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Predictable and Regioselective Insertion of Internal Unsymmetrical Alkynes in Rhodium-Catalyzed Cycloadditions with Alkenyl Isocyanates

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Abstract: A regioselective, rhodium-catalyzed cycloaddition between a variety of internal, unsymmetrical alkynes is described. We document the impact of both steric and electronic properties of the alkyne on reaction course, efficiency, and enantioselectivity. The substituent that better stabilizes a positive charge or the larger group, all else being equal, inserts distal to the carbonyl moiety in a predictable and controllable fashion. The reaction scope is broad and the enantioselectivities are high, providing an "instruction manual" for substrate choice when utilizing this reaction as a synthetic tool.

Introduction

Transition-metal catalyzed cycloadditions provide an efficient route to complex carbocyclic and heterocyclic compounds.[1] In particular, reactions involving three π-components, such as [2+2+2] cycloadditions, allow for access to many complex molecules. The use of isocyanates as one π-component allows for introduction of nitrogen functionality into the cycloadducts.[2] The pioneering work of Yamazaki,[3] Hoberg[4] and Vollhardt[5] on alkyne/isocyanate cycloadditions to form pyridones has recently been furthered by Itoh[6] and Louie.[7] Asymmetric pyridone-forming cycloadditions have appeared from the laboratories of Tanaka.[8]

Building on these key precedents, all of which report cycloadditions involving two alkynes as π components, we have recently described the asymmetric, rhodium-catalyzed cycloaddition between an isocyanate, tethered alkene and an exogenous alkyne.[9] Initial studies[9a] revealed that a catalyst formed from rhodium bis(ethylene) chloride dimer $[Rh(C_2H_4)_2Cl]_2$, in combination with a phosphine, gives rise to the formation of lactam and vinylogous amide products dependent on the nature of the symmetrical alkyne. Further development[9b] led to the discovery of successful reaction conditions employing TADDOL-phosphoramidite ligands (**L1**−**L3**, Figure 1), which allow the reaction to proceed asymmetrically with terminal alkynes. We have also shown that 1,1-disubstitution on the alkene is tolerated in the reaction.[9c] The nature of the terminal alkyne (aryl or alkyl) controls the product selectivity. Aryl groups and larger substitutions tend to favor vinylogous amide product (**4**), while alkyl and smaller substituents produce the lactam (**3**) as the major product with the TADDOL-based ligands (**L1**−**L3**). We have shown that a carbodiimide may be used in place of the isocyanate, leading to a profound influence on product selectivity due to their inherent steric bulk.[9d] More recently,[9e] we have reported an inversion in product selectivity with the use of a BINOL- or biphenol-phosphoramidite ligand (**L4**, **L5** in Figure 1) and aliphatic alkynes. The ability to predict product selectivity through alteration of the ligand allows for greater control within the reaction. Lastly, we have gained an insight into the coordination geometry of the active catalyst in the reaction of diarylalkynes and alkenyl isocyanates finding that excess alkyne substrate acts as a sixth ligand on octahedral Rh(III).[9f] Exploiting this sixth ligand effect has allowed us to manipulate enantioselectivities with the use of a nonparticipating additive.

These investigations greatly aid our understanding of this reaction, and have provided an arsenal of reaction conditions with which to tune new applications of this strategy. However, all the above studies focused on internal symmetrical alkynes or terminal alkynes, the latter having a large inherent difference in both steric bulk and electronic contributions across the π system. The use of internal, unsymmetrical alkynes in this chemistry has the potential to introduce additional substituents, complicated by potential problems of poor regiocontrol. In this respect, our prior work indicating that there are elements of both sterics and electronics influencing efficiency and selectivity was especially worrisome. We envisioned that there may be internal, unsymmetrical alkynes bearing contrasting substituent effects: small, electron-withdrawing groups or large, electron-releasing

