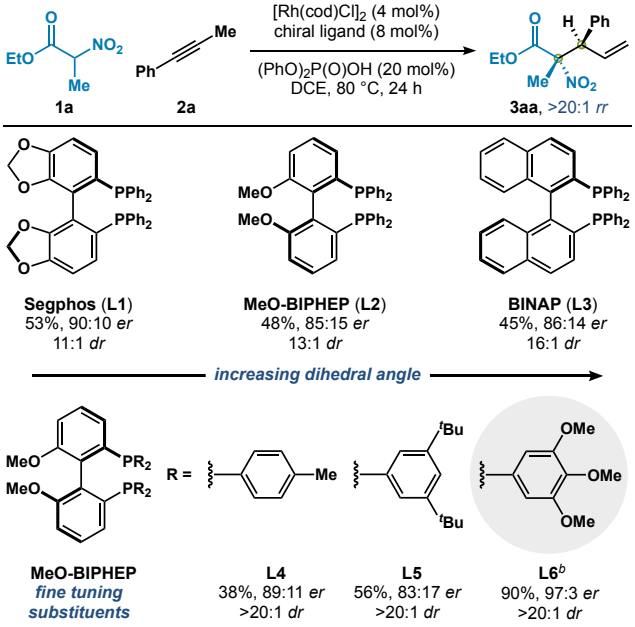
Table 1. Investigating various *α*-nitrocarbonyls.[a]



[a] See SI for reaction conditions. Yields determined by ^{1}H NMR referenced to an internal standard.

Next, we focused on an enantioselective variant for the coupling of *α*-nitroesters with alkynes because the resulting motifs are readily converted to *α*-AAs.[18] To identify the appropriate chiral catalyst, we selected *α*-nitroester **1a** and 1-phenyl-1-propyne (**2a**) as the model substrates (Table 2). Using atropoisomeric bisphosphine ligands **L1**–**L3** with a range of dihedral angles,[19] we observe the allylic *α*-AA surrogate **3aa** with moderate yields (45–53%) and enantioselectivities (85:15–90:10 *er*). Ultimately, we found that commercial MeO-BIPHEP ligand **L6** bearing bis(3,4,5-trimethoxyphenyl)phosphino groups affords **3aa** in 90% yield with 97:3 *er*, >20:1 *dr*, and >20:1 *rr* on preparative scale (1 mmol).[20,21]

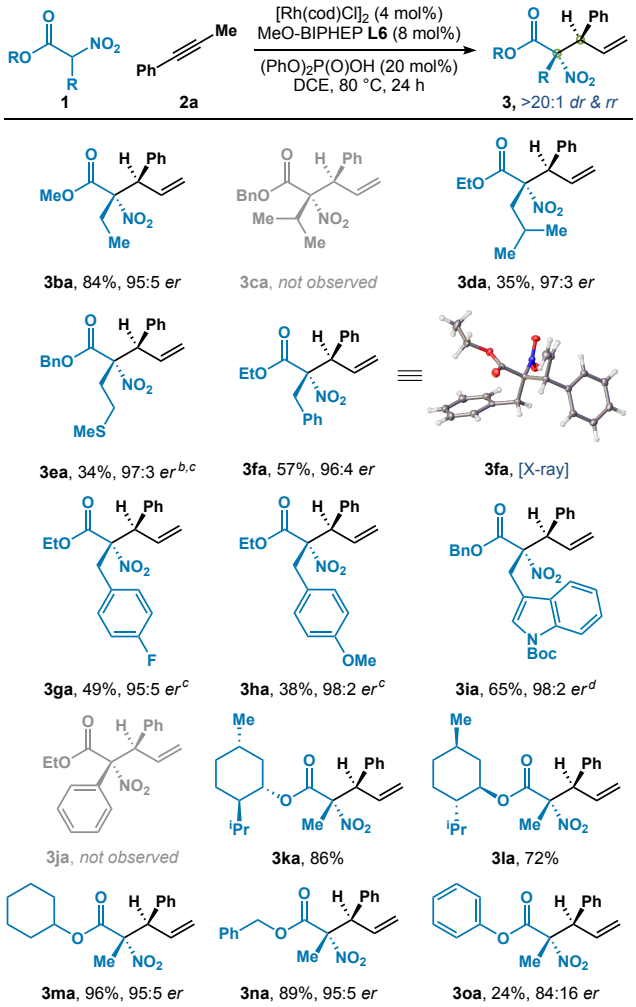
Table 2. Survey of chiral ligands.[a]



[a] See SI for reaction conditions. Yields determined by ^{1}H NMR referenced to an internal standard. [b] Isolated yield for a 1 mmol reaction.

