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Asymmetric Multicomponent Reactions for Efficient Construction of Homopropargyl Amine Carboxylic Esters

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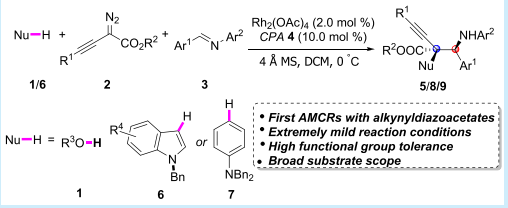
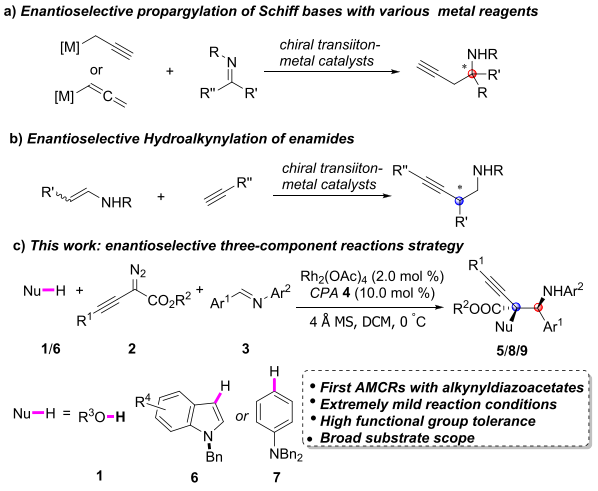
Supporting Information

ABSTRACT: Developing an efficient and highly enantioselective protocol to access homopropargyl amines is of high interest to the synthetic community and also remains a formidable challenge for organic chemists. Here, we present integrated $Rh_2(OAc)_4$- and BINOL-derived chiral phosphoric acid cooperatively catalyzed three-component reactions of alkynyldiazoacetates, imines with various nucleophiles including alcohols, indoles, and N,N-disubstituted anilines, affording the corresponding homopropargyl amines containing two vicinal chiral centers in satisfactory yields with high to excellent diastereo- and enantioselectivities.



Enantiomerically pure homopropargyl amines are versatile building blocks for the synthesis of many bioactive compounds and natural products,[1,2] such as indolizidine 209B[2a] and hederacine A.[2c,d] As such, developing enantioselective synthetic methods for these compounds is of great interest to the synthetic community.[3] A traditionally synthetic approach toward α-branched homopropargyl amines is enantioselective propargylation of Schiff bases with various propargyl or allenyl metal reagents[4] (Scheme 1a), and

Scheme 1. Efficient Construction of HPACEs



considerable efforts have been made to develop catalytically asymmetric methods, relying on developing novel chiral metal complexes.[5] However, these propargylation reactions that involve the use of stoichiometrically synthesized or pregenerated propargyl or allenyl metals would strongly limit the chemical and functional diversity of the final products. Although there have been few alternative strategies to access chiral β-branched homopropargyl amines[6] (Scheme 1b), demand for developing novel complementary strategies for the enantioselective synthesis of homopropargyl amines is expected to remain strong in this field.

Asymmetric multicomponent reactions (AMCRs) represent a powerful and efficient method for construction of enantiomerically pure organic compounds with complexity as well as skeletal diversity.[7] As intermediates of high interest, ylide or zwitterionic intermediates that were generated in situ by metal-associated carbenes derived from diazo compounds and an array of nucleophiles have been recognized as key intermediates in several novel AMCRs.[8−11] The reactivity profile of ylide or zwitterionic intermediates, which are heavily dependent on the structure of the substituents adjacent to the diazo carbon, have significant influence on the selectivity and efficiency of the AMCRs.[12,13] α-Aryldiazoacetates are among the most widely used substrates in AMCRs, and there are also limited elegant examples with α-alkyldiazoacetates[9f,13b] and α-alkenyldiazoacetates.[10a] In contrast, the AMCRs with alkynyldiazoacetates[14] remain unexplored according to our current best knowledge in this area. Herein, we present highly enantioselective three-component reactions of alkynyldiazoacetates, imines with three kinds of nucleophiles including alcohols, indoles, and *N*,*N*-disubstituted anilines, which provide an efficient access to α,β-disubstituted homopropargyl amine carboxylic esters (HPACEs) bearing a quaternary stereogenic center (Scheme 1c).