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(4) (a) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1982**, *234*, C35. (b) Hoberg, H.; Oster, B. W. *Synthesis* **1982**, 324. (c) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1983**, *252*, 359.
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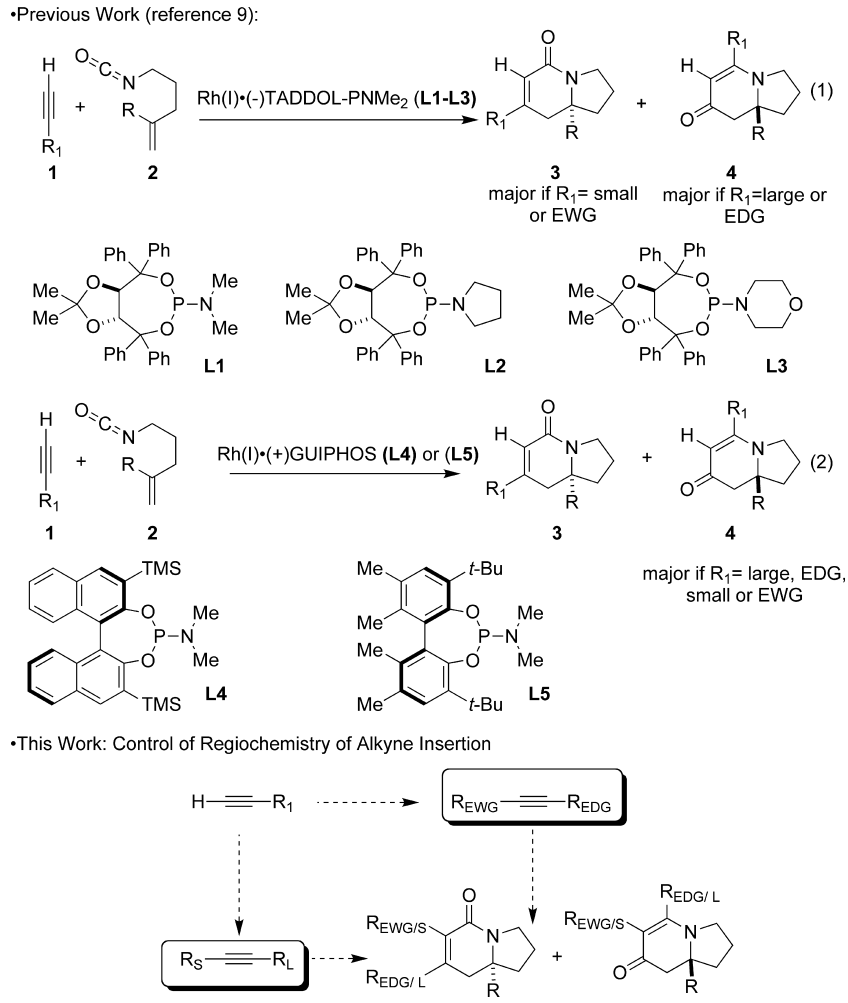

Figure 1. Reactions from previous work[9] and the current work.

groups that could participate predictably in cycloadditions. We embarked on the following study to elucidate the parameters governing reactivity while also providing a guide from which to apply unique, individual, hitherto under-developed internal alkynes to [2+2+2] cycloadditions.

The use of unsymmetrical, internal alkynes during metal-catalyzed cycloadditions is not without precedent. The obvious hurdle is to achieve regioselective insertion. A greater achievement still would be to realize the selectivity in a predictable and dependable fashion with a keen understanding of the forces driving the insertion. Several authors have pursued the problem in metal-catalyzed annulations onto alkynes[10] only to obtain poor selectivities. The use of internal unsymmetrical alkynes in metal-catalyzed cycloadditions, from [4+2],[11] [3+2],[12] [2+2+2],[13] and [2+2+1][14] has met with some success. Several reports have achieved success in selectively inserting unsymmetrical, internal alkynes. However, the examples tend to be limited to extreme differences (either in sterics or electronics),[15] limited scope,[16] or the selective insertion remains unexplained[17] thus making general use difficult.

Utilization of unsymmetrical, internal alkynes in metal-catalyzed [2+2+2] cycloadditions with a variety of substrates has been explored. As early as 1983, Vollhardt and co-workers[5a] showed that unsymmetrical, internal alkynes participate in cobalt-catalyzed [2+2+2] cycloadditions, eq 3 (Scheme 1). A single regioisomer was observed for trimethylsilyl-substituted alkynes. On the other hand, uniformly poor selectivity was seen

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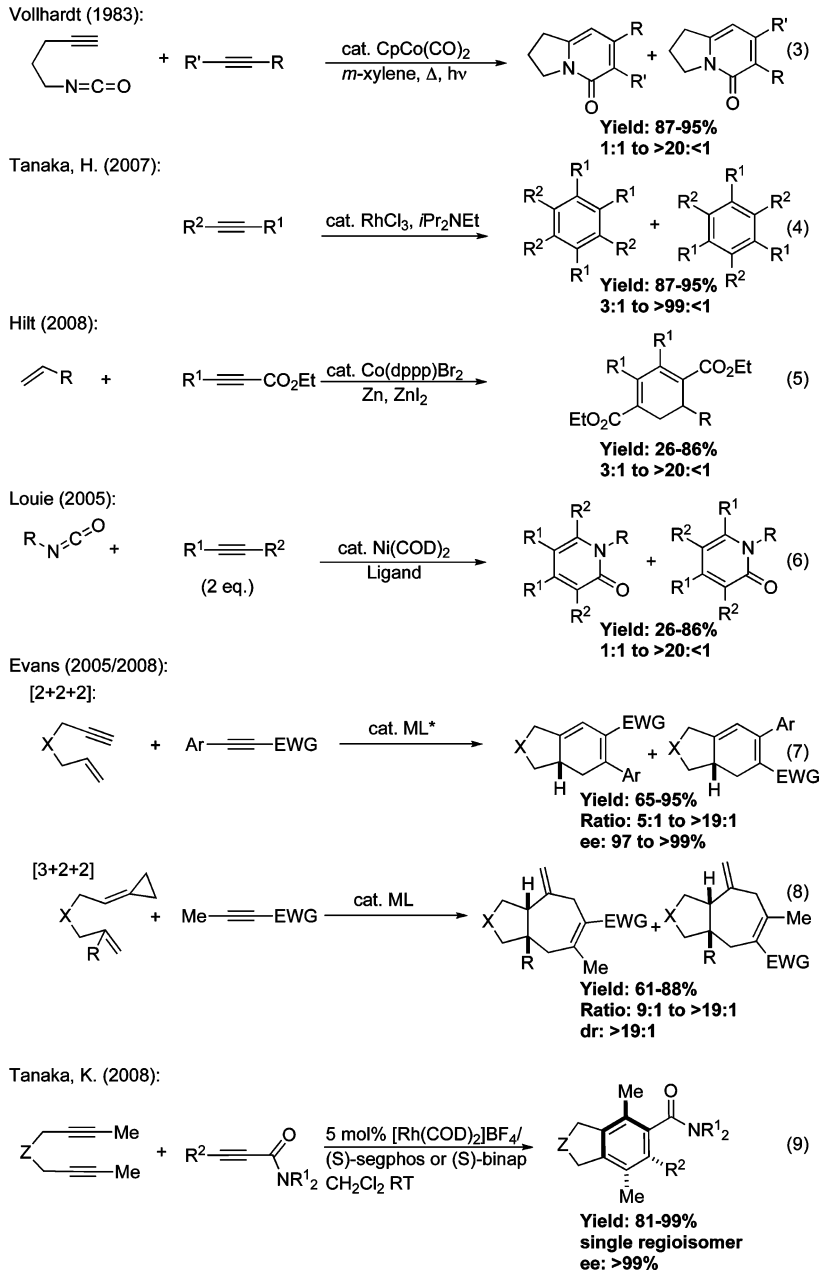
Scheme 1



