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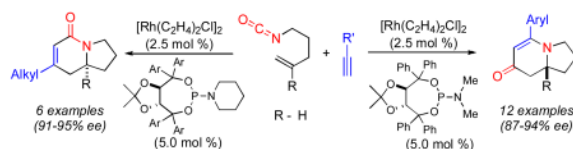
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Enantioselective Synthesis of Indolizidines Bearing Quaternary Substituted Stereocenters via Rhodium-Catalyzed [2+2+2] Cycloaddition of Alkenyl Isocyanates and Terminal Alkynes

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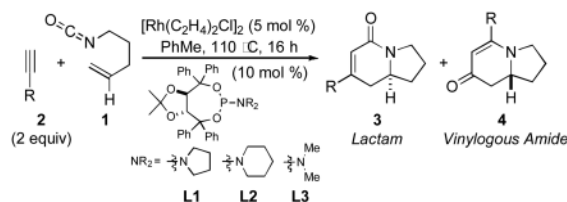
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Abstract



An enantioselective synthesis of indolizidines bearing quaternary substituted stereocenters by way of a rhodium catalyzed [2+2+2] cycloaddition of substituted alkenyl isocyanates and terminal alkynes is described. The reaction provides lactam products using aliphatic alkynes, while aryl alkynes give rise to vinylogous amide products. Through modification of the phosphoramidite ligand, high levels of enantioselectivity, regioselectivity, and product selectivity are obtained for both products.

Transition-metal-catalyzed $[m+n+o]$ type cycloaddition reactions have proven to be efficient methods for the construction of complex polycyclic carbocycles and heterocycles.¹ Of the functional groups that participate in these cycloadditions, isocyanates² have played an increasingly important role due to their reactivity and embedded nitrogen-containing functionality.³ Indeed, the [2+2+2] cycloaddition of isocyanates with diynes to generate 2-pyridones has been demonstrated with Co(I), Ru(II), Ni(0), and Rh(I).⁴ Our group has recently demonstrated⁵ that the [2+2+2] cycloaddition of unsubstituted pentenyl isocyanate **1** with alkynes **2** could be accomplished in the presence of a rhodium(I) catalyst to form either lactam **3** or vinylogous amide **4** – the result of an apparent CO migration.⁶ Moreover, the reaction of **1** with terminal aryl alkynes in the presence of phosphoramidite ligand **L1**,⁷ affords vinylogous amide **4** products with high levels of enantioenrichment (up to 94% ee) while reaction with terminal aliphatic alkynes in the presence of ligand **L2** affords lactam products **3** with only moderate enantioenrichment (76–87% ee).^{5b}

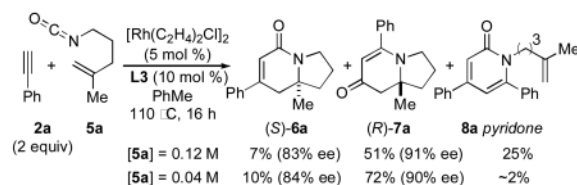


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 Supporting Information **Available**: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

We envisioned that this reaction would provide an expedient entry into a variety of indolizidine and quinolizidine natural products.⁸ We further noted that a number of these natural products possess additional substitution at various positions around the core including carbon groups at the bridgehead position (a quaternary substituted stereocenter).⁹ Two specific examples of such natural products include the marine alkaloids cylindricines A-F¹⁰ and the immunosuppressant FR901483.¹¹ We thus endeavored to extend this cycloaddition reaction to incorporate polysubstituted alkenes, in spite of considerable literature precedent which suggested that more substituted alkenes provide less stable alkene/metal complexes.¹² For example, ethylene binds to Rh(I) 13 times stronger than propylene while isobutylene binds 200 times less strongly than propylene.¹³ Indeed, the substitution of disubstituted alkenes in place of terminal olefins in catalytic reactions is not trivial.¹⁴ In light of these potential problems, it is particularly notable that a Rh(I)-phosphoramidite catalyst system has proven to be very accommodating of 1,1-disubstituted alkenes as partners in this chemistry. The development of this transformation is described herein.

In preliminary tests, we were pleased to discover that the methyl substituted isocyanate **5a** (0.12 M in toluene) reacts with phenylacetylene (2 eq) in the presence of $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ (5 mol %) and phosphoramidite **L3** (10 mol %) to give a 1:8 mixture of lactam **6a** and vinylogous amide **7a** (58% combined yield) as single regioisomers with good enantioselectivities, eq 2. The major byproduct in this reaction was 2-pyridone **8a**, the result of cycloaddition between the isocyanate and two equivalents of alkyne. Using more dilute conditions ($[\mathbf{5a}] = 0.04 \text{ M}$), the formation of pyridone **8a** could be suppressed, leading to the desired cycloadducts as a 1:7 mixture of **6a:7a** with similar ee's.



(2)

The reaction was further optimized by lowering the rhodium dimer catalyst loading to 2.5 mol %, a change which results in only a minor decrease in yield (Table 1, entry 1). A series of terminal alkynes were subjected to reaction with isocyanate **5a** using the optimized conditions (Table 1).

