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Rhodium-Catalyzed Regiodivergent [3 + 2] and [5 + 2] Cycloadditions of Quinolinium Ylides with Alkynes

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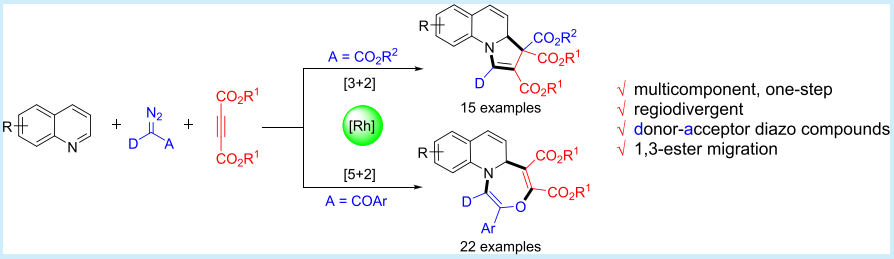
Supporting Information



ABSTRACT: Rhodium-catalyzed regiodivergent [3 + 2] and [5 + 2] cycloadditions of quinolinium ylides with alkynes are reported, providing highly functionalized five-membered indolizine derivatives and seven-membered 1,4-oxazepine compounds, respectively, in moderate to excellent yields under mild reaction conditions. Importantly, quinolinium ylides are derived from donor−acceptor diazo compounds, and different types of donor−acceptor diazo compounds exhibit distinct selectivity and reactivity for the reactions. The [3 + 2] cycloadditions involve an unusual 1,3-ester migration process.

N-Heterocycles represent long-standing targets for synthetic chemists because they are common skeletons of many natural products, pharmaceuticals, and agrochemical products.[1] Among them, five-membered indolizine derivatives and seven-membered 1,4-oxazepine compounds are unique structural units in the N-heterocycles, both of which widely exist in medicinal chemistry with remarkable biological activities and pharmaceutical interest.[2,3] Developing efficient and versatile routes toward these structural motifs is therefore highly desirable.

Pyridinium ylides, as a special type of azomethine ylide, are a class of important intermediates with wide applications in organic synthesis of N-heterocycles.[4] Compared with traditional strategies from pyridinium salts with the aid of base,[5] the metal-catalyzed formation of pyridinium ylides (**A**) from pyridines and diazo compounds[6] is a more efficient and greener strategy with respect to step economy (Scheme 1, a).[7−10] In 1993, Padwa and co-workers reported a rhodium-catalyzed [3 + 2] cycloaddition of pyridine, α-diazoacetophenone, and dimethyl acetylenedicarboxylate, which proceeds through the in situ generation of pyridinium ylide.[7] Afterward, Dowden and co-workers realized iron- or copper-catalyzed cycloadditions of pyridines, diazo compounds, and electron-deficient alkenes[8] or alkynes,[9] leading to highly functionalized tetrahydroindolines or indolizines. Recently, Wan and co-workers developed copper-catalyzed oxidative cycloadditions between quinolines, acceptor-H diazo compounds, and electron-deficient alkenes for direct construction of indolizine derivatives via quinolinium ylides.[10] To our surprise, little attention has been paid to the cycloaddition reactivity of pyridinium ylides derived from donor−acceptor diazo compounds with alkynes.[8a]

In contrast with catalytic 1,3-dipolar [3 + 2] cycloadditions of pyridinium ylides for preparing five-membered indolizine compounds, synthetic [5 + 2] cycloaddition strategies of pyridinium ylides as 1,5-dipoles for the construction of seven-membered N-heterocycles have been much less reported. In 2014, Yoo and co-workers discovered stable pyridinium zwitterion 1,5-dipoles (**B**) prepared via the rhodium-catalyzed reactions between pyridines with 1-sulfonyl-1,2,3-triazoles and developed various [5 + 2] cycloadditions to furnish seven-membered 1,4-diazepine derivatives (Scheme 1, b).[11] To the best of our knowledge, however, [5 + 2] cycloadditions of pyridinium ylides derived from diazo compounds as 1,5-dipoles with alkynes have no reports.