for any alkyne that did not possess the silyl group, including an alkyl alkynoate. In 2007, Tanaka and co-workers[18] performed cyclotrimerizations utilizing unsymmetrical internal alkynes. They generally observe a single regioisomer and explain the selectivity due to the electronics of the alkyne, eq 4 (Scheme 1). In 2008, Hilt and co-workers[19] used cobalt-based catalyst to cyclize two equivalents of alkyne with an alkene. The authors observe moderate selectivity and yields (∼4:1 and up to 48%) with the alkyl propiolate and a variety of alkenes, while the aryl propiolate shows excellent selectivity and better yield (>20:1, 45−86%), eq 5 (Scheme 1). The authors propose that both ligand and substrate control regioselectivity. Louie and co-workers[20] have developed Ni(0) catalyzed [2+2+2] cycloadditions with internal alkynes and isocyanates to form a variety of pyridones, eq 6 (Scheme 1). The authors report a wide range of selectivities (1:1 to >20:1) and good yields (63−94%), with the degree of selectivity highly alkyne dependent. The steric bulk of the ligand also appears to play a role. Also in 2005, Evans and co-workers[21a] explored [2+2+2] cycloadditions with alkynes and enynes, catalyzed by Rh(I) in combination with a phosphine. Impressively, these workers illustrate highly enantioselective synthesis of the cycloadducts using a variety of aryl propiolates, eq 7 (Scheme 1). In 2008, the Evans group again showed that a [3+2+2] cycloaddition could be performed in a similar fashion, eq 8 (Scheme 1). However, the internal alkynes were not used in the enantioselective reactions in this case.[21b] Also in 2008, Tanaka demonstrated control of axial chirality in

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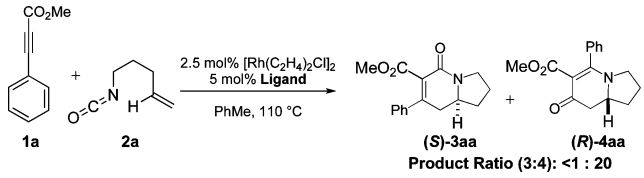
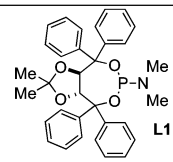
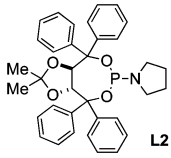
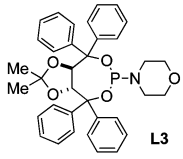
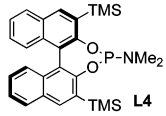
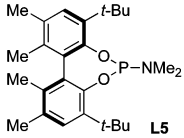
(21) (a) Evans, P. A.; Lai, K. W.; Sawyer, J. R. *J. Am. Chem. Soc.* **2005**, *127*, 12466. (b) Evans, P. A.; Inglesby, P. A. *J. Am. Chem. Soc.* **2008**, *130*, 12838.

Table 1. Ligand Screen



1a 2a

Entry[a]	Ligand	Yield (%)	ee(%)
1	 L1	68	58
2	 L2	50	73
3	 L3	31	58
4	 L4	68	86
5[b]	 L5	69	56

[a] All reactions conducted with **1a** (2 equiv), **2a** (1 equiv), $[Rh(C_2H_4)_2Cl]_2$ (0.025 equiv), **Ligand** (0.05 equiv) in PhMe at 110 °C, unless otherwise stated. [b] **1a** (1.2 equiv) used.

