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Dirhodium(II)/Xantphos-Catalyzed Relay Carbene Insertion and Allylic Alkylation Process: Reaction Development and Mechanistic Insights

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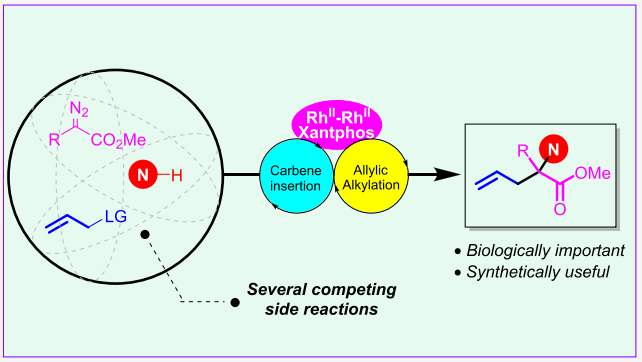
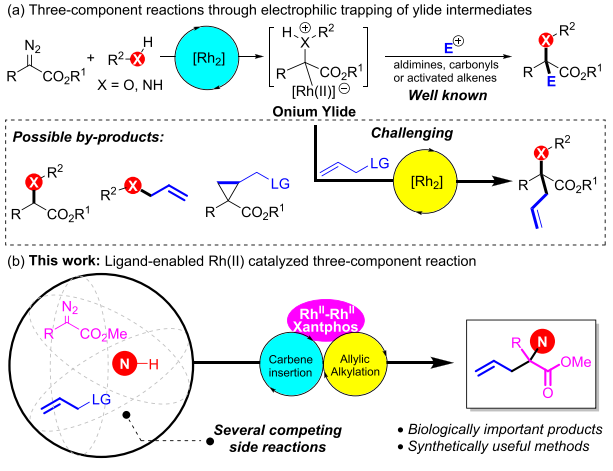
ABSTRACT: Although dirhodium-catalyzed multicomponent reactions of diazo compounds, nucleophiles and electrophiles have achieved great advance in organic synthesis, the introduction of allylic moiety as the third component via allylic metal intermediate remains a formidable challenge in this area. Herein, an attractive three-component reaction of readily accessible amines, diazo compounds, and allylic compounds enabled by a novel dirhodium(II)/Xantphos catalysis is disclosed, affording various architecturally complex and functionally diverse α-quaternary α-amino acid derivatives in good yields with high atom and step economy. Mechanistic studies indicate that the transformation is achieved through a relay dirhodium(II)-catalyzed carbene insertion and allylic alkylation process, in which the catalytic properties of dirhodium are effectively modified by the coordination with Xantphos, leading to good activity in the catalytic allylic alkylation process.



1. INTRODUCTION

Dirhodium(II) complexes of the tetracarboxylate type have been widely utilized in the discovery and development of valuable synthetic methodologies.[1−3] Especially, dirhodium(II) complexes-catalyzed multicomponent reactions (MCRs) involving electrophilic trapping of metal-associated onium ylide intermediates generated *in situ* from metal carbenoids with various nucleophiles have emerged as a powerful protocol for construction of structurally complex and diverse molecules (Scheme 1a).[4] Trapping of onium ylides by nucleophilic addition to aldimines, carbonyls, activated alkenes (Michael acceptors) and so on, as well as a few examples via the formal S_N1 pathway, have been reported.[5−9] Despite the recent progress and the great significance of allylic group in organic synthesis, the introduction of allylic moiety as the third component through allylic metal intermediate remains a formidable challenge in dirhodium(II)-catalyzed MCRs (Scheme 1a). To achieve this challenging transformation, the following issues must be addressed: (1) In principle, dirhodium(II) complex is unfavorable for two-electron oxidative addition to form allylic dirhodium species.[10,11] (2) The competitive direct allylic substitutions between the nucleophilic substrates and allylic substrates should be avoided.[12] (3) Dirhodium(II)-catalyzed cyclopropanation reaction between diazo compounds and C=C bond of allylic substrates may be a problematic side reaction.[1e,q]

Scheme 1. Introduction to Dirhodium(II) Complexes-Catalyzed Multicomponent Reactions by Trapping of Onium Ylides (a) and Our Work (b)



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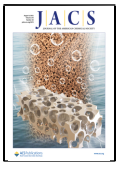

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The development of efficient methods for the preparation of unnatural α-tetrasubstituted α-amino acids continues to attract considerable research interest and has become a significant goal in the fields of medicinal chemistry and organic synthesis.[13,14] Here we disclose an unique reactivity of a Rh(II)/Xantphos catalytic system, which can efficiently catalyze a multicomponent reaction of readily available α-diazo esters, amines and allylic substrates, providing various architecturally complex and functionally diverse α-quaternary α-amino acid derivatives in an one-pot fashion (Scheme 1b). With an allyl group as a synthetic handle, the α-amino acid derivatives can serve as convenient starting materials to prepare some important intermediates for biologically active molecules. A relay dirhodium(II)-catalyzed carbene insertion and ligand-enabled [Rh_2]-catalyzed allylic alkylation process was proposed to explain the programmed assembly of these three components.