Comparing the lactam:vinylogous amide (**6:7**) selectivity obtained with phenylacetylene **2a** (1:8), *p*-methoxy-phenylacetylene **2b** (<1:20) and *p*-bromo-phenylacetylene **2c** (1:3), it is evident that electron rich alkynes favor formation of vinylogous amide products **7** while electron poor alkynes increase the formation of lactam products **6**, a situation we had also noted in our work with terminal alkynes and pentenyl isocyanate.^{5b} Unlike the product selectivity in entries 1-3, the yield (76-80%) and enantioselectivity (88-91% ee) remain relatively unchanged with shifting alkyne electronics. The reaction also proceeds smoothly with vinyl ether **2d** to yield vinylogous amide product in good yield and excellent enantioselectivity (91% ee).¹⁵

Terminal aliphatic alkynes also participate in the cycloaddition with isocyanate **5a**, albeit with a reversal in product selectivity (Table 2). With 1-octyne **2e**, a modest 2:1 ratio of lactam **6e** (84% ee) and vinylogous amide **7e** (71% ee) is obtained in 82% combined yield. Interestingly, phosphoramidite ligand **L4** (a ligand with little effect on the reaction of phenylacetylene¹⁶) greatly improves the enantioselectivity in the reaction with **2e** (entry 2). Further modification

of the ligand led to phosphoramidite **L5**, which affords the lactam in good product selectivity (6.5:1) and enantioselectivity (91% ee). A variety of terminal aliphatic alkynes, including those bearing silyl ethers, an ester, and alkyl chloride (entries 4-6, 8), are tolerated under the optimized conditions (60-83% yield, 92-95% ee). The generally high enantioselectivity and product selectivity obtained with ligand **L5** represents a marked improvement over the selectivity previously reported with **L3**.^{5b}

The range of alkenyl isocyanate substitution was also explored using *p*-methoxyphenylacetylene **2b** as the alkyne (Table 3). The ratio of lactam to vinylogous amide products obtained remains independent of the alkene substitution (<1:20 in all cases). The reaction proceeds in a consistent manner with alkyl substituents such as butyl, isobutyl, and benzyl (71-80% yield, 92-94% ee). As the steric size of the substituent is increased, as in the case with isopropyl and cyclohexyl isocyanates, an increase in pyridone byproduct and a corresponding decrease in vinylogous amide yield are observed (entries 4-5). We presume that the increased steric demand about the alkene decreases the rate of coordination and/or insertion of the alkene to the extent where intermolecular insertion of a second alkyne is competitive even under dilute conditions. Benzyl ethers **5g**, silyl ethers **5h** and terminal alkenes **5i**¹⁷ are all tolerated under these reaction conditions (74-77% yield, 88-92% ee).

We have shown that 1,1-disubstituted alkenes are competent partners in the Rh-catalyzed [2+2+2] cycloaddition reaction leading to the generation of tetrasubstituted carbinolamine stereocenters. We have also identified a new phosphoramidite ligand that provides improved product selectivity and enantioselectivity in the cycloaddition of aliphatic alkynes.¹⁸ Efforts aimed at understanding the subtle ligand effects and applications in total synthesis are currently underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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15. Attempts at generating quinolizidine systems using homologous substituted isocyanates resulted in exclusive formation of pyridone.
16. With L4, 6a:7a (1:7) are obtained in 76% combined yield (83% and 90% ee respectively).
17. We have observed no evidence to suggest the terminal olefin participates in this reaction. Homologous systems were not examined.
18. Internal alkynes also participate in this cycloaddition reaction but provide higher selectivities using a different ligand. These studies are currently ongoing.