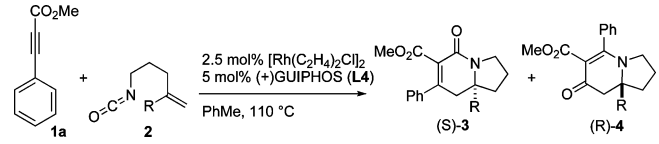
the [2+2+2] cycloaddition of diynes and tertiary alkynamides, eq 9 (Scheme 1).[22]

Our previous work[9] on the rhodium catalyzed [2+2+2] cycloaddition had introduced us to the potential challenges associated with unsymmetrical alkynes, the most significant being that the inherent steric and electronic difference present in the terminal alkynes would not necessarily be prevalent in internal alkynes. Extending the reaction to internal, unsymmetrical alkynes represents an important advance due to a great increase in reaction scope as well as a better understanding of the reaction mechanism. With these challenges in mind, we set out to determine the minimal steric and electronic difference necessary for the regio- and enantioselective [2+2+2] cycloaddition of internal alkynes with alkenyl isocyanates. Herein, we disclose our results.

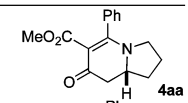
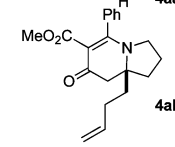
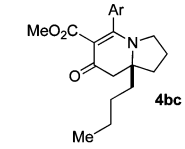
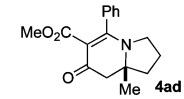
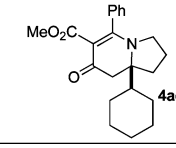
Results and Discussion

With the hope that a large electronic difference between ester and aryl functionalities would provide good selectivity, alkynoates were selected as our first unsymmetrical, internal alkynes. After choosing methyl phenylpropiolate (**1a**) as the test unsymmetrical alkyne, a brief ligand screen was conducted in order to determine amenable reaction conditions (Table 1). It should be noted that while all ligands gave a single regioisomer of the product (vinylogous amide **4**), GUIPHOS (**L4**) proved to be the best ligand for this substrate, both in terms of enantioselectivity and yield. Thus, this ligand was used to explore the unsymmetrical alkyne scope.

Table 2. Isocyanate Screen



1a 2

entry[a]	R	3 : 4[b]	yield (%)	ee (%) of 4[c]	Product
1	H, **2a**	< 1 : 20	68	86	 **4aa**
2	, **2b**	< 1 : 20	75	96	 **4ab**
3[d]	Me, **2c**	< 1 : 20	91	98	 **4bc**
4	Me, **2d**	< 1 : 20	90	98	 **4ad**
5	, **2e**	< 1 : 20	81	97	 **4ae**

[a] Reactions conducted with 2.5 mol % $[Rh(C_2H_4)_2Cl]_2$, 5 mol % GUIPHOS, 1 eq 2, 1.2 eq 1a in PhMe at 110 °C for 14 h, unless otherwise stated. [b] Regioisomers not observed by ^{1}H NMR (>20:1). [c] Determined by HPLC using a chiral stationary phase. [d] **1b** used in place of **1a**, due to ease of separation on HPLC.

After the initial success with GUIPHOS (**L4**) and the unsubstituted alkenyl isocyanate, we sought to explore the tolerance in the reaction to a variety of substitutions on the alkene (Table 2). While all reactions proceed in excellent yield, there is a marked increase in enantioselectivity when disubstituted alkenes are utilized. The constitution of this substitution does not appear to be important. In particular, entry 5 illustrates the efficiency that appears upon combination of an internal alkynoate and the catalyst based on GUIPHOS (**L4**). This result stands in stark contrast with the behavior of isocyanate **2e** with TADDOL-$PNMe_2$ (**L1**) and a terminal, aryl alkyne (19% yield).[23]

Due to the increased selectivity with substituted isocyanates (**2b**-**2e** vs **2a**, Table 2), the scope was broadened in two parallel

(22) Suda, T.; Noguchi, K.; Hirano, M.; Tanaka, K. *Chem.—Eur. J.* **2008**, *14*, 6593..

(23) From ref 9c:

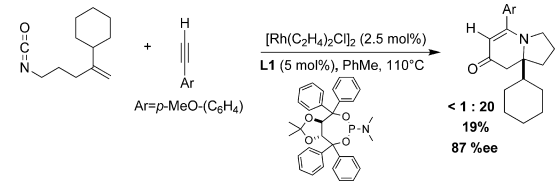
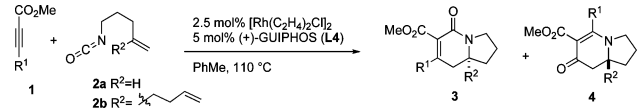
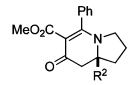
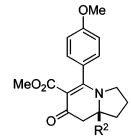
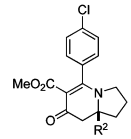
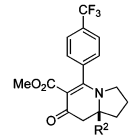
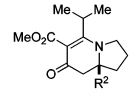
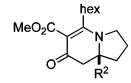
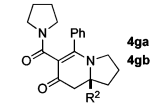
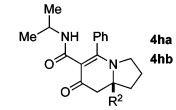
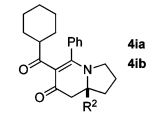
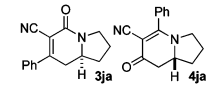
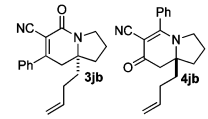
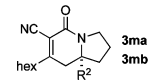