2. RESULTS AND DISCUSSION

2.1. Reaction Discovery. We initiated our study by examining a Rh(II)/Pd(0) dual system in the reaction of *N*-methylaniline **1a**, α-diazo ester **2a**, and allylic substrate **3a**, based on a hypothesized domino Rh(II)-carbene-induced N–H insertion and Pd-catalyzed allylic alkylation process (Scheme 2; for details, see the Supporting Information (SI)).[15] In the absence of added ligand or additional Pd catalyst, the mixture of **1a**, **2a** and **3a** gave only the product (**4a**) of carbene insertion reaction between **1a** and **2a** (Scheme 2a), while the direct allylic amination product **5a** was formed in 95% yield using $Pd_2(dba)_3$/Xantphos as the sole catalyst (Scheme 2b). Additionally, only a minor amount of **6a** (16%) was observed when combining $Rh_2(Oct)_4$, $Pd_2(dba)_3$, and Xantphos together as the catalyst, along with **5a** as the major product (Scheme 2c). Surprisingly, the combination of a catalytic amount of $Rh_2(Oct)_4$ and Xantphos afforded the target product **6a** in 91% yield (Scheme 2d). Neither the carbene insertion product **4a** nor allylic amination product **5a** was detected in this case. It is worth mentioning that no any cyclopropanation product **7a** was observed in all the cases (Scheme 2a–d). Intriguingly, changing the rhodium source from a Rh(II) carboxylate to a Rh(I) or a Rh(III) salt mainly gave the product **5a**, suggesting the corresponding Rh species preferably catalyze allylic amination reaction, rather than the carbene insertion reaction (Table 1, entries 2 and 3). Further screening of the ligands including ^{t}Bu-Xantphos, BINAP, PPh_3, $P^tBu_3{\cdot}HBF_4$, and ^{i}Pr-NHC provided the carbene insertion product **4a** as the major product, which indicated that Xantphos should play a unique role in the allylic alkylation process (entry 1 vs 4–8). When the amount of Xantphos was decreased to 1.5 mol%, the reaction still gave the product **6a** in 91% yield (entry 9). Further decreasing the amount of Xantphos to 1.0 or 0.5 mol% resulted in slightly lower yield of **6a** (86% and 82% yield, respectively, entries 10, 11). The results indicated that at most 1.0 equiv Xantphos per Rh dimers is involved in the three-component reaction. It is worth mentioned that although CH_3CN can coordinate to dirhodium complex, the dirhodium-catalyzed reaction of **1a** with phenyldiazoacetate **2a** could happen smoothly in CH_3CN at room temperature, which might be attributed to the fast dynamic coordination–dissociation in solution between free and axial-coordinated ligand (solvent and so on).[1a,16]

Scheme 2. Preliminary Attempt on the Reactions of 1a, 2a, and 3a Using Different Catalysts: $Rh_2(Oct)_4$ (a), $Pd_2(dba)_3$/Xantphos (b), $Rh_2(Oct)_4$/$Pd_2(dba)_3$/Xantphos (c), and $Rh_2(Oct)_4$/Xantphos (d)

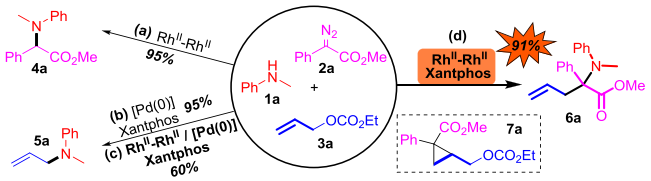

Table 1. Optimization for Dirhodium(II)/Xantphos-Catalyzed Multicomponent Reaction of 1a, 2a and 3a[a]

			yield (%)[b]		
entry	cat.	ligand (mol%)	4a	5a	6a
1	$Rh_2(Oct)_4$	Xantphos (2.0)	0	0	91
2	$[Rh(COD)_2](BF_4)$	Xantphos (2.0)	0	>99	0
3	$RhCl_3{\cdot}3H_2O$	Xantphos (2.0)	4	72	2
4	$Rh_2(Oct)_4$	^{t}Bu-Xantphos (2.0)	83	<1	11
5	$Rh_2(Oct)_4$	BINAP (2.0)	69	<1	26
6	$Rh_2(Oct)_4$	PPh_3 (4.0)	30	0	0
7	$Rh_2(Oct)_4$	$^tBu_3P{\cdot}HBF_4$ (4.0)	95	0	5
8[c]	$Rh_2(Oct)_4$	^{i}Pr-NHC (4.0)	89	0	11
9	$Rh_2(Oct)_4$	Xantphos (1.5)	0	0	91
10	$Rh_2(Oct)_4$	Xantphos (1.0)	4	0	86
11	$Rh_2(Oct)_4$	Xantphos (0.5)	8	0	82
12	$Rh_2(Oct)_4$	–	95	0	0

[a]Unless otherwise noted, all reactions were carried out using **1a** (0.25 mmol), **2a** (0.40 mmol), **3a** (0.35 mmol), Rh catalyst (1.0 mol%), ligand (2.0 mol%), and Cs_2CO_3 (150 mol%) in CH_3CN (2.0 mL) under Ar at r.t. for 9.0 h. $Rh_2(Oct)_4$ = rhodium(II) octanoate dimer. [b]GC yield. [c]^{i}Pr-NHC = 1,3-bis(2,6-di-isopropylphenyl)-4,5-dihydroimidazol-2-ylidine.

