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Ruthenium(II)-Catalyzed Regioselective Reductive Coupling of α-Imino Esters with Dienes

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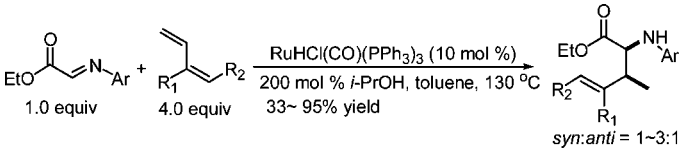
ABSTRACT



A method for the highly regioselective reductive coupling reaction of *N*-aryl-α-imino esters with dienes is described. The method utilizes the $RuHCl(CO)(PPh_3)_3$/*i*PrOH catalytic system under an Ar atmosphere and provides α-branched allylic α-amino acid derivatives. Application of this transformation to the concise synthesis of a natural plant growth regulator is demonstrated.

Transition-metal-catalyzed regioselective reductive coupling of two organic π-bond containing molecules provides very powerful methods available for the construction of C−C bonds. The direct catalyzed reductive coupling of alkyne/alkyne,[1] alkene/alkyne,[2] alkene/alkene,[3] diene/carbonyl (via an alcohol),[4] allene/carbonyl,[5] alkyne/carbonyl,[6] and enyne/carbonyl[7] partners have been widely explored. Recently, the coupling of activated alkene/imine couples[8] catalyzed by metal complexes or organic small molecules has attracted particular attention because this

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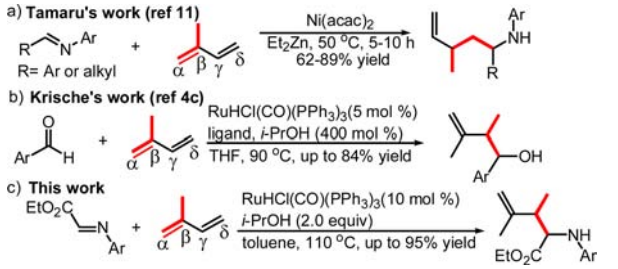
type of transformation can result in the formation of more valuable nitrogen-containing compounds including aza-heterocycles, but most olefin substrates were limited to functionalized α,β-unsaturated carbonyl compounds,[8a−h] enol derivatives,[8i] and allylboranes[8j] or allylsilanes.[8k] In comparison, the use of an unactivated olefin as one of the π-coupling partners is highly uncommon possibly due to its poor reaction activity.[9] Additionally, unactivated olefins easily react with *N*-aryl imines to produce heterocycles via aza-Diels−Alder cyclization[10] instead of linear coupling. Nevertheless, Tamaru reported that Ni(0)-catalyzed reductive coupling of unfunctionalized dienes with aldimines using Et_2Zn as a reductant and this transformation could realize the homoallylation of aldimines in which a C−C bond was formed between the α-carbon atom of the alkene and the aldimine carbon atom (Scheme 1a).[11] Moreover, Krische also reported that Ru(II)-catalyzed reductive coupling of dienes with aldehydes could furnish homoallyl alcohols in which a C−C bond formation occurs highly regioselectively at the γ-carbon atom of dienes (Scheme 1b).[4c]

Scheme 1. Transition-Metal-Catalyzed Reductive Coupling of Imine or Aldehyde/Diene



On the other hand, α-imino esters have served as versatile acceptors of nucleophiles, and their corresponding addition reaction with organometallic reagents, Mannich donors, etc. provided a concise synthetic approach to α-amino acid derivatives.[12] Our research interests in exploring methods for the rapid assembly of α-substituted α-amino acid derivatives[13] prompted us to investigate the direct coupling reaction of olefins with α-imino esters. Herein, we disclose the first Ru(II)-catalyzed diene/iminoester reductive coupling reaction to give various γ, δ-unsaturated α-amino acid derivatives in which a C−C bond formation occurs highly regioselectively at the γ-carbon atom of dienes (Scheme 1b). Most of the products described in this report are α-branched allyl substituted α-amino acid derivatives, and their corresponding derivatives could be further used as fundamental building blocks in many pharmacologically active molecules such as Cyclomarin A[14] and antimalarial lipopeptides.[12b] The previous synthesis of α-branched allylic α-amino acid derivatives generally suffers from tedious reaction steps and harsh reaction conditions.[12b,14,15]