With this protocol, we explored the asymmetric coupling of various *α*-nitroesters with **2a** (Table 3). Analogs of ethylalanine (**3ba**), leucine (**3da**), methionine (**3ea**), phenylalanine (**3fa**), 4-fluoro-phenylalanine (**3ga**), tyrosine (**3ha**), and tryptophan (**3ia**) are generated with moderate to high yields (34-84%) with excellent levels of enantioselectivity (≥95:5 *er*). The absolute configuration of **3fa** was confirmed by X-ray crystallographic analysis.[20,21] In the case of lower yielding substrates, we often recover *α*-nitroester **1**.[20] The bulkier *β*-branched *α*-nitroesters **1c** and **1j** do not couple to **2a** to form analogs of valine (**3ca**) and phenylglycine (**3ja**), respectively. Alkyl-substituted esters **3ka**-**3na** provide higher reactivity than aryl ester **3oa**. We see high levels of diastereocontrol (>20:1 *dr*) for forming **3ka** and **3la**, which suggests the C–C bond is forged by catalyst control.

Table 3. *α*-Nitrocarbonyl scope.[a]

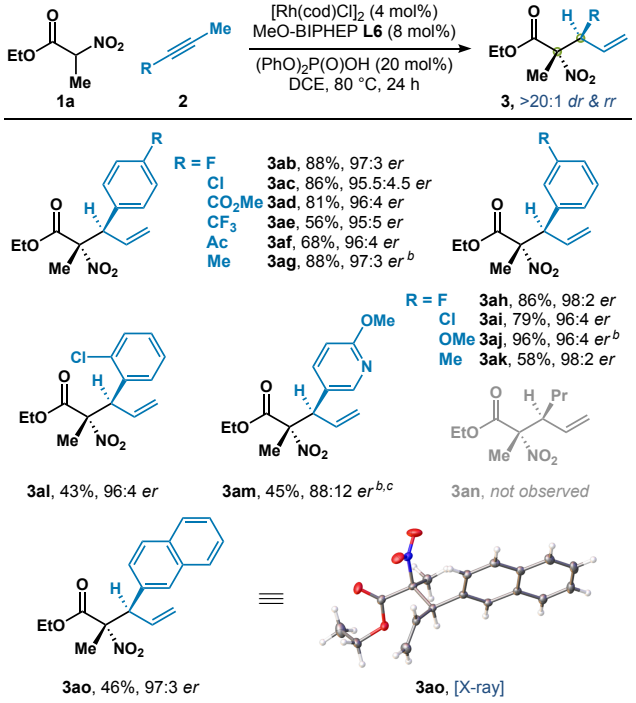


[a] Isolated yields. See SI for reaction conditions. [b] 6:1 *dr*. [c] Yields based on recovered starting material (brsm): **3ea** (76%), **3ga** (96%), and **3ha** (65%). [d] [Rh(cod)Cl]$_2$ (8 mol%) and **L6** (16 mol%) instead of standard conditions.

Table 4 captures results from our study on the coupling of **1a** with various alkynes **2**. Aryl alkynes possessing a variety of electronics and substitution patterns participate in the asymmetric coupling (**3ab**–**3al** and **3ao**). Alkynes bearing halides (**2b**, **2c**, **2h**, **2i** and **2l**), carbonyls (**2d** and **2f**), and extended *π*-systems (**2o**) transform to the corresponding allylic *α*-nitroesters **3**. Aryl alkynes

with electron-donating substituents (**1g** and **1j**) display lower conversion under standard conditions. Increasing the catalyst loading results in improved yields of **3ag** and **3aj** (88% and 96%, respectively), while maintaining high stereoselectivity (≥96:4 *er* and >20:1 *dr*). The presence of an ortho-substituent on alkyne **2l** imparts lower reactivity (46%), presumably due to steric hindrance. Pyridyl alkyne **2m** converts to allylic *α*-nitroester 3am with a higher catalyst loading. It appears that an aromatic or heteroaromatic substituent on the alkyne is critical for reactivity (see **3an**). The absolute configuration of **3ao** was confirmed by X-ray crystallographic analysis.[20,21]

Table 4. Alkyne scope.[a]



[a] Isolated yields. See SI for reaction conditions. [b] $[Rh(cod)Cl]_2$ (7.5 mol%) and **L6** (15 mol%) instead of standard conditions. [c] 15:1 *dr*.