2.2. Scope and Synthetic Applications. With the optimized reaction conditions in hand, the generality of this reaction was explored (Scheme 3a). To our delight, *N*-ethylaniline **1b** and indoline **1c** reacted smoothly with substrates **2a** and **3a** under the standard conditions, giving the corresponding products **6b** and **6c** in 84% and 72% yield, respectively. Surprisingly, primary amines, such as $BocNH_2$ and aniline, were also well tolerated, affording the corresponding products **6d** and **6e** in good yields (77% and 87%). Various anilines with different groups on the benzene ring, including *o*-Me, *o*-Br, *m*-F, *m*-Cl, *m*-Br, *m*-I, and *p*-Me, performed well in the reactions with **2a** and **3a**, providing the corresponding products (**6f–6l**) in 69%–90% yields. Compared with the substrate **1m** containing an electron-donating methoxy group on the *para* position, substrates **1n** and **1o** with electron-withdrawing groups (*p*-CN, *p*-CF_3) gave much better yields in the reactions (40% vs 85% and 92%). Additionally, for *ortho*,*para*-dibromo-substituted aniline and α-naphthylamine, the reactions also proceeded smoothly, giving the products **6p** and **6q** in good yields, respectively. Moreover, the structures of **6d** and **6n** were unambiguously determined by X-ray crystallographic analysis (see the SI).

On the basis of these results, the scope of the α-diazo esters **2** in the reactions with aniline (**1e**) and allyl ethyl carbonate (**3a**) was further investigated. As shown in Scheme 3b, changing methyl ester to ethyl ester had no obvious influence on the reaction outcomes, providing the product **6r** in 79% yield. However, the diazo compound with ^{t}Bu ester gave

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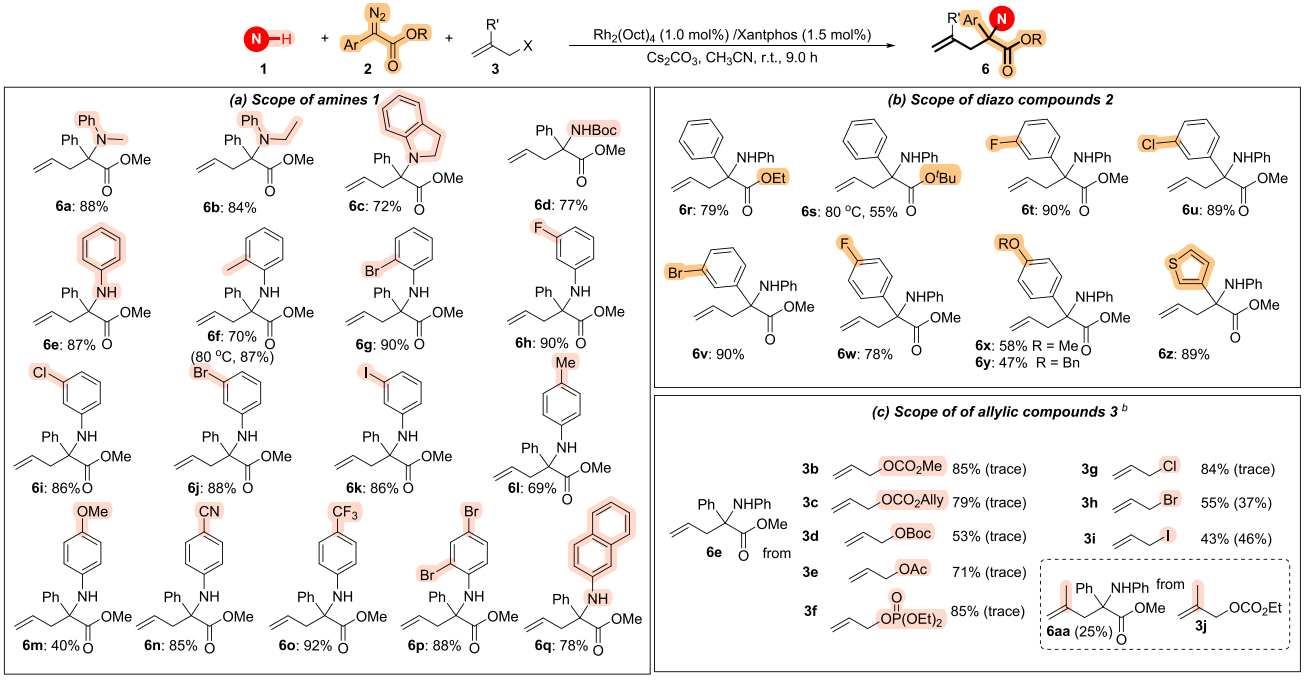
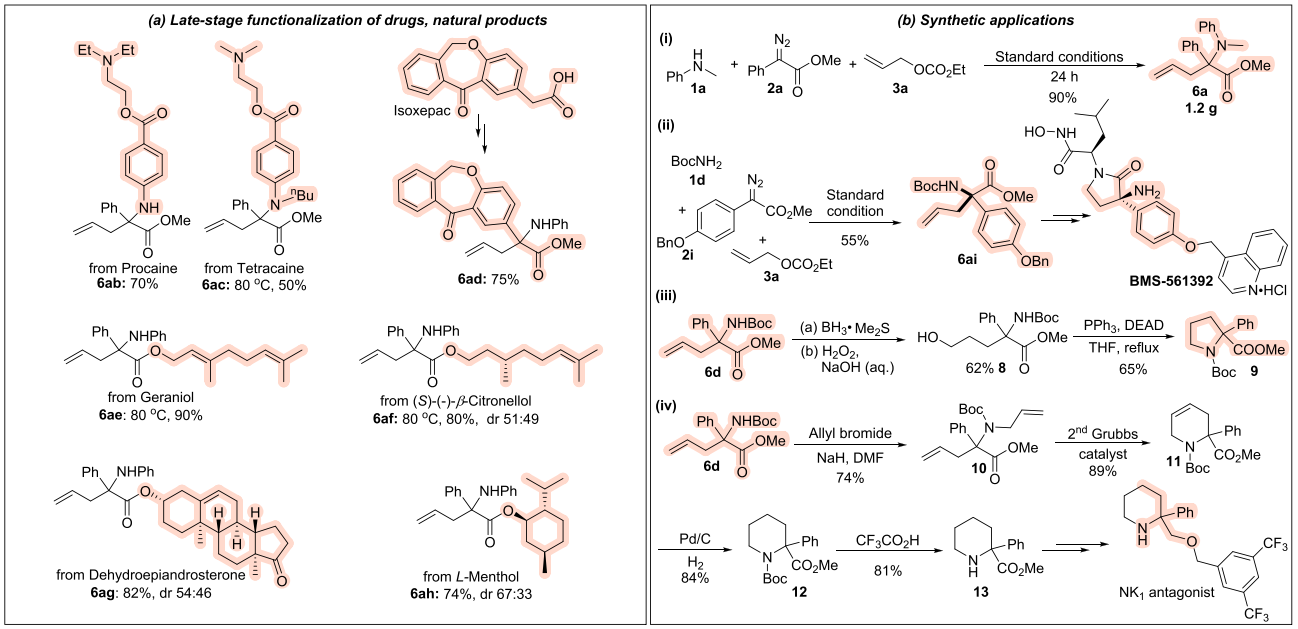
Scheme 3. Substrate Scope of Amines (a), Diazo Compounds (b), and Allylic Compounds (c)[a]