Inspired by the former reports, herein, we report rhodium-catalyzed multicomponent and regiodivergent cycloadditions of quinolines, donor−acceptor diazo compounds, and electron-deficient alkynes, which result in [3 + 2] indolizine derivatives through 1,3-ester migration and [5 + 2] 1,4-oxazepine compounds, respectively (Scheme 1, c).

Initially, quinoline **1a**, dimethyl acetylenedicarboxylate **2a**, and phenyl diazoacetate **3a** were utilized as model substrates to optimize the reaction conditions (Table 1). When the reaction was performed in toluene at room temperature without catalyst

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Scheme 1. Cycloadditions of Pyridinium Ylides

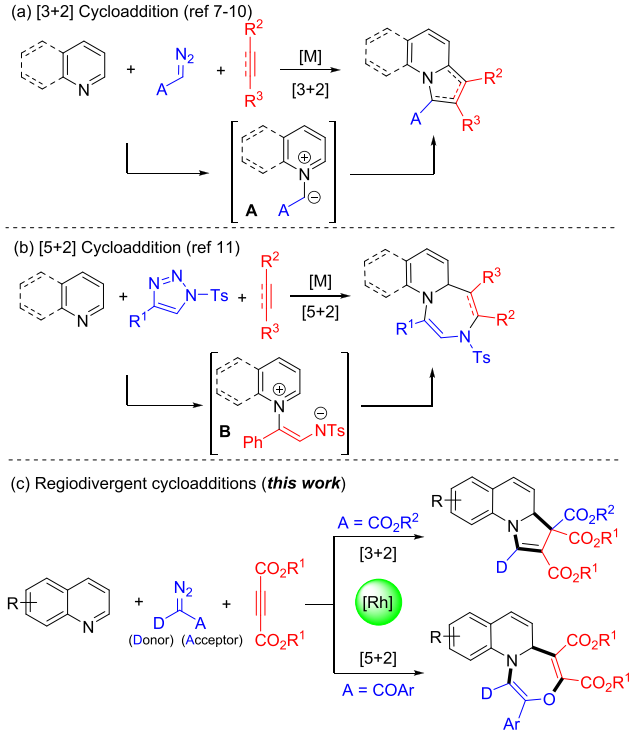
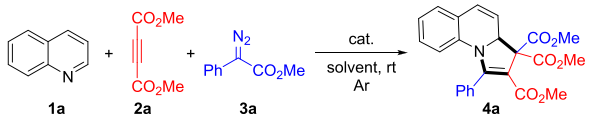


Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a 4a

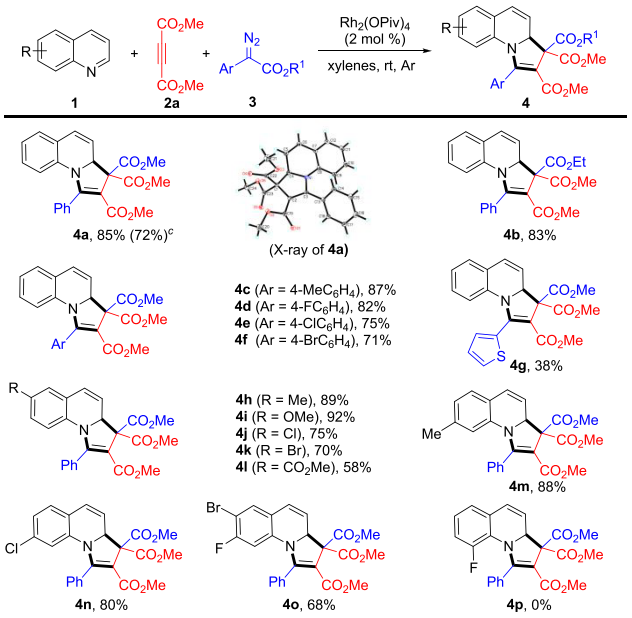
entry	catalyst	solvent	yield (%)[b]
1	-	toluene	-
2	$[(MeCN)_4Cu]PF_6$	toluene	-
3[c]	$(Ph_3P)_3AuCl$	toluene	-
4	$Rh_2(OAc)_4$	toluene	-
5	$Rh_2(Cap)_4$	toluene	-
6	$Rh_2(tfa)_4$	toluene	-
7	$Rh_2(pfb)_4$	toluene	-
8	$Rh_2(TPA)_4$	toluene	-
9	$Rh_2(Oct)_4$	toluene	58
10	$Rh_2(esp)_2$	toluene	60
11	$Rh_2(OPiv)_4$	toluene	74
12	$Rh_2(OPiv)_4$	CH_2Cl_2	46
13	$Rh_2(OPiv)_4$	THF	30
14	$Rh_2(OPiv)_4$	DMF	-
15	$Rh_2(OPiv)_4$	xylenes	85
16[d]	$Rh_2(OPiv)_4$	xylenes	<10
17[e]	$Rh_2(OPiv)_4$	xylenes	51

