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Copper(II)-Catalyzed Amidations of Alkynyl Bromides as a General Synthesis of Ynamides and *Z*-Enamides. An Intramolecular Amidation for the Synthesis of Macrocyclic Ynamides

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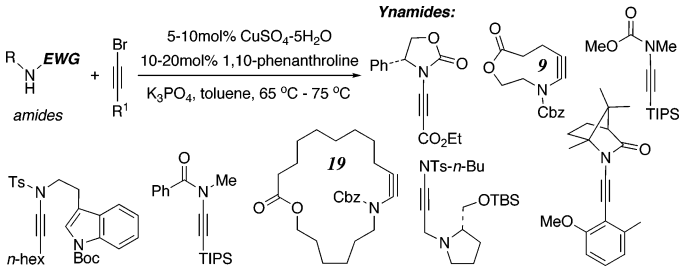

A general and efficient method for the coupling of a wide range of amides with alkynyl bromides is described here. This novel amidation reaction involves a catalytic protocol using copper(II) sulfate-pentahydrate and 1,10-phenanthroline to direct the sp-C−N bond formation, leading to a structurally diverse array of ynamides including macrocyclic ynamides via an intramolecular amidation. Given the surging interest in ynamide chemistry, this atom economical synthesis of ynamides should invoke further attention from the synthetic organic community.

Introduction

Ynamides have attracted much attention from the synthetic community in recent years.[1−4] A large number of new methodologies have been developed employing ynamides as a versatile organic building block, leading to the synthesis of a structurally diverse array of useful functional groups and carbocycles as well as heterocycles.[3,4] Depending on the reactivities involved, these transformations can be classified into two major categories: (1) those ynamides with reactivities similar to simple alkynes, such as metal-catalyzed cycloadditions, RCM, addition reactions, cross-coupling reactions, radical cyclizations, and other tandem reactions, and (2) those with reactivities based on the *in situ* generated ketene iminium intermediates such as sigmatropic rearrangements, Pictet−Spengler reactions, and enyne cyclizations.

At the very same time, the synthesis of ynamides[2,5−7] had largely suffered from harsh reaction conditions, laborious

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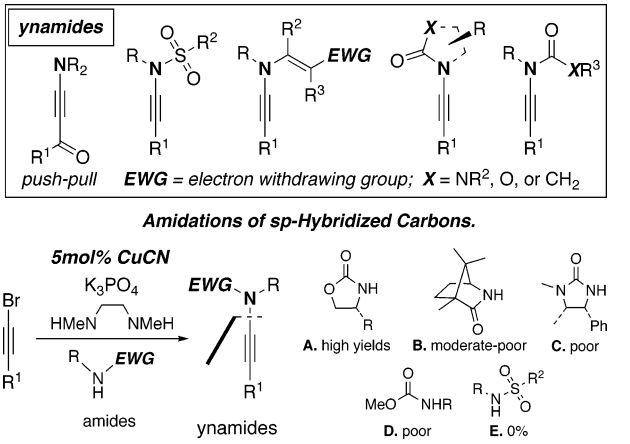
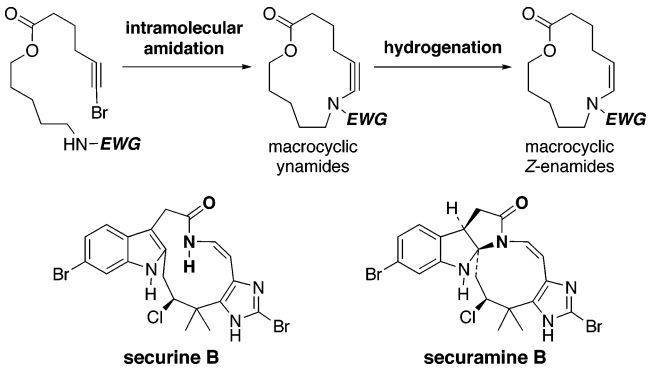
reaction sequence, and narrow substrate scope. This deficiency had seriously hindered the development of this field. Inspired by the seminal work from Buchwald's group on copper-catalyzed amidation of aryl halides,[8−13] known as the Goldberg reaction,[9] we communicated a methodology[14] for the ynamide synthesis that involved a direct cross-coupling of alkynyl bromides and amides catalyzed by Cu(I) salts (Scheme 1). This methodology represents the first practical C−N bond formation process involving sp-hybridized carbons[15] and offered an atom economical entry toward a more ideal synthesis of ynamides over the previously existing protocols.[5−7]

However, there had remained an unacceptable limitation within this new protocol, with oxazolidinones being the most useful amide substrates for the transformation. Other important classes of amides such as lactams, imidazolidinones, acyclic carbamates, and sulfonamides were all poor coupling partners.

SCHEME 1. Ynamides and Amidations of Alkynyl Bromides



SCHEME 2. An Intramolecular Amidation



Shortly after, Danheiser addressed this limitation by developing a stoichiometric copper(I)-mediated amidation protocol.[16] In their work, a stronger base, KHMDS, was employed to generate the desired copper amide species. A distinctly attractive feature of this coupling reaction is that it can proceed at room temperature, thereby allowing the preparation of thermally sensitive ynamides. Subsequently, Urabe and Sato[3k] documented their success examples of using sulfonamides in CuI-catalyzed amidation of alkynyl halides exactly where we had failed.

Despite these practical modifications, we decided to reinvestigate the effect of different combinations of copper salts and ligands on the efficiency of this C−N bond formation method. Consequently, we communicated a more efficient and general method for the synthesis of ynamides and heterocycle-substituted ynamines, featuring a copper sulfate−pentahydrate-1,10-phenanthroline driven catalytic system.[17] This success further allowed us to explore the possibility of achieving an intramolecular amidation for the synthesis of unique macrocyclic ynamides that can lead to macrocyclic enamides (Scheme 2). The inspiration came from macrocyclic enamide-containing natural products such as securine B and securamine B.[18] We report here the entire synthetic scope of this amidation of alkynyl halide, an interesting competing *N*-alkynylation, and development of an intramolecular amidation of alkynyl halides.