[a]Reaction conditions: the mixture of **1** (0.25 mmol), **2** (0.40 mmol), **3** (0.35 mmol), $Rh_2(Oct)_4$ (1.0 mol%), Xantphos (1.5 mol%), and Cs_2CO_3 (150 mol%) in CH_3CN (2.0 mL) was stirred at room temperature for 9.0 h. Isolated yields of the products are reported. [b]The isolated yields of the reactions in the absence of Xantphos are presented in parentheses in (c).

Scheme 4. Late-Stage Functionalization of Complex Architectures (a) and Synthetic Applications (b)



relative lower yield (**6s**, 55%), probably due to the large steric hindrance of the ester moiety. Diazo compounds with either electron-withdrawing (F-, Cl-, Br-) or electron-donating (MeO-, BnO-) groups on the aryl group performed well affording the corresponding products smoothly in moderate to excellent yields (**6t**–**6y**, 47%–90%). The thienyl motif in diazo ester was also tolerated very well, giving the corresponding product **6z** in 89% yield. Next, allylic substrates **3** bearing various leaving groups were investigated in the reactions with aniline (**1e**) and α-diazo ester **2a** (Scheme 3c). All the tested allylic alcohol esters **3b**–**3f** and allylic chloride **3g** performed well in this reaction, providing the product **6e** in moderate to good yields (53%–85%). It is noteworthy that, in the absence of Xantphos, the reactions gave only a trace amount of product **6e** in these cases, with isolation of the N–H insertion product as the major product instead, thus highlighting the unique effect of the ligand in the allylic alkylation again. When allyl halides **3h** and **3i** were used in the reaction, the product **6e** was obtained in moderate yields with or without Xantphos, along with some allylic amination product, which might be due to