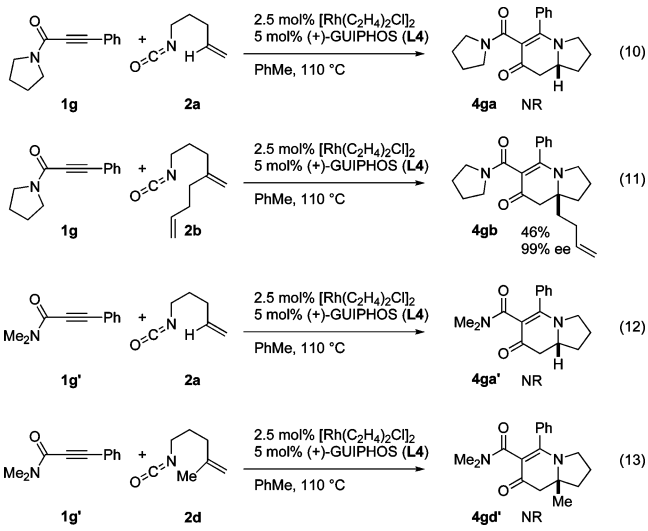
Table 3. Electron-Deficient Alkyne Scope



entry[a]	EWG—≡—R[1]		isocyanate	3 : 4	yield (%)	ee 3 (%)	ee 4 (%)	Major Product[b]	
1	MeO_2C—≡—Ph	**1a**	**2a**	< 1 : 20	68	-	86		**4aa**
2			**2b**	< 1 : 20	75	-	96		**4ab**
3	MeO_2C—≡—OMe	**1b**	**2a**	< 1 : 20	80	-	70		**4ba**
4			**2b**	< 1 : 20	94	-	93		**4bb**
5	MeO_2C—≡—Cl	**1c**	**2a**	<1 : 20	83	-	77		**4ca**
6			**2b**	<1 : 20	57	-	94		**4cb**
7	MeO_2C—≡—CF_3	**1d**	**2a**	< 1 : 20	33	-	82		**4da**
8			**2b**	< 1 : 20	29	-	96		**4db**
9	MeO_2C—≡—CHMe$_2$	**1e**	**2a**	<1 : 20	39	-	74		**4ea**
10			**2b**	<1 : 20	46	-	>99		**4eb**
11	MeO_2C—≡—hex	**1f**	**2a**	1 : 7	60	62	65		**4fa**
12			**2b**	1 : 2.5	60	62	96		**4fb**
13			**2a**	NR	-	-	-		**4ga**
14		**1g**	**2b**	<1 : 20	46	-	99		**4gb**
15			**2a**	<1 : 20	91	-	11		**4ha**
16		**1h**	**2b**	<1 : 20	85	-	56		**4hb**
17			**2a**	<1 : 20	40	-	90		**4ia**
18		**1i**	**2b**	<1 : 20	40	-	95		**4ib**
19	NC—≡—Ph	**1j**	**2a**	1 : 1	39	48	2		**3ja** **4ja**
20	NC—≡—Ph	**1j**	**2b**	1 : 1.5	61	32	87		**3jb** **4jb**
21	NC—≡—hex	**1k**	**2a**	> 20 : 1	31	80	-		**3ma**
22			**2b**	> 20 : 1	68	95	-		**3mb**

[a] See Table 2. [b] Single regioisomer detected by ^{1}H NMR. Regioisomer structure determined by NOE for select examples, with the rest assigned by analogy. See Supporting Information.

Scheme 2

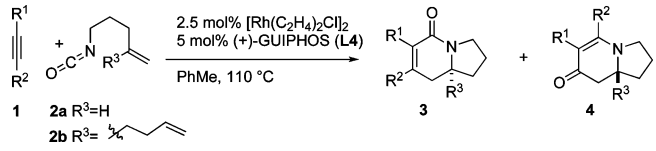


directions. We performed the cycloaddition with each new alkyne with the unsubstituted alkyne (**2a**) and a substituted counterpart (**2b**)[24] allowing for an investigation into whether or not the trend of increasing enantioselectivity held true for a variety of alkynoates. The results (entries 1−12, Table 3) show that the pattern holds for all alkynoates: substituted alkenyl isocyanates proceed with greater enantioselectivity (94−99%) when coupled with alkynoates compared to the unsubstituted counterparts. It should be noted that the obvious expansion to use carbodiimides[9d] as a π-component was attempted (∼25−30% yield); however, the products were extremely prone to oxidation that eliminated the stereocenter.

Electronic variation of the aryl alkynoates reveals a strong influence on reaction efficiency, with the most electron deficient alkyne (**1d**) proceeding in only 33% yield (entries 7, 8). This parallels the reactivity trend previously seen with electron-deficient terminal aryl alkynes.[9b] Steric hindrance appears to have the same effect on yield (entries 9, 10), with a more modest effect on enantioselectivity (entries 9 vs 11, 10 vs 12). The cycloadditions proceed with excellent product selectivity favoring the vinylogous amide product. A single regioisomer is observed in all cases (>20:1 regioselectivity determined by ^{1}H NMR). We next varied the nature of the electron-withdrawing group. The tertiary alkynamide **1g** does not behave as expected; **2b** reacts to provide product in moderate yield and excellent enantioselectivity. In contrast, **2a** fails to react with alkyne **1g**. Secondary amide **1h** did not present the same problem with reactivity. Both isocyanates (**2a**, **2b**) participate in the reaction with excellent yields. However, the enantioselectivities are surprisingly poor. This may be due to the coordination of the basic amide oxygen to the rhodium catalyst. The corresponding cyclohexyl ketone (entries 17, 18) behaves in a similar fashion

(24) **2b** was chosen due to its availability in bulk quantities.