The initial proof-of-concept experiment was performed under a dinitrogen atmosphere with methyl 2-diazo-4-(trimethylsilyl)-but-3-ynoate **2a** added to a solution of 4-bromobenzyl alcohol **1a** and imine **3a** in the presence of $Rh_2(OAc)_4$ (2.0 mol %) and BINOL-derived chiral phosphoric acid (CPA) **4a** (10.0 mol %)

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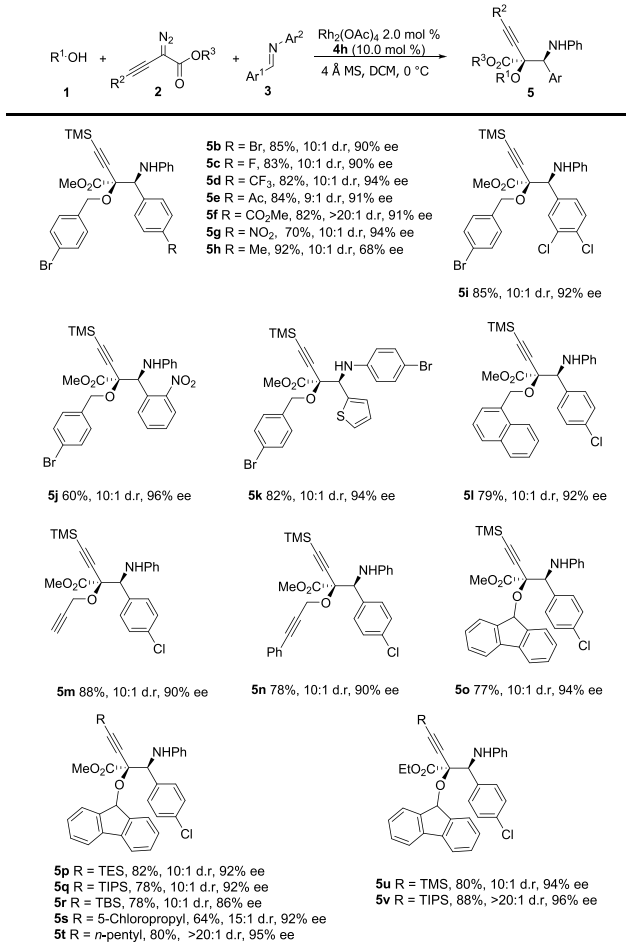
via a syringe pump for 15.0 min at 0 °C. The desired product **5a** was obtained in 90% yield with dr 5:1 and 12% ee. Then various BINOL-derived CPAs **4** were screened. The substituents on the BINOL-derived CPAs had a significant impact on the diastereo- and enantioselectivity, albeit a negligible impact on the yield of the three-component product **5a**. Gratifyingly, the BINOL-derived CPAs **4h** with a bulky triphenylsilyl group ($SiPh_3$) afforded the three-component product **5a** in 91% yield with dr 9:1 and 94% ee; replacement of dirhodium tetraacetate with several dirhodium catalysts including $Rh_2(TFA)_4$, $Rh_2(esp)_2$, and $Rh_2(Oct)_4$did not give any enhanced results. Other Rh(I), Pd(0), Pd(II), Cu(I), Cu(II), Au(I), and Ag(I) catalysts, have been proven to be unsuitable in our current system. We then explored different solvents in the three-component reaction. DCE and PhMe were capable of this transformation, albeit in lower yield and decreased diastereo- and enantioselectivity of the product **5a**, whereas THF dramatically diminished the yield. Moreover, a decrease or increase in temperature failed to improve the enantioselectivity of this transformation (see the Supporting Information for details).

With the optimized reaction conditions in hand, we then investigated the substrate scope of imines for this transformation. As shown in Table 1, a variety of imines with electron-withdrawing groups such as Br, F, CF_3, Ac, CO_2Me, and NO_2, some functional groups that are problematic in traditionally synthetic approaches, were well tolerated in the three-component reaction (products **5b**−**g**), furnishing the corresponding three-component products in good to excellent yields (70−85%), with good to excellent dr (9:1 to >20:1) and excellent ee (90−94%). The methyl-substituted imines was also suitable for this reaction, affording the product **5h** in the highest yield (92%), but with lowest ee (68%) and average dr (10:1). To our delight, imines with *meta*- and *ortho*-substituents successfully afforded the corresponding products **5i** and **5j** in acceptable yield (60−85%) with good dr (10:1) and excellent ee (92−96%). Furthermore, the aldimine containing sulfur-substituted heterocyclic rings, (*E*)-N-4-Br-phenyl-1-(thiophene-2-yl)-methanimine, was proven to be compatible with this reaction (product **5k**). Next, the scope of this transformation with respect to the alcohol component was investigated. For different types of alcohols, this asymmetric three-component reaction proceeded smoothly to provide the corresponding three-component products in a satisfactory manner (products **5l**−**o**). To test the steric tolerance of the reaction, we chose the very bulky fluorenol as the alcohol component, and an array of alkynyldiazoacetates were investigated. A variety of methyl/ethyl alkynyldiazoacetates containing silyl groups including TMS, TES, TBS, and TIPS were well tolerated in this transformation (products **5p**, **5q**, **5r**, **5u**, and **5v**). Interestingly, alkynyldiazoacetates containing a chloro functional group and a long alkyl chain successfully gave the corresponding products **5s** and **5t** in satisfactory yields (64−80%) with excellent dr (15:1−>20:1) and ee (92−95%).