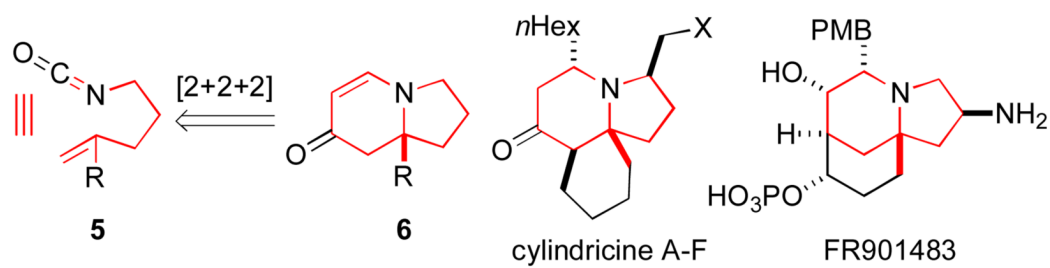
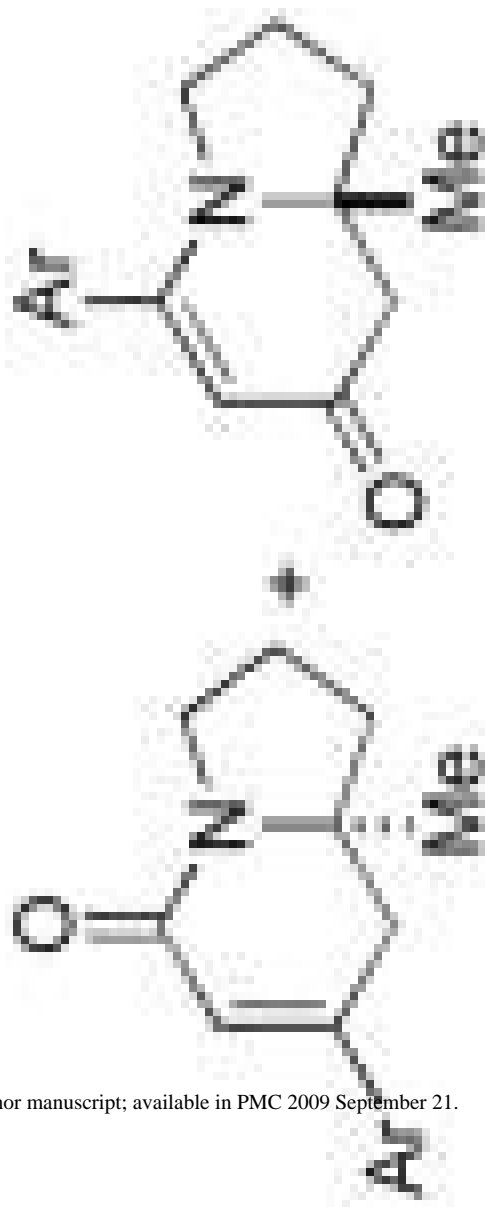
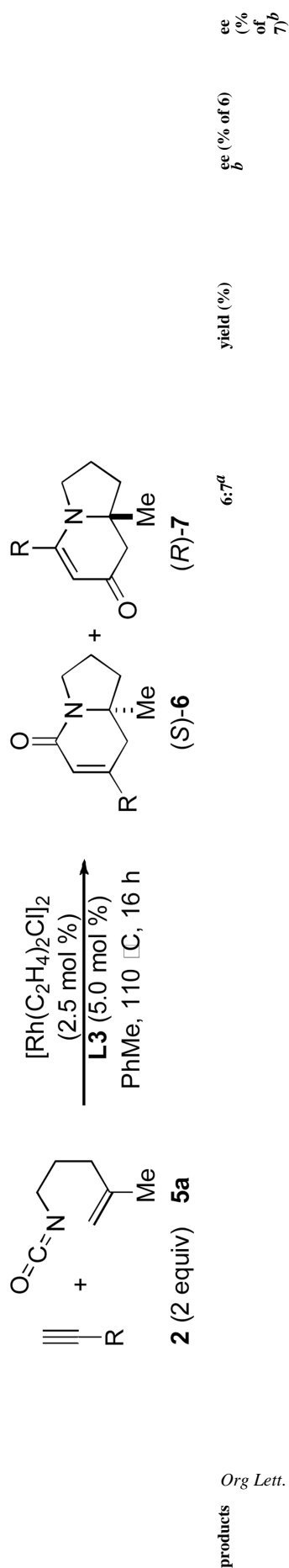


Figure 1.
Indolizidines Bearing Quaternary Substituted Stereocenters

Table 1

Alkyne Scope



7a

7b

7c

7d^c

1:8

< 1:20

1:3

1:9

76

80

77

64

84

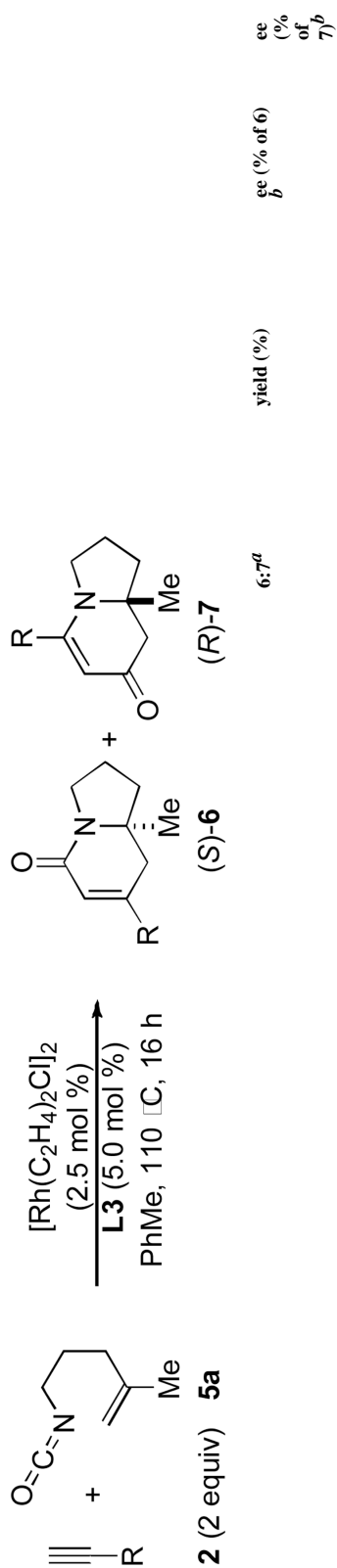
-

82

90

91

88^d



products

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selectivity determined by ¹H NMR of the unpurified mixture.

