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Cascade C−H Functionalization/Amidation Reaction for Synthesis of Azepinone Derivatives

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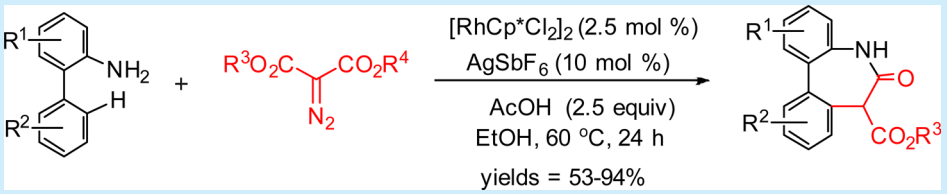
Supporting Information



ABSTRACT: A cascade C−H functionalization/amidation reaction of aminobiaryls with diazomalonates has been developed under rhodium catalysis, affording new azepinone derivatives in moderate to excellent yields.

Currently, nitrogen-containing group directed C−H functionalizations by transition-metal catalysis have emerged as a powerful and environmentally friendly strategy for the construction of C−C and C−hetero bonds.[1] Among the nitrogen-containing groups, amino groups are one of the best candidates for directing and assisting C−H functionalizations, such as amino groups without *N*-substituents (i.e. free amino groups),[2,5] with *N*-monosubstituents[3] and *N*-disubstituents.[4] In recent years, great attention has been paid to using 2-aminobiaryls as substrates to perform C(sp^2)−H functionalization for efficient synthesis of fused heterocycles and coupling products.[5] In 2012, Zhang et al. reported that biaryl-2-amines reacted with alkenes to give phenanthridines via their C(sp^2)−H functionalization under palladium catalysis.[5a] The following year, Zhu and co-workers developed a C(sp^2)−H aminocarbonylation of 2-aminobiaryls with CO for an efficient synthesis of phenanthridinones by palladium catalysis.[5b] In 2015, Luan et al. disclosed an oxidative annulation of 2-aminobiaryls with alkynes through C(sp^2)−H functionalization under palladium catalysis, affording dibenzo[*b*,*d*]azepines.[5c] To the best of our knowledge, there is no report on the C−H functionalization of 2-aminobiaryls with diazo compounds through cross-ring C(sp^2)−H activation directed by amino groups.

Recently, diazo compounds have been widely used in nitrogen-containing group directed C−H functionalization, such as benzamides,[6a,c] oximes,[6d,e] imines,[6f,g] *N*-heterocycles,[6h,i] hydrazines,[6j,k] *N*-oxides,[6l,m] secondary amines,[6d] and ammonium salts.[6n] However, to the best of our knowledge, free-amine directed C−H functionalization with diazo compounds remains unknown. Thus, we focused on the C−H functionalization of 2-aminobiaryls with diazomalonates through cross-ring C(sp^2)−H activation directed and assisted by amino groups. It can be further envisioned that the C(sp^2)−H functionalization followed by amidation can produce azepinone derivatives. Azepinones as seven-membered *N*-heterocycles are important structural motifs in many alkaloids, pharmaceuticals, and other bioactive molecules.[7] As we know, a cascade reaction combines two or more bond-forming reactions into one process and need not isolate intermediates. This type of reaction reduces resource consumption and environmental impact and has been widely used in the synthesis of natural products, pharmaceuticals, and other bioactive molecules.[8] In view of these points, we embarked on the investigation of a cascade C(sp^2)−H functionalization/amidation reaction of 2-aminobiaryls with diazomalonates for an efficient synthesis of azepinone derivatives.

Initially, 2-aminobiaryls **1a** and diazomalonate **2a** were chosen as model substrates to explore and optimize the cascade C−H functionalization/amidation reaction. When $[IrCp^*Cl_2]_2$ (2.5 mol %) and $AgSbF_6$ (10 mol %) were employed as a transition-metal catalytic system, and in the presence of AcOH in ethanol at 60 °C, the cascade C−H functionalization/amidation reaction was able to occur to give the desired azepinone derivative **3a**, albeit in low yield (entry 1, Table 1). However, use of $[RhCp^*Cl_2]_2$ instead of $[IrCp^*Cl_2]_2$ resulted in a remarkable increase of the yield of **3a** to 83% (entry 2, Table 1). When other silver salts, such as $AgNTf_2$ and AgOAc, were employed, only a trace amount of **3a** was obtained (entries 4−6, Table 1). In the absence of $[RhCp^*Cl_2]_2$ or $AgSbF_6$, no or a trace amount of **3a** was obtained, respectively. If AcOH was replaced with CsOAc, no desired reaction occurred, which suggests that proton may be very useful in the reaction (entries 7 and 8, Table 1; also see the SI). Using another solvent instead of ethanol, such as MeOH, DCE and CH_3CN, was not beneficial to the cascade reaction (entries 9−11, Table 1). The effect of temperature on this reaction was