[a]Reaction conditions: **1** (0.2 mmol), catalyst ([Rh] 2 mol %, [Au] 5 mol %, [Cu] 10 mol %), **2** (0.24 mmol), **3** (0.3 mmol), and xylenes (2.0 mL), rt, 8 h, Ar. [b]Isolated yields. [c]$NaBAr_F$ (5 mol %). [d]At 0 °C, 24 h. [e]At 80 °C.

or with $[(MeCN)_4Cu]PF_6$ or $(Ph_3P)_3AuCl$ as catalyst, the reaction did not occur (entries 1−3). Next, different rhodium catalysts were examined, and $Rh_2(OAc)_4$, $Rh_2(Cap)_4$, $Rh_2(tfa)_4$, $Rh_2(pfb)_4$, or $Rh_2(TPA)_4$ were all inactive in this reaction (entries 4−8). Gratifyingly, product **4a** was obtained in similar yields when $Rh_2(Oct)_4$ or $Rh_2(esp)_2$ was employed (entries 9 and 10). Switching the catalyst to $Rh_2(OPiv)_4$ resulted in better yield (entry 11). Next, different solvents were screened, and xylene was the best choice (entry 15). Other solvents such as methylene dichloride (CH_2Cl_2), tetrahydrofuran (THF), and *N*,*N*-dimethylformamide (DMF) were not suitable for the reaction (entries 12−14). Finally, the reaction was sluggish under low temperature (entry 16), and high temperature was detrimental to the reaction (entry 17).[12]

With the optimal reaction conditions in hand, we next set out to investigate the generality and limitations of this reaction (Scheme 2). Both diazo compounds and quinolines were

Scheme 2. Scope for [3 + 2] Cycloadditions[a,b]



[a]Reaction conditions: **1** (0.2 mmol), $Rh_2(OPiv)_4$ (2 mol %), **2** (0.24 mmol), **3** (0.3 mmol), xylenes (2.0 mL), rt, 8 h, Ar. [b]Isolated yields. [c]Yield of 5 mmol scale in parentheses.

examined. Gratifyingly, a wide range of aryl diazoacetates with different substitutions could be utilized in this reaction, providing the corresponding indolizine products in moderate to excellent yields (**4a−g**). Both electron-donating and electron-withdrawing groups were tolerated on the aryl ring of the diazoacetates (**4c−f**). Additionally, a diazo compound containing thiophene was also compatible with this transformation and delivered the desired product **4g** in moderate yield. Next, various commercially available quinolines were subjected to this reaction. Quinolines with various 6- and 7-substituents could be converted to the corresponding indolizine products in good to excellent yields (**4h−n**). Notably, 6-bromo-7-fluoroquinoline was also suitable for this transformation and afforded **4o** in excellent yield. However, the target product **4p** was not obtained from the reaction with 8-fluoroquinoline under standard reaction conditions, possibly due to steric hindrance to inhibit quinolinium ylide formation.[13] The structure of **4a** was confirmed by X-ray crystallographic analysis.