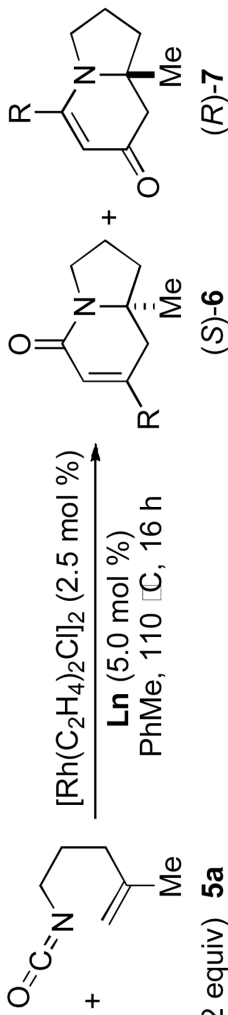
determined by HPLC using a chiral stationary phase.

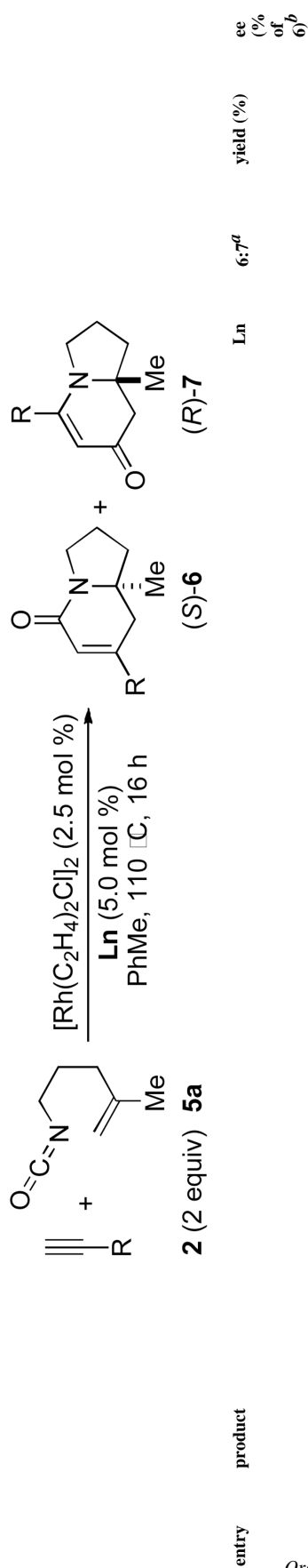
product E:Z = 97:3.

stereochemistry determined by X-ray.

Table 2

Aliphatic Alkyne Scope

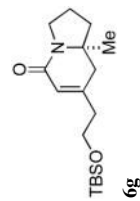
entry	product	Ln	6:7 ^d	yield (%)	ee (% of 6) ^b
	 <p> $\text{R}-\text{C}\equiv\text{C}-\text{C}(\text{Me})=\text{CH}-\text{N}(\text{O})-\text{C}_2\text{H}_4$ (2) + $\text{O}=\text{C}-\text{N}(\text{O})-\text{C}_2\text{H}_4-\text{C}(\text{Me})=\text{CH}-\text{N}(\text{O})-\text{C}_2\text{H}_4$ (5a) </p> <p> $\xrightarrow[\text{PhMe, 110 } ^\circ\text{C, 16 h}]{[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2 (2.5 \text{ mol } \%), \text{Ln} (5.0 \text{ mol } \%)}$ </p> <p> $(S)\text{-6}$ + $(R)\text{-7}$ </p>				
	 <p><i>n</i>-Hex</p> <p>6e</p>	L3	2:1	82	84
	6e	L4	3:1	75	95
	6e	L5	6.5:1	88	91