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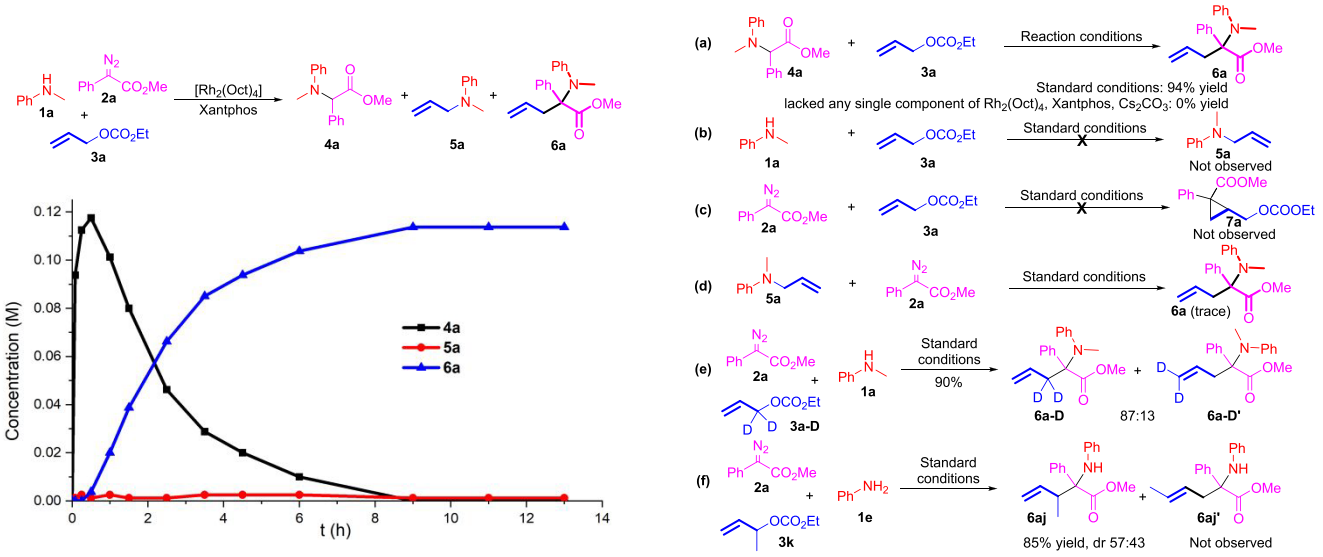
Scheme 5. Reaction Profiles of the Three-Component Reaction (Left) and Controlled Experiments (Right, a–f)



their relatively higher electrophilicities. For 2-methyl-substituted substrate **3j**, the reaction gave the desired product **6aa** in only 25% yield, probably caused by the large steric hindrance effect.

To show the applicability of the methodology developed herein, the transformations using natural products, pharmaceuticals, or their derivatives as the reaction partners for the three-component process were carried out. Notably, two interesting drugs with free NH groups (procaine and tetracaine) could be directly applied as the amine sources in this three-component reaction with **2a** and **3a**, generating quaternary α-amino acid derivatives **6ab** and **6ac** smoothly in good yields (Scheme 4a, 70% and 50%, respectively). Moreover, α-diazo esters derived from isoxepac, worked smoothly in this MCR with **1e** and **3a**, successfully introducing synthetically important allylic and amine groups into the α position of the acid derivative (**6ad**, 75% yield). Additionally, a series of alcohols, such as geraniol, (*S*)-(−)-β-citronellol, dehydroepiandrosterone, and L-menthol, can be readily transformed into the corresponding α-diazo esters, which were subjected to the reactions with **1e** and **3a**. To our delight, all the catalytic reactions proceed smoothly to afford **6ae**–**6ah** in moderate to good yields (74%–90%), showing good functional group compatibility with ketone and olefins. All these results indicated that this approach opens new opportunities for direct late-stage functionalization of some drugs and natural products, which may assist new drug discovery in future.

The synthetic utility of this approach was further demonstrated in the reactions shown in Scheme 4b. Gram-scale reaction of **1a**, **2a**, and **3a** proceeded smoothly with little decrease in efficiency (Scheme 4b-i). The reaction of **1d** and **3a** with **2i** gave the desired product **6ai** in 55% yield, which has been utilized as the key intermediate for the synthesis of BMS-561392, a tumor necrosis factor-α converting enzyme inhibitor (Scheme 4b-ii).[17] 2,2-Disubstituted pyrrolidines and piperidines having at least one aryl substituent represent an important series of pharmaceutically relevant molecules.[18] Starting from the product **6d**, α-phenylproline derivative **9** was conveniently synthesized through hydroboration–oxidation of the double bond and Mitsunobu reaction (Scheme 4b-iii, 40% overall yield for two steps). In addition, treatment of **6d** with allylic bromide smoothly furnished the compound **10** in 74% yield, which then underwent a ring-closing metathesis reaction and a Pd/C-catalyzed hydrogenation to afford the piperidine derivative **12** (75% yield for two steps). Finally, the deprotection of *N*-Boc of **12** delivered the key intermediate **13** in 81% yield, which could be transformed to NK_1 receptor antagonist (Scheme 4b-iv).[18a]

2.3. Mechanistic Studies. As shown in Scheme 5, the kinetic profiles of this reaction under the standard conditions clearly indicated that carbene insertion product **4a** was generated in the first 5 min and further converted to the final product **6a**. Additionally, the reaction of **1a** with **2a** and **3a** in CD_3CN was monitored by ^1H NMR spectroscopy, and the results further identified the real intermediate to be **4a** rather than metal-dissociated free ylide (for details, see the SI). Moreover, treatment of **4a** with the allylic substrate **3a** under the standard conditions indeed gave the final product **6a** in a remarkably high yield. However, no **6a** was observed in the absence of any single component of $Rh_2(Oct)_4$, Xantphos or Cs_2CO_3 (94% vs 0%, Scheme 5a). These results above suggested a relay carbene-induced N–H insertion and [Rh_2]/Xantphos-catalyzed allylic alkylation process, which is different from the well-known binuclear Rh(II)-catalyzed MCRs, wherein a mechanism involving an oxonium ylide generated *in situ* and trapped by the third component directly.[4] Notably, neither the allylic amination nor cyclopropanation reaction was favorable when **3a** was treated with **1a** or **2a** under the standard conditions (Scheme 5b,c, respectively), which could be the key factors for the success of the titled three-component reaction. Additionally, Xantphos remained unchanged in the presence of diazo compound **2a** in CH_3CN, suggesting the phosphine-azine compound is not likely involved in this multicomponent reaction (for details, see the SI).[19] Furthermore, the reaction between allylic amination product **5a** and α-diazo ester **2a** only gave trace amount of product **6a**, indicating the [2,3]-sigmatropic rearrangement is unlikely to be responsible for the formation of the target product (Scheme 5d).[3d,20] To further understand the allylic substitution process, deuterated allylic substrate **3a-D** was treated in the reaction and two products **6a-D** and **6a-D′** were observed in 87:13 ratio

