How to cite: *Angew. Chem. Int. Ed.* **2021**, *60*, 4599–4603
International Edition: doi.org/10.1002/anie.202014015
German Edition: doi.org/10.1002/ange.202014015

Tandem Catalysis

Enantioselective Addition of α-Nitroesters to Alkynes

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Abstract: *By using Rh–H catalysis, we couple α-nitroesters and alkynes to prepare α-amino-acid precursors. 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 enabled innovative medical applications.[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. 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 co-workers 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 precursors. This atom-economical[8] coupling exploits two simple functional groups and provides rapid access to synthons for the building blocks of life.[9]

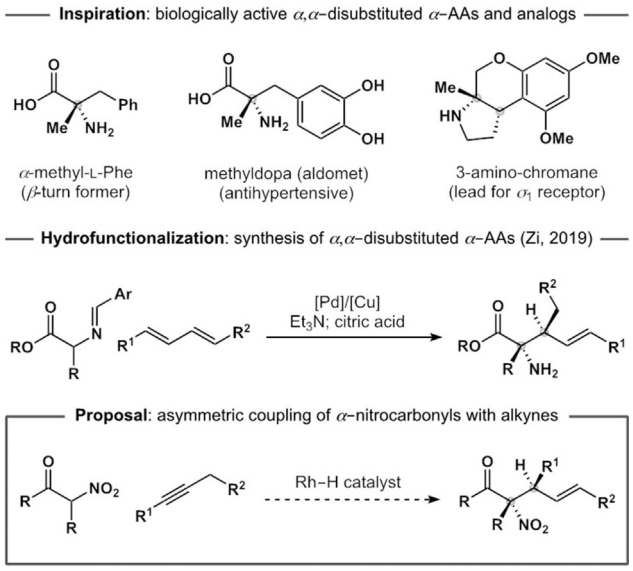

Figure 1. Enantioselective addition of α-nitroesters to alkynes.

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 synthons **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] We previously reported 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 co-workers expanded this approach for the coupling of ketones with alkynes, however, an achiral amine co-catalyst furnishes the branched products with little to no diastereocontrol.[13c]

In related studies, we and Breit independently reported 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 challeng-

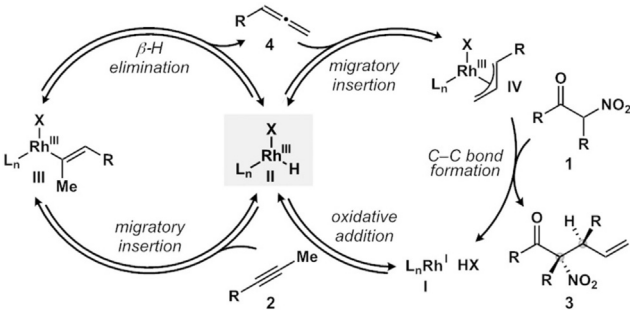

Figure 2. Proposed mechanism for Rh-catalyzed allylation.

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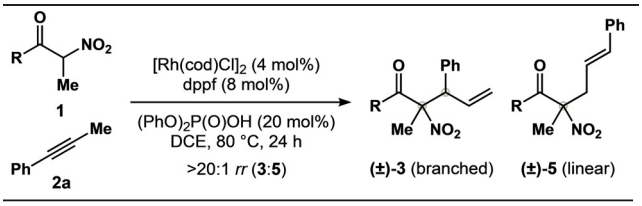
ing. It occurred to us that α-nitrocarbonyls display comparable chelation aptitude[15] and acidity (pK_a = ca. 8)[16] to 1,3-dicarbonyls. Thus, we imagined α-nitrocarbonyls would be suitable nucleophiles for trapping Rh–π-allyl species **IV**. With this design in mind, we set out to couple α-nitrocarbonyls and alkynes with enantio- and diastereocontrol.