We next set out to investigate α-diazoketones as substrates, which have been used as three-atom 1,3-dipole synthons in a few transition-metal-catalyzed cycloadditions.[14] Thus, we envisioned that pyridium ylides of α-diazoketones could act as active 1,5-dipole intermediates to intrigue [5 + 2]

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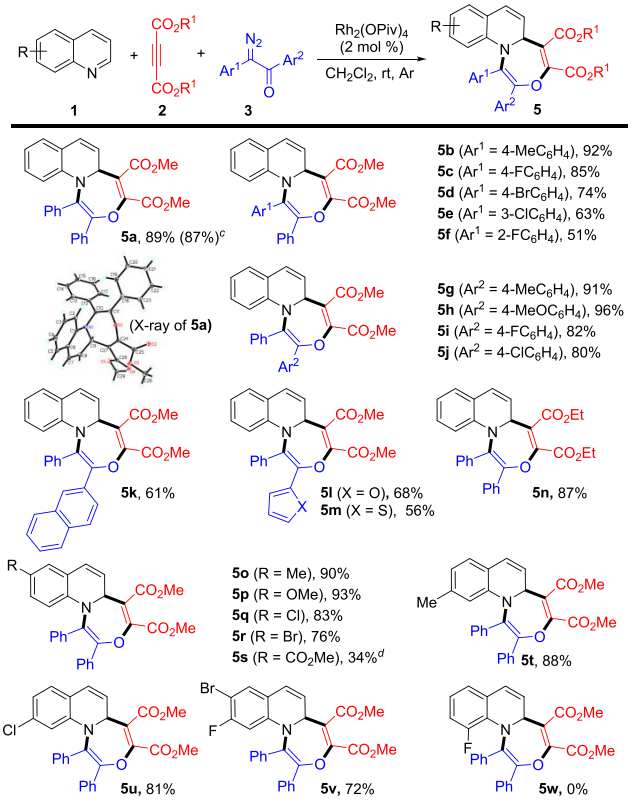
cycloadditions with electron-deficient alkynes, which would afford a novel approach to synthesize highly substituted 1,4-oxazepine structures.[15] Under optimized reaction conditions,[16] the expected [5 + 2] cycloaddition product **5a**, confirmed by X-ray crystallographic analysis, was obtained in 89% yield when quinoline **1a**, dimethyl acetylenedicarboxylate **2a**, and 2-diazo-1,2-diphenylethanone **3h** were utilized as model substrates. Next, we examined the substrate scope for the synthesis of 1,4-oxazepines (Scheme 3). A variety of α-diazoketones with

Scheme 3. Scope for [5 + 2] Cycloadditions[a,b]

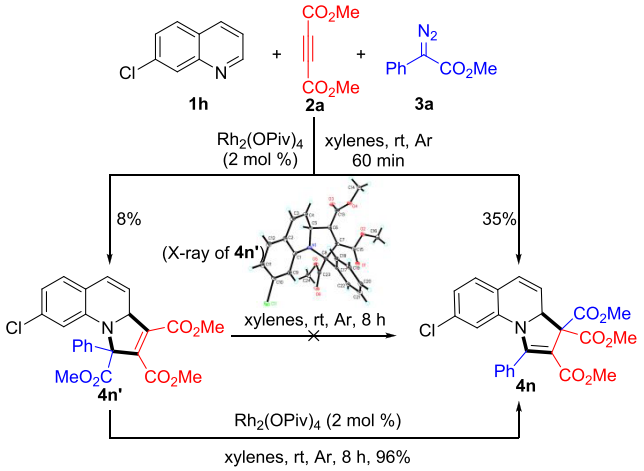


[a]Reaction conditions: **1** (0.2 mmol), $Rh_2(OPiv)_4$ (2 mol %), **2** (0.24 mmol), **3** (0.3 mmol), CH_2Cl_2 (2.0 mL), rt, 8 h, Ar. [b]Isolated yields. [c]Yield of 5 mmol scale in parentheses. [d]At 40 °C.

different substitutions on both aryls were first examined in this reaction, providing the corresponding products in moderate to excellent yields (**5a**−**5m**). Both electron-donating and electron-withdrawing groups were tolerated on both aryl rings of the α-diazoketones (**5a**−**5j**). Notably, diazoketones containing a bulky 2-naphthyl group, furan, and thiophene were all suitable for this reaction, affording the desired product **5k**, **5l**, and **5m** in 61%, 68%, and 56% yields, respectively. Diethyl acetylenedicarboxylate was compatible for this reaction (**5n**). Then various quinolines were tested, and the corresponding products were also obtained in moderate to good yields (**5o**−**5v**), except that **5w** was not obtained from 8-fluoroquinoline.[13]