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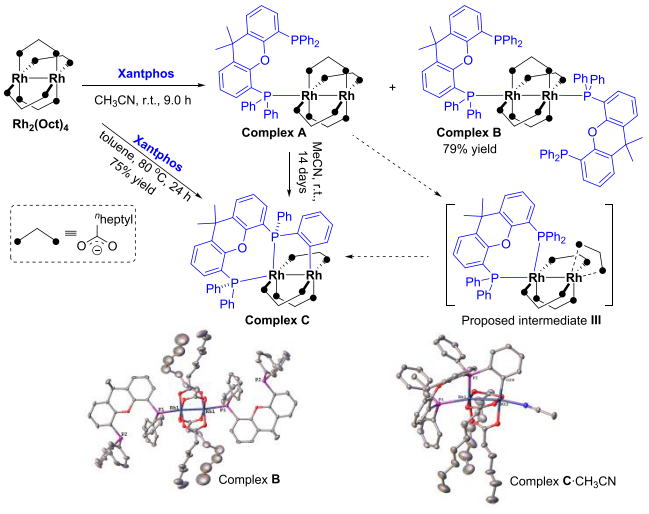
(Scheme 5e).[10a] Furthermore, the reaction of substrate **3k** only gave the branched product **6aj**, suggesting the mechanism that insertion of C═C bond followed by the β-oxygen elimination of **3k** is unlikely to be involved in the reaction (Scheme 5f). Both the results in Scheme 5e,f provided evidence in supporting the intermediacy of a σ-bound allylic rhodium complex, which is consistent with the general rhodium-catalyzed allylic substitution.[10]

It is well known that mono-rhodium complexes can catalyze allylic substitution reactions.[10,11b−k] In contrast, only one example regarding dirhodium(II) was reported by Tsuji's group in 1984, in which $Rh_2(OAc)_4$ together with $^nBu_3P$ was used as catalyst for allylic alkylation (at 65 °C).[11a] To investigate the possibility for the generation of monomeric Rh(I) and/or Rh(III) species in the catalytic reaction conditions,[2a,d,16] a mixture of $Rh_2(Oct)_4$, Xantphos, and Cs_2CO_3 was stirred at room temperature in CH_3CN for 9.0 h. However, the ^{31}P NMR signal corresponding to Rh(I) or Rh(III)/Xantphos was not observed in the reaction mixtures. Notably, a single peak at −22.7 ppm and a doublet of doublets which might be due to coupling to $^{103}Rh_1-^{103}Rh_2$ at −36.0 ppm (J = 93.7, 30.8 Hz) were observed at 9.0 h, and the other two doublet of doublets at 2.5 ppm (J = 140.9, 5.7 Hz) and −57.0 ppm (J = 79.4, 67.4 Hz) appeared after prolonging the time to 4 days, indicating that some novel rhodium complexes formed between [Rh_2] and Xantphos along with the time (Figure S9 in the SI). Additionally, mono Rh/Xantphos and [Rh_2]/Xantphos show significantly different activity in allylic amination of **1a** and **3a**, suggesting it is unlikely to form mono Rh species from [Rh_2]/Xantphos under the standard conditions. Taking these factors into consideration, the binuclear Rh−Rh core structure is mostly likely retained in the reaction process, though the formation of a trace amount of mono-Rh species below the detection limit cannot be totally ruled out.

Although the isolation of the key Rh_2-allylic complex intermediate from the reaction of $Rh_2(Oct)_4$, Xantphos and various allylic substrates failed, some evidence of the interaction between [Rh_2] and Xantphos ligand was observed. As shown in Scheme 6, the combination of $Rh_2(Oct)_4$ (1.0 equiv) and Xantphos (1.5 equiv) in CH_3CN under room temperature for 9.0 h led to an orange slurry, in which two new