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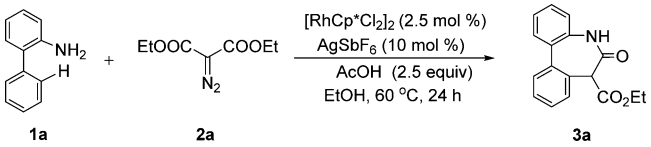
Table 1. Optimization of the Cascade C−H Functionalization/Amidation Reaction of 2-Aminobiaryl 1a with Diazomalonates 2a[a,b]



1a 2a 3a

entry	catalyst system	solvent	additive	yield[b] (%)
1	$[IrCp^*Cl_2]_2$/ $AgSbF_6$	EtOH	AcOH	19
2	**$[RhCp^*Cl_2]_2$/$AgSbF_6$**	**EtOH**	**AcOH**	**83**
3	−/$AgSbF_6$	EtOH	AcOH	0
4	$[RhCp^*Cl_2]_2$/ $AgNTf_2$	EtOH	AcOH	trace
5	$[RhCp^*Cl_2]_2$/ AgOAc	EtOH	AcOH	trace
6	$[RhCp^*Cl_2]_2$/−	EtOH	AcOH	trace
7	$[RhCp^*Cl_2]_2$/ $AgSbF_6$	EtOH	CsOAc	0
8	$[RhCp^*Cl_2]_2$/ $AgSbF_6$	EtOH	AcOH	0
9	$[RhCp^*Cl_2]_2$/ $AgSbF_6$	MeOH	AcOH	76
10	$[RhCp^*Cl_2]_2$/ $AgSbF_6$	DCE	AcOH	45
11	$[RhCp^*Cl_2]_2$/ $AgSbF_6$	CH_3CN	AcOH	42
12[c]	$[RhCp^*Cl_2]_2$/ $AgSbF_6$	EtOH	AcOH	22[c]
13[d]	$[RhCp^*Cl_2]_2$/ $AgSbF_6$	EtOH	AcOH	61[d]

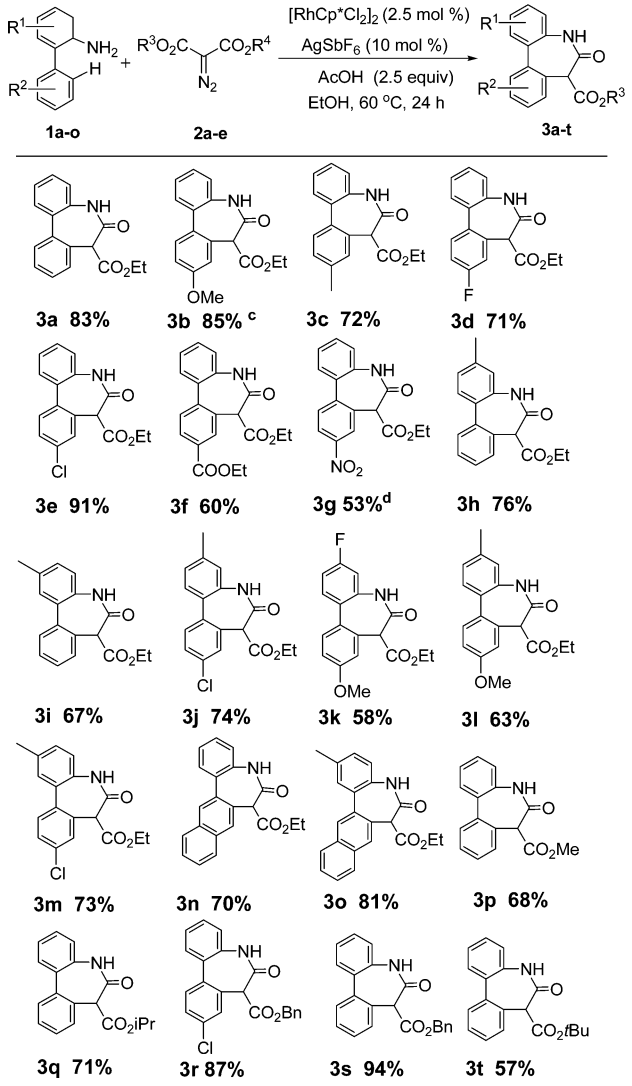
[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), additive (2 equiv), 60 °C, for 24 h. [b]Isolated yields. [c]30 °C. [d]100 °C.

also studied, and lower yields of **3a** were obtained when the temperature was elevated or reduced from 60 °C (compare entries 12 and 13 with entry 2, Table 1; also see the SI).