entry	product	Ln	6:7 ^d	yield (%)	ee (%) of 6) ^b
5		L5	9:1	70	95

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6f



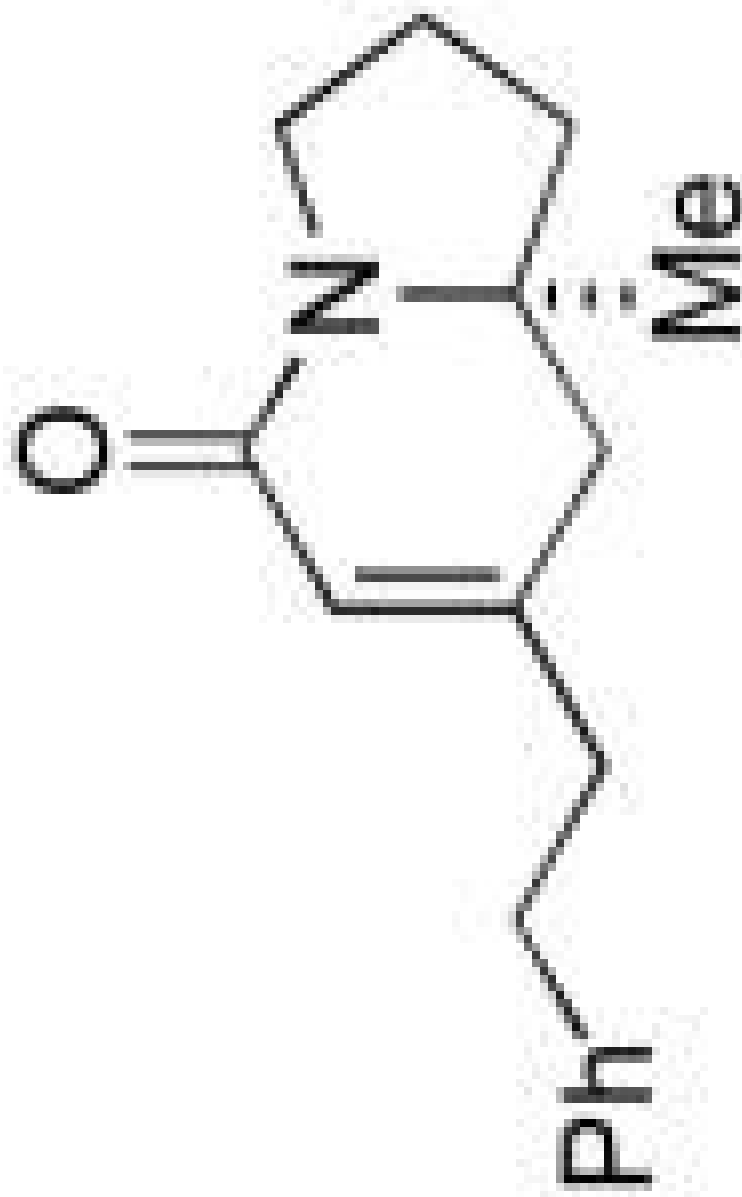
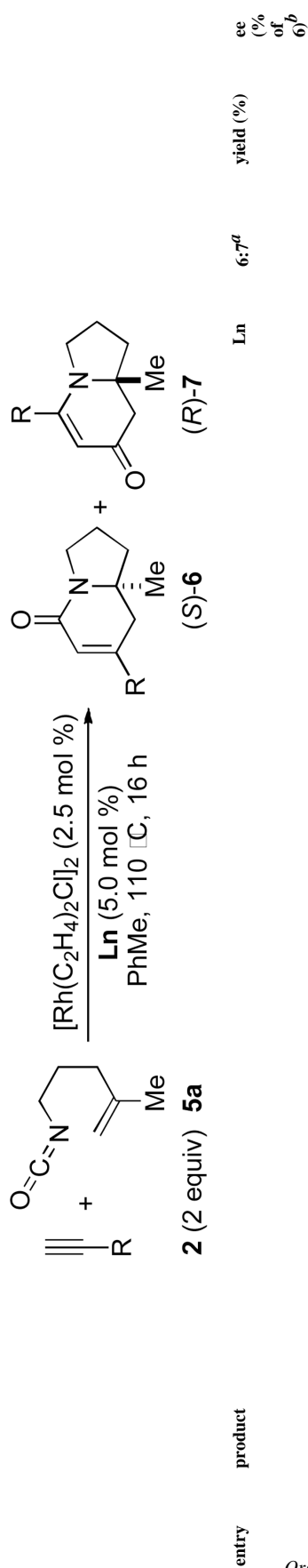
6g