A number of further experiments provide evidence in support of the mechanism depicted in Figure 2. First, we monitored a mixture of $[Rh(cod)Cl]_2$, MeO-BIPHEP **L6**, and diphenyl phosphate by ^1H NMR spectroscopy.[20] We observe a resonance in the spectrum at –16.2 ppm (after heating the mixture for 30 min at 80 °C). The observed resonance is consistent with reported values for Rh(III)-H complexes.[22] This resonance disappears in the ^1H NMR spectrum upon the addition of alkyne **2a**. Second, we subjected deuterated alkyne ***d*-2a** to the standard reaction conditions (Figure 3A). We observe deuterium scrambling into the *β*-, *γ*-, and *δ*-positions of allylic *α*-nitroester ***d*-3aa**. The incorporation of hydrogen atoms at the *δ*-position of ***d*-3aa** supports a reversible *β*-H elimination in the isomerization pathway. Third, to examine the plausibility of an allene intermediate in the catalytic cycle, we subjected 1-phenylallene (**4a**) to the standard conditions (Figure 3B). We observe **3aa** (14% yield) when using an excess of allene **4a**. Moreover, the remaining amount of allene **4a** is consumed. These results, which are in agreement with previous reports, suggest that maintaining a low concentration of the allene intermediate **4** slows competitive polymerization.[10i,12a,23,24]

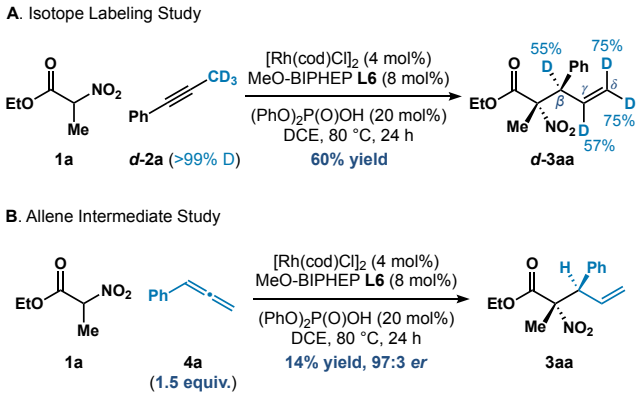
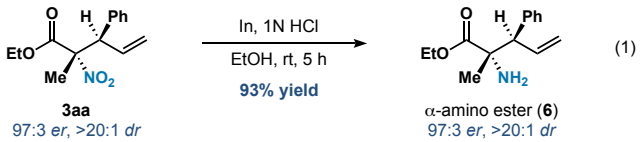


Figure 3. Mechanistic studies.

Treating allylic *α*-nitroester **3aa** with In powder readily yields the corresponding *α*-amino ester **6** in 93% yield (eq 1). This simple reduction allows for rapid access to *α*,*α*-disubstituted *α*-amino esters that contain two contiguous stereocenters, without the ablation of preset stereochemistry.



(1)

The use of Rh-H catalysis offers a complementary approach to novel *α*-AAs. The allylic *α*-AA surrogates prepared contain an olefin handle that can be used for protein modifications,[25] glycopeptide synthesis,[26] and cyclizations.[27] Our strategy offers a solution to the challenging preparation of contiguous stereocenters in an acyclic framework, with diastereo- and enantiocontrol. Insights from this study will guide related strategies to construct C–C bonds with transition-metal catalysis.

Acknowledgements

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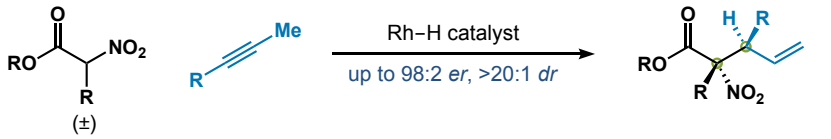
Table of Contents Graphic



readily available material *amino acid surrogates*