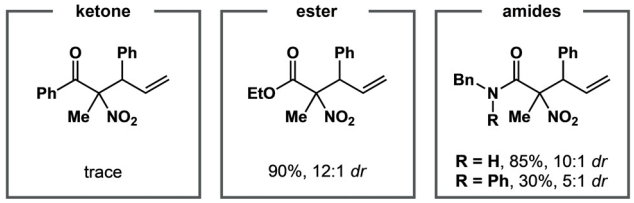
In preliminary studies, we discovered that various α-nitrocarbonyls add to the commercially available alkyne **2a** (Table 1). Using a combination of $[Rh(cod)Cl]_2$, dppf, and diphenyl phosphate, we observe allylic α-nitroketone, α-nitroester, and α-nitroamide products as single regioisomers (>20:1 *rr*) with moderate to high diastereoselectivity (5:1–12:1 *dr*).[17] 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 co-workers.[18] In Ooi's study, the use of allylic carbonates affords linear regioisomers with one stereocenter.

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.[19] To identify the appropriate chiral catalyst, we selected α-nitroester **1a** and alkyne **2a** as the model substrates (Table 2). Using atropoisomeric bisphosphine ligands **L1**–**L3** with a range of dihedral angles,[20] we observe the allylic α-AA precursor **3aa** with moderate yields (45–53%) and enantioselectivities (85:15–90:10 *er*). Ultimately, we found that commercial MeO-BIPHEP ligand **L6** affords **3aa** in 90% yield with 97:3 *er*, >20:1 *dr*, and >20:1 *rr* on preparative scale (1 mmol).[21,22] This coupling relies on the use of alkynes as the unsaturated partner instead of activated olefins, imines, propargylic carbonates, and allylic leaving groups.[18,19] Therefore, we explored the scope of this transformation to access unique β-aryl-α-nitroester motifs.

With this protocol, we explored the asymmetric coupling of various α-nitroesters with **2a** (Table 3). Analogs of ethyl-

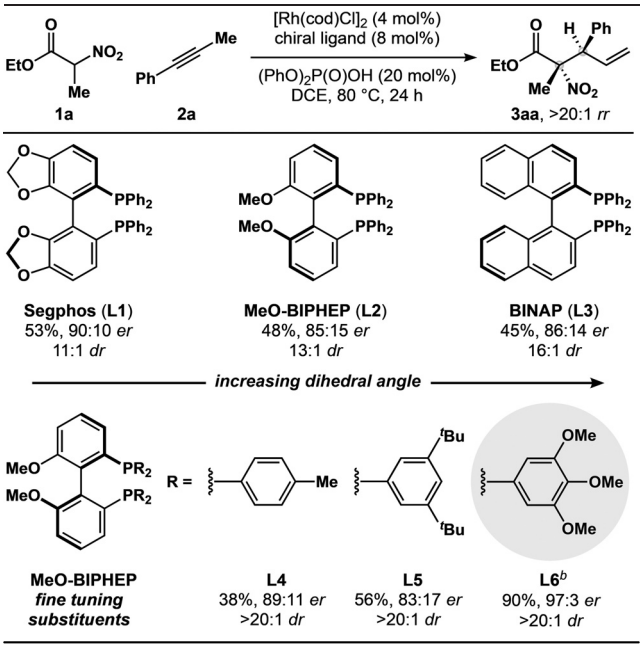
Table 1: Investigating various α-nitrocarbonyls.[a]





[a] **1** (0.10 mmol), **2a** (0.15 mmol), $[Rh(cod)Cl]_2$ (4.0 mol%), dppf (8.0 mol%), $(PhO)_2P(O)OH$ (20 mol%), DCE (0.20 mL), 80°C, 24 h. Yields determined by ^1H NMR referenced to an internal standard. Cod = 1,5-cyclooctadiene, dppf = 1,1′-bis(diphenylphosphino)ferrocene, DCE = 1,2-dichloroethane.