Table 4. Electron-Neutral Alkyne Scope



1 **2a** R^3=H
2b R^3=

entry[a]	R^1—≡—R^2		isocyanate	3 : 4	yield (%)	ee 3 (%)	ee 4 (%)	Major Product
1	Et—≡—Ph	**1l**	**2a**	1 : 11	84	-	76	**4la**
2			**2b**	<1 : 20	50	-	83	**4lb**
3	Me—≡—Ph	**1m**	**2a**	1 : 10	94	-	71	**4ma**
4			**2b**	<1 : 20	70	-	72	**4mb**
5[b,c]	Cl—≡—Ph	**1n**	**2a**	1 : 5[d]	78	12[d]	20	**4na**
6[b,c]			**2b**	<1 : 20	53	-	91	**4nb**
7	Me—≡—	**1o**	**2a**	<1 : 20	57	-	33	**4oa**
8			**2b**	<1 : 20	65	-	45	**4ob**

[a] See Table 2. [b] Reaction stirred over 4 Å molecular sieves to remove residual water present in alkyne. [c] Five mol % $[Rh(C_2H_4)_2Cl]_2$, 10 mol % GUIPHOS. [d] The lactam adduct is generated as an apparent 2:1 ratio of inseparable regioisomers (determined by ^{1}H NMR).

to the alkynoates. The enantioselectivities are excellent, increasing when isocyanate **2b** is used. The yield is low, presumably due to the steric bulk of the ketone. The use of alkynyl nitriles (entries 19−22) shows a possible influence of size on product selectivity. The nitrile is much smaller than any of the carbonyls used in the study, which is likely the cause of the change in product selectivity for entries 19 and 20. When the alkynyl-R^1 group is exchanged from an aryl to an alkyl moiety, the product selectivity switches completely to the lactam.

The failure of tertiary amide **1g** to participate in the reaction with isocyanate **2a** (entry 13, Table 3 and eq 10 in Scheme 2) is worth an additional comment. Similar attempts with the corresponding dimethyl amide also failed, eq 12 in Scheme 2. This profound difference in behavior between the terminal and 1,1-disubstituted olefin isocyanate is puzzling. We speculated that the presence of the tethered terminal olefin on isocyanate **2b** plays a role in modifying the Rh coordination sphere potentially by occupying a site and displacing a competitive ligand. In support of this hypothesis, we note that subjection of isocyanate **2d**, bearing a 1,1-disubstituted alkene but lacking the second olefin, and the dimethylamide of phenylpropiolic acid to the reaction conditions fails to deliver cycloadduct, eq 13 in Scheme 2. The impact of the butenyl side chain must be exerted in an intramolecular fashion on an intermediate in the catalytic cycle. The electronic and steric similarities between the terminal alkene in the butenyl group with the terminal alkene in isocyanate **2a** likely eliminates the possibility that these effects occur by simple intermolecular coordination of the alkene to Rh.

In an effort to determine the minimal extent of the steric/electronic difference necessary for selectivity, we investigated simpler alkynes, again surveying both **2a** and **2b** as the isocyanate component in the reaction (Table 4). Entries 1 and 2 illustrate that an electronic difference as small as aryl versus alkyl is enough for the reaction to proceed efficiently, generating a single regioisomer with high product selectivity. The enantioselectivities in these cases remain roughly the same (71−83% ee), regardless of alkene substitution, in contrast with the alkynoates. Entries 5 and 6 (20 and 91% ee) show dependence of ee on the isocyanate. The chloro phenyl acetylene, which had been previously used successfully in ruthenium catalyzed [2+2] reactions,[25] shows aberrant behavior; this alkyne generates vinylogous amide adduct as a single regioisomer but forms the lactam adduct with **2a** as a 2:1 mixture of regioisomers (entry 5, Table 4).[26] This remains the only unselective alkyne insertion we have observed, and given that it forms lactam adduct selectively in the absence of phosphoramidite ligands, we suggest it arises by a fundamentally distinct mechanism.[27,28] Entries 7 and 8 show that a large steric difference is enough to control the regioselectivity of alkyne insertion. The large group is also sufficient to control product selectivity, favoring the vinylogous amide. These results, along with the failure of **1g** to react with **2a**, indicate that sterics, alongside electronics, play a profound role in the reaction outcome.

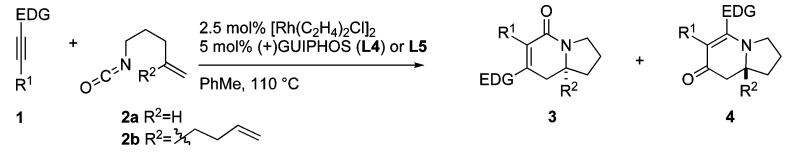
From the above results, it is clear that internal alkynes selectively form vinylogous amide products. That there is a large steric component to this effect is evident on the basis of our previous studies. Branched aliphatic terminal alkynes provide increased amounts of vinylogous amide adduct using the Rh•TADDOL system, as do aryl acetylenes.[9b] The use of both GUIPHOS (**L4**) and **L5** leads to selective formation of vinylogous amides even with small aliphatic alkynes such as 1-octyne.[9e] Diaryl alkynes provide vinylogous amides exclusively under the mediation of both Rh•PAr_3[9a] and Rh•GUIPHOS.[9f] We note that the steric model also explains the somewhat more modest selectivities seen for smaller alkynes. Alkyne **1f** provides the vinylogous amide in only 7:1 selectivity, comparable to that observed with 1-octyne (4:1).[9e] Lastly, the smallest alkyne investigated in this study, **1k**, leads to exclusive formation of lactam adduct.