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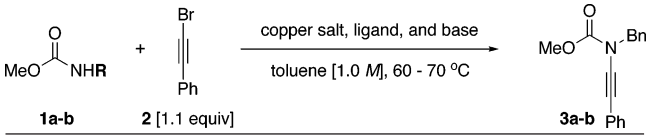
TABLE 1. Screening of Copper Salts, Ligands, and Bases



1a-b **2** [1.1 equiv] **3a-b**

entry	R	amide	copper salt[a] [mol %]	ligand[b]	base[c]	ynamide	% yield[d]
1	Bn	**1a**	CuCN [6.0]	DMEDA[e]	K_2CO_3	**3a**	0[f]
2	Bn	**1a**	CuCN [50.0]	DMEDA	K_2CO_3	**3a**	5−9[g,h]
3	Bn	**1a**	CuCN [5.0]	DMEDA	K_3PO_4	**3a**	7
4	Bn	**1a**	CuCN [20.0]	DMEDA	K_3PO_4	**3a**	17
5	Bn	**1b**	$CuSO_4$ [20.0]	DMEDA	K_3PO_4	**3a**	20
6	Bn	**1a**	$CuSO_4$ [10.0]	1,10-phen	K_3PO_4	**3a**	32[i]
7	Bn	**1a**	$CuSO_4$ [10.0]	1,10-phen	K_2CO_3	**3a**	5
8	Bn	**1a**	$CuSO_4$ [20.0]	1,10-phen	K_3PO_4	**3a**	73−79[h,j]
9	c-Hex	**1b**	$CuSO_4$ [10.0]	1,10-phen	K_2CO_3	**3b**	0[k]
10	c-Hex	**1b**	$CuSO_4$ [20.0]	1,10-phen	K_2CO_3	**3b**	15
11	c-Hex	**1b**	$CuSO_4$ [20.0]	1,10-phen	Cs_2CO_3	**3b**	0
12	c-Hex	**1b**	$CuSO_4$ [20.0]	1,10-phen	K_3PO_4	**3b**	46−60[l]

[a] $CuSO_4 = CuSO_4 \cdot 5H_2O$. [b] DMEDA = *N*,*N*′-dimethylethylenediamine; 1,10-phen = 1,10-phenanthroline. The ratio of copper salt:ligand = 1:2 in all cases, unless otherwise indicated. [c] 2.0 equiv was used in all cases. [d] Isolated yields. [e] 10 mol % of DMEDA was used. [f] Reported in entry 9 of Table 1 in ref 3b, and the temperature was 110 °C. [g] The temperature was 110 °C. [h] The range obtained from several trials. [i] Concentration = 0.5 M. The yield was only 19% when concentration = 1.0 M. [j] The yield was only 18% when the solvent and $CuSO_4$ were scrupulously dried. [k] Reported in entry 1 of Table 1 of ref 3b. [l] T = 80 °C and yields were lower at 50 and 110 °C.

Results and Discussion

1. Screening of Cu Salts, Ligands, and Bases. To develop a more general protocol for the preparation of ynamides, variables such as Cu salts, ligands, solvents, concentrations, and bases were carefully screened using acyclic carbamate **1a** and bromoalkyne **2** as the model substrates (see Table 1). Under original reaction conditions using 20 mol % of CuCN as the catalyst (entries 2−4) and 40 mol % *N*,*N*′-dimethylethylenediamine (DMEDA) as the ligand with K_3PO_4 as the base, the desired ynamide **3a**[19] was obtained in a best yield of 17% (entry 4) with the major reaction pathway being homocoupling of bromoalkyne **2**. Given this poor starting point, it was clear that a much better and more general amidation protocol was needed.

Without getting inundated by details of our screening efforts, which had been documented in our previous communications,[14,17] we re-examined the entire catalytic system. A brief screening of solvents confirmed that a nonpolar solvent such as toluene was the most effective in favor of the ynamide formation. Polar solvents such as DMF, NMP, and 2-ethoxyethanol favored homocoupling of bromoalkynes such as **2**. Subsequently, a series of readily available copper salts were carefully studied. While most of the copper species showed poor to moderate activities, an enhanced selectivity toward the ynamide formation was observed when using $CuSO_4 \cdot 5H_2O$ (entries 5−8). Further optimizations of ligands demonstrated that 1,10-phenanthroline is a more superior ligand than DMEDA while employing $CuSO_4 \cdot 5H_2O$ (entry 6 versus 5). When using 20 mol % of $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline as the ligand (entry 8), the desired ynamide **3a** was isolated in 73−79% yield. It is noteworthy that the yield dropped to 18% when $CuSO_4 \cdot 5H_2O$ was scrupulously dried.

However, another key difference is the base. Among the bases that we screened were K_3PO_4, K_2CO_3, Cs_2CO_3, KO*t*-Bu, and *n*-Bu_4NOH, and K_3PO_4 proves to be the base that led to the most consistent results, especially when amidations involve acyclic urethanes (or amides). Although our previous disclosures have suggested that the choice of the base is critical and that K_3PO_4 works the best for most amidations,[14,17] we would state here more explicitly that K_2CO_3 has failed in most amidations using *acyclic* urethanes (or *acyclic* amides) (see entry 2), as attested by Tam's recent report (entry 1).[3b] Even when employing the new catalytic system with $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline, K_3PO_4 remains a better choice than K_2CO_3 (entries 6 and 8 versus 7).

To further support the significance of using K_3PO_4 as the base in these amidations, we re-examined one of Tam's substrates (amidation using **1b**) that they had some real difficulties with[3b] (entry 9 in Table 1) even when employing $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline but with K_2CO_3 as the base.[3b] We repeated this reaction and found that, in our hands, we could only manage isolating the desired ynamides **3b** in 15% yield using K_2CO_3, even when we used 20 mol % of copper salt (entry 10). Interestingly, while Cs_2CO_3 gave 0% (entry 11), we isolated **3b** in 46−60% yield with several trials when K_3PO_4 was the base (entry 12). This difference is likely due to the pK_a's of amides, although we are not certain at this time of the exact rationale.

Finally, it is noteworthy that (1) the reaction was equally efficient in most cases using a sealed reaction flask without flushing and blanketing with an inert atmosphere and (2) the use of $CuSO_4 \cdot 5H_2O$ represents a catalytic protocol that is much cheaper and environmentally more acceptable than the original CuCN method. With a temperature range of 60−80 °C instead of 110 °C, this new protocol represents a much milder condition than the original one.

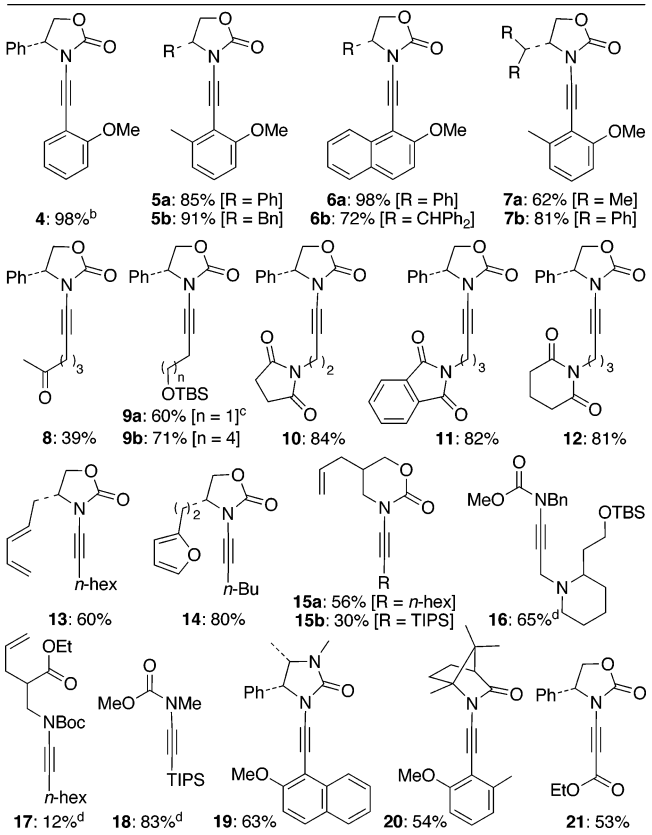
2. Carbamate, Urea, and Lactam-Substituted Ynamides. The scope of this new protocol was explored using a diverse array of bromoalkynes and amides (Table 2). We note that examples presented in this paper are new substrates that have not appeared in our previous communications.[14,17] These new coupling conditions employing $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline appeared to tolerate a wide range of substitutions on the bromoalkyne (Table 2). In addition to alkyl, aryl, and silyl groups, other relatively sensitive functional groups such as silyl ethers, imides, and ketones all survived the coupling conditions to afford the desired ynamides in good yields. Even sterically demanding alkynyl bromides coupled very efficiently to give the desired ynamides in very good yields (see **4**−**7**).