After the reaction conditions were optimized, it could be concluded that the cascade reaction should be performed under the catalysis of $[RhCp^*Cl_2]_2$ (2.5 mol %) and $AgSbF_6$ (10 mol %) in the presence of AcOH in ethanol at 60 °C. As shown in Scheme 1, various 2-aminobiaryls **1a−m** were able to undergo the cascade C−H functionalization/amidation reaction with diazomalonate **2a** expediently, affording desired azepinone derivatives **3a−m** in moderate to excellent yields under the optimized conditions. 2-Aminobiaryls bearing electron-donating groups **1b−c** on nonaniline rings resulted in the desired azepinone derivatives **3b,c**, and those bearing electron-withdrawing groups **1d−g** resulted in the azepinone derivatives **3d−g**. The structure of azepinone derivative **3e** was further determined by X-ray crystallography (Figure 1). The experimental results also indicated that functional groups on aniline rings in 2-aminobiaryls **1h−m** did not affect the cascade reaction, affording the corresponding azepinone derivatives **3h−m** in satisfactory yields. When 2-naphthylanilines were employed, amino groups in the aniline rings could also direct and assist the activation of C(sp^2)−H bonds in the naphthlene rings, affording the desired azepinone derivatives **3n,o** in good yields. Moreover, other symmetrical diazomalonates, such as dimethyl, diisopropyl and dibenzyl diazomalonates **2b−d**, also underwent the cascade reaction smoothly to afford the corresponding azepinone derivatives **3n−s** in good to excellent yields. As expected, when the unsymmetrical diazomalonate *tert*-butyl ethyl 2-diazomalonate **2e** was employed, the successive amidation in the cascade reaction occurred at the less bulky ethoxycarbonyl group and preserved the more bulky *tert*-butoxycarbonyl group in azepinone derivative **3t**.

Further experiments demonstrated that the C(sp^2)−H functionalization was also able to occur on some five-membered heteroaromatic rings through the direction and

Scheme 1. Cascade C−H Functionalization/Amidation Reaction of 2-Aminobiaryls 1 with Diazomalonates 2 for Azepinone Derivatives 3[a,b]



[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %), additive (2.5 equiv), 60 °C, for 24 h. [b]Isolated yields. [c]For 36 h. [d]80 °C, for 12 h.

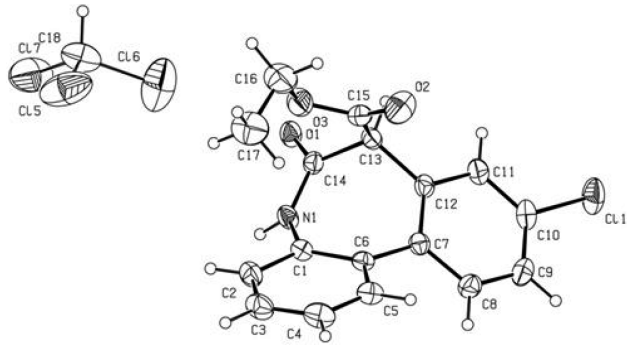


Figure 1. X-ray structure of azepinone derivative **3e**.

assistance of amino groups in benzene rings under optimized conditions. As shown in Scheme 2, 2-furylaniline **1u** and 2-thienylaniline **1v** performed the cascade/amidation reaction

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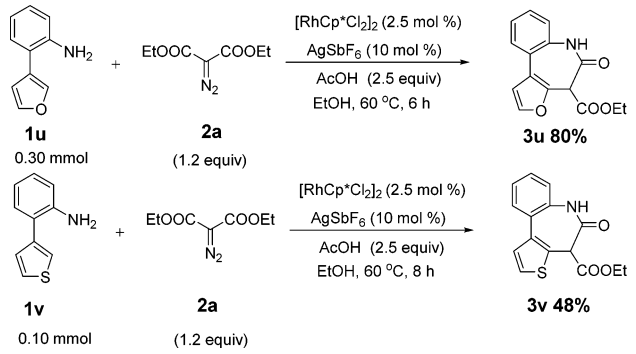
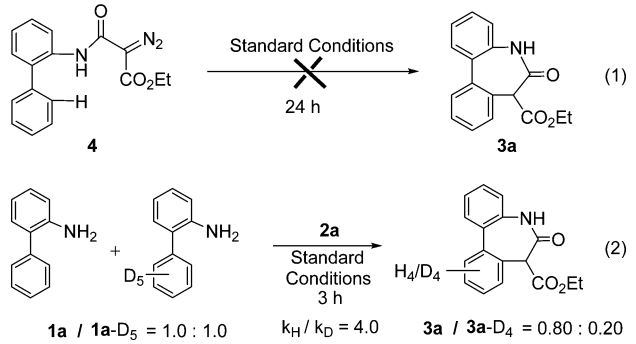
with diazomalonate **2a** to give corresponding azepinone derivatives **3u,v** expediently.