To rationalize regioselectivity in these reactions, which we have noted is extremely high for all vinylogous amide adducts in this study, a simple steric model cannot be applied in most cases. The regioselective insertion of alkyne **1o** in the metalacycle leading to the selective formation of products **4oa** and **4ob** is best explained by sterics, but the preponderance of evidence, vis a vis the successful insertion of many polarized alkynes, suggests there is an electronic component to regioselectivity. In all cases, the stronger electron-releasing group is placed alpha to the nitrogen in the vinylogous amide adduct.

If this hypothesis is true, based on the data seen thus far and utilizing electronics as the primary factor governing insertion of the unsymmetrical alkynes, it stands to reason that any substitution more electron-releasing than phenyl should dictate regioselectivity and lead to inversion, placing the phenyl ring proximal to the carbonyl. We examined several groups in this light (ynol ethers, ynamides[29] and enynes) in an effort to test

(25) Jordan, R. W.; Villeneuve, K.; Tam, W. *J. Org. Chem.* **2006**, *71*, 5830.
(26) The reaction generates an apparent ~2:1 ratio (determined by ^{1}H NMR) of inseparable regioisomers of the lactam adducts, but a single vinylogous amide adduct. The HPLC trace indicates the presence of two pairs of enantiomers. The ^{13}C NMR also indicates the presence of two compounds. Thus, the lactam adducts were not fully characterized.
(27) A control experiment run in the absence of phosphoramidite ligand generated lactam selectively in 25−30% yield, also as a 2:1 ratio of regioisomers.
(28) Although unprecedented, mechanisms involving oxidative addition of Rh into the C−Cl bond cannot be discounted.

Table 5. Electron-Rich Alkynes

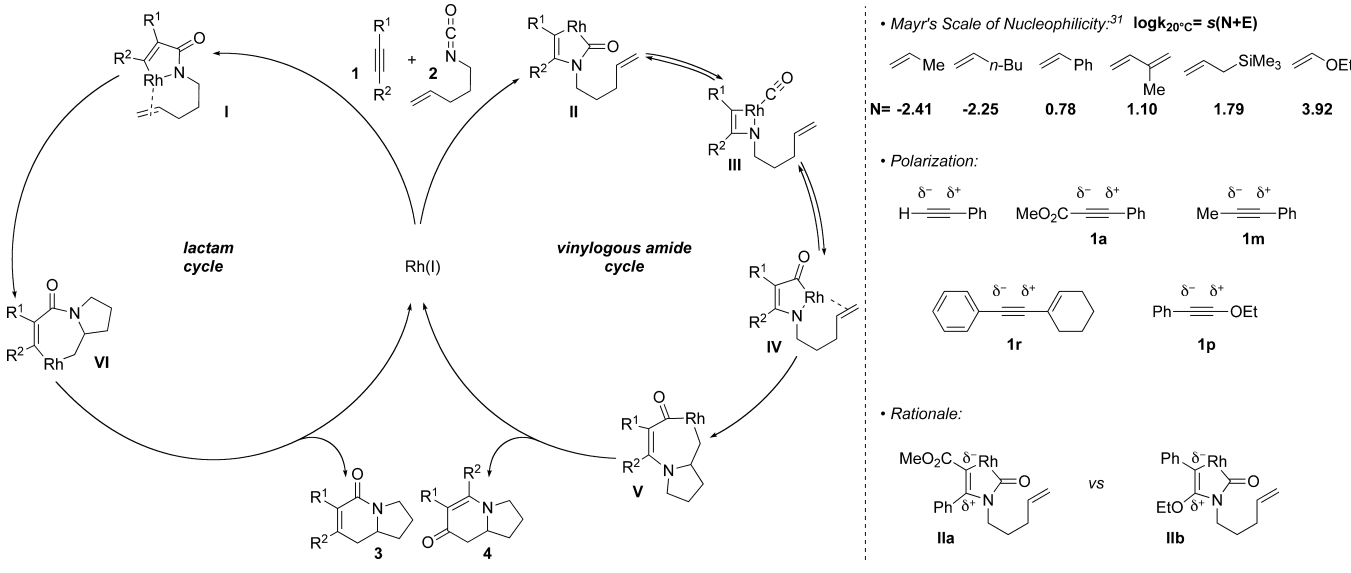


entry[a]	R^1—≡—EDG	isocyanate	3 : 4	yield (%)	ee (%) of 3	ee (%) of 4	Major Product
1	Ph—≡—OEt	2a	1 : 4	98	4	77	4pa
2	1p	2b	<1 : 20	98	-	97	4pb
3		2a	<1 : 20	56	-	52	4qa
4	1q	2b	<1 : 20	91	-	85	4qb
5		2a	<1 : 20[b,c]	90	-	90 minor 83 major	4ra
6	1r	2b	<1 : 20[b,d]	85	-	94 minor 92 major	4rb
7	Cy—≡—N	2a	<1 : 20[e]	80	-	ND	4sa
	1s						

major minor

[a] Regiochemistry was determined by NOE; see Supporting Information. [b] Inseperable mixture of regioisomers (10:1 favoring phenyl proximal to the carbonyl, **L5** as ligand). [c] The use of **L4** as ligand provides **4** with 5:1 regioselectivity. [d] The use of **L4** as ligand provides **4** with 3:1 regioselectivity. [e] Regioselectivity 1.2:1.