5

77

L5 11.5:1

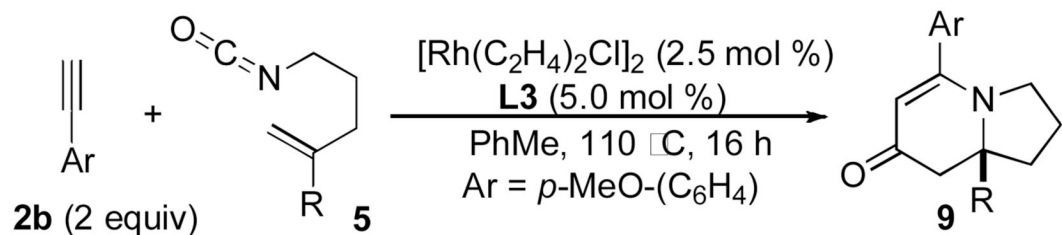
93



61

Table 3

Alkenyl Substitution Scope

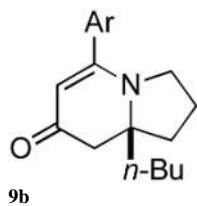


entry

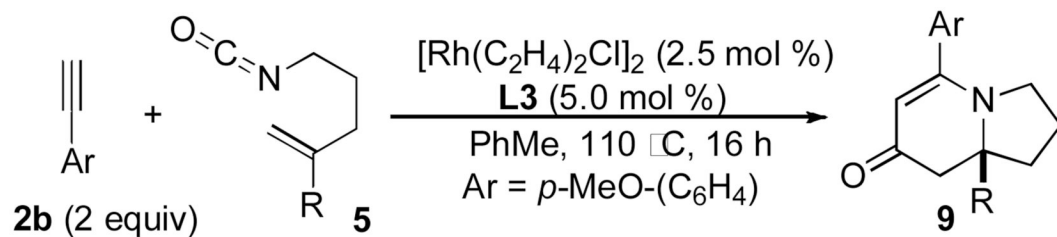
product

yield

1



71



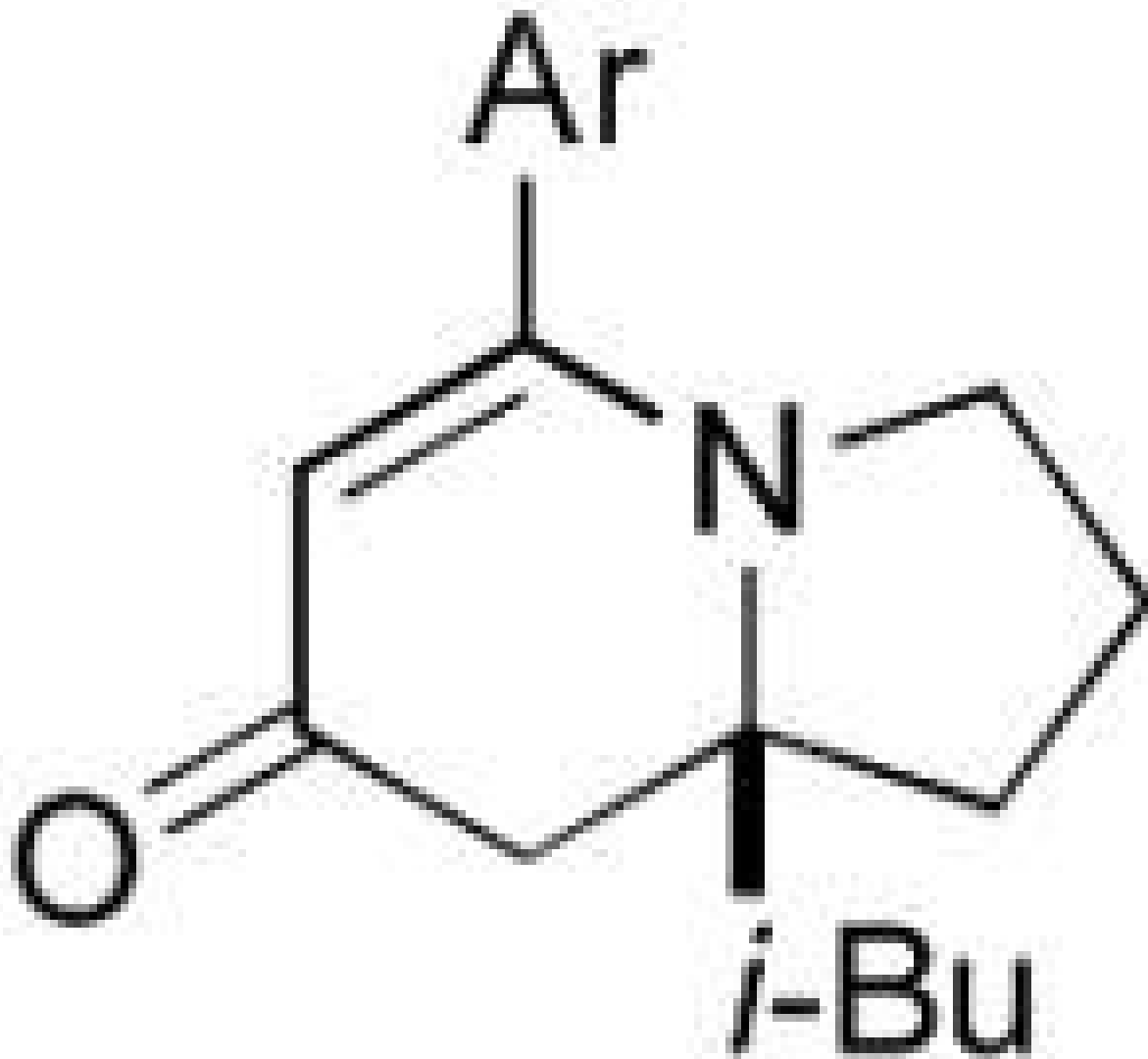
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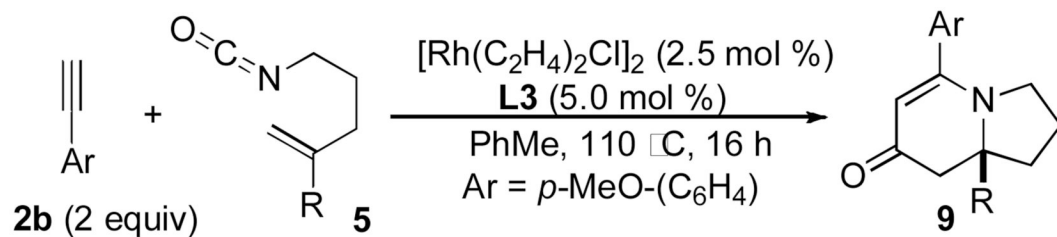
product