The Ru(II)-catalyzed reductive coupling of iminoester **1a** (0.20 mmol) with isoprene **2a** (0.80 mmol) was first investigated using $RuH_2(CO)(PPh_3)_2$ (10 mol %) as the catalyst in toluene (3.0 mL) at 130 °C for 24 h, and we quickly found that this transformation could provide a 12% yield of a branched-chain α-amino acid derivative (**3a**) in the absence of any additives (Table 1, entry 1). Considering the Ni-catalyzed homoallylation of aldimines with dienes is involved in the hydrogen-transfer process in the presence of Et_2Zn,[11] we tried to conduct this reaction further to screen various hydrogen sources to achieve satisfying yields (entries 2−6). To our delight, *i*-PrOH could afford **3a** in 70% yield (entry 6). Then, we investigated the effect of various Ru salts on the reductive coupling reaction. Among the tested Ru catalysts (entries 6−11), Ru-hydride catalysts were effective catalysts for this transformation, and $RuHCl(CO)(PPh_3)_3$ provided **3a** in up to 90% isolated yield (compare entries 6 and 11). However, other nonhydride ruthenium catalysts such as $RuCl_3$ gave trace amounts of **3a** (entries 7 and 9). Finally, we also investigated other reaction conditions to define the reaction parameters and found that variation of the catalyst loading (entry 12) and lower reaction temperature (entry 13) all resulted in poorer yields (see Supporting Information for more details).

Having established an efficient reaction protocol that enables the smooth reductive coupling transformation of particular isoprene, we next investigated its scope with regard to the *N*-aryl iminoester coupling partner. As shown in Table 2, aryl substitution on the imine nitrogen (R_1) showed no deleterious electronic effects, and the substrates with a *para*-electron donating group (4-MeO, 4-Me) or electron withdrawing group (such as 4-Cl, 4-Br, 4-NO_2, 3-CO_2Et) on the phenyl ring afforded the α-branched-chain allyl-α-amino acid derivatives in good to excellent yields (54−90%, entry 1). It is worth noting that the nitro-group-containing α-imino ester (**1g**) also gave a 17% yield of the unexpected product **3g-2** in which a C−C bond was formed between the β-carbon atom of isoprene and the imine carbon atom (entry 1). Compared with the *N*-phenyl imino ester (**1c**), *N*-(1-naphthyl)-α-iminoester (**1h**) underwent a slightly worse conversion and provided a moderate yield of **3h** (50%, entry 2) possibly due to the higher steric hindrance around the

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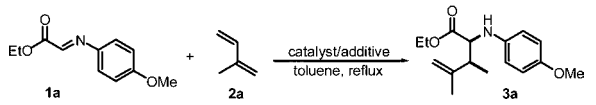
Table 1. Optimization Results for Ru-Catalyzed Reductive Coupling Reaction of **1a** with **2a**[a]



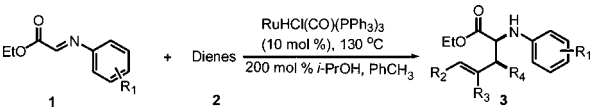
entry	catalysts	additive	yield (%)[b]
1	$RuH_2(CO)(PPh_3)_2$	–	12
2	$RuH_2(CO)(PPh_3)_2$	HCO_2H/Et_3N	16
3	$RuH_2(CO)(PPh_3)_2$	CH_3OH	21
4	$RuH_2(CO)(PPh_3)_2$	Et_3B	36[c]
5	$RuH_2(CO)(PPh_3)_2$	Et_2Zn	<5[d]
6	$RuH_2(CO)(PPh_3)_2$	*i*-PrOH	70
7	$RuCl_3$	*i*-PrOH	trace
8	$RuH_2(PPh_3)_4$	*i*-PrOH	8
9	$Ru_3(CO)_{12}$	*i*-PrOH	trace
10	$RuHCl(PPh_3)_3PhCH_3$	*i*-PrOH	47
11	$RuHCl(CO)(PPh_3)_3$	*i*-PrOH	90
12	$RuHCl(CO)(PPh_3)_3$	*i*-PrOH	76[e]
13	$RuHCl(CO)(PPh_3)_3$	*i*-PrOH	83[f]

[a] Unless otherwise noted, all the reactions were run with **1a** (0.2 mmol), **2a** (0.8 mmol), additive (0.4 mmol), catalyst (10 mol %), toluene (3.0 mL) under Ar in a sealed pressure tube at 130 °C for 24 h, followed by flash chromatography on SiO_2. [b] Isolated yield, and the ratio of cis/trans is 2.5:1. [c] We also got the byproduct 2-(4-methoxyphenylamino)-butyric acid ethyl ester (**3ab**) in 8% yield. [d] The major product is **3ab** (42% yield). [e] 5 mol % of catalyst used. [f] Carried out at 110 °C.