Scheme 6. Synthesis of the [Rh_2]/Xantphos Complexes



[Rh_2] complexes (**A** and **B**) were formed. (Note: Complexes **A** and **B** can be formed within 5.0 min; for details, see the SI.) By simple filtration, a purple filtrate containing complex **A** and an orange filter residue (Complex **B**, 79% yield) were obtained. Concentration of the filtrate mainly afforded mono-Xantphos-coordinated complex **A**, $Rh_2(Oct)_4$(Xantphos), which was characterized by NMR and MS techniques, and its ^{31}P NMR spectrum is consistent with the new signals that appeared in Figure S9a (for details, see the SI). Complex **B** was characterized as $Rh_2(Oct)_4(Xantphos)_2$ by single-crystal X-ray analysis. The structure of **B** shows that it is an axially ligated dirhodium(II) complex coordinated by two phosphorus atoms from two Xantphos ligands, each capping a Rh center with one of its PPh_2 moieties, while the other P is left free. The Rh−Rh bond length (2.453 Å) is longer than $Rh_2(OAc)_4(H_2O)_2$(2.385 Å), probably due to the strongly σ-donating nature of the axially ligating P atoms.[21] The Rh−Rh−P angle is 176.5°, which is 3.5° deviated from linearity. Additionally, the Rh−P distance (2.498 Å) is longer than that in the complex of $Rh_2(OAc)_4(PPh_3)_2$ (2.477 Å),[21a,d] which might be caused by the larger steric hindrance of Xantphos. Interestingly, slow evaporation of the purple solution of **A** in CH_3CN at room temperature for 2 weeks gave dark green crystals (complex **C**·CH_3CN, $Rh_2(Oct)_3(PPC)\cdot CH_3CN$). X-ray diffraction showed that the two Rh atoms are bridged by three carboxylate groups and by one molecule of Xantphos, where metalation has occurred at one of the phenyl rings of PPh_2 moiety. In this complex, Xantphos ligand acts as a P,P,C tridentate ligand, which means that one P atom bonds to the axial position of the Rh−Rh, while the other P atom and orthometalated phenyl group bond to the two Rh atoms respectively, replacing one of the original bridging (Oct) anions. The Rh−Rh bond length of complex **C**·CH_3CN (2.480 Å) is slightly longer than that of complex **B** (2.453 Å). The Rh−Rh−P angle is 167.7°, which is 12.3° deviated from linearity, completing the slightly distorted octahedral coordination around the metal atom. The P−Rh distance (2.548 Å) at axial position is longer than that in complex **B**, which might be caused by the rigid structure. It should be noted that structural chemistry of $Rh_2(O_2CR)_{4-x}(PC)_x$ (x = 1 or 2, wherein PC = $(C_6H_5)_2P(C_6H_4)$), have been well studied since their first synthesis reported by Cotton et al. in 1985.[22,23] Complex **C** can also be obtained in 75% yield from the reaction of $Rh_2(Oct)_4$ with Xantphos in toluene at 80 °C for 24 h, and its ^{31}P NMR spectrum is consistent with the new signals that appear in Figure S9b. The formation of complex **C** from complex **A** is probably caused by the release of an octanoate anion and the coordination of the second P atom to Rh to form intermediate **III**, followed by the subsequent metalation of the phenyl group.[23c,d] In this vein, a similar dirhodium(II) complex with a chelating *N*,*N*-ligand (2,2′-bipyridine) binding to one of the Rh(II) atoms and three bridging OAc^- groups has been reported in 1991,[24] further supporting that it is reasonable to propose the intermediate **III** wherein one metal center of the dirhodium core is chelated by the Xantphos ligand.

To this end, a parallel comparison of their catalytic performance of complexes **A**, **B** and **C** in the allylic alkylation of **3a** with **4a** was carried out by following the kinetic profiles of the reaction process (Figure 1). It was found that all three catalytic systems (complexes **A** and **B** and the *in situ* generated catalyst from $Rh_2(Oct)_4$ with Xantphos) resulted in the same reaction profiles, suggesting that a common active species

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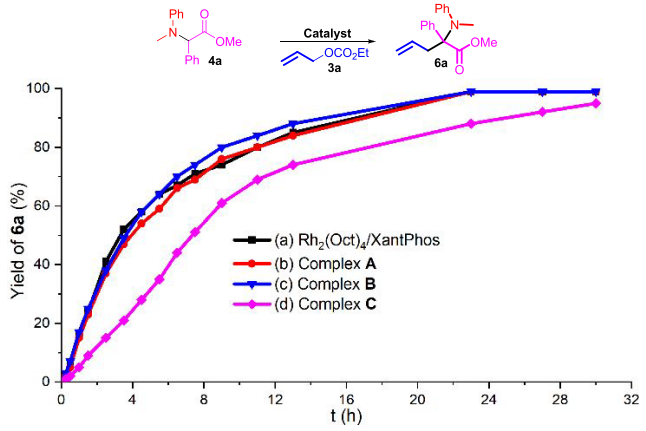
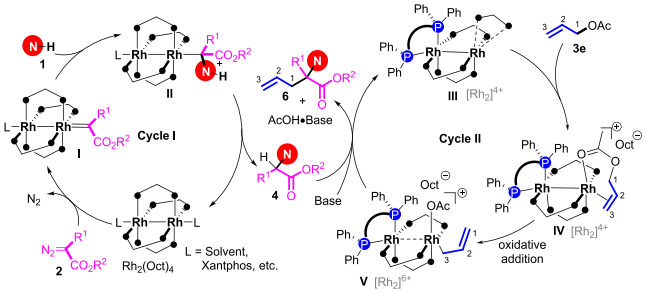


Figure 1. Reaction profiles of the two-component reactions. Reaction conditions: **3a** (0.70 mmol), **4a** (0.50 mmol), Cs_2CO_3 (150 mol%), r.t., CH_3CN (4.0 mL) as the solvent, Rh catalyst: (a) $Rh_2(Oct)_4$ (1.0 mol%), Xantphos (1.5 mol%), (b) complex **A** (1.0 mol%), (c) complex **B** (1.0 mol%), and (d) complex **C** (1.0 mol%).

might operate the catalytic system. However, the reaction using complex **C** as the catalyst precursor showed slower reaction rate, suggesting the partial transformation of complex **C** to active species might occur, which may also be in equilibrium with complex **A** or **B**. It is also possible that complex **C** acts as a less efficient active species, although the exact role of **C** is still unclear.