Oxazolidinones bearing different substitutions, including phenyl, benzyl, diene, and furyl substitutions, all participated in the coupling reaction with the desired oxazolidinone-substituted ynamides being isolated mostly in 60−98% yields (see **4**−**14**). Both K_2CO_3 and K_3PO_4 proved to be comparably efficient here for the cyclic oxazolidinone series. A six-membered ring carbamate was also reasonably effective for this amidation when Cs_2CO_3 or K_3PO_4 was used.

More importantly, formally poor substrates such as acyclic carbamates are now suitable for the coupling if K_3PO_4 was employed as the base (see **16**−**18**). As expected, the *N*-alkynylation of the Boc-protected carbamate proceeded at a much slower rate, which can be attributed to the steric effect of the bulky Boc group (see **17** isolated at <40% conversion). Finally, urea (see **19**) and lactam (see **20**) are also suitable for amidations, and we can effectively construct push−pull yna-

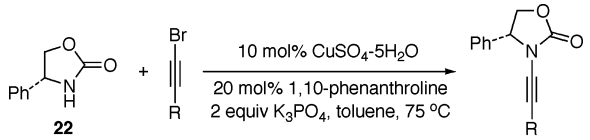
(19) See Supporting Information for details.

TABLE 2. Syntheses of Carbamate, Urea, and Lactam Substituted Ynamides[a]



[a] Reactions were carried out using 10 mol % $CuSO_4 \cdot 5H_2O$, 1,10-phen (2 equiv to copper), and 2.0 equiv of K_3PO_4, K_2CO_3, or Cs_2CO_3 in toluene (0.5−1.0 M based on amide) at 65−75 °C for 18−36 h. [b] Isolated yields. [c] 5 mol % CuCN and 10 mol % of DMEDA. [d] The reaction only proceeded well with the base being 2.0 equiv of K_3PO_4.

SCHEME 3. Large-Scale Preparations



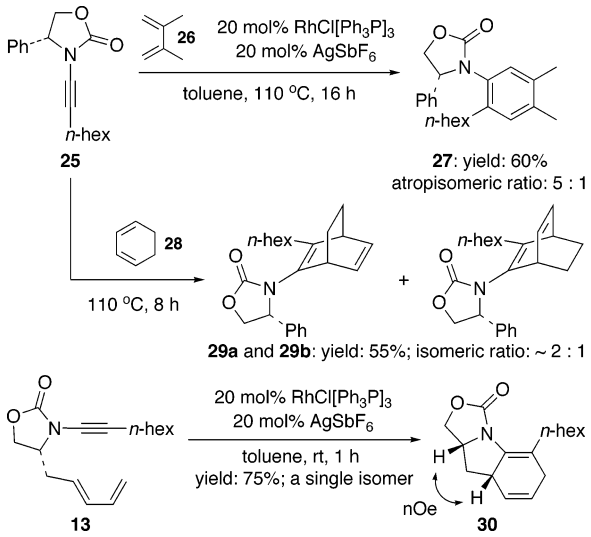
halide	R =	scale [mmols]	product	isolated yield [%]
23a	Ph	18	**24a**	60 [4.66 g]
23a	Ph	35	**24a**	71 [6.72 g]
23b	TIPS	48	**24b**	89 [14.63 g]
23b	TIPS	107	**24b**	86 [32.07 g]
23b	TIPS	109	**24b**	97 [35.73 g]

mides such as **21** by employing the $CuSO_4 \cdot 5H_2O$/1,10-phenanthroline catalytic system.

To demonstrate that this catalytic protocol is not limited in scale, we undertook a scale-up of our work. As shown in Scheme 3, ynamides such as **24a** and **24b** could be prepared in gram quantities. This realization is significant, because it allows one to envision ynamides being part of a linearly sequenced synthetic plan toward natural product syntheses.[4c]

The success in the preparation of diverse ynamides in a large quantity allows the flexibility to develop stereoselective methodologies employing chiral ynamides, which still represents a major directive that has not been undertaken at this point.[3b,k] We believe our amidation protocol should help advocate efforts toward this goal.

SCHEME 4. Rh(I)-Catalyzed Stereoselective Diels−Alder Cycloaddition



For example, as shown in Scheme 4, we were able to quickly demonstrate that Witulski's elegant intramolecular ynamide-Diels−Alder cycloaddition method[20,21] could be rendered stereoselective using chiral ynamides. While chiral ynamide **25** was feasible for intermolecular reactions, leading to interesting cycloadducts such as chiral anilide **27** and bicyclic chiral enamide **29a/b** (∼2:1 ratio, but unassigned), the stereoselectivity was not good. However, we could prepare tetrahydroindole **30** in 75% yield as a single diastereomer from chiral ynamide **29** via a Rh(I)/$AgSbF_6$-catalyzed[20] Diels−Alder cycloaddition.

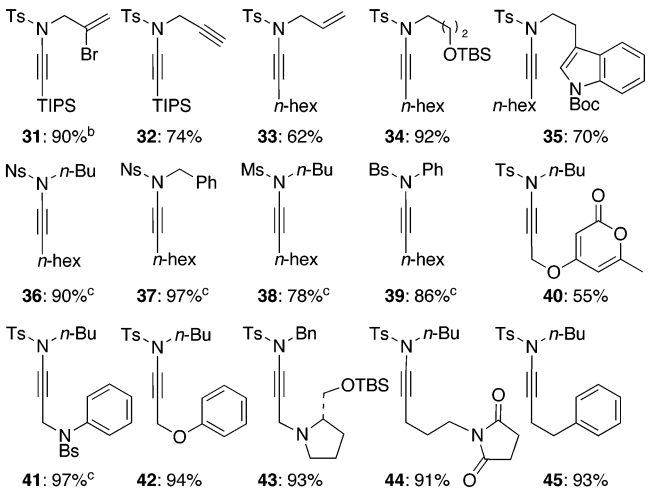
3. Sulfonyl-Substituted and Simple Ynamides. Most significantly, this new amidation protocol proves to be extremely efficient for the preparation of sulfonyl-substituted ynamides. Sulfonyl-substituted ynamides are important because they have been most prominently displayed in an array of elegant methodologies.[1−3] A diverse array of sulfonyl-substituted ynamides has been prepared to illustrate the range of functionalities on the amide nitrogen (Table 3).