C=N bond. In addition, *N*-(3-pyridyl)-α-iminoester (**1i**) was also a suitable substrate for this transformation and provided a 56% yield of the desired product **3i** (entry 3). Moreover, the scope of the procedure with regard to the diene coupling partner was then explored with *N*-(4-methoxylphenyl)-α-iminoester as the carbon electrophile. Except for the fact that *s-cis*-1,3-hexadiene **2g** afforded the *β*,*γ*-unsaturated α-amino acid derivative **3n** (entry 8), most of the 1,3-dienes reacted regioselectively at the *γ*-carbon atom of diene and provided the desired products with good yields (entries 4−6, 9, and 11). Cyclohexadiene **2e** showed low reactivity, and an almost 45% yield of α-iminoester was recovered even after 48 h (entry 6). It is interesting that the nonconjugated 1,5-diene **2f** could also be used in this transformation and gave the corresponding desired product **3m** possibly due to the fact that the ruthenium hydride catalyst can induce double bond isomerization and migration (entry 7). Unfortunately, no reaction occurred for the terminal disubstituted alkene **2i**, and α-iminoester **1a** was completely recovered (entry 10). Finally, we separated and obtained two pure diastereoisomers of **3g-1**; the structure of one isomer which was determined by means of the X-ray crystallographic analysis indicated that 1,2-*syn*-**3g-1** belongs to the major product (see Supporting Information for more details).[16]

(16) The major isomer 1,2-*syn*-**3g-1** was determined by X-ray single crystal structure. Assuming an analogous reaction mechanism, the corresponding diastereoselectivity ratio (*syn*/*anti*) of other α-amino acid derivatives was assigned as indicated in Table 2.

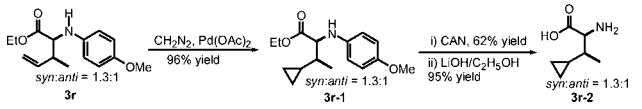
Table 2. Ru-Catalyzed Reductive Coupling Reaction of *C*-Acylimines with Various Dienes



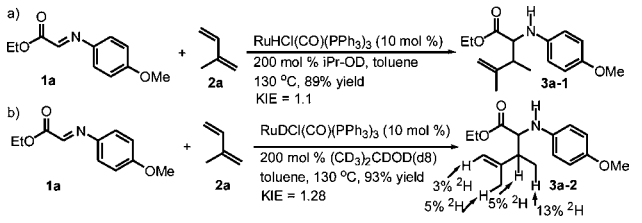
entry	C-acylimines	dienes	yield (%)[b] [ratio][c]
1	**1a**, R_1 = *p*-MeO **1b**, R_1 = *p*-Me **1c**, R_1 = *p*-H **1d**, R_1 = *p*-Cl **1e**, R_1 = *p*-Br **1f**, R_1 = *m*-CO_2Et **1g**, R_1 = *p*-NO_2	**2a**	**3a** 90 [2.5:1] **3b** 87 [2.3:1] **3c** 74 [2.0:1] **3d** 73 [2.4:1] **3e** 83 [1.4:1] **3f** 89 [1.5:1] **3g-1** 54 [2.1:1] **3g-2**: 17
2	**1h**	**2a**	**3h** 50 [1.7:1]
3	**1i**	**2a**	**3i** 56 [1.5:1]
4	**1a**	**2b**	**3j** 77 [1.7:1]
5	**1f**	**2c**	**3k**[17, d] 62 [1.1:1]
6	**1a**	**2e**	**3l**[e] 33 [1.0:1]
7	**1a**	**2f**	**3m**[c] 59 [1.4:1]
8	**1a**	**2g**	**3n** 65 [1.4:1]
9	**1a**	**2h**	**3o** 48 [1.5:1]
10	**1a**	**2i**	**3p** 0
11	**1a**	**2j**, R = Ph **2k**, R = H	**3q** 83 [3.0:1] **3r** 95 [1.3:1]

[a] Unless otherwise noted, all the reactions were run with **1** (0.20 mmol), **2** (0.80 mmol), IPA (0.4 mmol), catalyst (10 mol %), solvent (3.0 mL) under Ar in a sealed pressure tube at 130 °C for 24 h, followed by flash chromatography on SiO_2. [b] The overall yield of the diastereomeric mixture. [c] Ratio of *syn*/*anti*. [d] Carried out at 110 °C. [e] The reaction was carried out using 20 mol % of $RuHCl(CO)(PPh_3)_3$ for 48 h.