Scheme 2. Cascade C−H Functionalization/Amidation Reaction of 2-Heteroaryl Anilines 1u−v with Diazomalonates 2a



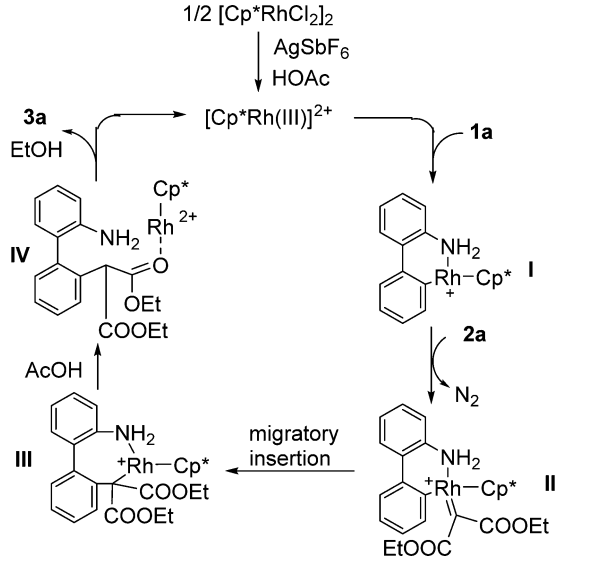
To gain insight into the mechanistic pathway of the cascade reaction, we performed a control experiment using diazo compound **4** to test its intramolecular C(sp^2)−H functionalization reaction (Scheme 3, eq 1). The experiment indicated that

Scheme 3. Primary Mechanistic Study



no azepinone derivative **3a** was obtained under the optimized conditions. This result supports that the cascade reaction probably first undergoes amine-directed C(sp^2)−H functionalization then amidation reaction. Furthermore, an intermolecular competition reaction between **1a** and **1a**-d_5 was conducted under the optimized conditions, and the value of the kinetic isotope effect (KIE) is 4.0. The KIE result suggests that the C−H activation may be involved in the rate-determining step of the cascade reaction (Scheme 3, eq 2). On the basis of the results of the experiment and precedent literature,[6c,d] a plausible mechanism for the cascade C(sp^2)−H functionalization/amidation reaction is proposed as follows (Scheme 4). First, under the direction and assistance of the amino group, $[Cp^*Rh(III)]^{2+}$ activates α-C(sp^2)−H in 2-aminobiaryl **1a** to form the six-membered rhodacycle intermediate **I**. Then diazomalonate **2a** reacts with the rhodacycle **I** to form a rhodium(III) carbene intermediate **II**. Migratory insertion of carbene group into the Rh−C bond in intermediate **II** results in the seven-membered rhodacyclic intermediate **III**. Protonolysis of intermediate **III** gives C(sp^2)−H functionalization intermediate **IV**. Finally, $[Cp^*Rh(III)]^{2+}$ may function as a Lewis acid to activate the carbonyl group in the ester moiety of intermediate **IV**,[6h] which promotes an intramolecular amidation

Scheme 4. Plausible Mechanism for the Cascade C−H Functionalization/Amidation Reaction



to give the desired azepinone derivative **3a** with regenerating $[Cp^*Rh(III)]^{2+}$.

In conclusion, we have developed a cascade C−H functionalization/amidation reaction of aminobiaryls **1** with diazomalonates **2** under rhodium catalysis. Various electron-withdrawing or electron-donating functional groups in 2-aminoaryls are compatible with the cascade reaction, affording new azepinone derivatives **3** in moderate to excellent yields. This synthetic method has the advantages of mild reaction conditions, broad substrate scope, good yields, and efficient synthesis. A plausible mechanism using rhodium(III) to activate both C(sp^2)−H bonds for functionalization and the carbonyl group in the ester moiety for amidation is also proposed. The novel cascade C−H functionalization/amidation reaction may have potential applications in the synthesis of related natural products and pharmaceuticals.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR, ^{13}C NMR and HRMS for new products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01140.

Experimental procedures and ^{1}H, ^{13}C NMR and HRMS spectra for new products (PDF)

X-ray crystallographic data for **3e** (CIF)

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Notes

The authors declare no competing financial interest.

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