In addition to simple alkyl and aryl, other functionalities such as vinyl bromide, propargyl, allyl, silyl ether, and Boc-protected indole can tolerate the coupling conditions to give the corresponding ynamides in good to excellent yields (see **31**−**35**). Successful formation of the ynamide **32**, bearing a terminal alkyne, is quite encouraging, since a copper-catalyzed Glaser-type coupling of the terminal alkyne with bromoalkyne was originally expected to be a major competing pathway. Substitutions on the sulfonyl groups were also studied, indicating that Bs, Ns, and Ms are also viable sulfonamides for the amidation (see **36**−**39**). No noticeable rate or efficiency difference was observed, with all the ynamides being obtained in excellent yields

The effect of various functionalized bromoalkynes on the efficiency of the coupling reactions was investigated (see **40**−

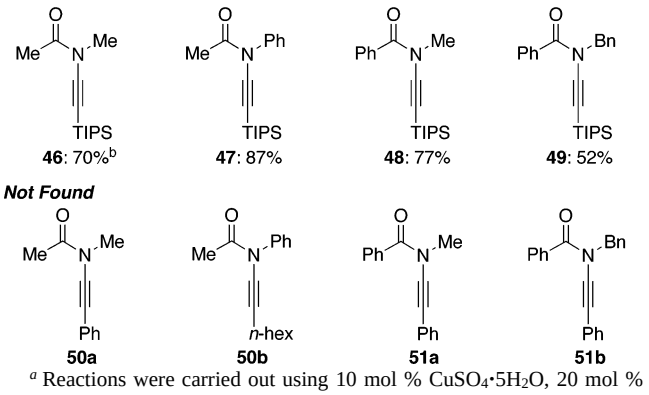
(20) Witulski, B.; Lumtscher, J.; Bergsträsser, U. *Synlett* **2003**, 708.
(21) For reviews, see: (a) Varela, J A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (b) Rubin, M.; Sromek, A. W.; Gervorgyan, V. *Sylett* **2003**, 2265. (c) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (d) Saito, S. Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (e) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (f) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (g) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523. (h) Hegedus, L. S. *Coord. Chem. Rev.* **1997**, *161*, 129. (d) Wender, P. A.; Love, J. A. In *Advances in Cycloaddition*; JAI Press: Greenwich, 1999; Vol. 5, pp 1−45.

TABLE 3. Syntheses of Sulfonyl Substituted Ynamides[a]



[a] Reactions were carried out using 10 mol % $CuSO_4 \cdot 5H_2O$, 1,10-phen (2 equiv to copper), and 2.0 equiv of K_2CO_3 in toluene (0.5−1.0 M based on amides) at 65−75 °C for 18−36 h. [b] Isolated yields. [c] Ns = 4-nitrobenzene sulfonyl; Ms = methane sulfonyl; Bs = benzene sulfonyl.

TABLE 4. Syntheses of Simple Ynamides[a]



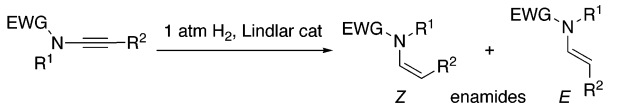
[a] Reactions were carried out using 10 mol % $CuSO_4 \cdot 5H_2O$, 20 mol % 1,10-phen, and 2.0 equiv of K_3PO_4 in toluene at 80 °C for 18−36 h. [b] Isolated yields.

45). To our delight, a wide range of ynamides with novel structural features on the alkynes, including propargyl pyrone, propargyl anilide, propargyl phenol, pyrrolidine, imide, and aryl were obtained efficiently using the new protocol. A relatively lower yield was observed on ynamide **40** due to the instability of the corresponding bromoalkyne. We should note that the nature of the base is not critical in these amidations.

Finally, the synthesis of simple ynamides such as **46**−**49** in which the nitrogen atom is substituted with a simple acetyl or benzyol group could be achieved in good yields employing $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline with K_3PO_4 as the base (Table 4). Although for reasons we are not certain of at this time, we were unable to prepare ynamides **50**−**51**, ynamides **46**−**49** should be more versatile given the removable TIPS group, and we have in part addressed a frequently asked question whether one can access these simple ynamides in lieu of other useful ongoing methodological development.

4. Stereoselective Synthesis of *Z*-Enamides. One of the simplest applications of ynamides would be to prepare enamides via Lindlar-type hydrogenations, which has not been accomplished. There had been no real reason to prepare enamides through this method when ynamides were not readily available, especially given the existing methods for the synthesis of

TABLE 5. Hydrogenations of Ynamides



entry	enamides	solvent	Pd-mol%[a]	T [°C]	time [h]	yield [%][*Z* : *E*][b]
1	**52a**: R = *n*-hex	EtOAc	5.0[c]	rt	0.5	91 [92 : 8]
2	**52a**: R = *n*-hex	CH_2Cl_2	5.0	rt	5	87 [≥ 95 : 5]
3	**52b**: R = TIPS	EtOAc	2.5	rt	7	90 [86 : 14]
4	**52b**: R = TIPS	EtOAc	2.5	0	20	90 [80 : 20]
5	**52c**: R = Ph	CH_2Cl_2	5.0	rt	24	95 [≥ 95 : 5]
6	**52d**: R = H	CH_2Cl_2	5.0	rt	0.5	95 [≥ 95 : 5]
7	**53**	CH_2Cl_2	5.0	rt	7	87 [≥ 95 : 5]
8	**54**	CH_2Cl_2	5.0	rt	18	60 [≥ 95 : 5]
9	**55**	CH_2Cl_2	5.0	rt	28	85 [≥ 95 : 5]
10	**56**	EtOAc	5.0	rt	4	42 [52 : 48]
11		EtOAc	5.0	0	1.5	46 [62 : 38]
12		EtOAc	1.0[c,d]	rt	4	70 [≥ 95 : 5]

[a] Lindlar catalyst: 5% w/w Pd on $CaCO_3$ support poisoned with Pb. The mol % here represents the actual amount of Pd present. [b] All are isolated yields. All *Z*:*E* ratios were determined by ^1H NMR. [c] Quinoline was added. [d] Pd on $BaSO_4$.

enamides.[2b,8,10,12,22,23] However, given that a diverse array of ynamides can be prepared via this catalytic amidation, preparation of enamides via hydrogenations of ynamides, especially those *Z*-enamides, which remains challenging kinetically, can represent a quite attractive option. More significantly, we pursued this endeavor because enamides represent another unique functional group that has not been widely studied,[22,24,25] and they are frequently found in natural products.[26]

As shown in Table 5, the concept of preparing a wide range of *Z*-enamides via Lindlar hydrogenations of ynamides can be established. While the yields of these hydrogenations are generally high as expected, the *Z*: *E* ratio is not great in some special instances (entries 3, 4, 10, and 11). Specifically, we found that bulky substituents such as TIPS (**52b**) and Ph (**52c**) tend to retard the rate of hydrogenation (entries 3−5), and while the rate may not play a role in the selectivity, it appears that the TIPS group presents a problem in attaining high *Z*-selectivity (entries 3 and 4), even when the hydrogenation was carried out at 0 °C. The other instance involved the synthesis enamide **56** (entry 10−12), but we were able to improve its ratio by