yield

2

75

**9c**



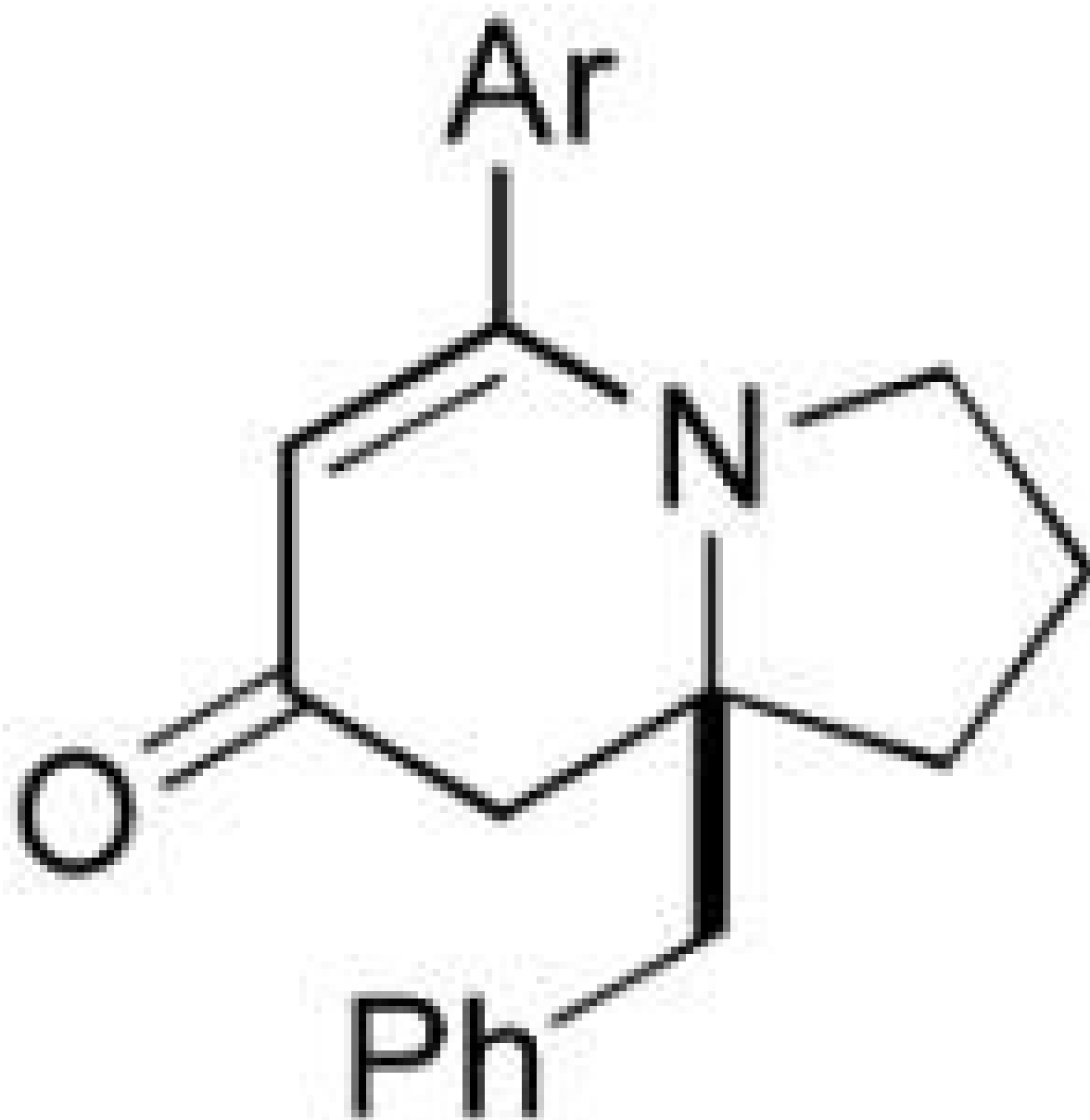
entry

product

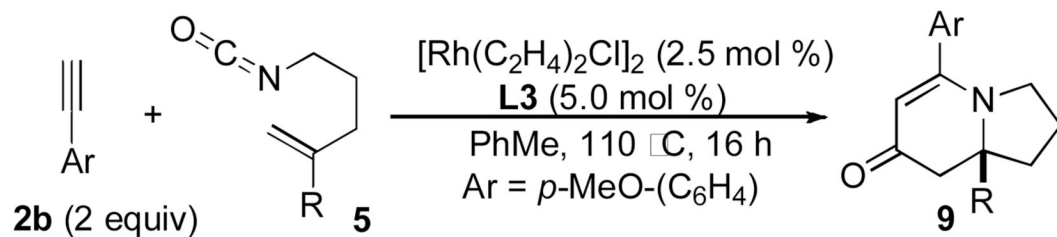
yield

3

80



9d



entry

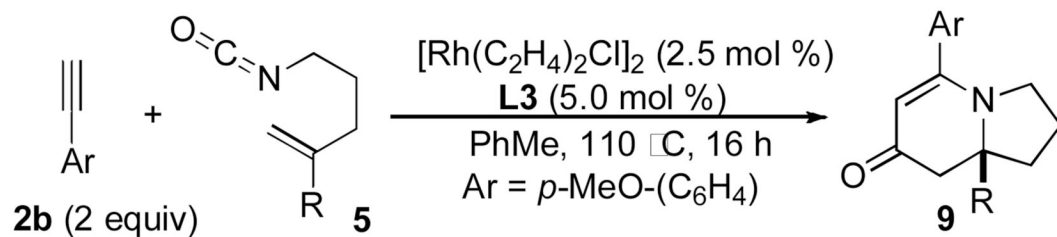
product

yield

6

77

**9g**



entry

product