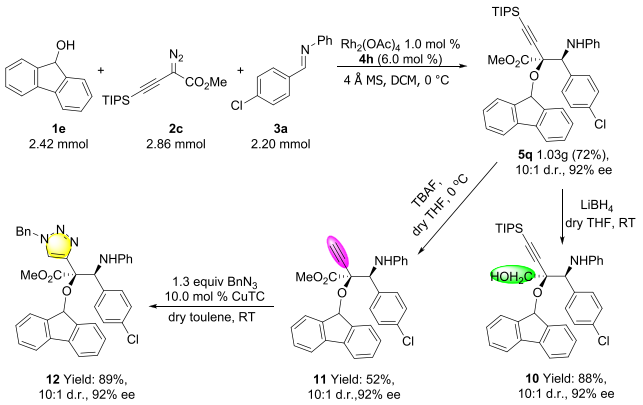
As shown in Scheme 2, to illustrate the synthetic utility of this transformation, a gram-scale experiment with fluorenol, diazo compound **2c**, and imine **3a** was carried out in the presence of $Rh_2(OAc)_4$ and **4h** at 0 °C in DCM for 2 h, affording 1.03 g of **5q** in 72% yield without diminishing the dr (10:1) and ee (92%). Furthermore, treatment of **5q** with lithium borohydride ($LiBH_4$) gave **10** in 88% yield with the same diastereo- or enantioselectivity. In addition, the TIPS group of **5q** could be efficiently removed by treatment with tetrabutylammonium fluoride (TBAF) in THF at 0 °C,[15] furnishing **9** in moderate yield. Compound **11** could be efficiently transformed into triazole compound **12** in 89% yield via a copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC).[16] The structure and absolute stereochemistry of **5q** and **11** were confirmed by X-ray crystallographic analysis of **12** (Figure 1a, CDCC 1902392).

Table 1. Substrate Scope of Three-component Reactions of 1 and 2 with 3[a]



[a]Reaction conditions: **1a**/**2a**/**3a**/**4**/ $Rh_2(OAc)_4$ = 0.36/0.36/0.30/0.03/0.006 mmol and **2a** in 1.0 mL of solvent was added into a solution of **1a**, **3a**, **4**, $Rh_2(OAc)_4$, and 100 mg 4 Å MS in 1.0 mL of solvent via a syringe pump under a dinitrogen atmosphere for 15.0 min, and the resulting mixture was stirred for another 1.0 h.

Scheme 2. Synthesis of Gram-Scale Transformations of 5q



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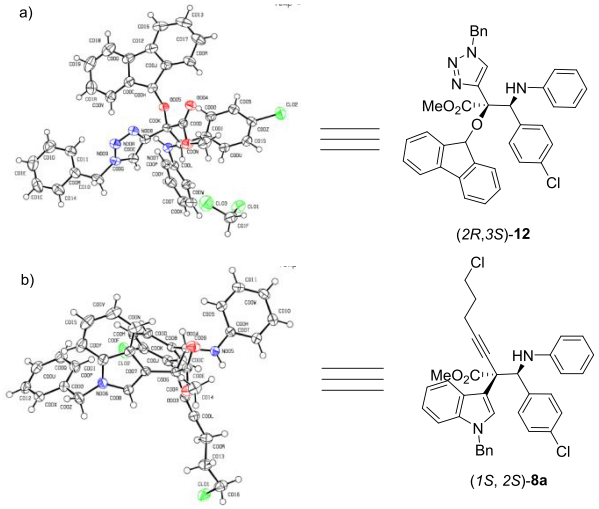
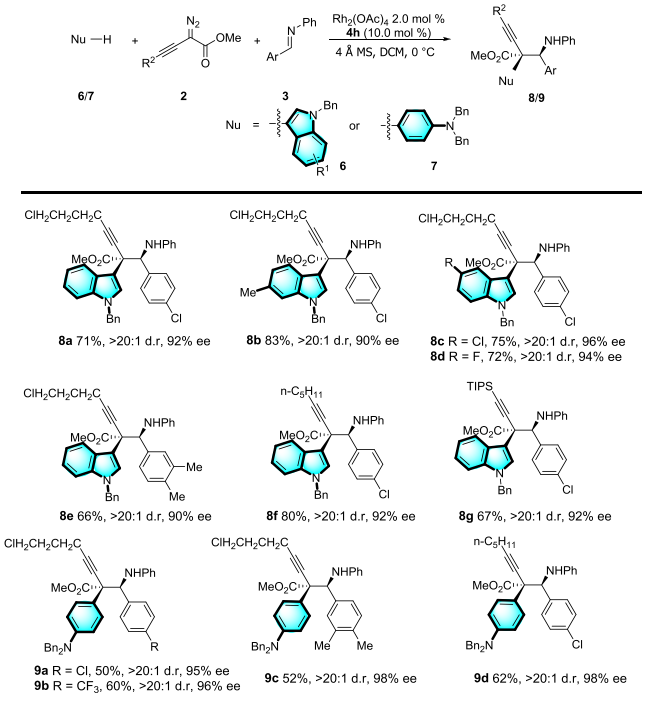