(22) Rappoport, Z. *The Chemistry of Enamides in the Chemistry of Functional Groups;* John Wiley and Sons: New York, 1994.
(23) For a recent elegant report on the synthesis of enamides, see: Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845.
(24) For recent applications of the chemistry of enamides, see: (a) Sivaguru, J.; Saito, H.; Poon, T.; Omonuwa, T.; Franz, R.; Jockusch, S.; Hooper, C.; Inoue, Y.; Adam, W.; Turro, N. J. *Org. Lett.* **2005**, *7*, 2089. (b) Robiette, R.; Cheboub-Benchaba, K.; Peeters, D.; Marchand-Brynaert, J.; *J. Org. Chem.* **2003**, *68*, 9809. (c) Poon, T.; Turro, N. J.; Chapman, J.; Lakshminarasimhan, P.; Lei, X.; Jockusch, S.; Franz, B.; Washington, I.; Adam, W.; Bosio, S. G. *Org. Lett.* **2003**, *4*, 4951. (d) Padwa, A.; Danca, M. D. *Org. Lett.* **2002**, *4*, 715. (e) Fuch, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3349. (f) Maeng, J.-H.; Funk, R. L. *Org. Lett.* **2000**, *2*, 1125.
(25) For our own work on the chemistry of enamides: see: Xiong, H.; Hsung, R. P.; Shen, L.; Hahn, J. M. *Tetrahedron Lett.* **2002**, *43*, 4449.
(26) Yet, L. *Chem. Rev.* **2003**, *103*, 4283.

SCHEME 5. *Z*- and *E*-Enamides

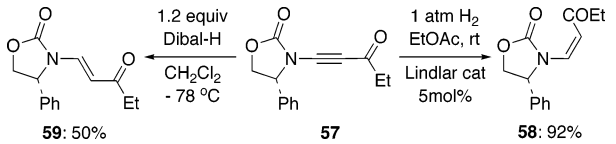
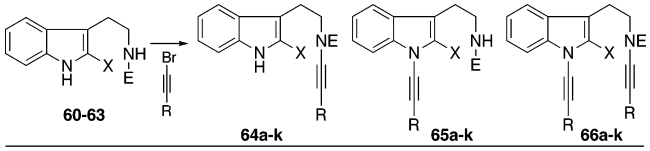


TABLE 6. Competing Amidation in the Indole Series[a]



entry	indole	X	E	R	products	% yields[b]/ ratios[c]	% yield **66a−k**
a	**60**	H	Ts	$(CH_2)_3Cl$	**64a**, **65a**	55/7:1	15
b	**60**	H	Ts	$(CH_2)_3OBn$	**64b**, **65b**	69/9:1	20
c	**60**	H	Ts	*n*-Hex	**64c**, **65c**	64/12:1	ND[d]
d	**60**	H	Ts	*n*-Bu	**64d**, **65d**	66/10:1	ND
e	**60**	H	Ts	Ph	**64e**, **65e**	63/11:1	ND
f	**60**	H	Ts	$CH_2OTBDPS$	**64f**, **65f**	64/18:1	ND
g	**60**	H	Ts	$(CH_2)_4OTBS$	**64g**, **65g**	60/10:1	ND
h	**60**	H	Ts	$(CH_2)_2CH(OEt)_2$	**64h**, **65h**	63/15:1	ND
i	**61**	H	Ns	*n*-Hex	**64i**, **65i**	55/≥25:1	ND
j	**62**	H	CO_2Me	*n*-Hex	**64j**, **65j**	62/≤1:25	ND
k	**63**	Br	Ts	*n*-Hex	**64k**, **65k**	65/≤1:25	15

[a] Reactions were carried out using 10 mol % $CuSO_4 \cdot 5H_2O$, 1,10-phen (2 equiv to copper), and 2.0 equiv of K_2CO_3 in toluene (0.5−1.0 M based on amide) at 65−75 °C for 18−36 h. [b] Isolated yields. [c] Ratios were determined using ^1H NMR. [d] ND = Yields not determined, for they were generally <5%.

employing quinoline-poisoned Pd−$BaSO_4$ (entry 12). We believe that the *E*-isomer is a result of isomerization during the reaction and/or purification thereafter.

Finally, we were able to employ the push−pull ynamide **57** to demonstrate that both *Z*- and *E*-enamide (**58** and **59**) could be accessed, respectively, in high selectivity depending upon the reductive conditions used (Scheme 5).

5. Observation of a Competing *N*-Alkynylation. It is very intriguing that a competing *N*-alkynylation was observed in the preparation of tryptamide-substituted ynamides. During our studies toward utilizing ynamides in the natural product synthesis,[4c] we needed to prepare a series of tryptamide-substituted ynamides **64a−k** (Table 6), a key precursor for the subsequent ketene iminium Pictet−Spengler cyclization reaction en route to total syntheses of indole alkaloids desbromoarborescidine A and C,[4c,27−29] However, in our attempts, we found unexpected competing *N*-alkynylation from the indolyl nitrogen atom, leading to ynamides **65** as well as bis-coupled product **66**.

Our studies revealed that the relative acidities of the indolyl NH and amide proton had likely played a significant role in the amidation reaction. While the desired ynamides **64a−h** were obtained as major products with a range of different alkynyl bromides when the tryptamine nitrogen atom was substituted with a Ts group (tryptamide **60** for entries a−h in Table 6), the indolyl *N*-alkynylation products **65a−h**, which are inseparable from ynamides **64a−h**, were produced consistently throughout as minor products with the ratio ranging from 7:1 to 18:1. Only when employing a stronger electron-withdrawing Ns group, as shown in tryptamide **61** (entry i), was production of the minor product **65i** completely eliminated. The bis-*N*-alkynylated products **66a−i**, however, were observed in all cases.

Intriguingly, our attempt to construct ynamide **64j** using the carbamate-protected tryptamide **62** led to the indolyl *N*-alkynylation product **65j** exclusively in 62% yield (entry j). Please note that K_2CO_3 was chosen as the base to be consistent with the other entries, and it turned out to be suitable in this particular amidation. Furthermore, substitutions on the indole also had a significant effect on the selectivity. The indolyl *N*-alkynylation product **65k** became the sole dominant product when *N*-*p*-toluenesulfonyl 2-bromotryptamide **63** was employed. The desired ynamide **64k** was not observed at all (entry k).

These selectivities are likely associated with their respective pK_a's, and the amidation favors the more acidic nitrogen site. For example, the pK_a of aryl sulfonamido-NH is ∼16.1 (in DMSO),[30] while the indolyl-NH is less acidic with a pK_a of 21.0 (DMSO),[31] Thus, the *N*-alkynylation favored the aryl sulfonamide nitrogen atom (entry a−h), and when using the Ns group, the *N*-alkynylation of sulfonamide was the only observed product, presumably because the acidity of Ns-NH is even higher (entry i). On the other hand, the pK_a of a urethane-NH is approximately 24.8 (in DMSO).[30] In this comparison, the indolyl-NH is now relatively more acidic with a pK_a of ∼21.0 (in DMSO),[31] the *N*-alkynylation in this case was observed to favor the indolyl nitrogen atom (entry j).