Although the exact mechanism of the reaction is still not clear, a tentative mechanism for this relay catalysis is proposed in Scheme 7 based on the results herein and previous studies.[4]

Scheme 7. Proposed Mechanism



Both the phosphine-free and Xantphos-coordinated $[Rh(II)_2]$ can catalyze carbene insertion reaction, affording the intermediate **4** (Cycle I). Considering the fact that bidentate phosphine-Xantphos is essential for the allylic alkylation step (Scheme 5a), whereas almost no **6a** but only **4a** was observed in this dirhodium-catalyzed MCRs using monophosphine ligand (such as PPh_3 and $^tBu_3P$; Table 1, entries 6 and 7), $[Rh_2]$ complex with a monodentate-coordinated Xantphos is unlikely to be responsible for the allylic alkylation. Additionally, a tridentate (P,P,C)-coordinated complex **C** has also been demonstrated less effective for the allylic alkylation. Thus, complex **III** bearing a chelate-coordinated Xantphos is proposed as the active species that can initiate the following allylic alkylation of intermediate **4** (Cycle II). It is notable that though the combination of a dirhodium(II) complex with a sophisticated ligand has led to some novel and attractive catalytic transformations, to thoroughly investigate and fully understand the origins of the novel catalytic activities still remain a challenge.[25,26] It is known that binuclear species can undergo bimetallic oxidative addition to activate small molecules, as a result of the beneficial electronic communication between the two metals.[27] For the dirhodium complexes, the $[Rh_2]^{4+}$ core can also undergo an oxidation process to generate $[Rh_2]^{6+}$ species under some oxidative conditions,[26f,27b,28] suggesting that the oxidative addition of $[Rh_2]^{4+}$/Xantphos with allylic substrate to form $[Rh_2]^{6+}$/Xantphos/allylic complex is possible. In this work, it can be expected that the electron density at $[Rh_2]^{4+}$ core is increased by the chelating σ-donation of Xantphos to one of the Rh atoms through the electronic communication between the two Rh atoms.[29,30] As a result, the $[Rh(II)_2]$ moiety of intermediate **III** is more susceptible to oxidation addition of allylic substrate **3** (in other words, nucleophilic attack of $[Rh(II)_2]$ core to electrophilic allylic substrate) as compared with the phosphine-free or mono-phosphine-coordinated $Rh_2(Oct)_4$.[10] Xantphos turns out to be the best ligand to bidentate coordinate with the $[Rh(II)_2]$ core and promote the oxidative addition to form the $[Rh_2]$-allylic intermediate, while labilizing one of the bridging carboxylate ligands to facilitate substrate coordination. Taking all the factors above together, it was tempting to tentatively propose that Xantphos-$[Rh]_2$ **III** undergo oxidative addition with allylic substrate to form a possible $[Rh_2]^{6+}$ allylic intermediate **V** via substrate-ligated **IV**. Subsequent nucleophilic attack by **4** takes place with the assistance of a base to give the final product **6** and regenerates the intermediate **III** (Scheme 7, Cycle II). It is also possible that CH_3CN coordinates to some dirhodium intermediates in the catalytic cycle. Due to the electronic communication between the two Rh atoms, the whole $[Rh_2]$ core can be considered as one catalytically active site in the $[Rh_2]$/Xantphos-catalyzed allylic alkylation process. For ease of understanding, it can also be considered that the allylic alkylation happens at one of the Rh atoms while the other Rh atom with the bound Xantphos plays a role in catalysis through electronic communication, which is similar to some mechanistic proposals for bimetallic-catalyzed reactions in the literature.[30a−h,31]

3. SUMMARY AND CONCLUSIONS

In summary, we have developed a Xantphos-enabled, Rh(II)-catalyzed, efficient and versatile three-component reaction of amines, diazo compounds, and allylic compounds, affording various architecturally complex and functionally diverse α-quaternary α-amino acid derivatives in good to excellent yields with high atom and step economy. Mechanistic studies indicate that the catalytic properties of the dirhodium carboxylate are tuned by the coordination with Xantphos, resulting in novel reactivity of dirhodium in catalytic allylic alkylation. As the dirhodium complex can be modified with additional ligands, further development of this catalytic system into asymmetric reactions and efforts to elucidate the reaction mechanism in more details are under way in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c05701.

Experimental procedures, complete characterization data, and NMR spectra (PDF)

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Accession Codes

CCDC 2050251−2050253 and 2050272 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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