Figure 1. X-ray single crystal structures of **12** and **8a**.

Very recently, our research group reported several AMCRs via trapping of active zwitterionic intermediates generated by metal carbenes with carbon-centered nucleophiles such as indoles and *N*,*N*-disubstituted anilines.[10a,13c] We further envisioned that this three-component strategy would enable highly efficient syntheses of enantiomerically rich *α*,*β*-disubstituted homopropargyl amines bearing an all-carbon quaternary stereogenic center, which is a particularly challenging task in modern organic synthesis. As shown in Table 2, we were very pleased to find that indoles and *N*,*N*-dibenzylanilines were suitable for this transformation under the above optimized reaction conditions. Various substituted *N*-benzylindoles underwent this transformation smoothly to give the corresponding products in good yields (products **8a**−**d**). Meanwhile, various imines and alkynyldiazoacetates were suitable for this asymmetric three-component reaction with *N*-benzylindole (products **8e**−**g**). The absolute configuration of **8a** was determined to be (1*S*,2*S*) by X-ray crystal diffraction analysis (Figure 1b, CDCC 1892221). Interestingly, improved results were obtained when we chose *N*,*N*-dibenzylaniline as the nucleophile component (products **9a**−**d**). Remarkably, excellent diastereo- and enantioselectivities were observed in all cases.

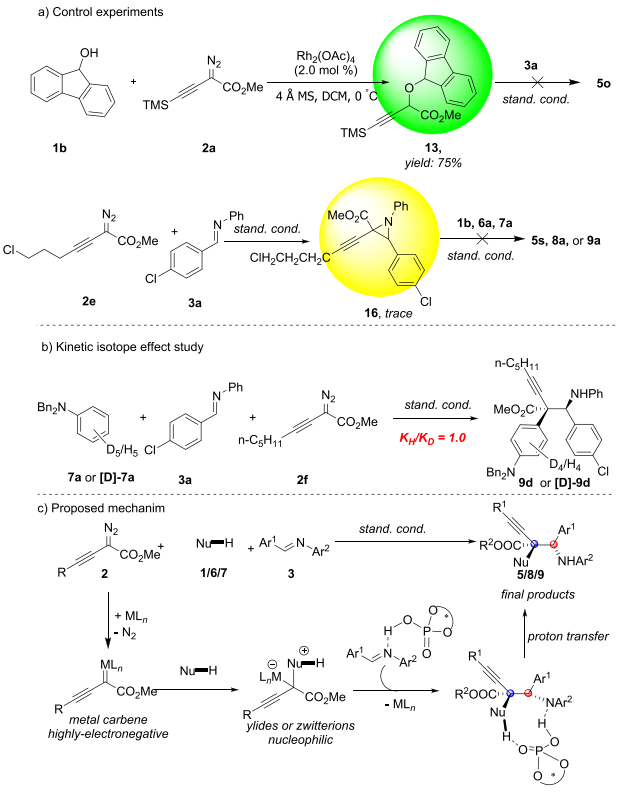
To gain more mechanistic insights of these novel three-component reactions, further control experiments and kinetic isotope effect (KIE) studies were performed. First, we prepared the O−H insertion product **13** form **1b** and **2a** with $Rh_2(OAc)_4$ as the catalyst (C−H insertion product **14** and **15**, see the Supporting Information for details). However, upon addition of imine **3a**, three-component product **5o** was not detected under standard reaction conditions (similar results were obtained with *N*-benzylindole **a** or *N*,*N*-dibenzylaniline **7a**; see the Supporting Information for details). In the novel three-component reactions, the aziridine **16** was also a possible intermediate that underwent a ring-opening process to form the observed three-component reaction products. To clarify this issue, we performed the reaction of **2e** and **3a** under standard reaction conditions, and only a trace of aziridine **16** was observed by LC−MS; further addition of **1b** (**6a** or **7a**) did not give any detectable three-component reaction products **5s** (**8a** or **9a**). These control reactions exclude the possibility that the three-component products (**5o**/**5s** and **8a**, **9a**) were formed from the addition of the O−H/C−H insertion products to **3a** or the aziridine ring-opening reactions with respective nucleophiles by a stepwise pathway (Scheme 3a). Additionally, a KIE experiment was performed with *N*,*N*-dibenzylaniline **7a** and its deuterated