Unfortunately, we could not find the exact pK_a of 2-bromoindolyl-NH in the literature, but 5-bromo-indolyl-NH is more than a magnitude more acidic than indolyl-NH,[32] and thus, 2-bromo indolyl-NH should approach the pK_a of aryl sulfonamide-NH or could actually be more acidic, leading to a favored *N*-alkynylation of the indolyl nitrogen atom. While mechanistically we have thus far followed those proposed by Buchwald[8,10] in amidation of vinyl halides given the similarity between these amidations, this selectivity has not been observed before. Thus, this could provide future mechanistic insights to this copper-catalyzed *N*-alkynylation and other related amidation reactions.

6. Intramolecular Amidations. To develop an intramolecular variant of this amidation,[33] we prepared amides **67a** and **67b** tethered to the alkynyl bromide motif (Scheme 6). Without much fanfare, the proposed intramolecular amidation proceeded smoothly to give 13-membered ring macrocyclic ynamides **68a** and **68b** in 80% and 96% yield, respectively, even with the base being K_2CO_3. Subsequent hydrogenation of **68a** gave macrocyclic enamide **69a** in 95% yield with exclusively *Z*-selectivity, thereby establishing in principle that we could pursue the synthesis of macrocyclic *Z*-enamide natural products such as securine B and securamine B[18] via this intramolecular amidation−Lindlar hydrogenation sequence. We were able to

(27) (a) For isolation of 10-desbromoarborescidine A, see: Johns, S. R.; Lamberton, J. A.; Occolowitz, J. L. *Aust. J. Chem.* **1966**, *19*, 1951. (b) For isolation of arborescidine A−D, see: Chbani, M.; Païs, M. *J. Nat. Prod.* **1993**, *56* 99.

(28) For total syntheses of arborescidine A, see: (a) Hua, D. H.; Bharathi, S. N.; Panangadan, J. A. K.; Tsujimoto, A. *J. Org. Chem.* **1991**, *56*, 6998. (b) Meyers, A. I.; Sohda, T.; Loewe, M. F. *J. Org. Chem.* **1986**, *51*, 3108.

(29) For total syntheses of arborescidine C, see: (a) Burm, B. E. A.; Meijler, M. M.; Korver, J.; Wanner, M. J. Koomen, G.-J. *Tetrahedron* **1998**, *54*, 6135. (b) Santos, L. S.; Pilli, R. A.; Rawal, V. H. *J. Org. Chem.* **2004**, *69*, 1283.

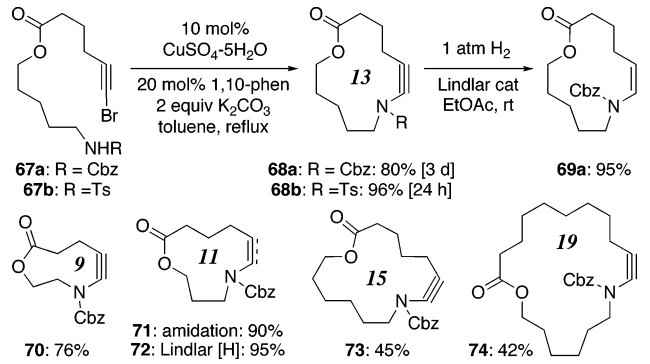
(30) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

(31) Bordwell, F. G.; Drucker, G. E.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 632.

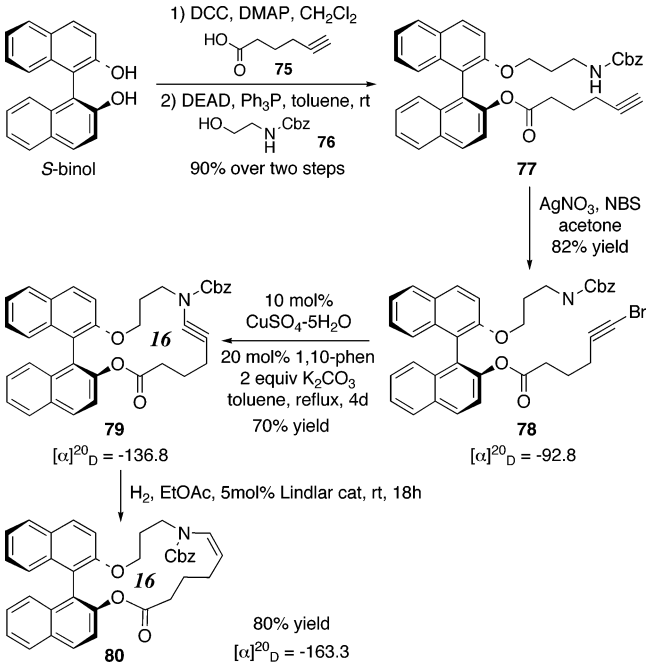
(32) Muñoz, M. A.; Guardado, P.; Hidalgo, J.; Carmona, G.; Balón, M. *Tetrahedron* **1992**, *48*, 5901.

(33) For some recent examples of Cu(I)-catalyzed intramolecular amidations, see: (a) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035. (b) Yang, T.; Lin, C.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2005**, *7*, 4781.

SCHEME 6. Intramolecular Amidations



SCHEME 7. A Chiral Macrocyclic Ynamide



explore the scope of this intramolecular amidation by preparing a nine-membered ring (**70**) all the way up to a 19-membered ring system (**74**), although yields began to diminish with increasing entropy.

While this intramolecular amidation should find applications in natural products syntheses, we prepared a chiral macrocyclic ynamide **79** and its corresponding macrocyclic enamide **80** from *S*-binol in good overall yields, employing a general sequence for the preparations of most of aforementioned amidation precursors (Scheme 7). These 16-membered chiral macrocyclic amides possess high optical rotations, and these rotations progressively increased from the acyclic compound (see **78**) to the *Z*-enamide **80**. This exercise suggests that the intramolecular amidation may find utilities in synthesizing structurally interesting macrocyclic materials for non-natural product oriented endeavors.

Conclusion

We have developed highly useful copper(II) salt catalyzed inter- and intramolecular amidations of alkynyl bromides that provide a general entry to a diverse array of ynamides. Given the emerging interest in ynamides, this synthetic protocol should have a significant impact on the future applications of ynamides in organic synthesis.

Experimental Section

A. For Ynamides from Tables 1−4. To a mixture of an amide (1.0 equiv), K_3PO_4 or K_2CO_3 (2.0 equiv), $CuSO_4 \cdot 5H_2O$ (0.10 equiv), and 1,10-phenanthroline (0.20 equiv) in a reaction vial was added a solution of a respective 1-bromoalkyne (1.1 equiv, 1.0 M) in toluene. The reaction mixture was capped and heated in an oil bath at 65−75 °C for 32 h while being monitored with TLC analysis. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc and filtered through Celite, and the filtrate was concentrated in vacuo. The crude products were purified by silica gel flash column chromatography (gradient eluent, EtOAc in hexane) to afford the desired ynamide.