Table 2: Survey of chiral ligands.[a]

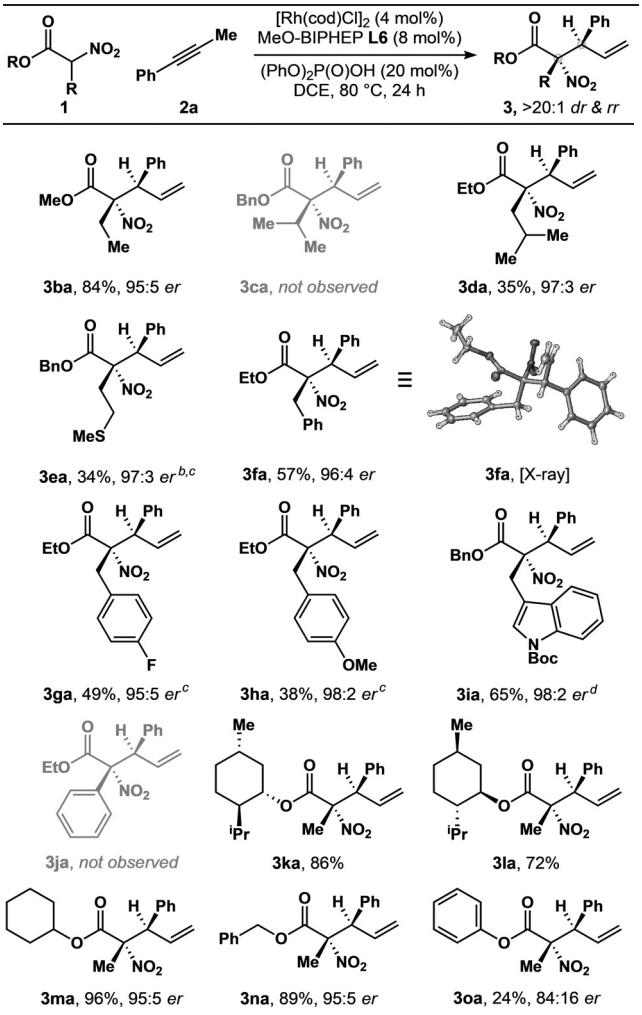


[a] **1a** (0.10 mmol), **2a** (0.15 mmol), $[Rh(cod)Cl]_2$ (4.0 mol%), chiral ligand (8.0 mol%), $(PhO)_2P(O)OH$ (20 mol%), DCE (0.20 mL), 80°C, 24 h. Yields determined by ^1H NMR referenced to an internal standard. [b] Isolated yield for a 1 mmol reaction.

glycine (**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%) and excellent levels of enantioselectivity (≥95:5 *er*). The absolute configuration of **3fa** was confirmed by X-ray crystallographic analysis.[21,22] In the case of lower yielding substrates, we often recover α-nitroester **1**.[21] 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.

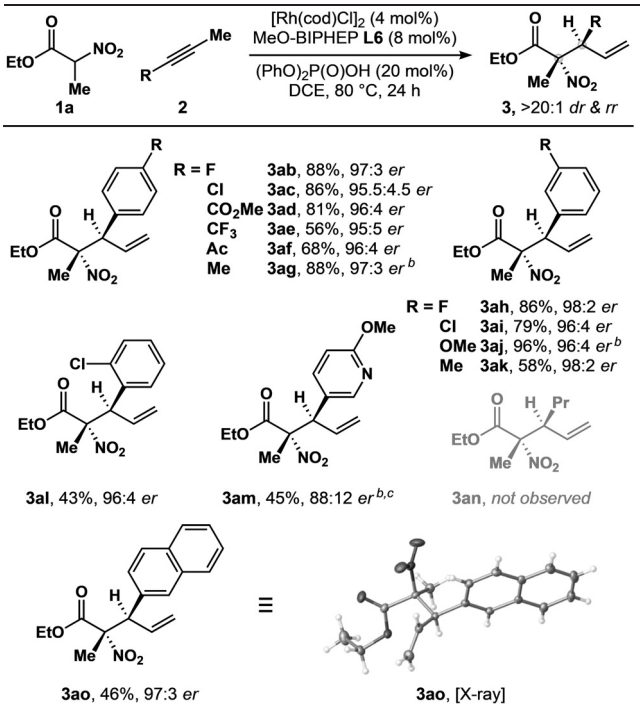
Table 4 captures results from our study on the addition of **1a** to various alkynes **2**. Aryl alkynes possessing a variety of electronics and substitution patterns participate in the asymmetric coupling (**3ab**–**3al** and **3ao**). Alkynes bearing halides (**2b**, **2c**, **2h**, **2i** and **2l**), 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 (43%), 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.[21,22]