Table 2. Substrate Scope of Three-Component Reactions of 6/7 and 2 with 3[a]



[a]Reaction conditions: the same as Table 2.

Scheme 3. Mechanism Studies of the Three-Component Reactions



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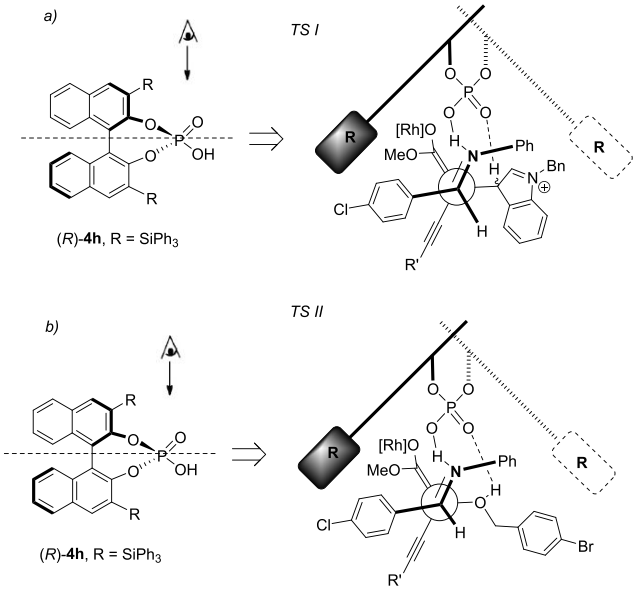
analogue [D]-**7a**. A KIE value of 1.0 suggested that the C−H bond cleavage of **7a** was not related to the rate-limiting step (Scheme 3b). Overall, these observations were consistent with our previously proposed mechanism via a trapping reaction reactive intermediate pathway[8a] (Scheme 3c).

The stereoselective outcome of the three-component reaction with alkynyldiazoacetates is in agreement with our previous observation on three-component reactions with aryl diazoesters.[10a] As shown in Scheme 4, with the interaction model

Scheme 4. Proposed Transition State for the Three-Component Reactions



proposed by Simón and Goodman,[17] the stereochemistry for these three-component reactions catalyzed by BINOL-derived CPA **4h** can be well rationalized (TS I). For example, the energetically favorable *E*-imine **3a**, activated by **4h** through hydrogen bonding between **4h** proton and the nitrogen of **3a**, is used to trap the zwitterionic intermediates generated in situ by metal-associated carbenes derived from alkynyldiazoacetates and *N*-benzylindole. Meanwhile, the direction of the **3a** *N*-phenyl group is proposed to be toward the empty side of the catalyst pocket; then the acidic C−H proton of the newly formed zwitterionic intermediates coordinates the Lewis basic phosphoryl oxygen atom via a weak hydrogen bond; further nucleophilic carbon attacks the imine and the following proton transfer occurs through the BINOL-derived CPA **4h** to give the product (1*S*,2*S*)-**8a** with the observed stereochemistry. Using the same model, the observed stereochemistry for the three-component reaction with alcohols can also be rationalized by a similar transition state (*TS II*) to give (2*R*,3*S*)-**5a**.

In conclusion, we have developed an array of highly efficient $Rh_2(OAc)_4$- and BINOL-derived CPA cooperatively catalyzed three-component reactions of alkynyldiazoacetates, imines, and a broad range of nucleophiles including alcohols, indoles, and N,N-disubstituted anilines. These transformations provide a novel complementary strategy for the synthesis of polyfunctionalized HPACEs. Moreover, this present reaction protocol creates two stereogenic centers in single step, including one (all-carbon) quaternary stereogenic center. This process proceeds under exceptionally mild reaction conditions and shows high functional group tolerance and broad substrate scope. Further investigations toward the biological activities of these polyfunctionalized HPACEs are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02139.

Experimental procedure and spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 1892221 and 1902392 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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