Scheme 3

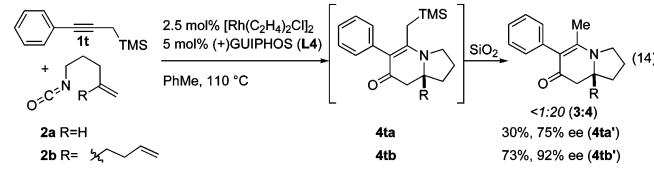


the limits of this hypothesis. Ynol ethers and ynamides each participate in the cycloaddition with a clean reversal of regioselectivity, placing the phenyl group proximal to the carbonyl moiety in the vinylogous amide (Table 5, entries 1−4). The low product selectivity observed with ynol ether **1p** and isocyanate **2a** is surprising but a control experiment run in the absence of phosphoramidite confirms the presence of a competing naked Rh-mediated cycloaddition forming the lactam.[30] Even a difference as small as cyclohexenyl versus phenyl (entries 5, 6) shows a distinct preference between regioisomers (10:1 with **L5**), which suggests that the electronic control is very sensitive.

Our proposed mechanism for the rhodium-catalyzed cycloaddition of alkenyl isocyanates and alkynes is shown in Scheme 3. Product selectivity is determined in the initial oxidative cycloaddition event generating intermediates **I** and **II**, entering the lactam and vinylogous amide catalytic cycles from a presumed common precursor. The high regioselectivities ob-

served in the alkyne insertion event may be explained using Mayr's scale of nucleophilicity.[31] To predict relative ability to stabilize an adjacent positive charge, we compared the Mayr nucleophilicities of several alkenes, (Scheme 3). The greater nucleophilicity (higher positive number) of a similar alkene corresponds to preference for insertion distal to the carbonyl group. However, one cannot exclude sterics entirely, as the large group also prefers to insert away from the carbonyl. To determine which property dominates, an alkyne was synthesized that possesses both an electronically donating group in addition to a sterically bulky group (entry 7, Table 5). Unfortunately, both sterics and electronics appear to exert similar control when placed in direct competition. Importantly, application of Mayr's nucleophilicity scale to alkyne substituents thus provides a polarization model that rationalizes observed selectivities. For example, the phenyl group better stabilizes a positive charge relative to both a carbomethoxy as well as an alkyl leading to alkyne polarizations for **1a** and **1m** (Scheme 3). On the other hand, the increased nucleophilicity of isoprene ($N = 1.10$) and ethyl vinyl ether ($N = 3.92$) relative to styrene ($N = 0.78$) results in an inversion of polarity of alkynes **1r** and **1p**, leading to the regioselective dichotomy between intermediates of type **IIa** and **IIb** (Scheme 3).

A closer examination of the Mayr scale suggests that propargyl silanes should participate with high regioselectivity, given the greater nucleophilicity of allylsilane relative to styrene (Scheme 3). The use of 3-phenyl propargyl silane **1t** in the cycloaddition exclusively provides vinylogous amide products with inversion of regioselectivity, eq 14. The intermediate γ-silyl enones (**4ta** and **4tb**) undergo a rapid protiodesilylation upon workup, affording a final product that is regioisomeric to the cycloadduct of phenylpropyne (contrast eq 14 with entries 3 and 4 in Table 4).



Conclusion

In summary, we have shown that unsymmetrical internal alkynes participate successfully in the rhodium-catalyzed [2+2+2] cycloaddition with alkenylisocyanates. We note nearly exclusive formation of vinylogous amide adducts in these reactions. We further observe very high regioselectivities with the vast majority of alkynes screened, and have delineated the factors responsible for controlling this sense of insertion. The successful development of this chemistry increases the synthetic utility of the rhodium-catalyzed [2+2+2] cycloaddition, thus allowing for predictable incorporation of internal unsymmetrical alkynes into indolizidine frameworks.

Acknowledgment. We thank NIGMS (GM80442) for support of this research. T.R. thanks the Monfort Family Foundation for a Monfort Professorship.

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

JA903899C

(29) Oppenheimer, J.; Hsung, R. P.; Figueroa, R.; Johnson, W. L. *Org. Lett.* **2007**, *9*, 3969.

(30) A reaction using 5 mol % $[Rh(C_2H_4)Cl]_2$, **1p** and **2a** in PhMe at 110 °C for 16 h provides lactam **3pa** in 34% yield with >20:1 product selectivity.

(31) (a) Mayr, H.; Ofial, A. R. *J. Phys. Org. Chem.* **2008**, *21*, 584. (b) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66.