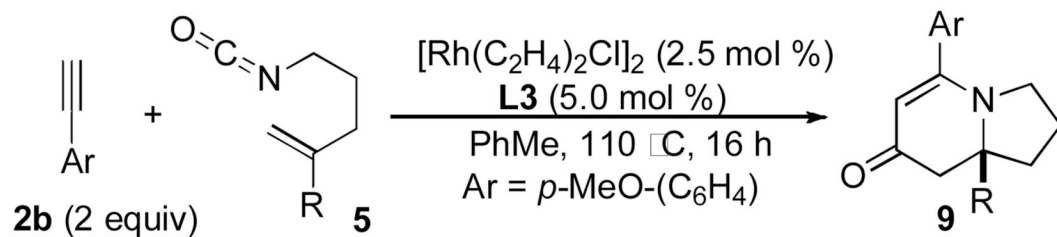
yield

7

74



9h



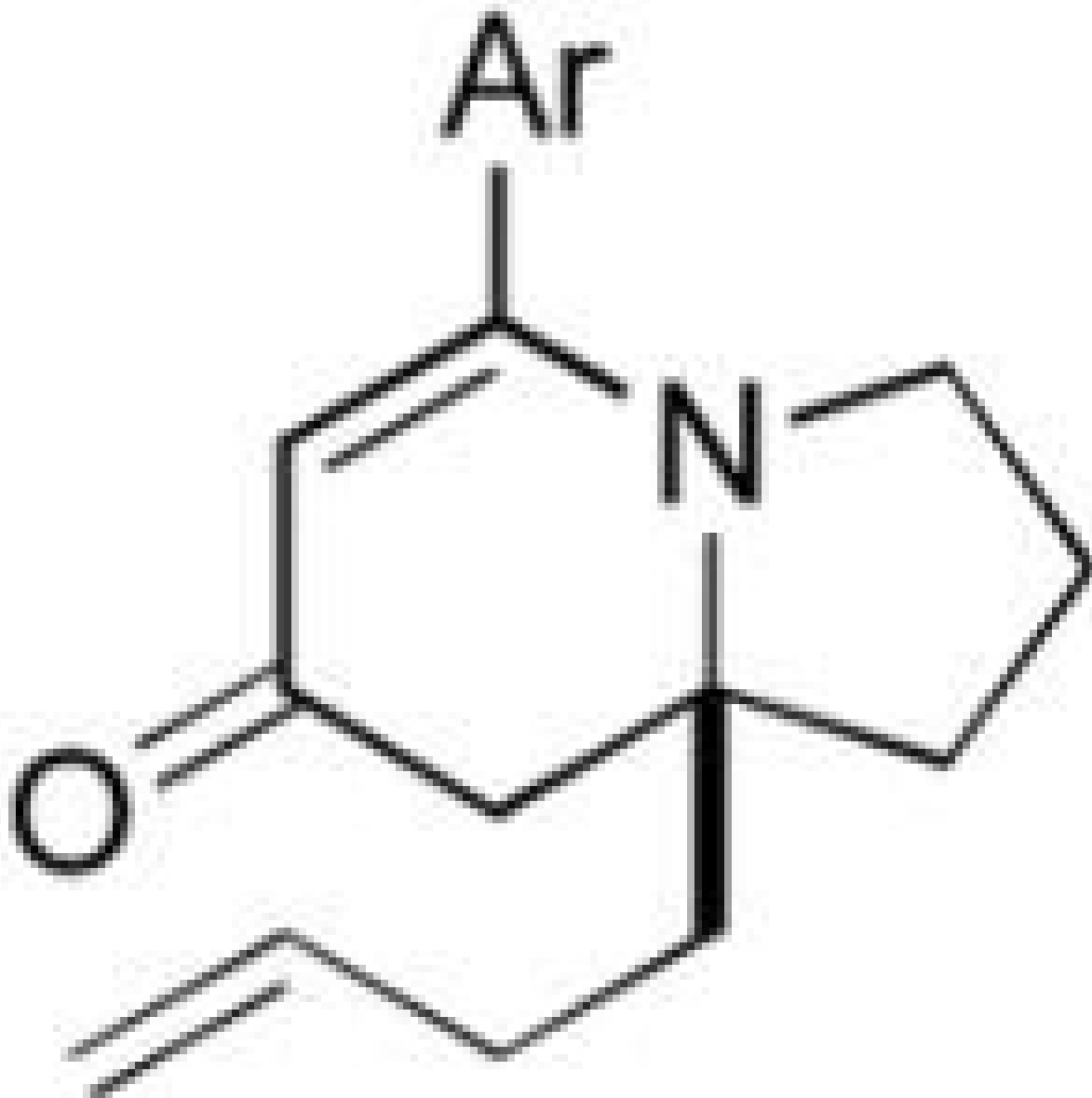
entry

product

yield

8

75



9i

^aDetermined by HPLC using a chiral stationary phase.

^b Major product isolated is pyridone (48% yield).