B. For Ynamides of the Indole Series in Table 6. To a mixture of an amide (1.0 equiv), K_3PO_4 (1.2 equiv), $CuSO_4 \cdot 5H_2O$ (0.1 equiv), and 1,10-phenanthroline (0.2 equiv) in a reaction vial was added a solution of respective 1-bromoalkyne (1.2 equiv, 0.66 M) in DMF/toluene (1/10). The reaction mixture was capped and heated in an oil bath at 75 °C for 32 h while being monitored with TLC analysis. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc, and filtered through Celite, and the filtrate was concentrated in vacuo. The crude products were purified by silica gel flash column chromatography (gradient eluent, EtOAc in hexane) to afford the desired ynamide.

Ynamide 4: $[\alpha]^{20}_D = -205.9$ (*c* 2.75, CH_2Cl_2); IR (thin film) 3070 (w), 2966 (w), 2254 (w), 1774 (s), 1596 (m), 1497 (m), 1460 (m), 1403 (s), 1250 (s), 1197 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.73 (s, 3 H), 4.32 (dd, 1 H, J = 7.0, 8.5 Hz), 4.78 (dd, 1 H, J = 8.5, 8.5 Hz), 5.17 (dd, 1 H, J = 7.0, 8.5 Hz), 6.81 (t, 1 H, J = 7.5 Hz), 6.82 (t, 1 H, J = 7.5), 7.18−7.25 (m, 2 H), 7.40−7.48 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 62.1, 69.0, 70.6, 81.5, 110.5, 111.2, 120.1, 126.8, 129.0, 129.2, 129.4, 133.2, 136.0, 155.3, 159.7; mass spectrum (APCI) *m*/*e* (% relative intensity) 294 (14) $(M + H)^+$, 268 (100), 250 (5), 120 (4); HRMS (ESI) calcd for $C_{18}H_{15}NO_3Na$ 316.0944, found 316.0946.

Ynamide 34: IR (film) 2955 (s), 2930 (s), 2859 (s), 2048 (s), 1686 (w), 1471 (w), 1090 (m) cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 1.20−1.57 (m, 8 H), 1.73−1.86 (quint, 2 H, J = 6.6 Hz), 2.25 (t, 2 H, J = 6.9 Hz), 2.43 (s, 3 H), 3.36 (t, 2 H, J = 6.6 Hz), 3.63 (t, 2 H, J = 6.3 Hz), 7.32 (d, 2 H, J = 8.1 Hz), 7.78 (d, 2 H, J = 8.1 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ −5.7, 14.1, 18.3, 18.5, 21.6, 22.6, 25.9, 28.5, 28.9, 31.0, 31.4, 48.6, 59.8, 70.2, 73.2, 127.7, 129.6, 134.6, 144.3; mass spectrum (ESI) *m*/*e* (% relative intensity) 474.3 (100) $(M + Na)^+$, 452.3 (18) $(M + H)^+$; HRMS (ESI) calcd for $C_{24}H_{41}NO_3SSiNa$ 474.2469, found 474.2473.

Ynamide 46: R_f = 0.50 (20% EtOAc in hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 21H), 2.35 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1, 18.4, 22.0, 35.8, 69.7, 99.6, 172.3; IR (thin film) 2944 (s), 2866 (s), 2171 (s), 1707 (s), 1463 (m) cm^{-1}; HRMS (EI) calcd for $C_{14}H_{28}NOSi$ $(M + H^+)$ 254.1935, found 254.1932.

Ynamide 64a: IR (thin film) 3414 (s), 3056 (w), 2924 (m), 2254 (m), 1597 (m), 1493 (w), 1457 (m), 1428 (w), 1354 (s), 1186 (w), 1166 (s), 1092 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.96 (q, J = 6.6 Hz, 2 H), 2.46 (s, 3 H), 2.53 (t, J = 6.6 Hz, 2 H), 3.13 (t, J = 7.5 Hz, 2 H), 3.64 (m, 4 H), 7.12−7.42 (m, 6 H), 7.59 (d, J = 7.8 Hz, 1 H), 7.76 (d, J = 8.4 Hz, 2H), 8.04 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 21.5, 24.0, 31.3, 43.5, 51.6, 68.4, 74.0, 111.1, 111.6, 118.4, 119.4, 122.0, 122.2, 127.1, 127.4, 128.9, 134.5, 136.1, 144.3; mass spectrum (APCI) *m*/*e* (% relative intensity) 413(100) $(M+H)^+$; HRMS (ESI) calcd for $C_{22}H_{23}ClN_2O_2SNa$ 437.1061, found 437.1070.

Ynamide 65j: IR (film) 3338 (brs), 2931 (s), 2858 (m), 2264 (m), 1723 (s), 1704 (s), 1530 (m), 1461 (m), 1256 (m), 1233 (m) cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.01 (t, 3 H, J = 6.9 Hz),

1.38−1.78 (m, 8 H), 2.54 (t, 2 H, J = 6.9 Hz), 2.97 (t, 2 H, J = 6.6 Hz), 3.53 (q, 2 H, J = 6.6 Hz), 3.68 (s, 3 H), 5.05 (s, 1 H), 7.09 (s, 1 H), 7.26 (ddd, 1 H, J = 0.9, 7.2, 8.1 Hz), 7.38 (ddd, 1 H, J = 0.9, 7.2, 8.1 Hz), 7.58 (dt, 1 H, J = 8.1, 0.9 Hz), 7.64 (d, 1 H, J = 8.1 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 13.7, 18.2, 22.4, 25.3, 28.4, 28.9, 31.2, 40.7, 51.6, 70.0, 71.5, 110.9, 114.9, 118.9, 121.0, 123.2, 126.4, 127.2, 138.6, 156.8; mass spectrum (ESI) *m*/*e* (% relative intensity) 349.3 (100) $(M + Na)^+$, 327.3 (4) $(M + H)^+$; HRMS (ESI) calcd for $C_{20}H_{26}N_2O_2Na$ 349.1886, found 349.1877.

Ynamide 66a: IR (thin film) 3060 (w), 2960 (m), 2925 (m), 2872 (w), 2264 (m), 1597 (m), 1464 (m), 1363 (m), 1168 (m), 1119 (m), 1092 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.89−1.96 (m, 2 H), 2.07−2.13 (m, 2 H), 2.43 (s, 3 H), 2.49 (t, 2 H, J = 7.2 Hz), 2.70 (t, 2 H, J = 7.2 Hz), 3.04 (t, 2 H, J = 7.2 Hz), 3.58−3.63 (m, 4 H), 3.76 (t, 2 H, J = 6.5 Hz), 6.94 (s, 1 H), 7.20 (t, 1 H, J = 8.0 Hz), 7.25 (d, 2 H, J = 8.0 Hz), 7.31 (t, 1 H, J = 8.0 Hz), 7.47 (d, 1 H, J = 8.0 Hz), 7.51 (d, 1H, J = 8.0 Hz), 7.66 (d, 2 H, J = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.0, 16.1, 21.7, 23.9, 31.5, 43.6, 43.7, 51.2, 68.2, 68.9, 72.7, 74.0, 111.2, 113.7, 118.9, 121.4, 123.5, 126.8, 127.1, 127.4, 129.6, 134.6, 138.4, 144.4; mass spectrum (ESI) *m*/*e* (% relative intensity) 537 (100) $(M + Na)^+$, 539 (80), 515 (15) $(M + H)^+$; HRMS (ESI) calcd for $C_{27}H_{28}Cl_2N_2O_2SNa$ 537.1141, found 537.1153.