Table 3: α-Nitrocarbonyl scope.[a]



[a] **1** (0.10 mmol), **2a** (0.15 mmol), $[Rh(cod)Cl]_2$ (4.0 mol%), MeO-BIPHEP **L6** (8.0 mol%), $(PhO)_2P(O)OH$ (20 mol%), DCE (0.20 mL), 80 °C, 24 h. Isolated yields. [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: Alkyne scope.[a]



[a] **1a** (0.10 mmol), **2** (0.15 mmol), $[Rh(cod)Cl]_2$ (4.0 mol%), MeO-BIPHEP **L6** (8.0 mol%), $(PhO)_2P(O)OH$ (20 mol%), DCE (0.20 mL), 80 °C, 24 h. Isolated yields. [b] $[Rh(cod)Cl]_2$ (7.5 mol%) and **L6** (15 mol%) instead of standard conditions. [c] 15:1 *dr*.

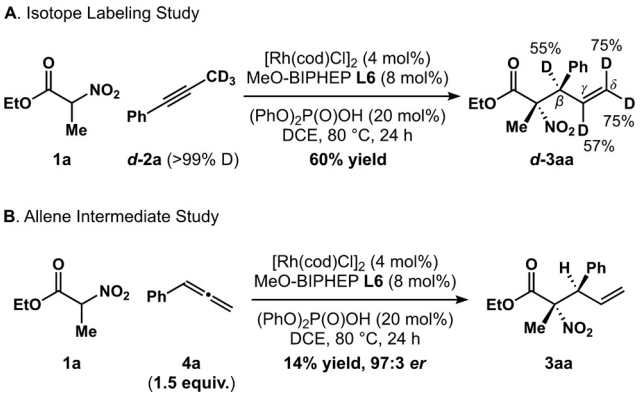
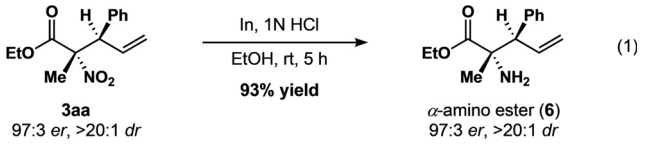


Figure 3. Mechanistic studies.

Further experiments provide support for 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.[21] We observe a resonance in the spectrum at −16.2 ppm. The observed resonance is consistent with reported values for Rh^{III}–H complexes.[23] 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 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 are in agreement with previous reports that suggest maintaining a low concentration of allene intermediate **4** slows competitive polymerization.[10i,12a,24,25]

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 stereoablation.

The use of Rh–H catalysis offers an approach to novel α-AAs. The allylic α-AA precursors prepared contain an olefin handle that is attractive due to its potential use for protein modifications,[26] glycopeptide synthesis,[27] and cyclizations.[28]



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 development of related α-nitrocarbonyl coupling reactions with alkynes. In particular, our laboratory has found initial success in the enantioselective addition of α-nitroamides to alkynes, which could provide a way to couple peptides containing α-nitroamide residues with alkynes.[21] Future studies will focus on widening scope and understanding the origins of stereocontrol. The high diastereocontrol achieved occurs without the need for a chiral amine (co-catalyst) as previously observed.[13a]

Acknowledgements

Funding provided by UC Irvine and the National Institutes of Health (R35GM127071). We thank Dr. Milan Gembicky (UC San Diego) for X-ray crystallographic analysis. We thank Solvias AG for donating commercial MeO-BIPHEP **L6**.

Conflict of interest

The authors declare no conflict of interest.

Keywords: alkynes · amino acids · nitroester · rhodium hydride · tandem catalysis

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[21] See the Supporting Information for more details.

[22] Deposition Numbers 2014416 (for **3fa**) and 2014415 (for **3ao**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/ structures. The absolute configurations of the remaining allylic α-AA precursors **3** were assigned by analogy.

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Manuscript received: October 19, 2020
Revised manuscript received: November 16, 2020
Version of record online: January 7, 2021