To gain the mechanistic insights into the unusual rhodium-catalyzed 1,3-ester migration process of the [3 + 2] cycloadditions,[17] control experiments were conducted (Scheme 4). The reaction of **1h**, **2a**, and **3a** was performed under standard reaction conditions within 60 min to afford **4n** and **4n′** in 35% and 8% yields, respectively. The structure of

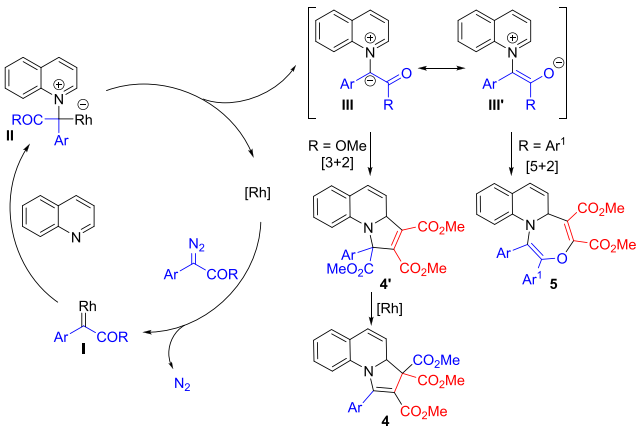
Scheme 4. Control Experiments



4n′ was confirmed by X-ray crystallographic analysis. Moreover, **4n′** was converted almost quantitatively to **4n** under standard reaction conditions. In contrast, **4n** was not obtained from **4n′** without catalyst.

On the basis of former investigations, a plausible mechanism has been proposed. As shown in Scheme 5, the reaction of

Scheme 5. Proposed Reaction Mechanism



rhodium complex with diazo compound generates rhodium carbene species **I** with the elimination of nitrogen. The nucleophilic addition of quinoline to **I** produces intermediate **II**. Subsequent dissociation of the rhodium salt gives rise to intermediates **III** and **III′**. Intermediate **III** undergoes 1,3-dipolar [3 + 2] cycloaddition with alkyne to give intermediate **4′**, which could be transformed to indolizine **4** through a metal-assisted 1,3-ester migration process, while intermediate **III′** would undergo 1,5-dipolar [5 + 2] cycloaddition with alkyne to afford seven-membered 1,4-oxazepine **5**.

In summary, we have developed rhodium-catalyzed regiodivergent [3 + 2] and [5 + 2] cycloadditions of quinolinium ylides with alkynes to provide five-membered indolizine derivatives and seven-membered 1,4-oxazepine compounds in moderate to excellent yields under mild reaction conditions. Importantly, quinolinium ylides are generated in situ from donor−acceptor diazo compounds, and different types of donor−acceptor diazo compounds exhibit distinct selectivity and reactivity for the reactions. Mechanistic investigations reveal that the [3 + 2] cyclo-

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additions proceed through a metal-assisted 1,3-ester migration process. These results contribute to expand the repertoire of the cycloadditions in which quinolinium ylides could be successfully involved to produce N-heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01765.

Experimental procedures along with characterizing data and copies of NMR spectra (PDF)

Accession Codes

CCDC 1914525 and 1914535−1914536 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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(12) Both adding sequence of starting materials and adding method are critical for this reaction. General procedure: A solution of alkyne **2** (0.24 mmol) and diazo compound **3** (0.3 mmol) in 1.0 mL of xylenes was added into a solution of quinoline **1** (0.2 mmol) and catalyst (2−10 mol %) in 1.0 mL of xylenes via an automatic syringe pump over 60 min at rt under dry argon atmosphere. Then the resulting solution was stirred at rt for 8 h (monitored by TLC). Please see the Supporting Information (Table S1) for details.

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(13) Pyridine (unsubstituted) was also tried as substrate under our optimized reaction conditions, but no desired [3 + 2] or [5 + 2] product was obtained.
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(16) Please see the Supporting Information (Table S2) for details.
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