Diels−Alder Cycloadditions. $AgSbF_6$ (7.6 mg, 0.022 mmol) was added to a solution of $RhCl(PPh_3)_3$ (20.5 mg, 0.022 mmol) in dry toluene (4.6 mL) under nitrogen. After stirring for 30 min at room temperature, ynamide **13** (29.0 mg, 0.11 mol in 1 mL dry toluene solution) was added and the reaction mixture was stirred at room temperature. After TLC showed all ynamide **13** was consumed, the reaction mixture was filtered through a small plug of Celite, the solvent was evaporated, and the resulting crude product was purified by column chromatography (Al_2O_3, III/N, gradient eluent). **30**: R_f = 0.40 (33% EtOAc in hexanes); $[\alpha]^{20}_D$ = −17.8 (*c* 0.61, $CHCl_3$); IR (film) 3033 (w), 2959 (m), 2924 (m), 2856 (m), 2814 (w), 1762 (s), 1704 (m), 1454 (m), 1382 (m), 1258 (m), 1119 (m), 1017 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 7.0 Hz), 1.23−1.54 (m, 9 H), 2.18−2.32 (m, 3 H), 2.56−2.63 (m, 1 H), 2.69−2.73 (m, 1 H), 3.12−3.22 (m, 1 H), 4.17−4.25 (m, 2 H), 4.50 (t, 1 H, J = 8.0 Hz), 5.80 (d, 1 H, J = 9.0 Hz), 5.83−5.88 (m, 1 H); ^{13}C NMR (125 MHz, CDC3) δ 14.2, 22.7, 27.9, 29.4, 31.4, 31.9, 33.9, 35.7, 41.8, 60.6, 66.1, 118.7, 126.3, 128.3, 131.4, 156.9; mass spectrum (ESI) *m*/*e* (% relative intensity) 284.2 (100) $(M + Na)^+$; HRMS (ESI) calcd for $C_{16}H_{23}NO_2Na$ 284.1621, found 284.1630.

Intramolecular Amidations. To a solution of bromide **67a** (41 mg, 0.1 mmol) obtained above in 20 mL of dry toluene were added K_3PO_4 (43 mg, 0.2 mmol) or K_2CO_3 (28 mg, 0.2 mmol), $CuSO_4 \cdot 5H_2O$ (2.5 mg, 0.01 mmol), and 1,10-phenanthroline (3.7 mg, 0.02 mmol). After the reaction mixture was refluxed for 24 h, 1.2 mg of $CuSO_4 \cdot 5H_2O$ and 1.8 mg of 1,10-phenanthroline were added. After reflux for another 24 h, 1.2 mg of $CuSO_4 \cdot 5H_2O$ and 1.8 mg of 1,10-phenanthroline were added and reflux continued for another day or two. Then the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduce pressure. The crude residue was purified via silica gel column chromatography (using EtOAc/hexane as eluent) to give the desired product **68a** in 80% yield.

Ynamide 70: R_f = 0.46 (33% EtOAc in hexanes); IR (film) 3032 (w), 2959 (s), 2926 (m), 2854 (w), 2237 (m), 1710 (s), 1498 (w), 1400 (m), 1295 (m), 1261 (w), 1236 (m), 1130 (m), 1038 (m), 1020 (w) cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 2.53 (t, 2 H, J = 7.0 Hz), 2.60−2.63 (m, 2 H), 3.80−3.94 (m, 2 H), 4.40−4.80 (br, 2 H), 5.18 (s, 2 H), 7.36−7.43 (m, 5 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 18.9, 33.2, 48.9, 64.8, 68.7, 77.0, 78.5, 128.2, 128.4, 128.6, 135.6, 153.5, 174.0; mass spectrum (ESI) *m*/*e* (% relative intensity) 296.1 (100) $(M + Na)^+$; HRMS (ESI) calcd for $C_{15}H_{15}NO_4Na$ 296.0893, found 296.0889.

Ynamide 68a: R_f = 0.41 (33% EtOAc in hexanes); IR (thin film) 2943 (m), 2259 (w), 1724 (s), 1450 (w), 1285 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53−1.64 (m, 2 H), 1.64−1.79 (m, 4 H), 1.87−1.98 (m, 2 H), 2.48−2.67 (m, 4 H), 3.52 (t, 2 H, J = 6.0 Hz), 4.25 (t, 2 H, J = 5.1 Hz), 5.24 (s, 2 H), 7.30−7.48 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 21.5, 21.7, 25.5, 26.7, 32.6, 48.6, 63.2, 67.9, 68.4, 74.8, 127.4, 127.9, 128.4, 136.0, 155.7, 173.4; mass spectrum (APCI) *m*/*e* (% relative intensity) 330 (18) $(M+1)^+$, 304 (21), 286 (100), 214 (38), 196 (12); HRMS (EI) calcd for $C_{19}H_{23}NO_4Na$ $(M + Na^+)$ 352.1519, found 352.1523.

Ynamide 79: R_f = 0.44 (33% ethyl acetate in hexanes); $[\alpha]^{20}_D$ = −136.8 (*c* 0.67, $CHCl_3$); IR (film) 2941 (m), 1755 (s), 1733 (s), 1652 (m), 1558 (m), 1243 (m), 1213 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03−1.12 (m, 1 H), 1.48−1.58 (m, 2 H), 1.76−1.98 (m, 2 H), 2.07−2.16 (m, 1 H), 2.22−2.39 (m, 1 H), 2.45−2.55 (m, 1 H), 3.27−3.37 (m, 1 H), 3.68−3.79 (m, 1 H), 3.95−4.03 (m, 1 H), 4.36−4.46 (m, 1 H), 5.21 (s, 2 H), 7.06 (d, 1 H, J = 8.0 Hz), 7.15 (d, 1 H, J = 8.0 Hz), 7.14−7.48 (m, 10 H), 7.83 (d, 2 H, J = 8.0 Hz), 7.92−8.00 (m, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 21.2, 22.9, 28.0, 32.6, 46.5, 64.4, 68.2, 80.8, 111.7, 113.6, 117.3, 121.7, 123.6, 125.1, 125.4, 125.5, 126.2, 126.5, 126.6, 127.0, 127.6, 128.1, 128.2, 128.6, 128.7, 129.0, 129.9, 131.7, 133.8, 133.9, 146.8, 154.0, 171.6; mass spectrum (ESI) *m*/*e* (% relative intensity) 592.2 (100) $(M + Na)^+$; HRMS (ESI) calcd for $C_{37}H_{31}NO_5Na$ 592.2094, found 592.2108.

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

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