Scheme 2. Synthetic Application of This Transformation



Scheme 3. Ru(II)-Catalyzed Reductive Coupling of Diene/*N*-Aryl-α-Iminoesters under Deuterio-Catalytic System[19]



An illustration of the utility of this reaction is shown in the concise synthesis of racemic 2-amino-3-cyclopropylbutanoic acid (**3r-2**) which is a novel plant growth regulator isolated from the mushroom *Amanita castanopsidis* Hongo[18] (Scheme 2). Cyclopropanation of **3r** occurred upon treatment with diazomethane in the presence of $Pd(OAc)_2$ (10 mol %) to provide the N-protected amino acid precusor **3r-1** in 96% yield, and the following CAN deprotection reaction and hydrolysis of **3r-1** furnished the ethyl 2-amino-3-cyclopropylbutanoate and racemic natural product (**3r-2**) in 62% and 95% yield, respectively. This procedure was accomplished in just three steps with an overall 57% yield from readily available **3r**.

The kinetic isotope effects of Ru(II)-catalyzed reductive coupling of **1a** with **2a** were readily obtained using the deuterium-labeled $RuHCl(CO)(PPh_3)_3$/*i*PrOD (RuHD) (κ_H/κ_D = 1.10) (Scheme 3a) and $RuDCl(CO)(PPh_3)_3$/*i*PrOH-d8 (RuDD) (κ_H/κ_D = 1.28) (Scheme 3b) system, respectively, and no significant isotopic effect was observed. The RuDD system provided deuterio-**3a-2** in which deuteriums were incorporated at the allylic methyl (^{2}H 5%), the allylic methine (^{2}H 5%), and the homoallylic methyl (^{2}H 13%). This pattern of deuterium incorporation likely resulted from reversible and regio-promiscuous hydrometalation of isoprene.

(17) The desired product from the reductive coupling of **1a** with **2c** could be detected by GC-MS, but it could not be purified even using preparative HPLC.

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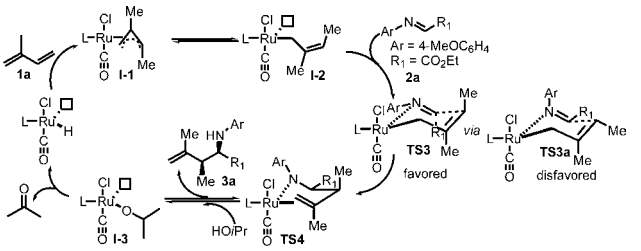
Scheme 4. Proposed Mechanism for the Transformation



The above-mentioned deuterium labeling experimental results illustrate that addition of a ruthenium hydride to **1a** gives π-allylruthenium complex **I-1**,[20] and the resulting complex **I-1** subsequently isomerizes to the more stable primary σ-allyl haptomer **I-2** (Scheme 4).[20] Then **I-2** reacts with an α-imino ester via a six-membered transition state **TS3** to furnish **3a** upon nucleophilic allylation and protonation; this process is similar to the reductive coupling of diene/aldehyde proposed by Krische.[4d] The corresponding diastereoselective outcome of this transformation may be explained on the basis of the indicated **TS3** and **TS3a** model. Finally, the alkoxy ruthenium intermediate **TS4** results in the formation of the RuH species via β-hydride elimination of **I-3** along with liberation of acetone, hence accomplishing the Ru(II) catalytic cycle.

In conclusion, we have developed the first Ru(II)-catalyzed reductive coupling of *N*-aryl-α-imino esters with dienes in which a C−C bond was formed regioselectively between the γ-carbon atom of dienes and the imine carbon atom. This method provides an efficient approach to access γ,δ-unsaturated α-amino acid derivatives upon removal of the *N*-(4-methoxy) phenyl group. The concise synthesis of a natural plant growth regulator was accomplished to demonstrate the utility of the method. Further studies on Ru-catalyzed asymmetric reductive coupling of this transformation are currently underway in our laboratory.

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Supporting Information Available. Details for experimental conditions, characterization data, copies of ^{1}H and ^{13}C NMR spectra for all isolated compounds, and crystallographic data for 1,2-*syn*-**3g-1** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.